The use of *Chiro*-Inositols in Asymmetric Synthesis

By

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Abstract

D- and L- *chiro*-inositols are readily and inexpensively available as their *O*-methyl ethers pinitol and quebrachitol. To date the use of the *chiro*-inositols in synthesis has not been exploited as fully as that of the more common isomer *myo*-inositol. The *chiro*-inositols were protected as either the di-isopropylidene or the di-cyclohexylidene systems to give them more steric bulk and were subsequently evaluated in the three areas of asymmetric synthesis;

- as chiral reagents
- as chiral auxiliaries
- as chiral ligands.

Outside of these areas was the successful application of methodology for the mono esterification of C-2 symmetric diols to these inositol systems. This allowed a series of molecules to be generated that proved useful in the areas outlined above.

For the use of *chiro*-inositols as chiral reagents, two reagents were investigated. The first was a hydroboration reagent similar to pinenyl borane. The second was the generation of a strained silacycle for use as a reagent in the enantioselective allylation of aldehydes.

In the area of chiral auxiliaries, these inositols were successfully used to give selectivity in the Michael reaction. Unfortunately this success was not repeatable in the aldol reaction. Investigations into the development of chiral ligands were unsuccessful in that we were unable to synthesize either a diamine or an amino alcohol from this system. A diol and an amino ether were trialed in asymmetric reactions but failed to provide any catalytic effect. This section of the project did lead to some interesting chemistry and a better understanding of this system that can be applied to future work.

Acknowledgements

One of the most important people in a PhD student's life (or perhaps the bane thereof) is their supervisor, I was lucky enough to have two. Thanks have to go to Dr John Hoberg who has supervised me for my entire time as a postgraduate student. I also owe thanks to Dr Andy Falshaw from IRL, we didn't mean all the Muppets comments. Thanks also to Dr Paul Teesdale-Spittle for both the modeling and the rugby.

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Finally a mention to everyone else in my life, first and foremost to my family, Dad (yeah it is chemistry), mum, Ash, Del, Haig and especially MICHAEL ROBERT LEE, thanks for all your love and support over the years. Also to everyone else who helped with my 'sanity' – Sam, Aimee, Emmett, Phil, Dacau, JK, Paula, Mike E, Scott, the band, Tom, Jay, Age, Amy and Derek.

Table of Contents

List of Reaction Schemes

List of Figures

List of Tables

Table of Abbreviations

Ac	Acetate
9-BBN	9-Borabicyclo[3.3.1]nonane
BINOL	1,1-bi-2-Napthol
Bn	Benzyl
BSA	*N,O*-bis(trimethylsilyl)acetamide
BuLi	Butyl Lithium
m-CPBA	m-Chloroperoxybenzoic acid
e.e.	Enantiomeric Excess
DAIB	(±)-3-*exo*-(dimethylamino)isoborneol
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
Cy	Cyclohexyl
DCI	D-*chiro*-inositol
d.e.	Diastereomeric Excess
DEAD	Diethylazodicarboxylate
DMAC	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DPPA	Diphenyl phosphorazidate
Et	Ethyl
FDA	United States Food and Drug Administration
GPI	Glycosyl Phosphatidyl Inositol
IR	Infrared spectrometer

IRL	Industrial Research Limited
Ipc	Diisopinocamphenyl
LA	Lewis acid
LAH	Lithium aluminium hydride
LCI	L-*chiro*-inostiol
LDA	Lithium diisopropylamine
LHMDS	Lithium hexamethyldisilazane
LTMP	Lithium tetramethylpiperidide
Me	Methyl
MeCN	Acetonitrile
Ms	Mesylate (methane sulfonyl)
MOM	Methoxy methyl
Ph	Phenyl
Piv	Pivaloyl (trimethylacetate)
psi	Pounds per square inch
py	Pyridine
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidne
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidne
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	Triflate (trifluoromethanesulfonyl)
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl

TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl

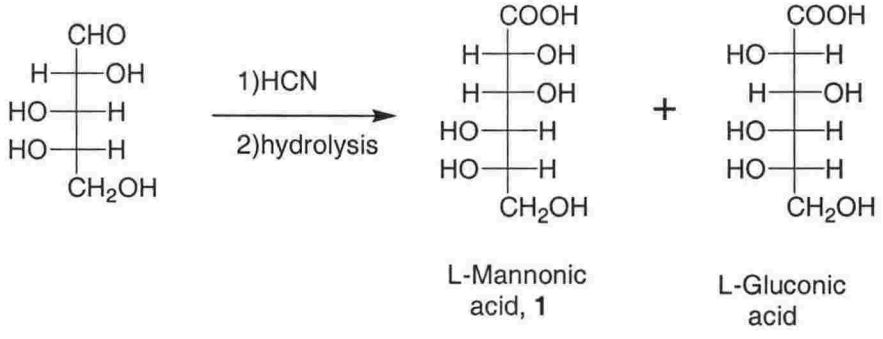
Chapter One - Introduction

> *"Synthesis is the central arena of modern organic chemistry providing specifically designed and precisely constructed materials on which many other services rely. The current high level of precision demanded of synthesis, including the provision of single enantiomers as well as single diastereomers, makes the understanding of the factors which allow control of the stereo-selectivity in organic synthesis an essential and fundamental topic for all students of chemistry."*

As Davies says in the above quote[1] asymmetric synthesis is a vital, and still growing part of modern organic chemistry; receiving recognition in 2001 with the awarding of the Nobel Prize to three chemists who have been at its forefront.[2] The origins of chirality are a hotly debated topic with many varying opinions published on the subject.[3] These range from pointing out that chirality appears to contravene the second law of thermodynamics and thus the theory of evolution must be doubted[3b] to many other more scientifically reasoned proposals none of which can be categorically proven. However chirality did originate, it is a concept that is fundamental to daily life affecting acts as simple as putting on a shoe or the taking of many modern medicines. Chirality means that molecules can exist as enantiomers and while they have identical physical and chemical properties they will interact with chiral environments such as biological systems differently. Thus the need for syntheses that can form one enantiomer (or diastereomer) preferentially is becoming increasingly important.

Most chemists will be familiar with the story of Pasteur and his serendipitous discovery of enantiomers while working with the $NaNH_4$ salts of tartaric acid; with the

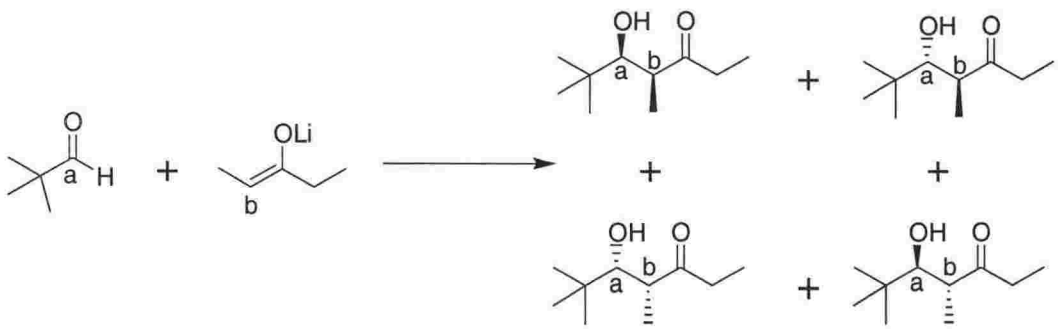
term *Chirality* being proposed by Kelvin in 1904.[3c] After discovering and describing the phenomenon of chirality, Pasteur began attempts at an early type of stereoselective synthesis. His initial investigations into inducing asymmetry included running reactions in a centrifuge and modifying the chirality of natural products by rotating plants. He also attempted a type of kinetic resolution by growing crystals in a magnetic field to induce enantiomeric resolution. As amusing as this may sound today, the use of physical forces in asymmetric synthesis has continued to be investigated. Included in a review by Feringa[3d] is the use of linearly polarized light in a magnetic field (1953), the use of electric and magnetic fields, the earths gravitational field (1978-1980) and more successfully asymmetric photochemical reactions. The first successful stereoselective synthesis, occurring in 1890, is credited to the father of carbohydrate chemistry, Emil Fischer.[4] After reacting L-arabinose with hydrogen cyanide, Fischer noticed that the resulting product was roughly two thirds L-mannonic acid, **1**, and one third its diastereomer, gluconic acid, scheme 1.1.



Scheme 1.1

Asymmetric synthesis was defined in 1904 by Marckwald as "*a reaction which produced optically active substrates from symmetrically constituted compounds with the*

intermediate use of optically active materials but with the exclusion of all analytical processes".[5] The modern view of asymmetric synthesis is broader in scope, in practice it is any reaction in which an achiral molecule or moiety is converted into a chiral one giving the products, whether enantiomers or diastereomers, in unequal amounts. It is also useful to note the difference between stereoselective and stereospecific reactions although this difference is often not acknowledged and it is common for the terms to be used interchangeably. A stereospecific reaction is one in which the reaction gives a specific stereochemistry in the product that is derived from particular stereochemistry in the starting material. Thus in a stereospecific reaction there is only one possible product stereoisomer for each starting stereoisomer. A stereoselective reaction is one in which two or more stereoisomers can be formed with one formed in excess. Examples are the formation of one or more new stereogenic centres in a chiral substrate, such as in the nucleophilic addition to a ketone or aldehyde. An example is the formation of new stereocentres from the reaction of two prochiral substrates, as in the aldol reaction shown in scheme 1.2.



Scheme 1.2

Stereoselective synthesis involves the formation of new stereogenic centres with one stereoisomer predominating. These reactions can be either enantioselective or diastereoselective. Emil Fischer first proposed the concept of diastereoselective synthesis, realizing that the ratio of formation of diastereomers in a product could be influenced by chirality already present in a molecule. A diastereoselective reaction will go through diastereomeric transition states, thus the ratio of isomers formed or diastereomeric excess (de) is reliant on the energy difference between the two transition states, figure 1.1. As shown, approach of the phenyl nucleophile on the same side of the C_3 phenyl moiety (as in the left hand case) increases the transition state energy relative to the nucleophile approaching from the opposite side (as in the right hand case).

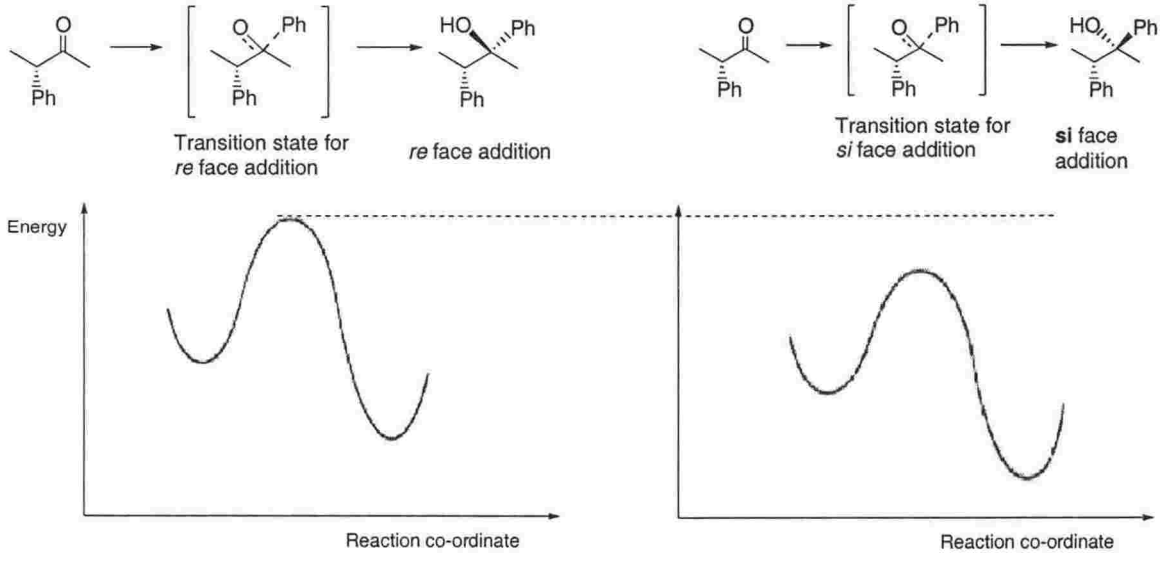


Figure 1.1-Diastereomeric transition states leading to diastereomeric products

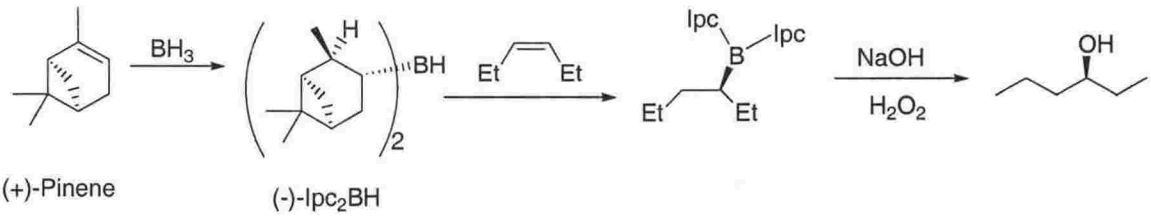
An enantioselective reaction is one in which one enantiomer is formed in excess. This type of selectivity can only be achieved by chiral methods. For a reaction to be

stereoselective there must be a discriminating factor that forces the reaction to occur preferentially from one face in a prochiral molecule. Many methods have been investigated to achieve this. Some, such as the use of chiral solvents or the use of circularly polarized light, have very limited success.[4] The strategies that are more successful are the use of chiral reagents, chiral auxiliaries, and chiral catalysts. As the focus of my research is in these areas the basics, with examples, will be presented.

1.1 Chiral reagents.

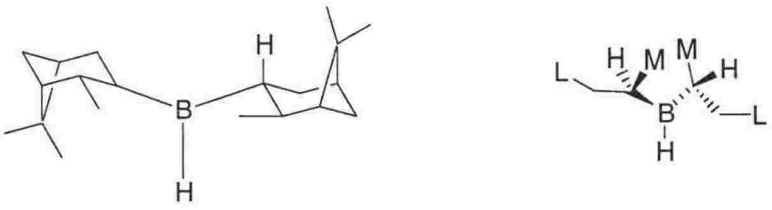
A chiral reagent is a reagent that within the course of a reaction induces stereochemistry in a prochiral starting material. For this strategy to be effective, the reagent must be present as a single enantiomer and used stoichiometrically, which can make the cost of reagents an issue. However, very high levels of selectivity can be achieved as long as the stereochemistry of the reagent is fixed. A good starting point for the generation of chiral reagents are natural products as they are inexpensive and in some cases both enantiomers are available. One of the best-known examples of this are the pinenes, which are easily converted into chiral organoborane reagents. The regio- and stereoselective hydroboration of (+)-α-pinene ($[\alpha]_D$ + 47.6° neat), gives the reagent (–)-Ipc_2BH ($[\alpha]_D$ –37.1°, THF), scheme 1.3. Conversely, hydroboration of (–)-α-pinene gives (+)-Ipc_2BH.[6] Like most other mono and dialkyl borane systems this reagent will, unless co-ordinated to a strong Lewis acid, exist as a dimer. However, it is usually written and shown as the monomer for convenience. One of the many areas in which these molecules have been used as chiral reagents is in the synthesis of chiral alcohols by the asymmetric hydroboration of *cis* olefins. An early example of their use was reported by Mandal and

Yoon, who used (–)-Ipc_2BH to hydroborate *cis*-hex-3-ene to give R-(-)-hexan-3-ol in 95% ee, scheme 1.3.[7]



Scheme 1.3

The hydroboration reaction involves the addition of a hydrogen atom to one end of a double bond while an alkyl boron group adds to the other end. This occurs in a concerted fashion with *syn* addition. By using a chiral reagent such as Ipc_2BH, the steric hindrance provided by the pinene groups allows for stereocontrol over the reaction. The stereoselectivity exhibited by this reagent can be explained via a model that is based on the most stable conformation of (–)-Ipc_2BH. In this conformation, the borane group and the *trans* methyl group on the pinene are equatorial. This model is shown as **2** in figure 1.2 and can be further simplified into **3**.



2 **3**

Figure 1.2-(-)Ipc_2BH reagent

In this model, M represents the methylene of the pinene ring and L the methyl group. There have been two different models proposed for the co-ordination of a *cis* olefin to this system, these are shown in figure 1.3. The first transition state model **4** is favored over **5** as there is less steric interaction between the methyl group from the olefin and the pinene methylene and this agrees with the observed stereoselectivity.

4 **5**

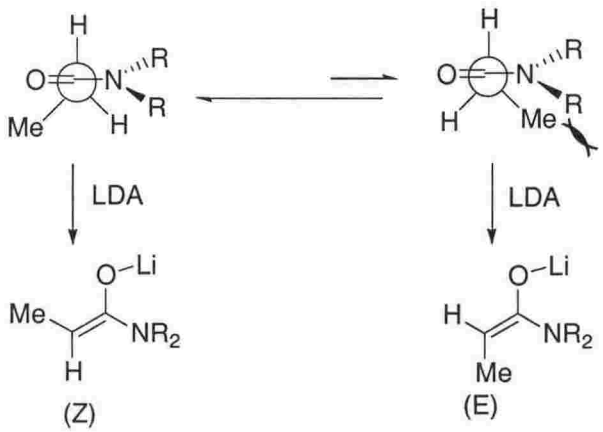
Figure 1.3-Coordination of a *cis*-olefin to Ipc_2BH

1.2 Chiral Auxiliaries.

A chiral auxiliary is a species that is covalently attached to a prochiral starting material and undergoes a reaction converting the entire molecule into a diasterotopic species. Chiral auxiliaries can be expensive as they must be used stoichiometrically, however the benefit of using these are the reaction products are diastereomers not enantiomers making them easier to separate. If the auxiliary is well designed, removal of the auxiliary from the substrate will enable its recovery and re-use. The important design features of a good chiral auxiliary are:

- Recyclable,
- Easily synthesized,
- Available as both enantiomers,
- Give high de's.

Evans pioneered this area developing it into a useful area of synthesis with his work on the formation and application of chiral enolates.[8] His groups early work investigated the use of amides, which undergo deprotonation with amide bases, scheme 1.4. They noticed that the formation of enolates in these systems is highly stereoselective, and with the enolization of *N,N*-dialkylamides the Z-enolate was formed preferentially over the (E).



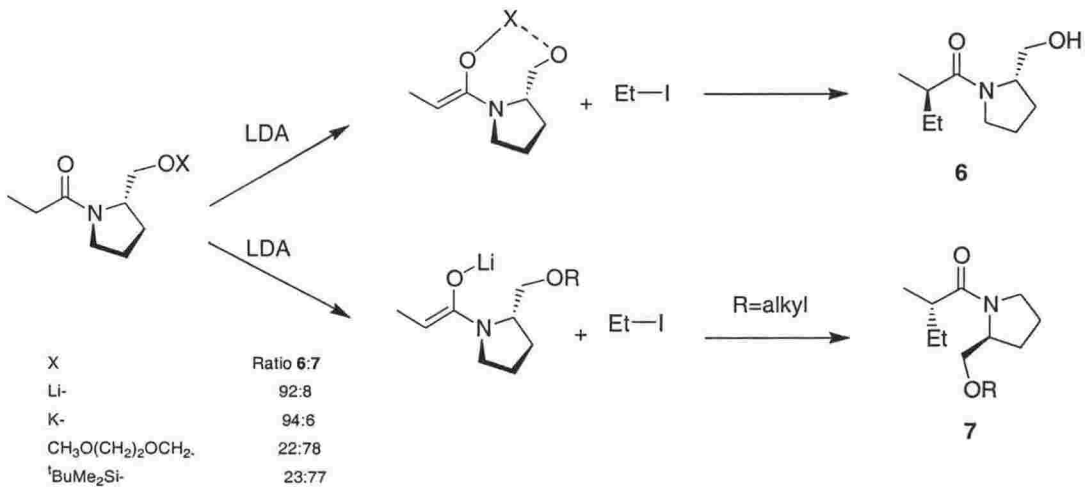
Scheme 1.4

This was rationalized by using conformational arguments in which the (E) product is disfavoured due to steric factors pushing the methyl away from the NR_2 group.[8] Alternatively, when enolates of *N*-acyloxazolidinones are generated, the (*E*) isomer has the favoured conformation due to co-ordination between the lithium ion and the carbonyl oxygen on the auxiliary, figure 1.4. The formation of enolates can also be controlled by incorporating sterically bulky groups into the molecule, as conformational restrictions will force the enolate into either the (*E*)- or (*Z*)- geometry.

Z-enolate *E*-enolate

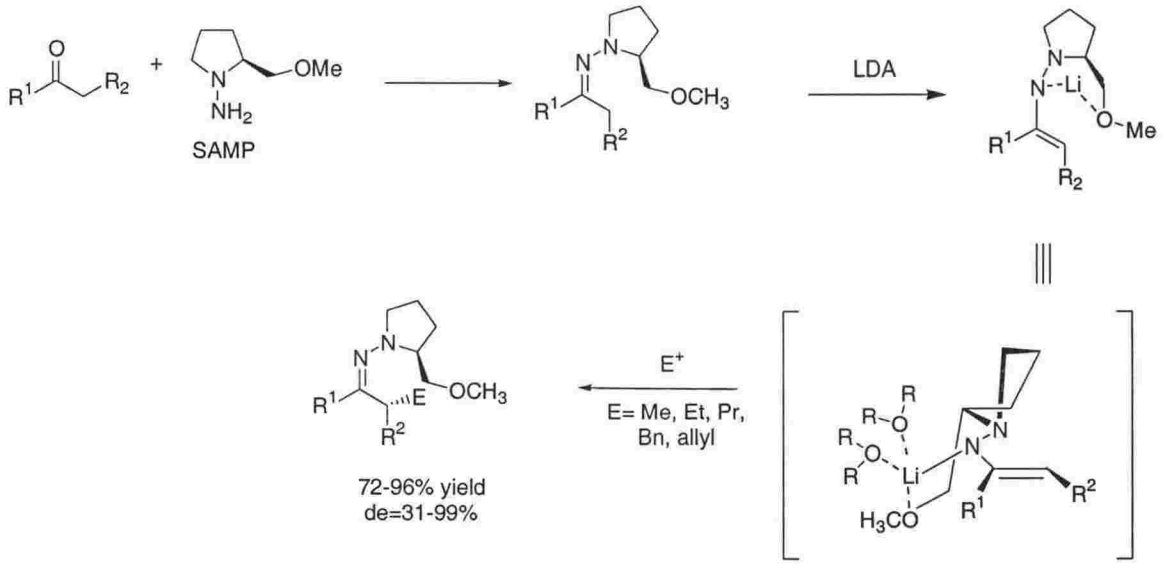
Figure 1.4- *Z*- and *E*- enolates

Evans applied this work to a variety of reactions that involve enolate intermediates, these included asymmetric Aldol reactions and α-substitutions. In reactions where an electrophile attacks the enolate, the chirality transferred was found to be dependent on the substitution of the hydroxymethyl moiety of the ligand, scheme 1.5. This selectivity difference arises from electrostatic forces governing the two cases. In the formation of **6**, the metal ion chelates to both the carbonyl and the ligand oxygen atoms. This blocks the bottom face of the molecule forcing the electrophile to attack from the top face. When the metal ion is absent, the repulsive electrostatic forces between the carbonyl oxygen and the oxygen on the ligand dominate. This forces the auxiliary to rotate leaving the chiral ligand blocking the top face thus forcing the electrophile to attack from below to give **7**.



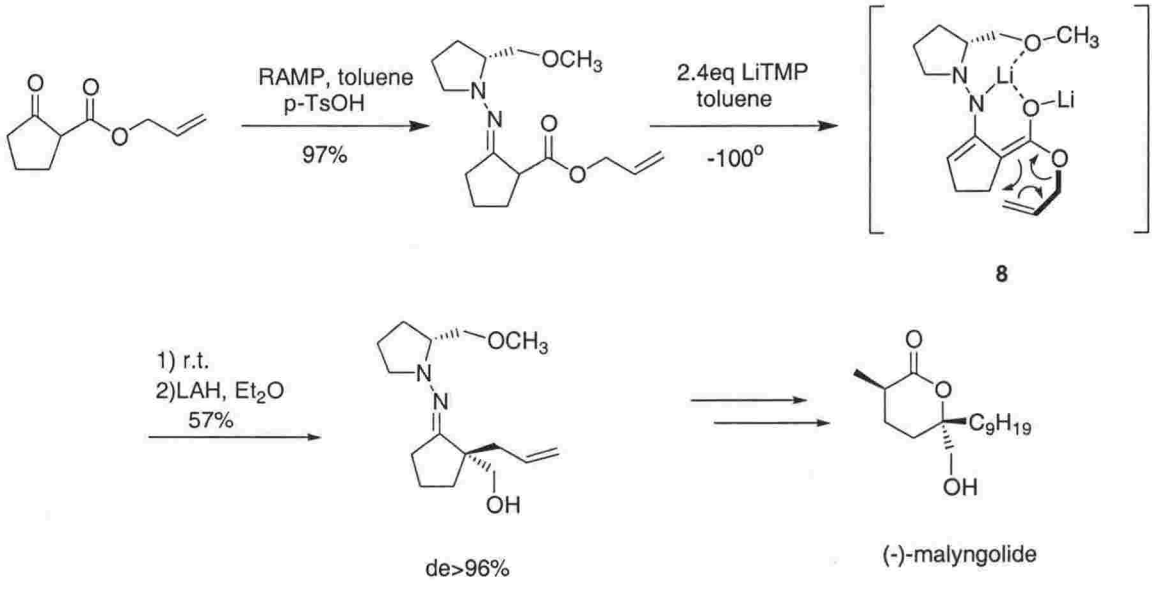
Scheme 1.5

Obvious starting points for the generation of these chiral auxiliaries are again natural products. The first asymmetric synthesis using a natural product derived auxiliary was published by Yamada and co-workers in 1969 with an (*S*)-proline derived auxiliary.[9] Evans' early work also included L-Valinol derived oxazolidinones as auxiliaries. Also derived from (*S*)-proline is (*S*)-1-amino-2-methoxymethylpyrrolide or SAMP, first reported by Enders and colleagues in 1976 and synthesized in a four-step procedure in 58% yield.[10] The (*R*)- isomer (RAMP) is also available in six-steps starting from (*R*)-glutamic acid in 35% yield;[10] other more sterically demanding analogues of these moieties are also available. SAMP and RAMP are readily converted into chiral hydrazones, which are then deprotonated by lithium diisopropylamide (LDA) or similar bases to give the corresponding enamines with high geometrical selectivity, scheme 1.6. These undergo a variety of reactions such as aldol condensations, Michael additions or the alkylation as shown.



Scheme 1.6

The Carroll rearrangement generates unsaturated ketones via the [3,3] sigmatropic shift of allyl acetoacetates. SAMP/RAMP chemistry has been used to develop an asymmetric variant of this reaction.[11] The auxiliaries were reacted with β-ketoallylesters to form hydrazones, which were doubly deprotonated by treatment with a base, typically LDA, leading to a species that underwent an asymmetric Carroll rearrangement. A Lewis acid mediated version of this reaction was used in the asymmetric synthesis of (–)-malyngolide, a lactone with potential as an antibiotic that was isolated from *Lyngbys majuscula*, a marine blue-green algae.[12] Early in this synthesis, the RAMP hydrazone was deprotonated to initiate the asymmetric Carroll rearrangement and the product reduced with lithium aluminium hydride (LAH) to give an α-quaternary hydrazone. The reaction, as shown in scheme 1.7, goes through the transition state **8** with the proposed intramolecular chelation of the Li to the methoxy group on the RAMP auxiliary. This forces the allylic group to approach from the less hindered front face leading to *si*-attack. The auxiliary was then cleaved with ozone in a 78% yield with no epimerisation.



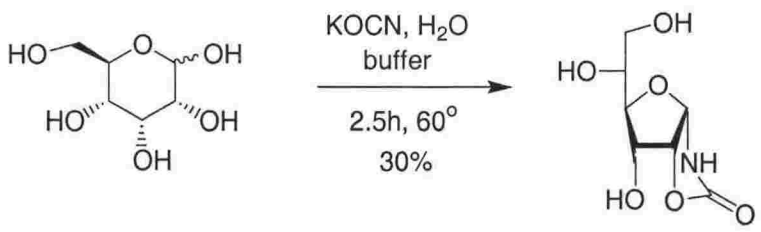
Scheme 1.7

More recent work on natural product derived auxiliaries has involved L-Valinol and L-phenylalaninol derived 2-imidazolidinones.[13] Schneider and Reece converted *t*-Leucine into *N*-enoyl 1,3-oxazolidin-2-ones, which were used as auxiliaries for asymmetric conjugate additions.[14] The yields were only between 58 and 63% but selectivity was very high with the lowest de being 90%. This is a good example of the importance of conditions to these reactions. When carried out in the presence of a metal catalyst chelation led to attack of the nucleophile from the front face, figure 1.5. However, when a Lewis acid such as BF_3 was used, the auxiliary was able to rotate to lessen the repulsive electronic effects between the two carbonyl oxygen atoms leading to backside attack.

Figure 1.5-Effects of chelation in conjugate addition reactions

Other natural product starting points have included modified guanidines,[15] camphor derivatives,[16] and cyclitols, which will be discussed later as they are of relevance to this research into the use of inositols in asymmetric synthesis. Wang and co-workers have used a D-fructose derivative to generate α-hydroxy carboxylic acids,[17]while Köll and co-workers have carried out a more comprehensive study into the use of

monosaccharides as auxiliaries. They have prepared a range of sugar derived cyclic carbamates or glyco-oxazolidinones. Over the ten years they have been generating these compounds they have utilized most pentoses and hexoses including D-mannose, D-galactose, D-xylose, D-ribose, L-arabinose and of course D-glucose.[18] The cyclic carbamates are synthesized by treatment of the sugar moiety with potassium cyanate in buffered aqueous solutions as illustrated in scheme 1.8. Since the first report of these carbamates in 1991, they have been used for asymmetric α-alkylations, α-acylations, α-halogenations and aldol reactions.[19]



Scheme 1.8

1.3 Chiral Catalysts.

Where chiral auxiliaries are chemically attached to the achiral starting material and thus are used stoichiometrically, chiral catalysts effect the transition state of a reaction and are therefore required in much smaller quantities. This is an attractive feature both economically and environmentally. The other major difference between a chiral auxiliary and a chiral catalyst is that where an auxiliary gives diastereomers a catalyst can give enantiomers. The importance of catalytic asymmetric reactions is highlighted in the literature with an annual review published in *Perkin Transactions,* covering developments in asymmetric catalysis for a preceding calendar year.[20] However,

the quantity of literature published on this topic is so vast that the authors specifically state no attempt has been made to make these reviews fully comprehensive.

Modern chemists have a very good working knowledge of which metals catalyze a given reaction, such as palladium for carbon-carbon coupling or ruthenium for metathesis. The majority of work going into new catalysis is involved with the design of new ligands or the 'tweaking' of older ones to improve selectivity and/or yield. There are key properties a molecule must have for it to be successful as a ligand. Firstly, the molecule must be able to form a sufficiently stable complex with the appropriate metal for a given reaction. Secondly, the ligand cannot de-activate the metal center, and finally for the ligand to give selectivity it must force the reactant to approach the metal center from a specific direction. This is usually achieved by using geometrically designed ligands to occupy specific areas of space around the metal ion forcing the incoming substrate to coordinate in a specific conformation, figure 1.6.[21]

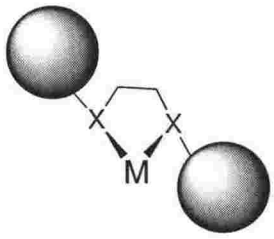
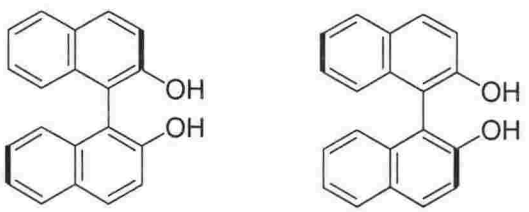


Figure 1.6- Schematic of ligand design

A valuable class of ligands are those that have a C_2 axis of symmetry. This symmetry in the ligand increases the selectivity of the catalyst as there is a reduction in the number of possible diastereomeric transition states due to the equivalent asymmetric environments imposed on the molecule.

Modern computational techniques have been applied to ligand design by computer aided functionality mapping. Functionality mapping involves looking at the transition state of a given reaction and identifying optimal interactions between the transition state and a set of selected functional groups. Using energy calculations, ligands are then proposed that should have optimized selectivity and activity.[22] A ligand can coordinate to a metal cation through any electronegative atom including O, S, N, C, and P. For the ligand to have a stable conformation on the metal, it has to be reasonably rigid and is traditionally bidentate. This last point has in recent times proven to be unnecessary as there have been examples of monodentate ligands such as monophos, which achieves selectivities as high as some bidentate ligands.[23] Probably the best-known bidentate diol ligand is the axially chiral BINOL (1,1-bi-2-napthol) and its various derivatives including the diamine BINAP.[24] BINOL is commercially available in both enantiomeric forms (*R*)-BINOL and (*S*)-BINOL, figure 1.7.

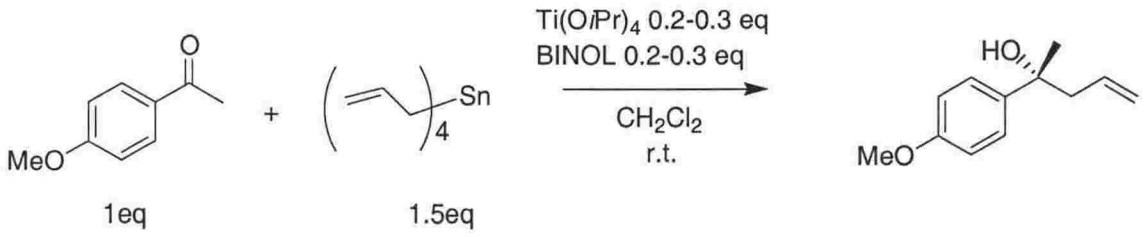


(R)-BINOL (S)-BINOL

Figure 1.7- (*R*)- and (*S*)- BINOL

The essence of BINOL as a ligand is that it will chelate to a wide variety of metal ions. Examples are known where it is used as a ligand on main group elements,[25] transition metals,[25] f-block metals[26] and bimetallic combinations of the above groups.[27] Titanium is the metal that is very often used with BINOL as it bonds strongly to oxygen.

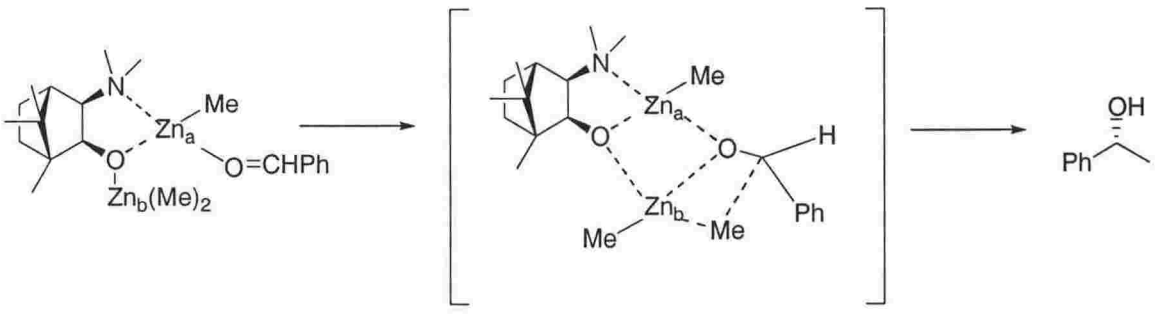
The variety of titanium reagents available allows the catalyst to be 'fine tuned' by variation of the electronic properties of the other ligands.[28] The asymmetric allylation of carbonyl compounds is a useful organic transformation. However it had proven difficult to carry out this reaction catalytically. Walsh and co-workers generated a catalyst for this reaction from BINOL (20-30mol%), $Ti(O^iPr)_4$, (20-30mol%) and 2-propanol (20mol%).[29] The inclusion of the 2-propanol appears to be a serendipitous discovery as it was found that when the catalyst was prepared in situ without removal of the liberated 2-propanol the ee of the reaction when carried out on 3-methylacetophenone rose from 51% to 73%. They then used this catalytic system to alkylate a series of ketones with an example shown in scheme 1.9. Yields ranged from 67% to 99% with ee's from 76% to 96%.



Scheme 1.9

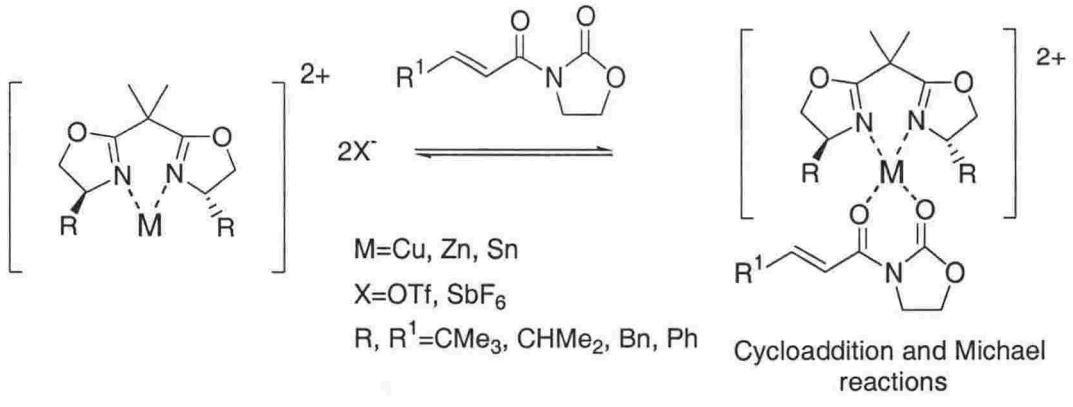
Amino-alcohols also have good precedence as ligands in asymmetric synthesis. An example is the addition of alkyl zincs to carbonyls and related compounds. Catalysts that have proven very successful in this area are the camphor derived 3-*exo*-(dimethylamino)isoborneol (DAIB). (–)-DAIB was first reported by Chittenden and Cooper in 1970[30] and was applied to the asymmetric addition of dialkylzincs to aldehydes by Noyori and co-workers.[31] They compared its catalytic properties with *cis*-1-

(dimethylamino)-2-hydroxycyclohexane and *cis*-1-(dimethylamino)-2-hydroxycyclopentane. DAIB proved to be the superior of the three requiring 2 mol% to catalyze the reaction of diethyl zinc with benzaldehyde (1.2:1 molar ratio) at 0 °C giving (*S*)-phenylpropan-1-ol in 97% yield and 98% ee. In further studies on this system, it was found that the stoichiometry of the DAIB, aldehyde and alkylating agent is vital to this reaction. While the reaction works very well with catalytic DAIB, the reaction does not occur if no DAIB or a stoichiometric amount is present. When a stoichiometric amount of DAIB is used, the carbonyl is not alkylated but benzyl alcohol is formed at a very slow rate. A variety of mechanisms and transition states have been considered in the past. Noyori, who has done much of the work on this system including theoretical studies, has proposed the one thought most accurate for dimethylzinc and benzaldehyde at present.[32] This proposed alkyl transfer mechanism is shown in scheme 1.10. The carbonyl oxygen complexes preferentially to Zn_a over Zn_b due to the increased Lewis acidity of Zn_a and the alkyl group is then transferred from Zn_b to the carbonyl. An example of the application of this catalyst is in the total synthesis of (+)-aspicillin, a macrocyclic lactone isolated from a lichen. In this synthesis, (–)-DAIB was used in the macrocyclization step forming an 18-membered lactone ring in 60% yield and 91% de.[33]



Scheme 1.10

A final example of chiral ligands that have been extensively used are the chiral bis(oxazoline) complexes developed by Evans. These ligands have been successfully used for asymmetric cyclopropanations, aziridations, Michael reactions, enol amination, aldol reactions and hetero Diels-Alder reactions.[34] Their general design strategy is shown in scheme 1.11, with a selected catalyst-substrate complex also shown.[35]



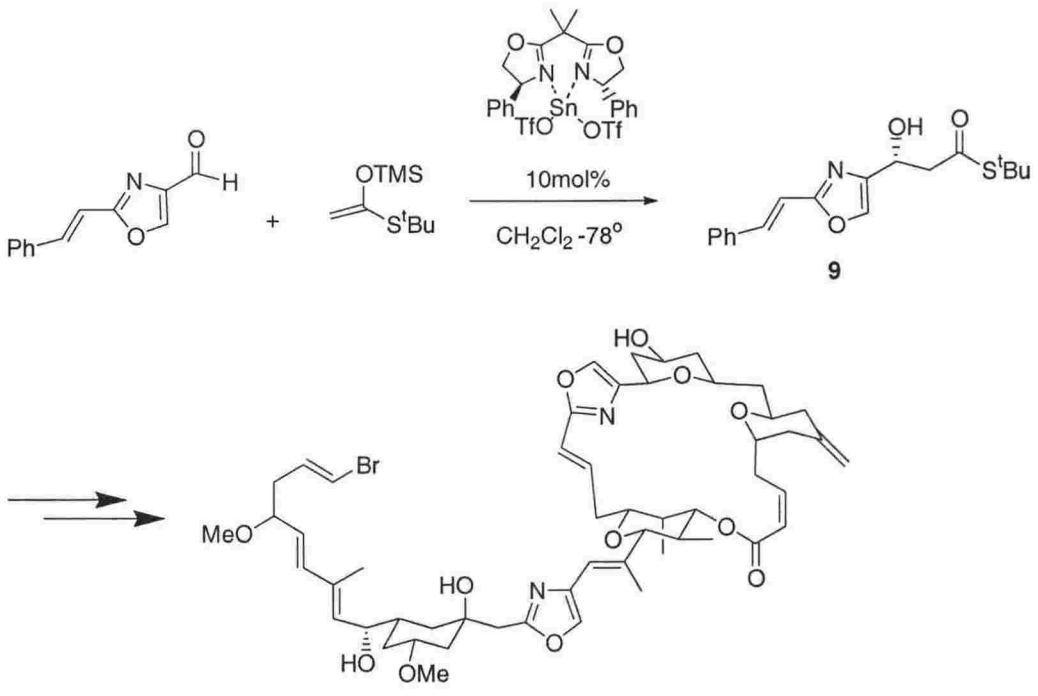
Scheme 1.11

As shown in the scheme above, Zn(II) and Sn(II) have been used with this system however Cu(II) is the metal of choice as it forms the most stable ligand-metal complexes for divalent ions, this is consistent with the Irving-Williams order

(Mn<Fe<Co<Ni<Cu>Zn).[36] Jahn-Teller factors, such as Cu(II) favouring the coordination of a bidentate substrate in the equatorial plane and the increased labilization of axial ligands, give the Cu(II) bis(oxazoline) complexes high stability and lead to the formation of well defined complexes. A small but worthy point to note is that the catalyst counter ions and their ability to modulate the Lewis acidity of the catalyst are also important. For Diels-Alder, reactions it was found that $[Cu(box)](SbF_6)_2$ complexes reacted up to 20 times faster and had better selectivity than the comparable triflates.[35] The selectivity in these reactions comes from the C-2 symmetry in the molecule and the bulk of the R groups. The catalyst backbone is essentially flat with the two bulky R groups projecting into defined areas of space as was shown in figure 1.6. In the complexation step, the incoming substrate can bind in two ways, however given the C-2 axis of symmetry, the two complexes are identical. After substrate chelation, the incoming reagent is forced to approach from a specific area of space due to the steric constraints of the R groups. This leads to very high selectivity with ee's most often in the 95-99% range.

These catalysts have been used in a variety of syntheses, one example is the total synthesis of Phorboxazole B.[37] Phorboxazole B is a macrolide found in a species of Indian ocean sponge found off the coast of Western Australia. To construct the C_{13}-C_{19} fragment of this molecule a Sn(II) catalyzed Mukiyama-aldol reaction was used as shown in scheme 1.12. The product **9** was formed in 91% yield with a 94% e.e. As with any highly successful strategy in chemistry many others have adapted and used these molecules. Ghosh, Mathivanan and Cappiello have comprehensively covered many of these in a report published in 1998.[38] It should be mentioned that the optimal system in

scheme 1.11 is R=*t*Bu, however this ligand is very expensive and only one enantiomer is readily available.



Scheme 1.12

1.4 Inositols

The inositols are carbocyclic members of the carbohydrate family. They are classed as carbohydrates as they fufill the definition of a carbohydrate by having the general formula $C_n(H_2O)_n$. However, the all carbon ring makes aspects of their chemistry very different to that of sugars. In particular, all the hydroxyl groups in the molecule are secondary, and the lack of a carbonyl group leads to the absence of anomeric reactions. The term inositol refers specifically to the members of the cyclitol family having a six-membered ring and their derivatives. There are nine possible inositol isomers, which include a pair of enantiomers, figure 1.8. Four of these (*myo-*, *scyllo-*, *L-chiro-*, and *D-*

chiro-) occur relatively abundantly in nature, two more (*neo*- and *muco*-) can be found in trace amounts. The final three inositols (*epi*-,*allo*- and *cis*-) are synthetically derived.

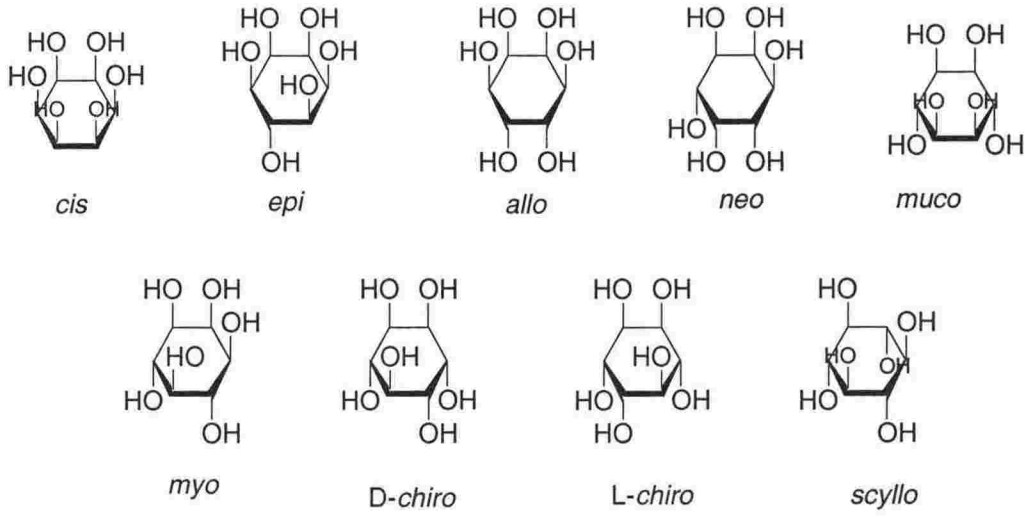


Figure 1.8-The Inositols

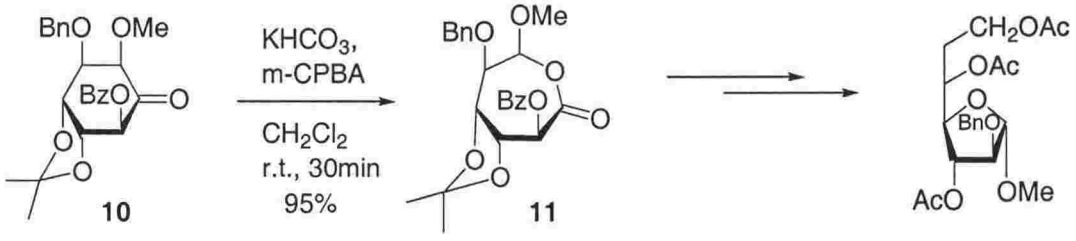
The most widely occurring of the inositols is *myo*-inositol, which was first found by Scherer in meat extract in 1850 and can also be found in plants as its methyl ethers bornesitol, sequoyitol or ononitol.[39] *Myo*-inositol is found in the cells of almost every living organism and is physiologically vital. It has been investigated as a growth factor for microorganisms and as a vitamin and lipotropic agent for animals. All animals require *myo*-inositol for the synthesis of phospholipids, which have a vital role in intercellular signaling.[40] The byosynthesis of *myo*-inositol from D-glucose and the reverse reaction have been established.[41] It was proven that animals can synthesize *myo*-inositol by the feeding of ^{14}C labeled D-glucose to rats and embryonic chicks, although it is likely that only certain animal organs can carry out this synthesis and subsequently supply the inositol to other body tissues. The conversion of *myo*-inositol into D-glucose was

demonstrated in rats by the use of deuterated and ^{14}C labeled *myo*-inositol. This reaction does not proceed by direct ring cleavage; *myo*-inositol is converted *in vitro* into DL-glucuronic acid which is subsequently converted via known metabolic pathways into D-glucose, although this is not the only way by which *myo*-inositol is metabolised.

Scyllo-inositol has been isolated from plants, several species of insects and mammals. Notably it is found in mammalian urine where it is thought to be formed by the metabolism of *myo*-inositol.[41] *Muco*-inositol is found as its methyl ether in plants while *neo*- is found in low amounts in soil phytate; the only practical way of obtaining it is through synthesis. *Epi-*, *allo-*, and *cis*- inositols are purely synthetic compounds. D- and L- *chiro*- inositols are found in plants as their methyl ethers pinitol and quebrachitol, respectively. The occurrence of these ethers in plants tends to be specific to families with only very rare examples of both being found in one family. Pinitol is commercially extracted from pine trees in New Zealand by New Zealand Pharmaceuticals and quebrachitol is extracted from natural rubber serum, a waste product from rubber processing. Both can be de-methylated by literature procedures to give the corresponding cyclitols.[42]

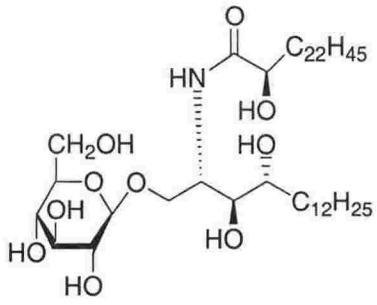
Given the low cost of both pinitol and quebrachitol and the availability of both enantiomers of *chiro*-inositol, it would be thought that they would be widely used in asymmetric synthesis. However, the majority of reports of synthesis from and/or with inositols has been carried out with *myo*-inositol. With the exception of specific research groups there has been little interest in the *chiro*-inositols. There have been some reports on the use of these materials, especially quebrachitol. Kiddle reviewed this molecule's use in the synthesis of bioactive molecules in 1995, and a short synopsis of this will be

discussed here.[43] The first reported synthesis of a natural product from quebrachitol was by Angyal, a name synonymous with most of the early work done on inositols. Angyal and Hodsin used L-quebrachitol to synthesize L-mannitol,[43] a sugar which had not been found in nature at the time. In recent times Ogawa, Chida and colleagues have reported the majority of the work on inositols in this area. They provided an early example in 1989 using quebrachitol to synthesize D- and L- galactose derivatives, scheme 1.13. They used a regioselective Baeyer-Villiger oxidation of protected quebrachitol **10** to give the seven membered lactone **11**. Lactone **11** was subsequently transformed into a variety of sugar derivatives.[44]

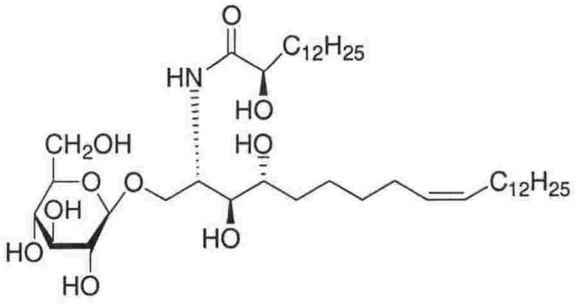


Scheme 1.13

More recently quebrachitol has been used as a starting point for the synthesis of glycosyl phosphatidyl inositols (GPI's). These molecules are found on the surface of all eukaryotic cells and have important roles in cellular interactions and differentiation. It was recently found that many GPI's have a phytosphingosine (4-hydroxysphinganine) as part of their structure. Two examples of these are Acanthacerebroside A and Astrocerebroside A, figure 1.9.



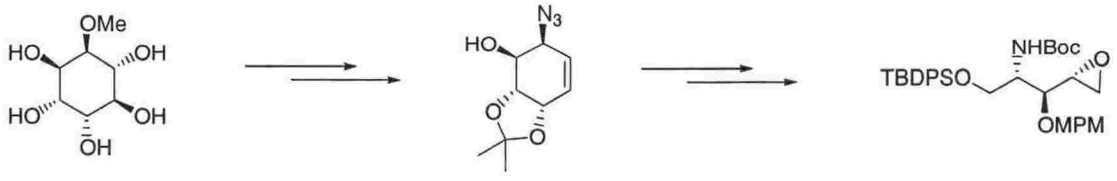
acanthacerebroside A



astrocerebroside A

Figure 1.9-Molecules synthesized from quebrachitol

Chida and co-workers synthesized these two compounds from a chiral epoxide derived from L-quebrachitol.[45] The chiral epoxide **13** is a common pre-cursor for various phytosphingosines. The azide **12** was prepared from L-quebrachitol in eight steps and then converted to epoxide **13** via a further nine reactions, scheme 1.14.



L-quebrachitol

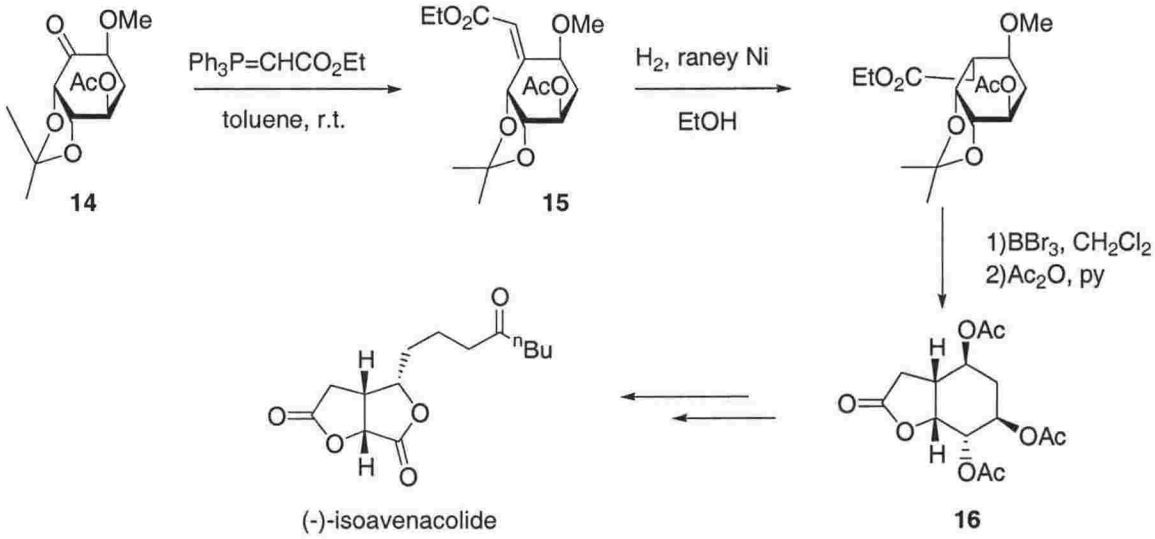
12

13

Scheme 1.14

A series of phosphatidyl-*myo*-inositols[46] and fluorinated inositol isosteres[47] were prepared from quebrachitol and pinitol by Kozikowski and colleagues. These were used in studies to investigate their effects on cellular growth. Finally, Ogawa and co-workers used quebrachitol as a starting point for the total synthesis of (–)-isoavenacolide, an anti fungal mould metabolite isolated from *Aspergillis avenaceus*.[48] This synthesis, like most

in carbohydrate chemistry, involved an extensive protection and deprotection strategy leading to the ketone **14**, scheme 1.15. This was converted via a Wittig reaction into **15** that was hydrogenated and converted into the γ-lactone **16**. This eventually led to (–)-isoavenacolide.



Scheme 1.15

Many optically active amino-gylcoside antibiotics and enzyme inhibitors have been synthesized from quebrachitol including the aminocyclitol valienamine synthesized by Paulsen and Heiber.[43] Again Ogawa and Chida have been prolific in this area using quebrachitol as a starting point for many compounds including the azahexoses galactostatin and 1-deoxygalactostatin, which are potent α- and β- galactosidase inhibitors. They have also synthesized the algycan structural component of simmondsin and the acyclic segment of (–)-oudemansin X a potent antibiotic, figure 1.10.

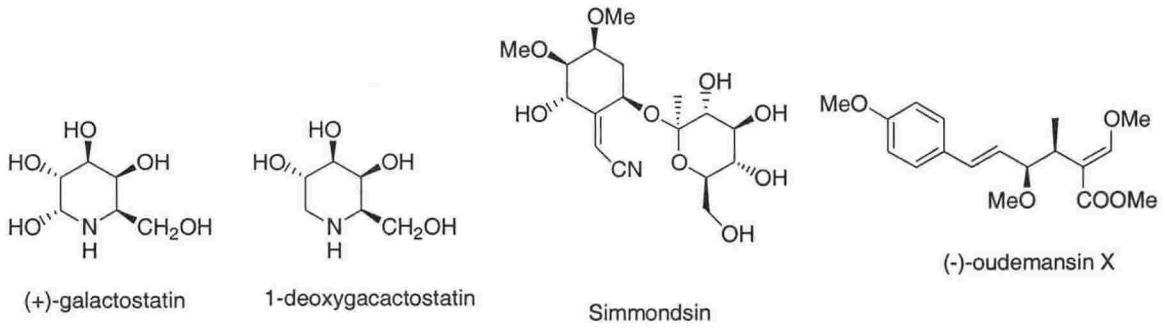
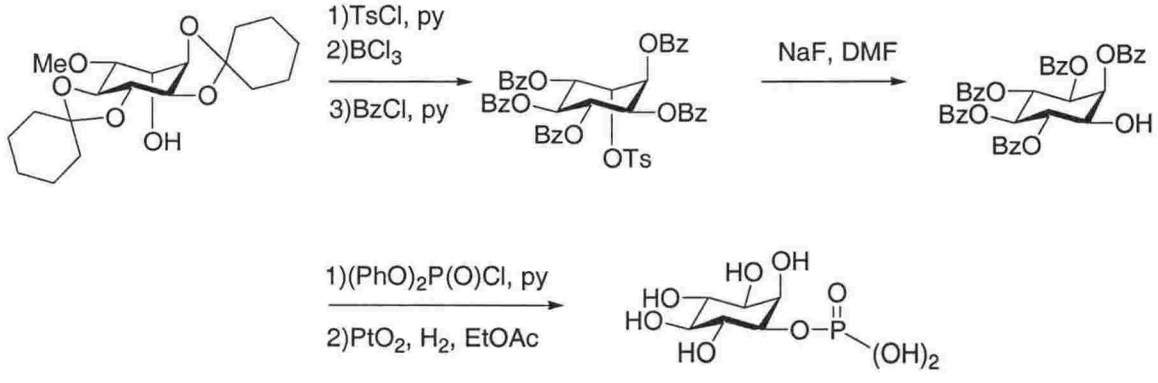


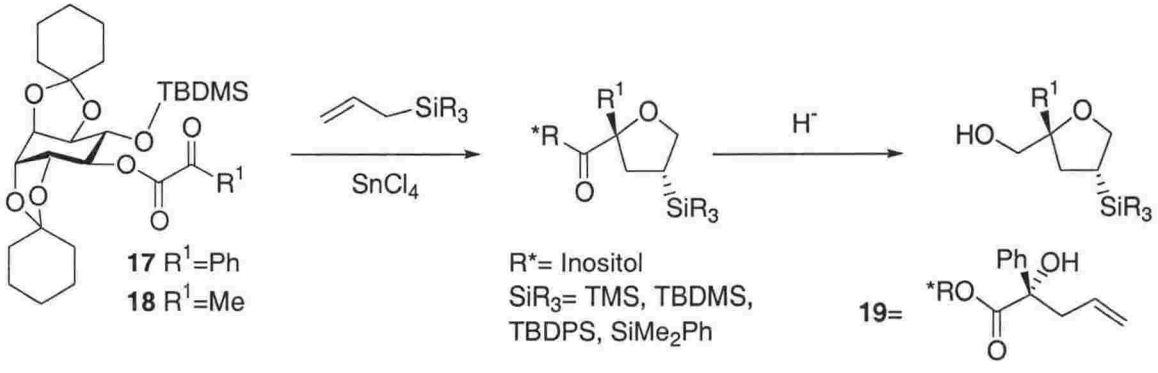
Figure 1.10-Enzyme inhibitors synthesized from quebrachitol

The final area Kiddle reviewed was the use of quebrachitol to synthesize other inositols. At the time this review was published, the only reported synthesis of an inositol isomer from quebrachitol was that of *muco*-inositol by Angyal and Odier. Quebrachitol has however, been used for two different syntheses of the naturally occurring D-*myo*-inositol-1-phosphate. The first synthesis was reported by Ozaki and co-workers, the second by Barnett and colleagues, both beginning with dicyclohexylidene protected quebrachitol. Ozaki's synthesis is long at 12 steps, while Barnetts, shown in scheme 1.16 took only six.



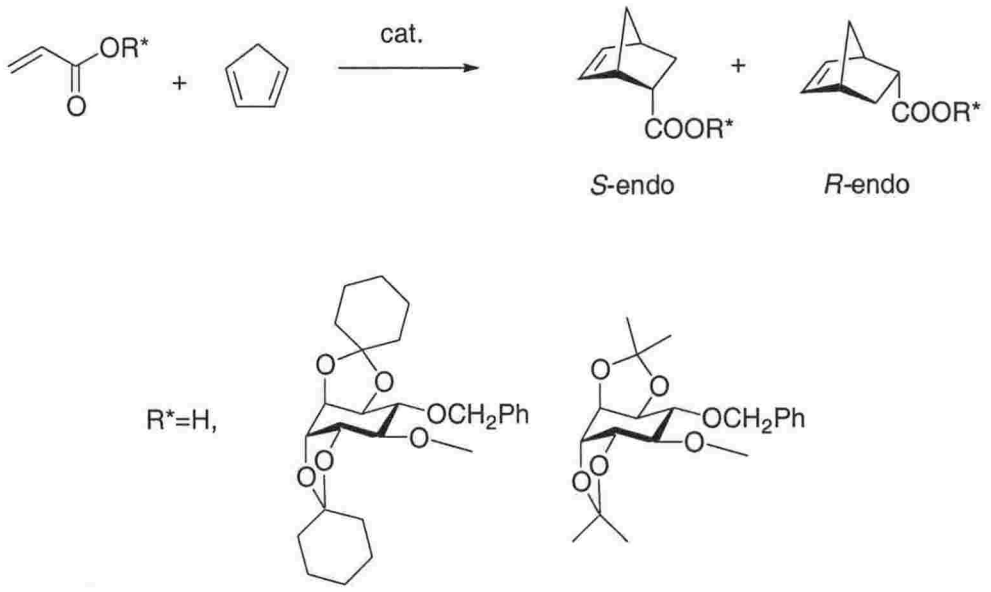
Scheme, 1.16

As mentioned previously inositols have been used as chiral auxiliaries. Ozaki and colleagues have developed a range of inositol derivatives that they have used to carry out many asymmetric reactions. They converted L-*chiro*-inositol into the dicyclohexylidene protected esters **17** and **18** by treatment of L-*chiro*-inositol with cyclohexanone with catalytic p-TsOH, followed by TBDMSCl and the appropriate acid chloride. These were treated with Grignard reagents, allyl silanes and were subjected to the tin(IV) chloride mediated addition of silyl enol ethers. Additionally, they have been used for [3+2] cycloadditions of allyl silanes as shown in scheme 1.17.[49] Yields for these reactions ranged from 48-85%, however when R^1=Ph and SiR_3=$SiMe_3$ and $SiPhMe_2$ the by-product **19** was formed in 20-22% yield. The ee's for this reaction were mostly greater than 95%.



Scheme 1.17

Another area where similar auxiliaries have been used is for Diels-Alder reactions, scheme 1.18.[50] Four catalysts were investigated; $AlCl_3$, Et_2AlCl, $TiCl_4$ and $SnCl_4$ along with a variety of solvents and conditions. Yields ranged from 0-97% with the highest product ratio attained being an endo to exo of 99:1.



Scheme 1.18

This is another example where additives control the stereochemical outcome, with $AlCl_3$ and Et_2AlCl forming endo in preference to exo but $SnCl_4$, which was able to chelate, giving the reverse selectivity. The model shown in figure 1.11 can rationalize this selectivity.

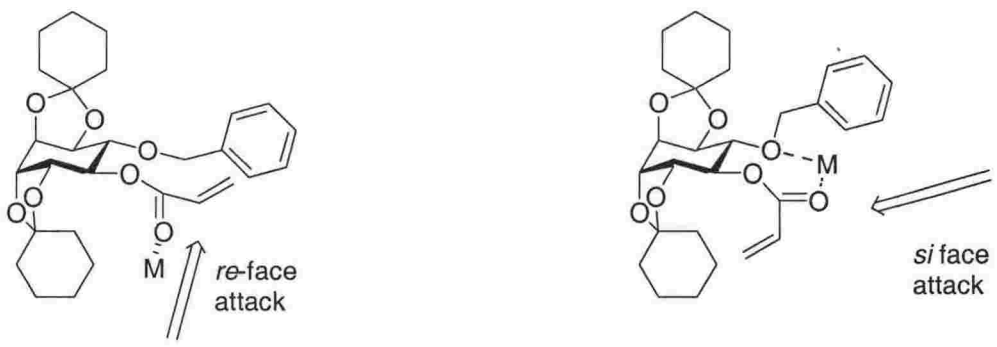
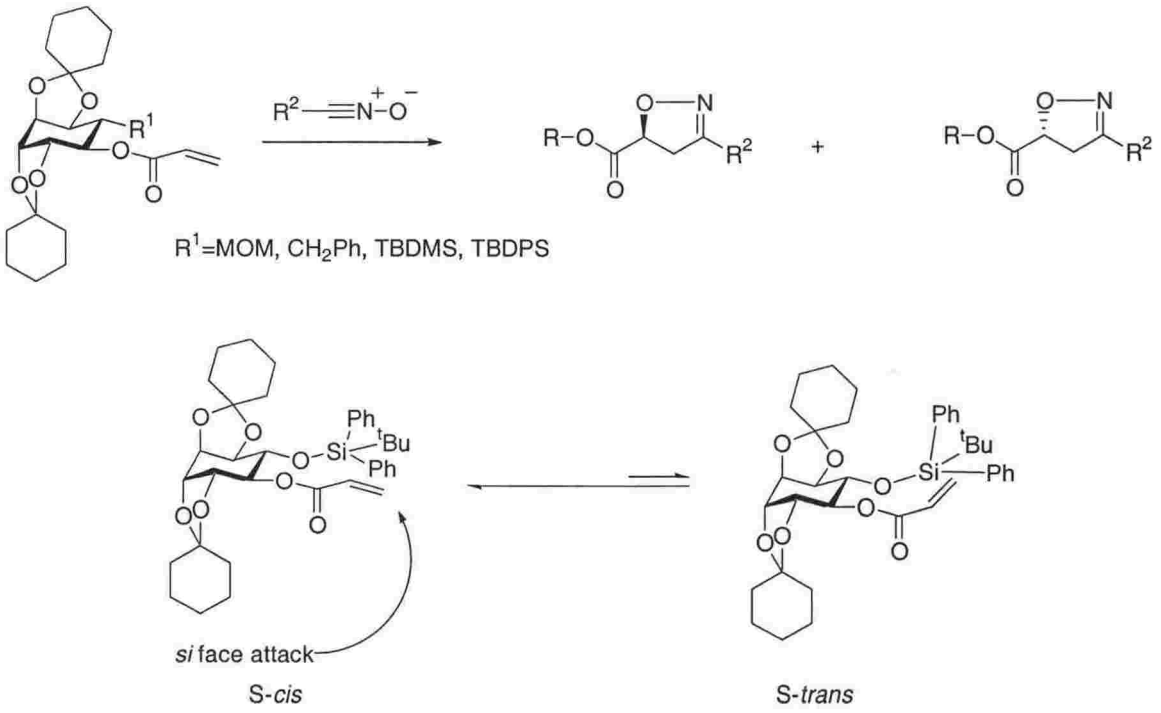


Figure 1.11-Transition state model for the Diels-Alder reaction

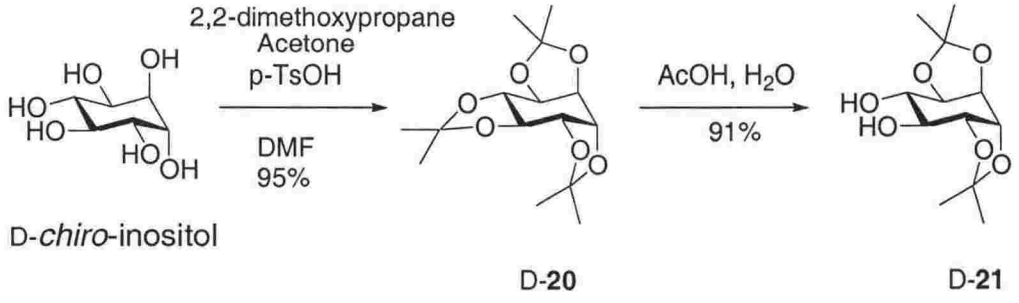
These systems have also been applied to the reduction of α-keto esters[51] and the addition of nitrile oxides to chiral acryloyl esters.[52] This last example leads to the formation of optically active Δ^2-isoxazolines, which are useful intermediates in the preparation of β-hydroxy carbonyl compounds. A range of auxiliaries were prepared and reacted with nitrile oxides, scheme 1.19. Yields varied from 81-89% and selectivities were from 1:1 (R^1=Bn) to 95:5 (R^1=TBDPS). The isoxazolines were then cleaved off the auxiliaries with L-selectride. The high selectivity in the case of TBDPS can be rationalized by the steric bulk of both the cyclohexylidene protecting groups and the TBDPS group. This bulk restricts the incoming reactant to attack from the front giving *si*-face attack as shown in scheme 1.19.



Scheme 1.19

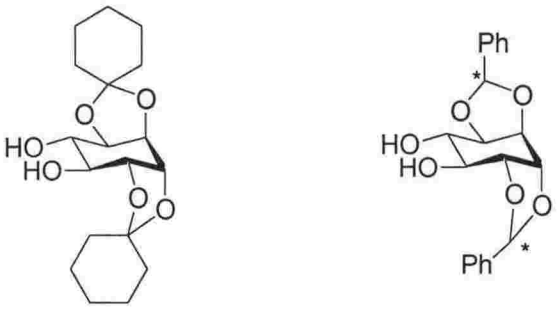
This selectivity can again be rationalized by the model shown, in the case of the *s-cis* conformer the bulky TBDPS group blocks the *re* face leaving the *si* face free for attack, this is the conformation that forms the major products. The minor products are formed by the less favoured *s-trans* conformation, where the alkene is interacting with the silyl protecting group.

As is shown by the above examples *chiro*-inositols protected with bulky groups have potential in asymmetric synthesis as both chiral auxiliaries and chiral catalysts. The configuration of the *chiro*-inositols means it is an easy process to protect the two pairs of *cis* diols with large groups. The 1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositols were first prepared by Angyal and coworkers in 1965.[53] The *chiro*-inositol is initially converted into the tri-*O*-cyclohexylidene moiety, then transformed to the diol by selective deprotection of the *trans*-cyclohexylidene acetal. A similar strategy is used in the preparation of the diisopropylidene variant. By taking the *chiro*-inositol and treating it with acetone and 2,2-dimethoxypropane in DMF with catalytic *p*-TsOH the triacetonide D-**20** is formed.[54] This is deprotected to the diol D-**21** via treatment with glacial acetic acid and water in an overall yield of 87%, scheme 1.20.



Scheme 1.20

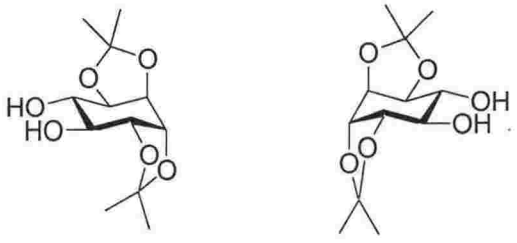
The two diols **21** and **22,** in both enantiomeric forms, will be the starting points for this project. A third diol **23** was also considered, figure 1.12. However, as this molecule is formed as a mixture of epimers at the indicated centers it was discounted as it could adversely affect the asymmetric chemistry we are developing using these systems.



D-**22** **23**

Figure 1.12- Starting Materials

Where we have used both *chiro*-enantiomers they will be distinguished by the use of D- and L- in front of the appropriate compound number for example the two enantiomers of **21** are shown in figure 1.13.

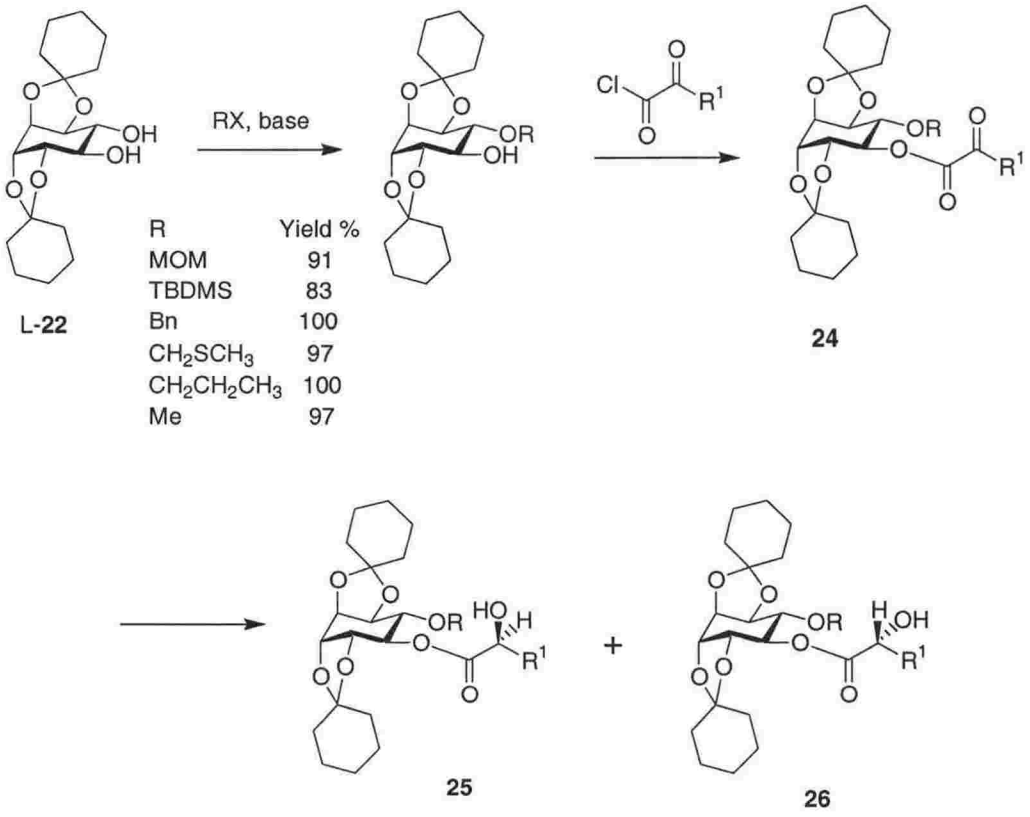


D-**21** L-**21**

Figure 1.13 – D and L enantiomers of **21**

Chapter Two - Mono-esterification of Diols 21 and 22.

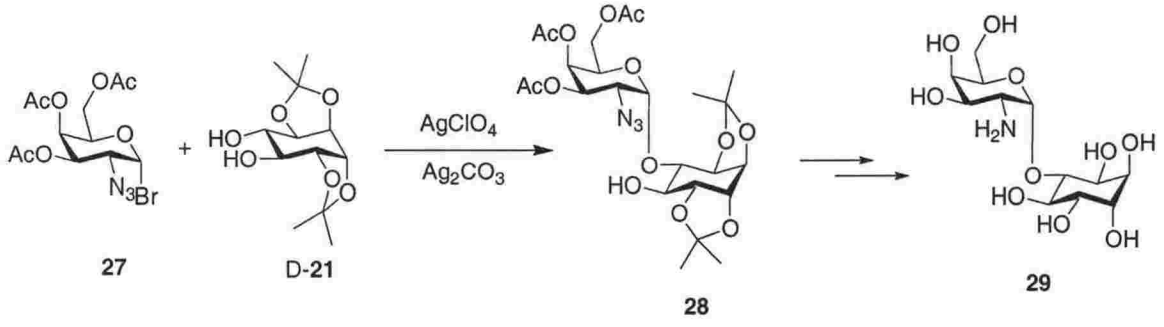
The C-2 symmetric inositol diols di-isopropylidene **21** or dicyclohexylidene **22** inositols are easily synthesized. However, the conversion of these diols into synthetically useful structures often proves to be non trivial. To expand on the usefulness of these molecules, investigations were begun into the mono protection of the free hydroxyl functionalities. Examples in the literature of similar moieties have been used with great synthetic utility. Ozaki and co-workers have used inositol L-**22** as a chiral auxiliary for the diastereoselective reduction of α-ketoesters, scheme 2.1.[51] In the first step, the authors have proposed that the mono protection enroute to **24** is assisted by the size of the cyclohexylidene protecting groups.



Scheme 2.1

The two R^1 groups were Ph and Me which were synthesized from the mono alcohols with phenyl pyruvic acid chloride/Et_3N and pyruvic acid, dipyridyl disulfide and PPh_3, respectively. The reducing agents surveyed were: $NaBH_4$, *i*-Bu_2AlH, Red-Al, $LiBH_4$, $Li[BEt_3H]$ and K-Selectride. Yields for the reduction reactions ranged from 15%-93% with selectivities for **25**:**26** from 1:1 (R^1=Ph , R= MOM, with $LiBH_4$) to as high as 97:3 (R^1= Ph, R=MOM, with K-selectride®).

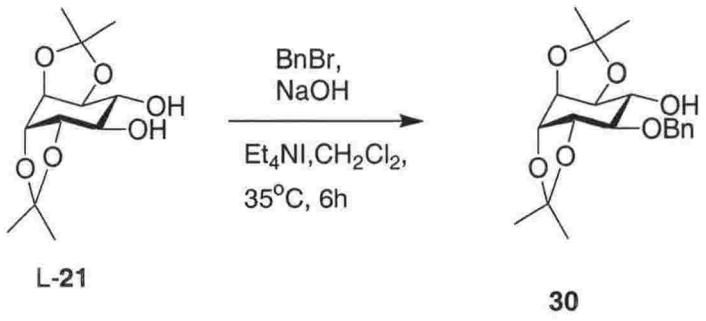
While the size of the cyclohexylidene protecting groups may assist in the mono-protection of the diols in this example, the same is not observed with all examples. For example, D-**21** was used in the used in the synthesis of 2-amino-2-deoxy-D-galactosyl-α-1→3-D-*chiro*-inositol, **29**[55] a member of the GPI family. The key intermediate in this synthesis, **28**, was formed after a three day coupling reaction of D-**21** with **27** which proceeded in only 30% yield with equal molar amounts of the disubstituted product formed, scheme 2.2.



Scheme 2.2

As this example shows, the mono fuctionalization of the hydroxyl moities of inositols has proven to be non trivial. Despite this some mono-functionalisations have been reported. One such example is the mono benzylation of L-**21**, scheme 2.3,[54b] this

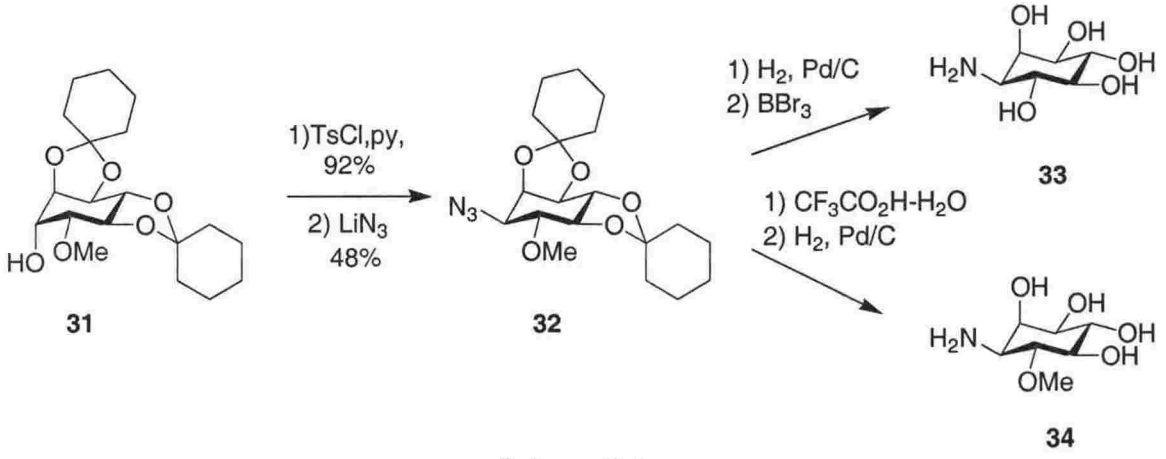
reaction is reported to proceed in 87% yield with a reaction time of only six hours at 35 °C.



L-21 **30**

Scheme 2.3

In any attempts I have carried out to generate **30** via this and other methods have resulted in yields varying from 0% to 45%. With inositol derivatives, other strategies for circumventing this problem have been developed. One example is to use the naturally occurring *O*-methyl ethers pinitol and/or quebrachitol.[43] This strategy usually requires selective protection of the molecule followed by cleavage of the methyl ether. Baker and co-workers have reported an example of work carried out using this methodology.[56] As part of a study on the inhibition of phosphatidylinositol synthase by 1D-*myo*-inositol, they converted the cyclohexylidene derivative **31** into an amino ether, scheme 2.4.

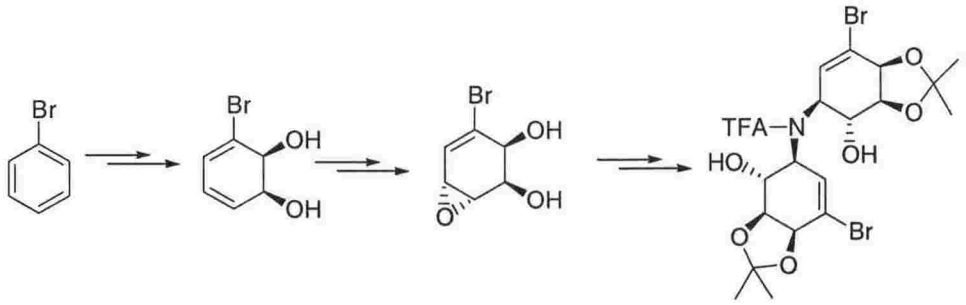


Scheme 2.4

The ability of the oncogenic mouse polyomia virus to transform cells and induce tumors in mice is dependant on its ability to bind phosphatidylinositol 3-kinase through the middle T oncoprotein. By selectively modifying position 3 in 1D-*myo*-inositol, the synthesis of these inositide 3-phosphates would be interrupted. To achieve this, the hydroxyl moiety on quebrachitol derivative **31** was tosylated and then displaced with lithium azide to give the required stereochemistry and blocking group in compound **32**. This was reduced with hydrogen and Pd/C then deprotected with BBr_3 in a CH_2Cl_2/MeOH mix to give 1D-3-amino-3-deoxy-*myo*-inositol **33**. Alternately, it was treated with CF_3CO_2H-H_2O, followed by hydrogen and palladium on carbon to give 1D-3-amino-3-deoxy-4-*O*-methyl-*myo*-inositol **34**. Of the compounds prepared by the authors 1D-3-amino-3-deoxy-*myo*-inositol **33** showed the highest activity.

Another strategy, reviewed by Carliss,[57] involves enzymatic conversions of benzene derivatives into chiral cis-diene diols by *E.coli* followed by stepwise and specific chemical conversions. Recent examples of this strategy include work done by Hudlicky and coworkers in making novel unnatural oligosaccharide mimics, scheme 2.5.[58] This

strategy builds the inositol in a stepwise manner, with concurrent protections, and hence circumvents the diol differentiation problems.

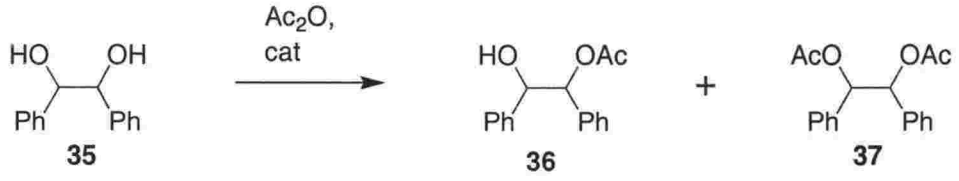


Scheme 2.5

Given the extensive strategies discussed above, a general method for all inositols appears to be needed. Partial and selective acetylation has been used successfully in carbohydrate chemistry,[59] although this selectivity is due to the stereochemical differences between hydroxyl groups inherent in sugars. The monoacetylation of non-sugar diols has proven to be more of a challenge. This is especially true in C-2 symmetric diols where there are no steric, electronic or conformational factors differentiating between the reactivities of the two hydroxyl groups. Methods used to overcome this selectivity problem are time consuming and require complicated isolation techniques, e.g. continuous extraction[60] or use solid supported systems.[61] These supports include ion exchange resins, alumina and silica with either the diol or a rare earth metal adsorbed onto it. An alternate strategy is to form a cyclic acetal, by treatment of the diol with a carbonyl compound then opening under acidic conditions to give the mono protected species.[62] With this strategy, toxic tin reagents have been used, often

stoichiometrically. The multiple steps also make yields less attractive than via other methods.

A different approach is to use an activating agent such as a Lewis acid or transition metal salt. This activates the acylating agent leading to nucleophilic attack by one hydroxyl group. Initially this method used a solid support, however recently Clarke and co-workers developed the technique into a simple, solution phase, one-step procedure for the monoacylation of C-2 symmetrical diols.[63] Their initial investigations with *meso*-hydrobenzoin **35** surveyed a wide range of Lanthanide salts using acetic anhydride to give the mono hydroxy ester **36** and diester **37**, scheme 2.6.



$CeCl_3$	90%	05%
$DyCl_3$	89%	11%
$YbCl_3$	95%	05%

Scheme 2.6

Clarke's group surveyed $DyCl_3$, $YbCl_3$, $CeCl_3$ and $Yb(OTf)_3$ using Ac_2O in THF. The results for $YbCl_3$ and $CeCl_3$ were very similar, providing higher selectivity than $DyCl_3$. $YbCl_3$ had an additional advantage of taking only four hours to react compared with 16 hours for $DyCl_3$ and 23 hours for $CeCl_3$. The final catalyst $Yb(OTf)_3$ was investigated because of its increased Lewis acidity due to the greater electron withdrawing nature of

the triflate groups.[64] Presumably this would increase its potential as an acylating agent. Unfortunately, it was non-selective giving exclusively diacetyl compound **37** in under one hour. It was also found to be catalyzing polymerization and ring opening reactions of the THF solvent. Having found the optimal catalysts, the effect of solvent was investigated by carrying out the mono benzoylation of **35** in THF, petrol, CH_2Cl_2, EtOAc, DMF, MeCN, ether and water. All solvents were inferior to THF with the exception of CH_2Cl_2, which increased reaction rates slightly. This was attributed to CH_2Cl_2 being a non-coordinating solvent, thus leaving the Lewis acid more readily available for coordination to the reactants. As a final step, they attempted the reaction under air with the hydrated lanthanide salt and undried solvents, which usefully led to no loss of yield or selectivity.

Recognizing the potential application of the above to our work, this methodology has been adapted and applied to diols **21** and **22**. Previous attempts to generate mono fuctionalized derivatives of these diols by treatment with one equivalent of reagent and careful monitoring lead to mixtures of the di-functionalized moieties and unreacted diol. This has led to a number of compounds being prepared with no evidence of the mono functionalized moiety, figure 2.1. Some of these compounds have proven useful and their chemistry will be discussed in the following chapters.

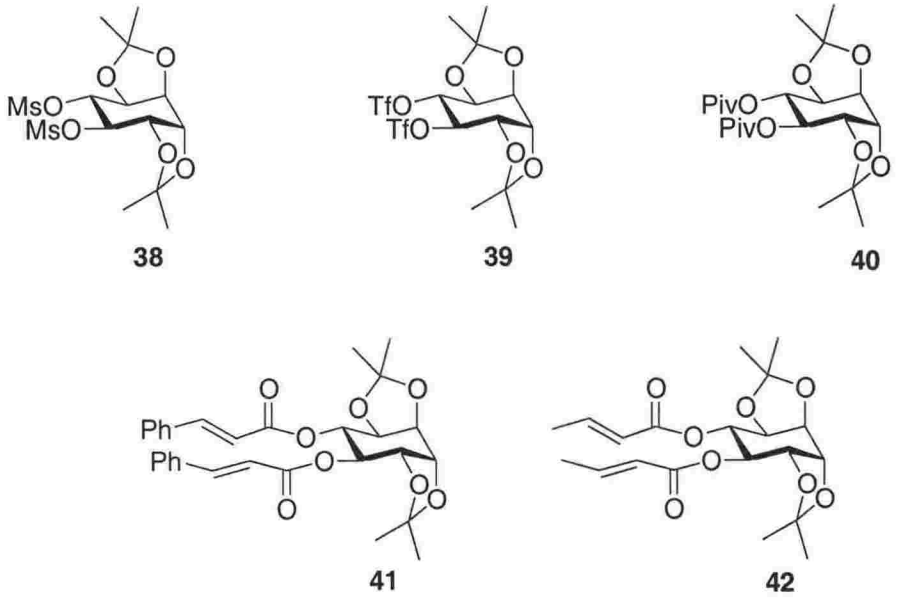
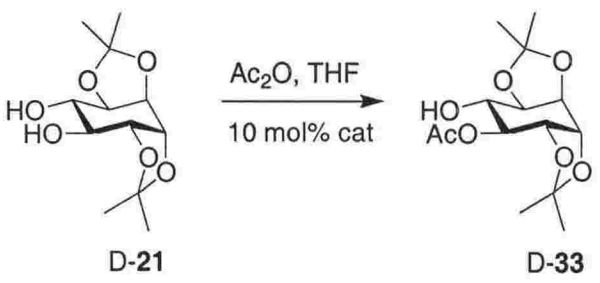


Figure 2.1 - Diesters generated from D-**21**

Initially Clarkes' conditions were applied to diol D-**21** with ten molar equivalents of acetic anhydride and either $CeCl_3.7H_2O$ and $YbCl_3.6H_2O$, scheme 2.7.

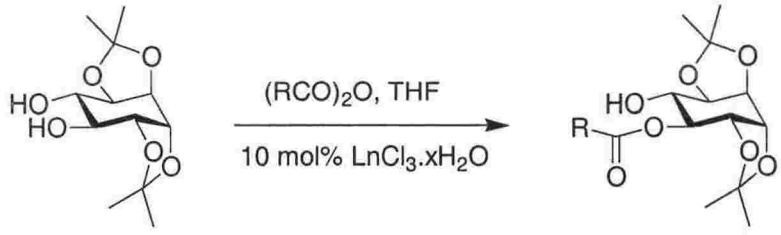


Scheme 2.7

This resulted in the formation of **33** in yields of 78% with ytterbium trichloride and 83% with cerium trichloride with no evidence of the diester. The amount of anhydride was

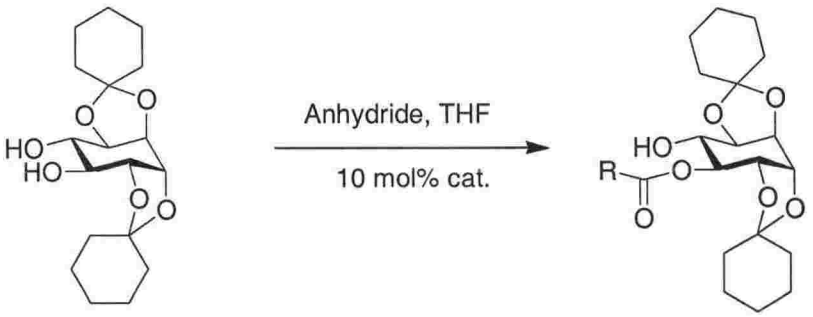
then reduced to five equivalents with no loss of yield. Using these conditions, the nine monoesters in table 2.1 have been prepared.

Table 2.1: Mono Protection of *chiro*-inositol derivatives



D-21 **43-48**

Anhydride	Reaction Time	Product (R=)	Ln (yield)
Chloroacetic	3h	D-(**43**) $ClCH_2$	Yb (95%)
	3h		Ce (48%)
	3h (from L-**21**)	L-(**43**)	Yb (90%)
Acetic	4h	D-(**44**) Me	Yb (78%)
	2.5h		Ce (83%)
Propionic	6h	D-(**45**) Et	Yb (76%)
	8h		Ce (74%)
Crotonic	6h	D-(**46**) (*E*) MeCH=CH	Yb (65%)
	7h		Ce (60%)
Benzoic	24h	D-(**47**) Ph	Yb (11%)
	24h		Ce (24%)
Pivalic	12h	D-(**48**) $(CH_3)_3C$	Yb (83%)
	24h		Ce (47%)



D-**22** **49,50**

Anhydride	Reaction Time	Product (R=)	Ln (yield)
Chloroacetic	4h	D-(**49**) $ClCH_2$	Yb (73%)
	5h		Ce (85%)
Acetic	6h	D-(**50**) Me	Yb (65%)
	8h		Ce (65%)

For products **43**, **45** and **48** better yields were obtained using Yb, although overall the Ce catalyst tended to give products that were easier to purify. The use of dichloromethane as a solvent proved less successful giving lower yields, and heating was also required to drive the reaction to completion. To expand the utility of this reaction, preliminary investigations were carried out into the use of this reaction to generate moieties with one sulfonate ester. The reaction was attempted with Tf_2O, Ts_2O and Ms_2O, in all cases generating intractable black oils. It was decided entry into this type of compound was more promising via other methods, which will be discussed later.

An interesting point to note is the absence of any diester when using **21** or **22**. While Clarke was able to avoid formation of the diester in his systems it was only under carefully controlled reaction conditions. In my examples, the diester was only formed when the reaction was carried out in the absence of the metal catalyst, under these conditions formation of the mono ester was not observed, the reaction times to form the

diesters were also longer being at least 24 hours in most cases. In these protected inositol systems, the rigidity of the protecting groups distorts the central inositol ring so that instead of sitting in a chair conformation it is skewed into almost a flat ring.[65] This has an interesting impact on the reactivity of the diol. In both this research and with work at IRL it has been found that attempted reaction of one hydroxyl group of **21** by careful control of reagents and conditions still leads to a mixture of di-substituted product and starting diol. It has been proposed that after one of the hydroxyl groups has reacted the other is activated and reacts at a faster rate than the unreacted diol.

However both the isopropylidene and cyclohexylidene groups are very sterically large, in the work by Ozaki this attribute was exploited to generate the mono protected moiety by using cyclohexylidene acetals. So the non-existence of diester could be attributed to steric hindrance, once the mono ester is formed there is too much steric hinderance around the metal for the free hydroxyl to attack another anhydride molecule. The contribution of these steric effects is further seen by, comparing the results for **21** and **22** in table 2.1, it is seen that in all instances **21** reacted faster and with higher yield. However, given that the diesters can be formed in good yield this cannot be the main reason for the mono selectivity. It is also interesting to note the low yields attained with benzoic anhydride, at 11% and 24% with $YbCl_3$ and $CeCl_3$, respectively as catalysts, are considerably lower than all others. As a sterically more hindered anhydride (pivalic) gives high yields, the low yield may be attributed to the electron rich nature of the benzoyl group, as the other anhydrides are comparatively more electron poor. In standard nucleophilic attack at a carbonyl, the electron withdrawing carbonyl oxygen pulls electron density away from the carbonyl carbon leaving it electropositive. Thus

nucleophilic attack occurs readily. Furthermore with electron poor anhydrides an even more electropositive carbonyl carbon results making it more attractive to nucleophilic attack from the inositol hydroxyl. In the case of benzoic anhydride, which is electron rich, electron density moves back toward the carbonyl carbon making it less attractive to nucleophilic attack. This is further supported by the reaction of crotonic anhydride, which is also electron rich (but somewhat smaller in size) and produces a modest 65% yield.

Although investigations into the exact mechanism of this reaction are still ongoing by Clarkes group,[63] two models have been adapted to these inositol systems. In the first, the metal coordinates to one hydroxyl from the diol and a carbonyl from the anhydride. This leaves the uncoordinated hydroxyl free to attack the activated anhydride carbonyl, figure 2.2.

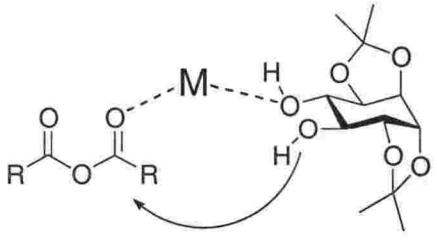
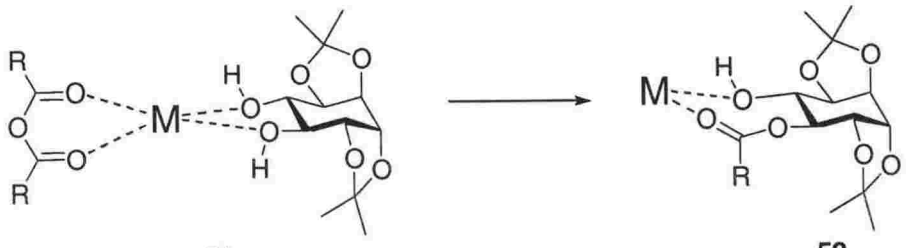


Figure 2.2 - Proposed mechanism

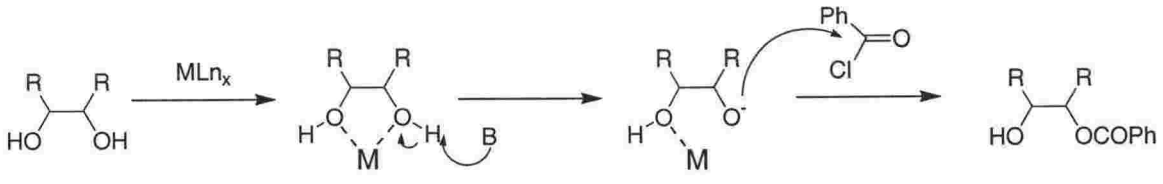
Alternately, both the diol and the anhydride undergo metal chelation to give **51**. The acyl group then transfers from the anhydride to the diol to give the seven-member chelate **52**, figure 2.3. This is replaced by a new diol molecule to regenerate the five-membered chelate **51** that is energetically more stable. The mono selectivity comes from the chelated diol **51** reacting at a faster rate than a non-chelated substrate **21**.



51 52

Figure 2.3 - Seven Membered Chelate vs Five Membered Chelate

In the ongoing mechanistic studies by Clarkes group, an acyl chloride generated in situ from the anhydride and the metal chloride was considered as the active acyl. However, in experiments using acyl chlorides, they found that the yield of diester increased. This led them to believe that acyl chlorides do not play a part in this mechanism. Interestingly however the monobenzoylation of C-2 symmetric diols using benzoyl chloride has been investigated with a selection of other metals, most extensively with tin and copper.[66] The proposed mechanism for that reaction is shown in scheme 2.8.



Scheme 2.8

This is an example of the difference metals can make to a reaction mechanism. In these two examples the same reaction is seemingly being carried out but by changing the Lanthanide to a main group metal the mechanism changes.

The use of this methodology has led to the generation of a new range of di-*O*-isopropylidene and di-*O*-cyclohexylidene monoester protected *chiro*-inositols. These results have recently been published in *Carbohydrate Research*[54a] and have proven useful in investigations into the use of *chiro*-inositols in asymmetric synthesis. These results will be discussed in the following chapter(s).

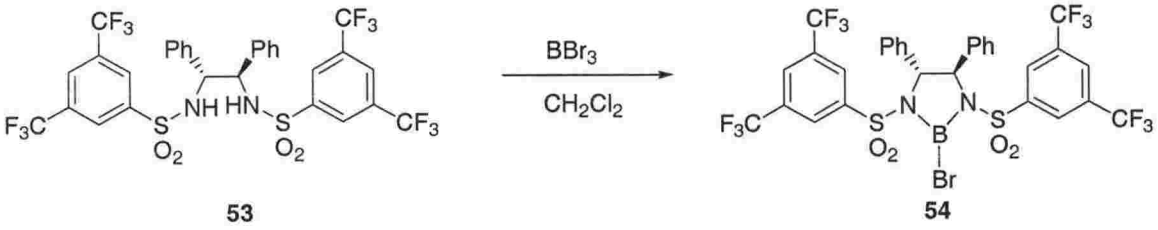
Chapter Three – *Chiro*-Inositols in synthesis as Chiral Reagents.

As defined in the introduction, a chiral reagent is a reagent which functions by inducing stereochemistry in a prochiral starting material during the course of a reaction. Many of the reagents used in asymmetric synthesis today are boron reagents, such as the isopinocampheyl borane $(Ipc)_2B$– hydroborating reagents or allyl$B(Ipc)_2$. The $(Ipc)_2$Borane system does have a major limitation that is found with most boron reagents, the difficulty in removing the Ipc– by-products from the desired product at the end of a reaction. Another problem associated with these reagents is they are not recyclable, once the reaction is complete the chiral moiety is unrecoverable. Inositols, if developed for this type of chemistry, should avoid these problems. Isopropylidene protected inositols are generally easy to separate via flash chromatography, however should this prove difficult then treatment of the protected insitol with a strong acid would cleave the isopropylidenes to give a water soluble by-product, which could be removed by aqueous washing. Either of these techniques would allow the inositol to be recovered. Although exhaustive investigations were not carried out into developing a chiral reagent the inositol system was applied in the following two areas.

3.1 Chiral Boron Triflate Reagent.

One very important use for boron reagents is for the formation of boron enolates that can subsequently be used in aldol reactions.[67] While aldol reactions that give *syn* products have become routine,[67] the formation of products with the *anti* configuration is far more challenging. While there are examples of *anti* aldol reactions, the methodology has been hindered by reaction conditions, the application of the methodology to a specific

substrate or even the availability of reagents. Therefore, research has focused on the *anti* selective aldol reaction mediated by boron reagents, especially boron triflates.[68] With an aldol reaction, both the relative and the absolute stereochemistry of the product must be considered. Reagents such as Cy_2BOTf will give *anti* products but as a racemic mixture; therefore in order to obtain optically active products a chiral reagent must be used. There are two examples of chiral boron reagents that have been successfully used to give optically active *anti* products. The first was reported in 1986 by Masamune and co-workers using (*S,S*)-2,5-dimethylborolane trifluoromethane sulfonate.[69] The yields they attained for the aldol reaction were 85-95% with ee's from 71-96%. The second example was reported by Corey and Kim in 1990, in which **53** was prepared from (*R,R*)-1,2-diamino-1,2-diphenylethane, 3,5-bis(trifluoromethyl)benzenesulfonyl chloride, diethyl amine and 4-dimethylamino pyridine (DMAP), and subsequently converted into **54**, scheme 3.1[70] Formation of enolates from propionate esters with **54** and triethylamine followed by reaction with aldehydes gave *anti* aldol products in 80-93% yields and 75-98% ee. However, in both the above examples the synthesis of the starting borane is highly complex.

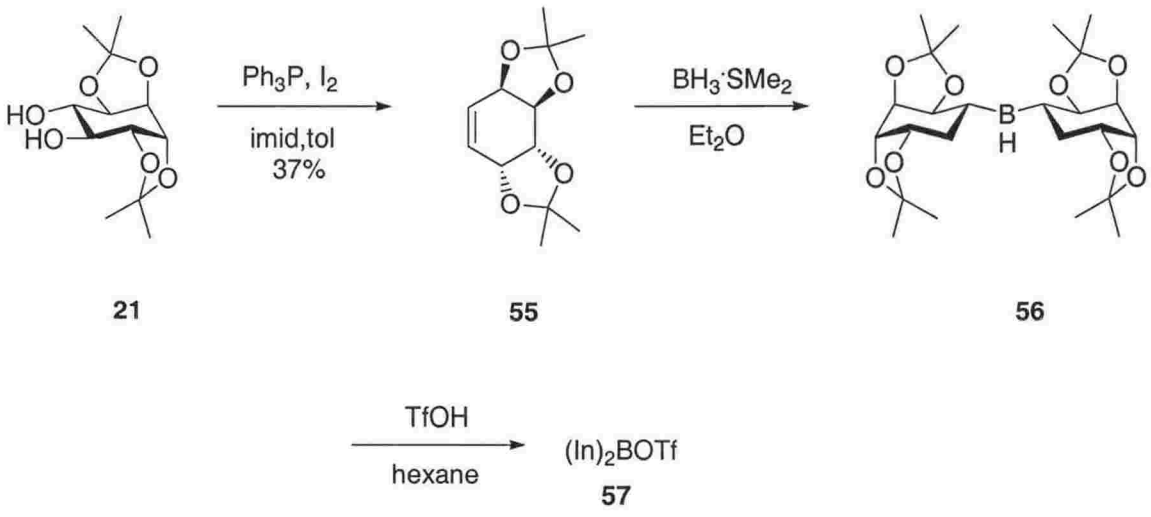


53 **54**

Scheme 3.1

It was postulated that **21** could be developed into a reagent similar to those described above as inositols are six membered carbocycles like the commonly used

cyclohexyl groups in Cy_2BOTf. Given that *chiro*-inositols are also chiral this would lead to an asymmetric reagent without the purification problems associated with Ipc containing moities. The strategy we followed to develop a chiral reagent of this type was to convert **21** into alkene **55**, which could be treated with $BH_3{\cdot}SMe_2$ to generate **56**. Treatment of **56** with triflic acid would then form **57**, scheme 3.2. To form **55,** the conditions reported by Mureyala and Pannala were employed. They used 1,2-diols from *myo*-inositol treating them with Ph_3P, iodine and imidazole in refluxing toluene to give an elimination product.[71,72] These conditions were applied to **21** yielding alkene **55** in a 37% yield after five hours. The yield could not be increased with extra reaction time.

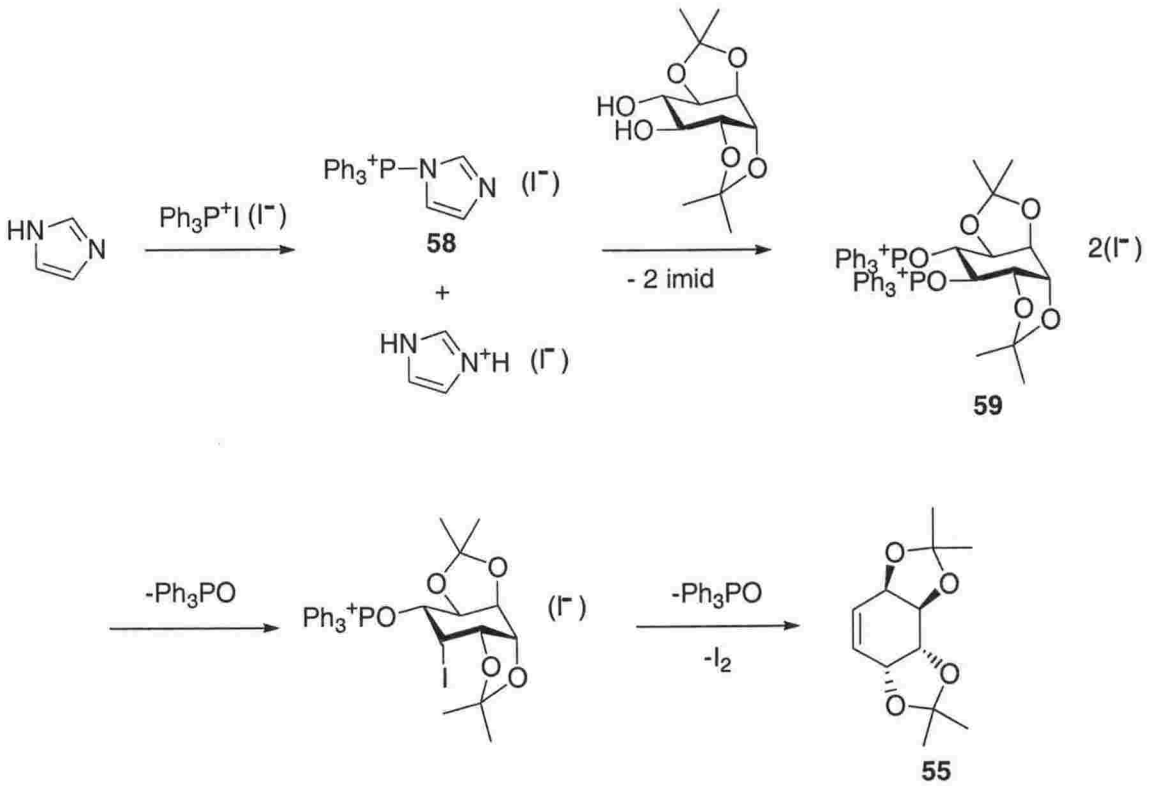


21 **55** **56** **57**

Scheme 3.2

Mechanistically, the imidazole, required in four molar equivalents with respect to the diol, acts as a base and leaving group to form complex **58** with PPh_3 and I_2, scheme 3.3. The diol then adds to this activated phosphine giving **59**. Complex **59** then looses Ph_3PO to form **55**, darkening as I_2 is liberated and the reaction progresses. This methodology

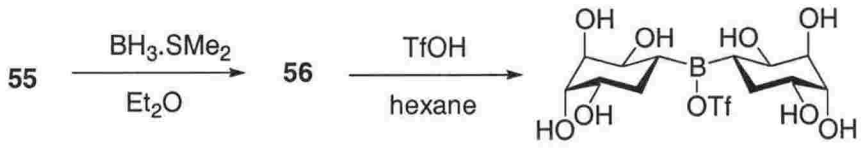
will only work on *trans* diols, for *cis* diols one equivalent of tetrabutylamminium iodide and excess potassium iodide are used.



Scheme 3.3

55 was then treated with $BH_3 \cdot SMe_2$ followed by triflic acid based on literature precidence.[73] This involved placing **55** under an inert atmosphere in anhydrous Et_2O at 0 °C then adding $BH_3 \cdot SMe_2$ dropwise over 30 minutes. As occurs with the Ipc reagents, a white solid was produced. This white solid, assumed to be **56,** was allowed to settle, was dried under reduced pressure, and was subsequently used without purification as borane complexes are known to be air sensitive. **56** was placed in anhydrous hexane and triflic acid was added over 30 minutes, stirred for one hour and then allowed to sit for a further

two hours. Following this, a semi-solid phase separated out, the liquid phase was cannulated into an argon purged flask and kept at –40 °C for 36 hours; over this time no more solid product formed. The white solid was dried under reduced pressure and subsequently proved to be insoluble in organic solvents. This insolubility is attributed to the isopropylidene groups being lost from the inositol as shown in scheme 3.4



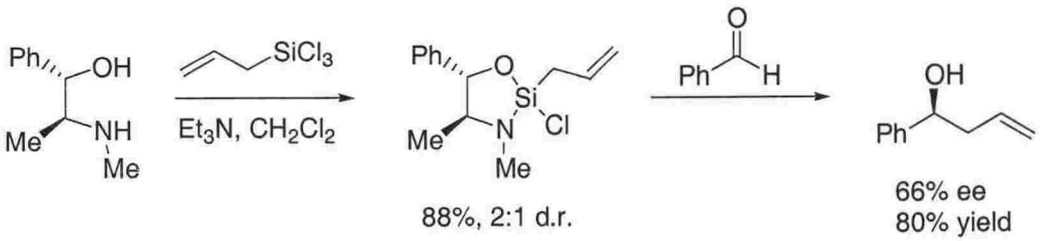
Scheme 3.4

In theory, the bis-tetraol could be re-protected to give an organic soluble moiety, however with the low yield in the formation of **55**, the concept was deemed too inefficient to be of synthetic use. However, future work with more robust protecting groups should solve this problem.

3.2 Strained Chiral Silacycle.

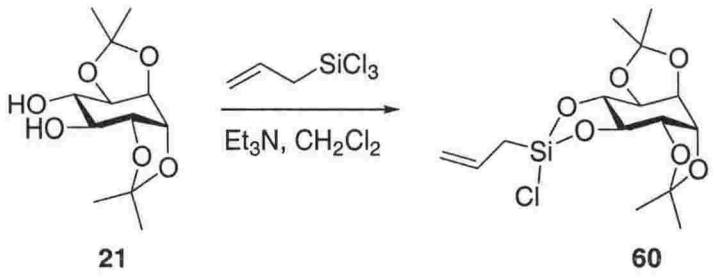
The asymmetric allylation of aldehydes is a very useful reaction in synthetic organic chemistry, often carried out with allylsilanes in the presence of Lewis acids.[74] In 1992, work carried out by Myers and co-workers found that the incorporation of silanes into small rings increased the rate of reaction in the silicon directed allylation reaction, scheme 3.5.[75] It was subsequently shown that when the silicon was constrained in a four or five membered ring, the Lewis acidity of the system increased to the extent that the addition of other Lewis acids to a reaction was unnecessary.[76] Leighton and co-workers

expanded this by incorporating the silane into a chiral species, which was then used for the enantioselective allylation of aldehydes, scheme 3.5.[76b]



Scheme 3.5

While the majority of their work was carried out with amino alcohols, they also screened 1,2-diols and 1,2-diamines. It was envisioned that **21** would be an ideal system for this type of reagent, being chiral and able to form a five membered silacycle. Thus, **21** was converted into a strained silane by adding to a solution of allyltrichlorosilane in CH_2Cl_2 Et_3N, and **21**. The reaction was monitored by TLC at 0 °C for two hours, at this point no reaction appeared to be occurring so the system was warmed to ambient temperature. After stirring at ambient temperature overnight no starting material was evident and silane **60** was isolated in 23% yield, scheme 3.6.



Scheme 3.6

In this example **60** will not be formed as two diastereomers as the C-2 symmetry of **21** with give two equivalent moities.

The allylation reaction with **60** will involve co-ordination of the carbonyl oxygen to the silicon followed by formation of the new carbon-carbon bond. Due to the isopropylidene groups blocking two of the possible approaches to the silane, the aldehyde is expected to co-ordinate as depicted by **61**, figure 3.1, (note this is showing the D isomer). This transition state will lead to the *S* product **62**.

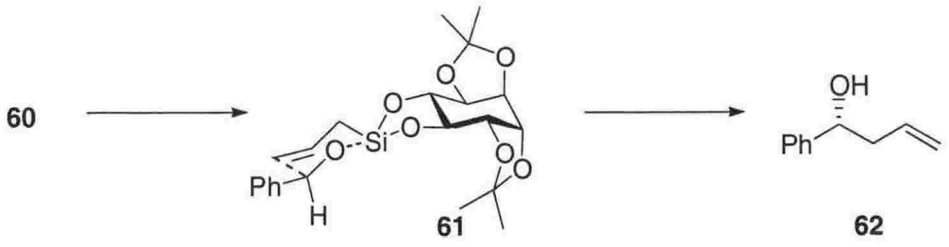


Figure 3.1 - Proposed transition state and expected product of allylation

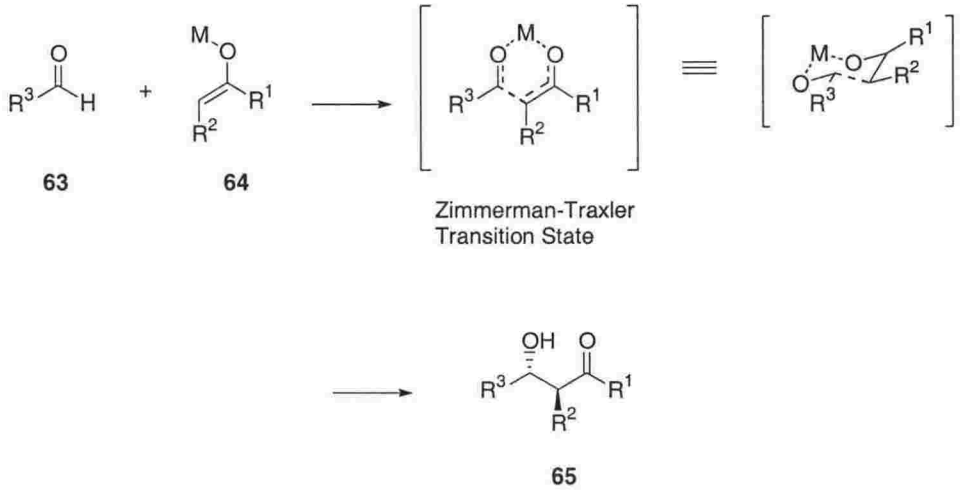
To trial this reaction benzaldehyde was chosen due to its reactivity. In the work carried out by Leighton, allylation was performed at –10 °C and in most cases the reactions were complete in two hours. With **60**, the reaction was initially attempted at 0 °C, upon no reaction, the temperature was raised to ambient temperature and finally until the toluene solvent was refluxing. This reaction was monitored by both thin layer chromatography (T.L.C.) and NMR, after two days, with no observed reaction the silane began decomposing. The reaction was then attempted in the presence of $BF_3{\cdot}OEt_2$ to increase the Lewis acidity, however this only increased the rate of decomposition of the silane.

As mentioned in chapter two, the isopropylidene groups pull the inositol ring in this system out of the usual chair conformation. This conformational restriction severely

hinders the flexibility of the molecule including that of the two unprotected hydroxyl groups. This restriction obviously results in a reduction in reactivity in the case of **60**, other examples of this will be discussed in the following chapters.

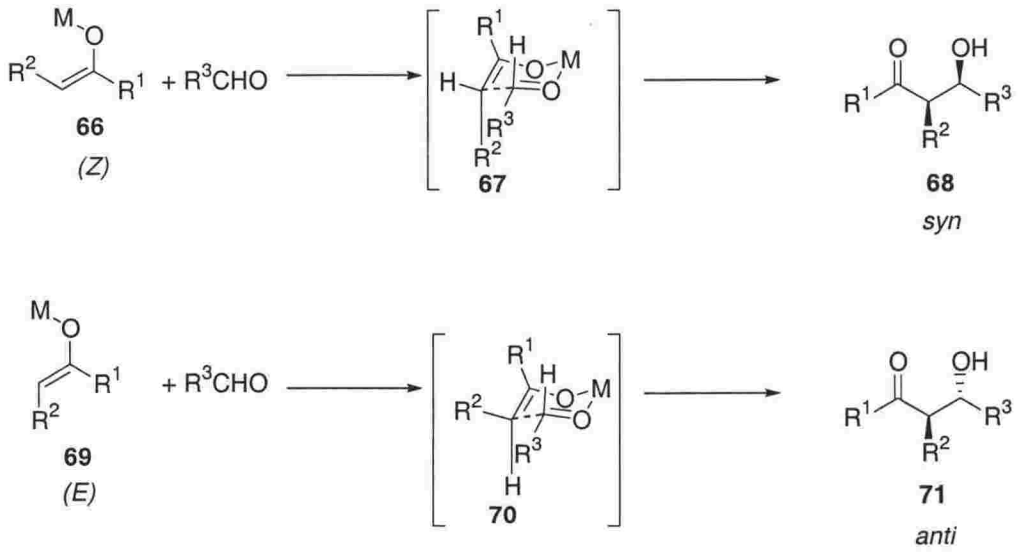
Chapter Four – *Chiro*-Inositols as Auxiliaries in the Asymmetric Aldol Reaction

The Aldol reaction involves the reaction of two carbonyl-containing compounds and is one of the fundamental methods for carbon-carbon bond formation. In a typical aldol reaction, one carbonyl compound is treated with a base converting it into an enolate. This enolate then adds to the remaining carbonyl via nucleophillic attack to give a tetrahedral intermediate that is protonated to give the final product. While this reaction is a useful way of forming a new carbon-carbon bond, the two possible new stereogenic centers can be formed as a complex mixture of all four possible isomers, i.e. two diastereomeric pairs of enantiomers. The progression of an Aldol reaction generally takes place through a highly ordered transition state known as the Zimmerman-Traxler transition state. In this, the enolate counter ion coordinates to the carbonyl oxygen bringing the two moieties together allowing the reaction to occur, scheme 4.1.[1] The carbonyl approaches the enolate perpendicularly, complexes to the metal, and the reaction then proceeds via a pericyclic intermediate with the large R^3 group of **63** adopting an equatorial geometry.[77]



Scheme 4.1

An important feature in defining the relative stereochemistry of the products is the geometry of the enolate. Under kinetic conditions, the R^2 group will occupy an equatorial position, and R^1 from the enolate adopting a pseudo equatorial position. Therefore with a *Z* enolate, R^2 will be forced into an axial position as depicted by **67**, giving *syn* addition, while in an *E*-enolate R^2 will be equatorial as shown by **70**, giving *anti* products, scheme 4.2.

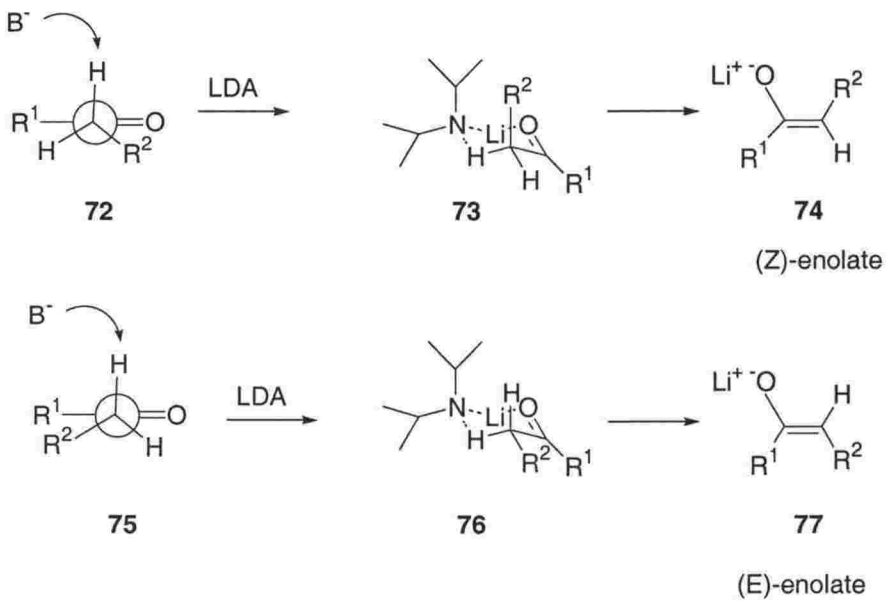


Scheme 4.2

If the reaction is under thermodynamic control, the reaction will proceed through the most thermodynamically stable transition state, this will have the maximum number of substituents equatorial and will lead to the *anti* product. Thus, we can see that by controlling the enolate formation and the reaction conditions we have a large degree of control over the stereochemical outcome of the reaction.

Enolate formation is a reasonably complex process with many factors playing a role. However a number of generalizations can be made. The size of the alkyl

substituents on the carbonyl are critical in determining which enolate will be formed. Under kinetic control, the majority of enolizations will produce a (Z)-enolate, this is rationalized in scheme 4.3 in which the proton undergoing abstraction is parallel to the π-system, thus producing a conjugated π-system. Steric interactions between the R and R^1 groups lead to the favored conformation as depicted by **73**.



Scheme 4.3

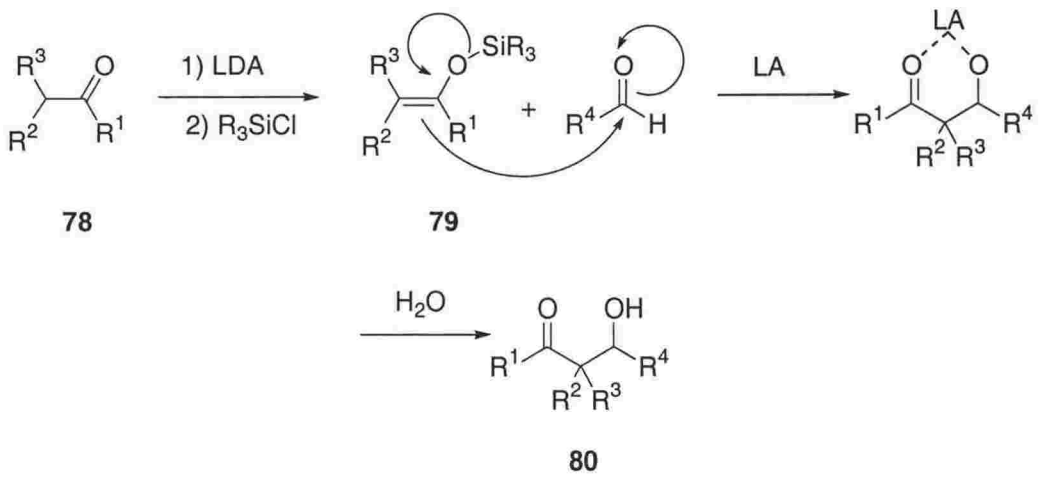
This effect is dependant on the inclusion of large R groups like Ph, whereas for smaller groups such as OMe or Et the selectivity decreases.[78] Furthermore an example where careful control of reaction conditions can influence the outcome is the Aldol reaction with cyclohexylethyl ketone.[79] If this molecule is treated with 9-borabicyclononane (9-BBN) triflate and N,N-diisopropylethylamine, the (Z)-enolate is formed and undergoes reaction with an aldehyde to give the *syn* product in up to 97:3 selectivity. If however, the base used in the enolization step is dicyclopentylboryl triflate and diisopropylethyl

amine, the (*E*)-enolate if formed and the *syn* to *anti* selectivity is 14:86. Additionally the use of chelating divalent cations such as Zn^{2+} or Mg^{2+} will cause thermodynamic control to predominate and *anti* products are formed.[78]

As mentioned initially two new stereogenic centers can be formed in an aldol reaction, thus there are four possible isomers as shown in the introduction, scheme 1.2. Therefore control of enolate geometry is not the only factor that must be considered for a successful stereoselective aldol reaction. Also of critical importance is the π-facial selectivity of the aldehyde. A commonly used method for attaining this selectivity is by the use of a chiral auxiliary. An appropriate auxiliary has the ability to control selectivity by blocking one face of the enolate forcing the aldehyde to approach the opposite face preferentially.

Given the synthetic use of this reaction as a method of generating new carbon-carbon bonds there has been a push to find a reliable catalytic methodology. The possibility of a catalytic variant of this reaction was made possible by the development of the Mukiyama aldol or Lewis acid mediated aldol reaction.[79] The Mukiyama aldol reaction involves the formation and trapping of the enolate as its silyl enol ether. This is subsequently reacted with an aldehyde in the presence of a Lewis acid, although Lewis base mediated reactions are also known.[80] One of the problems with a standard aldol reaction is the reaction products are often thermodynamically less stable than the reactants, thus pushing the reaction to completion can be a problem. Under standard aldol conditions the retro reaction can occur very easily, this can lead to a complex mixture of products. The Mukiyama aldol reaction helps negate this problem as the stable Lewis acid chelate stops the retro reaction, and leads to the desired aldol

products.[79] Simple hydrolysis removes the Lewis acid leading to the formation of the aldol product **80**, scheme 4.4.



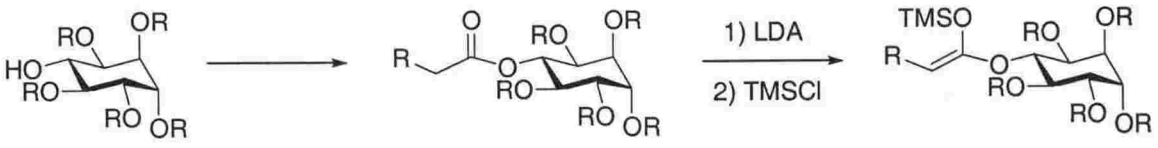
Scheme 4.4

Numerous methods for the formation of silyl enol ethers have been reported. However, the most commonly used method is to form the enolate of a carbonyl compound using a large sterically hindered base such as LDA or LHMDS, then trap this with a silyl chloride.[84] Other methods have been reported[81-83] and are used for unreactive or sensitive systems.

In Mukiyama reactions, π-facial selectivity can result from the use of a chiral silyl enol ether, chiral carbonyl compounds or by the use of a chiral Lewis acid. The use of a chiral, optically active enol ether is an example of the use of a chiral auxiliary to promote selectivity and examples of this type of aldol reaction have included silyl enol ethers attached to camphor derivatives, such as DAIB, and N-methylephedrine derivatives with excellent ee's being attained.[85] Addition to chiral carbonyl compounds takes advantage of the inherent steric hindrance, where stereochemistry already present in the molecule

directs the outcome of the reaction. Finally, use of a chiral Lewis acid allows for a catalytic asymmetric reaction.[86,87]

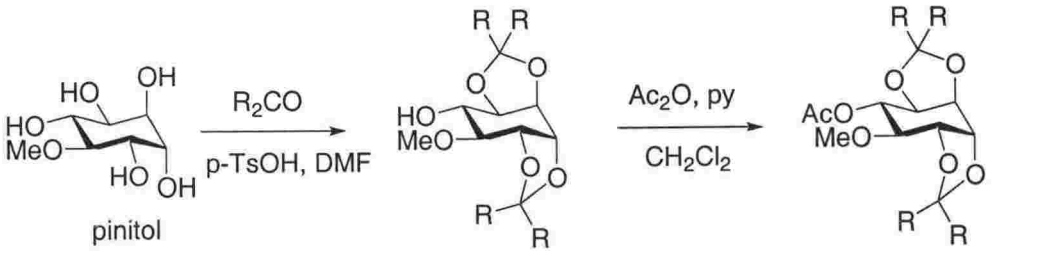
As mentioned, sugars have been used as chiral auxiliaries for the aldol reaction with some success,[19d] this led into investigations into the use of *chiro*-inositols as auxiliaries for use in the asymmetric aldol reaction. To achieve this, a simple esterification of an inositol, followed by conversion to a silyl enol ether was planned, scheme 4.5.



Scheme 4.5

This strategy would enable a Mukiyama aldol reaction to be attempted using the inositol as the chiral auxiliary. Earlier work from the literature has reported the dicyclohexylidene protected quebrachitol being acetylated and used as an auxiliary.[88] In the reported example, the acetyl was converted into an alkene by either Tebbes' or Petasis' reagent and then reduced to the isopropyl ether.

Since acetylation of carbohydrates is straightforward, it was decided to begin with acetylation of the protected pinitol derivatives D-**81** and D-**82**, scheme 4.6. If successful, groups larger than the methyl could be used by applying the monoesterification methodology discussed in chapter two, thus modifying the selectivity.



81 R=Me
82 R,R= -$(CH_2)_5$-

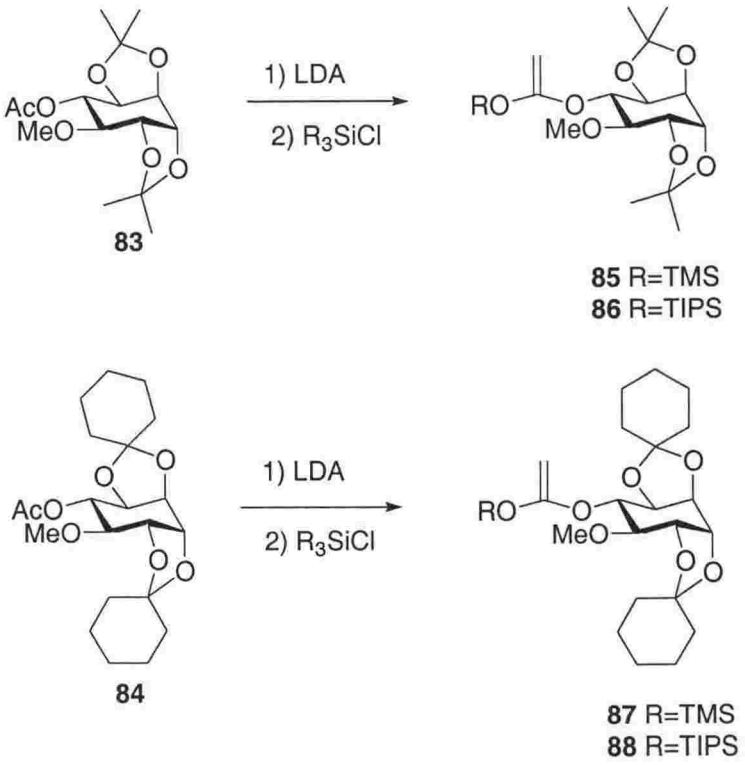
83 R=Me
84 R,R= -$(CH_2)_5$-

Scheme 4.6

Pinitol was treated with acetone, 2,2-dimethoxypropane and p-TsOH in DMF to form the diisopropylidene pinitol **81** in an 84% yield. The synthesis of **82** involved the treatment of pinitol with cyclohexanone and p-TsOH in DMF. This reaction required gentle heating and gave a slightly lower yield of 69%. Acetylation of the remaining hydroxyl to the respective acetates was achieved by standard treatment with acetic anhydride and pyridine in CH_2Cl_2. This reaction worked readily giving excellent yields of 94% for **83** and 90% for **84**. 1-D-3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol was also converted into the corresponding acetate although this was never taken further. Initially it was decided to use only **83** and **84** to investigate the conditions to carry out the Mukiyama aldol. The use of these acetates leads to only one possible enolate, should the strategy be successful R groups would be substituted for an acetate proton. This will allow *syn* and *anti* additions to be investigated.

The Mukiyama version of the aldol reaction was initially focused on, thus began investigations were begun into the conversion of **83** and **84** into silyl enol ethers. To generate the silyl enol ethers, an adaptation of the method published by Fukuzumi and co-workers was used.[84] This involved treating either **83** or **84** with LDA at –78 °C, the

resulting mixture was stirred for one hour then treated with HMPA and after a further 10 minutes with the trialkyl silane. After the silyl chloride was added, the reactions were stirred at –78 °C until TLC indicated no starting material remained. The times required for this are shown in table 4.1. Using this methodology four new structures were generated which were assigned the structures as shown below, scheme 4.7.



Scheme 4.7

Table 4.1- Formation of silyl containing compounds

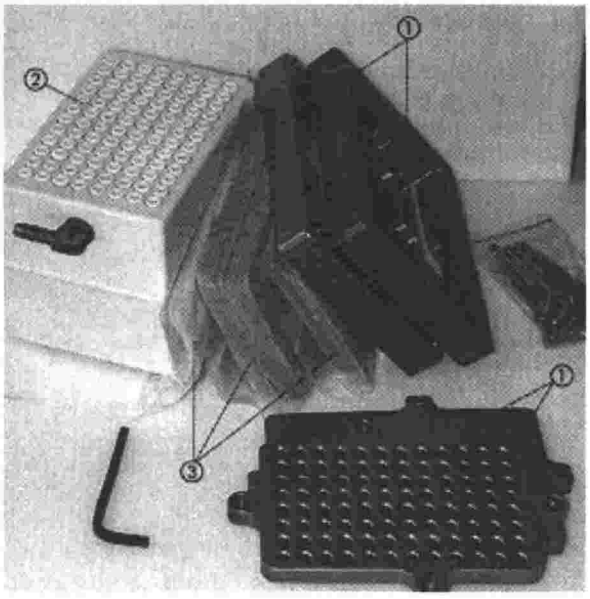
Entry	Substrate	Product	Time (hours)	Yield
1	**83**	**85**	2.5	69%
2	**83**	**86**	3	63%

3	**84**	**87**	4	54%
4	**84**	**88**	5	51%

Attempts to generate the corresponding compounds with *tert*-butyldimethylsilyl (TBDMS) or *tert*-butyldiphenylsilyl (TBDPS) groups failed. This failure can be attributed to the large size of both the TBDMS and TBDPS groups, as a comparison of the successful reactions show that the smaller TMS ether was formed in better yield and more rapidly than the TIPS (entry 1 compared to 2 and entry 3 compared to 4 table 4.1). The same comparison between the diisopropylidene and the dicyclohexylidene protected moieties show that the diisopropylidene was slightly more reactive and gave improved yields (entry 1 compared to 3 and 2 compared to 4). LHMDS was also tested as a sterically hindered base as it has been used in silyl enol ether formation, however, for this system LDA proved to be the optimal choice giving better yields.

Upon formation of the enol ethers, their use was investigated in the Mukiyama aldol reaction. Initial attempts involved reacting the enol ethers with benzaldehyde in the presence of $TiCl_4$ as based on literature methodology.[77,79,89] At –78 °C, no reaction occurred and as the temperature of the reaction was slowly raised we decomposition of the silyl reagents to give **81** and **82** was observed. The use of the weaker Lewis acids, $Ti(O^iPr)_4$ and $BF_3{\cdot}OEt_2$, at a variety of temperatures gave no reaction. As formation of the silyl enol ethers was achieved, it seemed obvious that they should undergo an aldol reaction. In order to obtain a successful aldol reaction, a variety of conditions using **85** were investigated via parallel screening. This enol ether was chosen as it was the easiest to form and was synthesized in the best yields, table 4.1.

This experiment was carried out using a Calypso®, multi-temperature reaction block for solution phase synthesis, figure 4.1. This system consists of a reaction block containing 48 individual wells that are covered with a gas manifold, allowing the system to be placed under an inert atmosphere. The reaction block is channeled allowing the temperature to be adjusted from –80 °C to +180 °C. Each well is capable of being set up to carry out a reaction under slightly different conditions with the exception of temperature.



Multi-Temperature Solution-Phase Reaction Block Kit

1) Reaction Block Frame
2) Multi-Temperature Solution-phase Reaction Block
3) Speta

Figure 4.1 – Caylpso Reaction Block Kit

For this parallel screening two solvents were used, CH_2Cl_2 and MeCN and four Lewis acids were tested: $TiCl_4$, $BF_3{\cdot}OEt_2$, TMSOTf and $SnCl_4$. This selection gave a range of strong acids ($TiCl_4$ and $SnCl_4$) to moderate ($BF_3{\cdot}OEt_2$) and a Lewis acid optimal to silyl compounds (TMSOTf). In addition to benzaldehyde, butyrlaldehyde was also used as an enol acceptor. These two gave an acceptor of higher reactivity but increased size (PhCHO) and a smaller more flexible but less reactive acceptor (butyl). Important in

this decision is that the approach of the acceptor is subjected to steric hindrance from the protecting groups on the inositol. For this experiment, 16 different reactions were trailed, involving preparation of a 0.05 mmol solution of the silyl enol ether that was loaded into the cells followed by two equivalents of both the Lewis acid and the aldehyde. The experiment was run over 26 hours beginning at –31 °C and kept at this temperature for three hours before being slowly warmed to –20 °C. The initial temperature was due to mechanical failure of the cooling unit, however previous results had shown no reaction at temperatures lower than this. After a further two hours, the cells were warmed to 0 °C before being left at ambient temperature. The reaction progress was monitored hourly by mass spectrometry, screening selected reactions for the first 14 hours and then at the end of the experiment. MS was used to verify a successful reaction based on the masses corresponding to the structures shown in figure 4.2. Unfortunately no masses corresponding to either of these structures were observed, which verified our earlier results that the silyl enol ethers are either unreactive or slowly decompose to **81**.

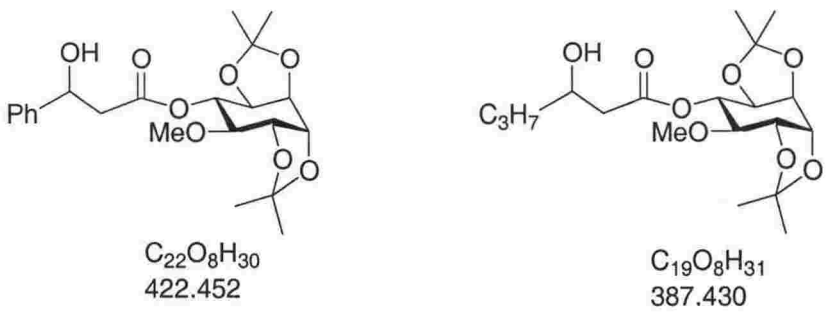


Figure 4.2 - aldol products

Given the steric hindrance inherent in this system a traditional aldol reaction was also attempted. However, treatment of **83** or **84** with LDA followed by benzaldehyde also

failed to provide the desired products. If the Mukiyama aldol had failed because of steric interactions between the silyl enol ether and the incoming aldehyde then the traditional aldol with a smaller lithium counter ion would have been more successful. The failure of this reaction led to re-examination of structures **85-88**. These compounds if they do have the structures as assigned contain a ketene-acetal functionality, these are well known to be highly reactive. When the enolates of **85-88** are generated by treatment with LDA there are two possible tautomeric structures with the most energetically favuored form being the enolate, figure 4.3.

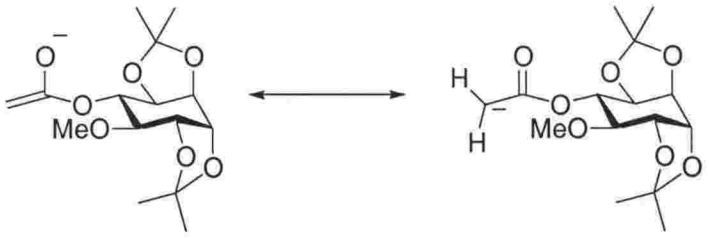
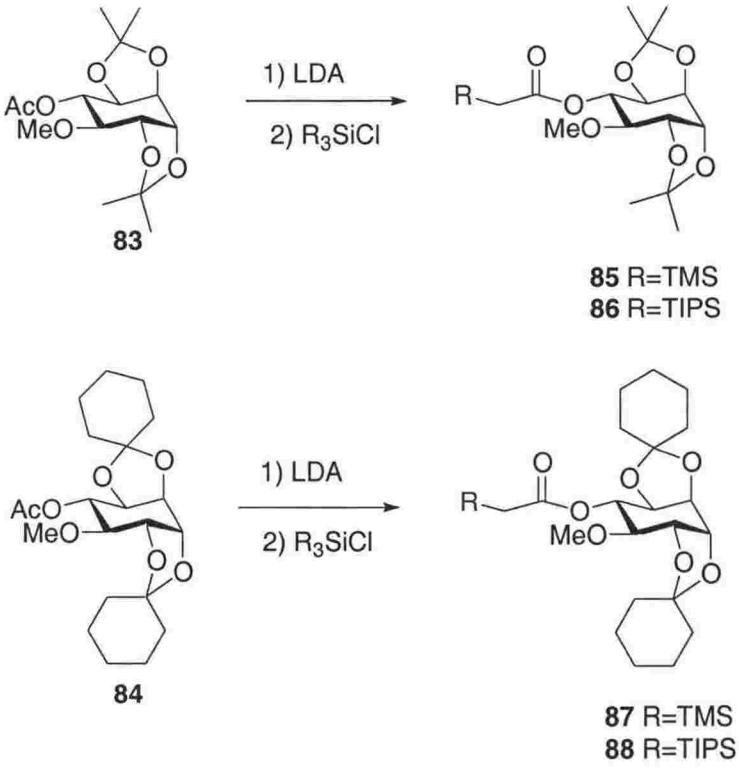


Figure 4.3

Inspection of the ^{13}C and the IR spectrum of **85-88** indicates the presence of carbonyl groups in these structures. This would suggest the trialkyl silane is not trapping the enolate but the less energetically favoured tautomer thus producing the carbon silylated moieties depicted in scheme 4.8.



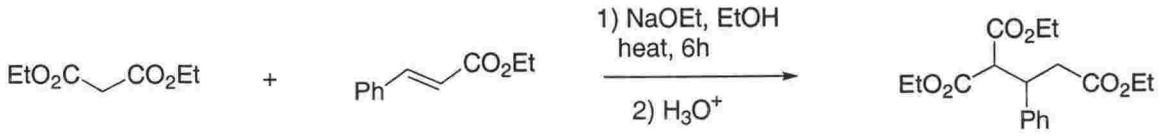
Scheme 4.8

This result can again be attributed to the steric constraints enforced on this system by the isopropylidene and cyclohexylidene protecting groups. These groups hinder this molecule to the extent that the reactive tautomer in this system is the least energetically favoured, while the enolate tautomer is showing no sign of reaction.

Whilst four new carbon silylated compounds have been generated from *chiro*-inositols these will not undergo an aldol reaction, and have limited synthetic utility. Again this was caused by the encumbered inositol ring system, given this the next obvious step is to remove the reactive site in the molecule further from the inositol ring. This strategy will be discussed in the following chapter.

Chapter Five – *Chiro*-Inositols as Auxiliaries for Asymmetric Conjugate Addition.

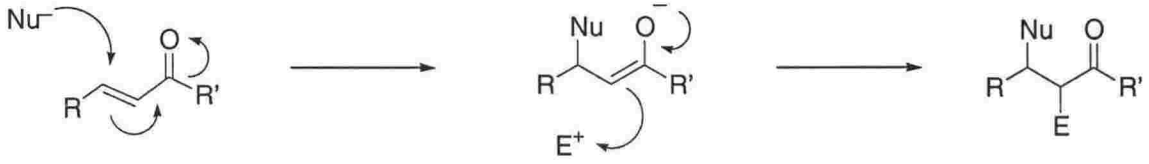
Conjugate addition involves the reaction of a nucleophile with an unsaturated system that is conjugated to an electron withdrawing group, usually a carbonyl. This type of addition has become an important method of carbon-carbon bond formation. The first example of conjugate addition was reported in 1883 by Kommenos,[90] involving the addition of diethyl sodium malonate to diethyl ethylenemalonate. The true pioneer of conjugate addition was Arthur Michael (1853-1942). In 1887, he reported the base promoted additions of the sodium salts of malonates and β-keto esters to ethyl cinnamate, scheme 5.1. From this work, the 1,4-conjugate addition to unsaturated systems in conjugation with a carbonyl has become known as the Michael reaction.[91]



Scheme 5.1

Conjugate addition reactions can take place at any site that is conjugated to the carbonyl and is 2n atoms distant from the carbonyl carbon with the most common being 1,4- addition. The determining factor on whether a nucleophile will attack 1,2- or 1,4- is dependant on how 'hard' or 'soft' it is. Hard nucleophiles such as Grignard reagents will attack at the 2 position, softer nucleophiles such as cuprates will attack in a 1,4- manner. In 1,4 conjugate addition, the nucleophile attacks the 4 position to form an intermediate enolate, which subsequently traps an electrophile to form the final product, scheme 5.2.

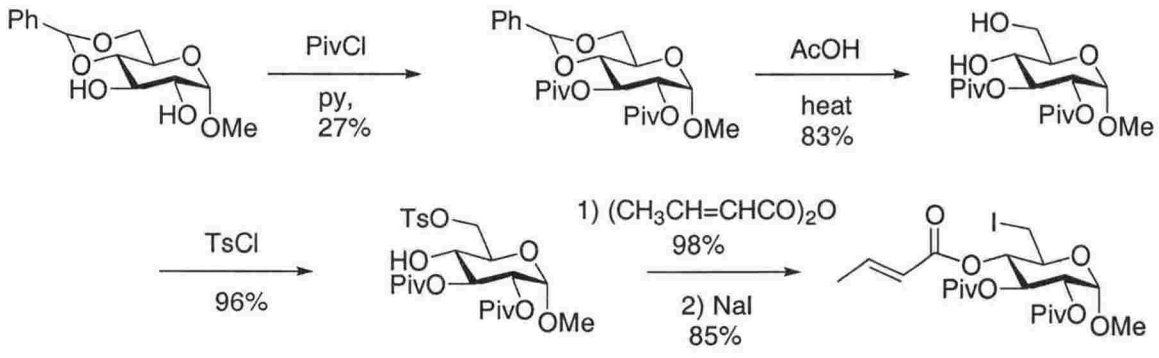
As with the aldol reaction, there are two new stereogenic centers formed leading to four possible isomeric products.



Scheme 5.2

5.1 Michael Acceptors

A Michael acceptor is any conjugated system containing an electron withdrawing group such as an ester. Tadano and co-workers have reported the successful use of sugars as chiral, ester auxiliaries for the asymmetric Michael reaction.[91] Their work used methyl α-D-gluco-, α-D-manno- and α-D-galactopyranosides- as asymmetric auxiliaries. In these studies, the sugar was tethered as an unsaturated ester at either the C-3, C-4 or C-6 position of a suitably protected sugar. These sugars were prepared through elaborate protection and deprotection strategies as shown in scheme 5.3.



Scheme 5.3

The synthesis, components of which are well known,[92] gave an overall yield of 18% for the six steps not including the initial methylation. Using similar procedures, they synthesized the range of Michael acceptors shown in figure 5.1. These molecules were subjected to copper mediated Michael reactions where the organocuprate was formed from $CuBr.Me_2S$ and a Grignard reagent. Addition using a range of nucleophiles gave yields of 51-92% with de's of 10-82%. Cleavage of the sugar and subsequent benzyl protection was reported to give yields of 80-94% with ee's 80 to 96%.

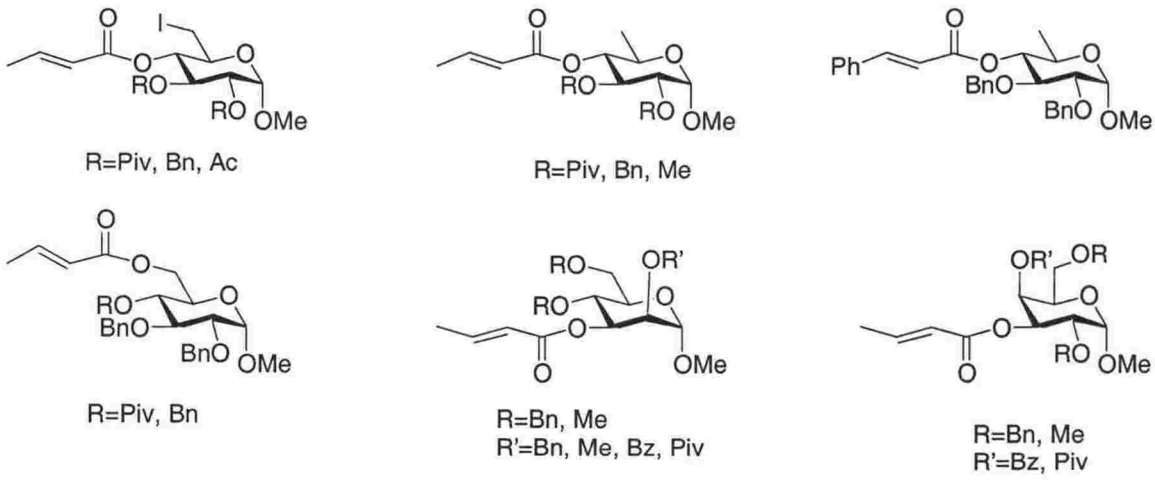
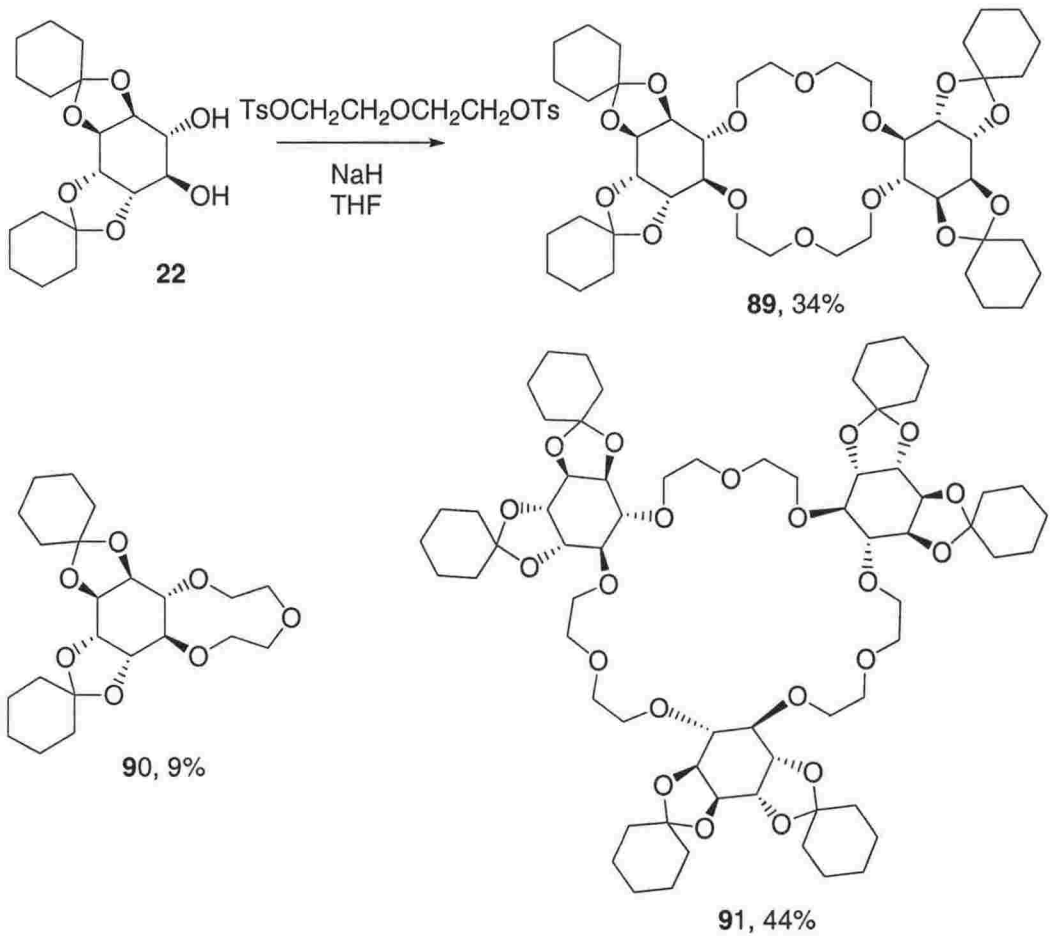


Figure 5.1-Chiral Michael acceptors derived from sugars

Given the success of this work, a logical step was to use inositols in the asymmetric Michael reaction and this will be the topic of this chapter. While this thesis was being written Akiyama and co-workers published a *chiro*-inositol derived system as a catalyst for the asymmetric Michael reaction.[93] This work reported the crown ether **89** derived from L-**22**, which was also formed with **90** and **91**, scheme 5.4. Catalytic amounts of **89** (0.2 eq) along with *t*-BuOK were used to catalyze the asymmetric reaction

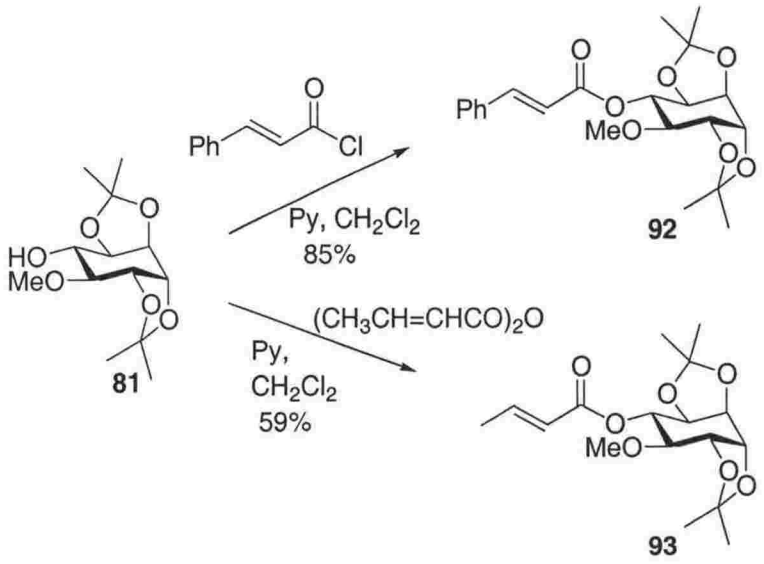
between glycine imine and a series of Michael acceptors. Yields of 65-80% and ee's of 46-96% were achieved in this 1,4-addition reaction.



Scheme 5.4

Attaching a Michael acceptor to the inositol system will move the reactive site in the molecule further away from the ring, thus the hindrance from the constrained inositol ring will be reduced. The first Michael acceptors synthesized were again from pinitol derivatives. Initially these were prepared using a DCC/DMAP coupling between the lone alcohol on **81** and the appropriate carboxylic acids to give yields of 62% (**92**) and 57% (**93**). Although **92** and **93** were successfully synthesized by these methods, better yields

resulted when **81** was reacted with cinnamoyl chloride to give **92** and crotonic anhydride for **93**, scheme 5.5.



Scheme 5.5

5.2 Organocuprate Mediated Michael Reactions.

One of the more common methods of inducing conjugate additions is by the use of organocuprates. The usual method of forming these organocuprates is by the transmetallation of an organometallic reagent with a copper salt. Much of the early work in this area was carried out by Gilman, including the formation of lithium dimethylcuprate from methylcopper and methyllithium, scheme 5.6.[94]

Scheme 5.6

Cuprates of the type $Li[CuR_2]$ have since become known as Gilman reagents due to this work, and in many Michael reactions the organocuprates are formed in situ. The reacting species formed in solution can be thought of as $[CuR_n]^{m-}$ fragments that are complexed to metal ions. In reality, the state in which the organocuprates exist is not as simple as we often describe. These fragments are able to aggregate together and form complex cluster molecules, especially in the formation of lower order cuprates where there will often be strong Lewis acid counter cations. The presence of anions from the Cu salt also contributes to the formation of these clusters. Theoretical calculations have proposed a myriad of structures that these clusters can adopt, with the most stable structure as depicted in figure 5.2.

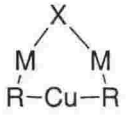
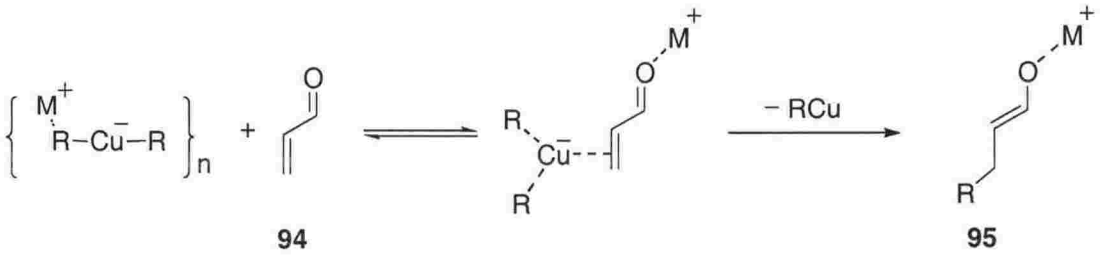


Figure 5.2 - Stable organocuprate cluster

This structure is often the ground state structure for Gilman reagents and the formation of these aggregates can be prevented by the use of solvents such as Me_2S or Et_2O, or by reacting LiR with CuR to stop salt formation. The later strategy has an associated problem in that working with simple organocopper moieties is often difficult. A good example is CuMe which is explosive and has poor solubility. Whether the presence of these aggregates effects the reaction mechanism for lower order cuprates or not, remains a point for discussion; with the general consensus being that they do not. Theoretical studies have indicated that as the transition state is not affected by these aggregates the

mechanism is also not affected. There is not full agreement on this point, and alternate views have been published.[95]

The currently accepted mechanism for enolate formation by the organocuprates proposed by recent studies is outlined in scheme 5.7.



Scheme 5.7

Krause and coworkers have examined this reaction using stopped flow techniques and found evidence to support a first order mechanism, with the rate determining step being the formation of the new carbon-carbon bond to give **95**. In an enone such as the generic acrolein structure **94**, there are two sites that can potentially bind; the π-electron cloud and the lone pairs on the carbonyl oxygen. The oxygen will complex preferentially to 'hard' species such as Lewis acids where as the π cloud will coordinate to 'soft' species such as the cuprate fragments discussed above. The binding of the $[CuR_2]^-$ fragment has been the subject of many theoretical studies, this work suggests that the cuprate binds at an angle of ~150°.[98] At this angle, the HOMO of the cuprate is able to interact with the π* orbital of the double bond leading to back donation as described by the Dewar-Chatt-Duncanson model, figure 5.3. These structures can be characterized by the upfield shift in the ^{13}C NMR of the alkene carbons by –40 to –80ppm and the downfield shift of the carbonyl carbon by +1 to +10ppm.

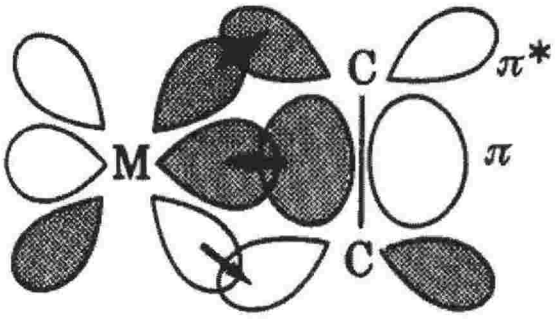
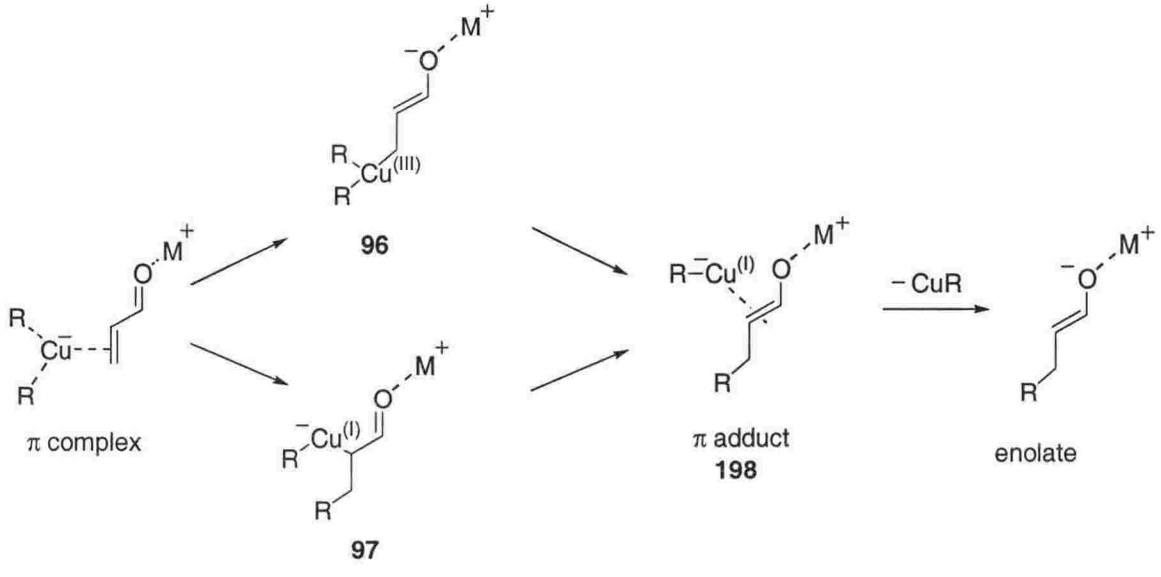


Figure 5.3 - Dewar-Chatt-Duncanson Model

For the rate determining step, formation of the new carbon-carbon bond, only indirect methods are able to be used to examine the mechanism and thus there is still debate on how it exactly occurs. The two currently proposed pathways are shown in scheme 5.8.[94]



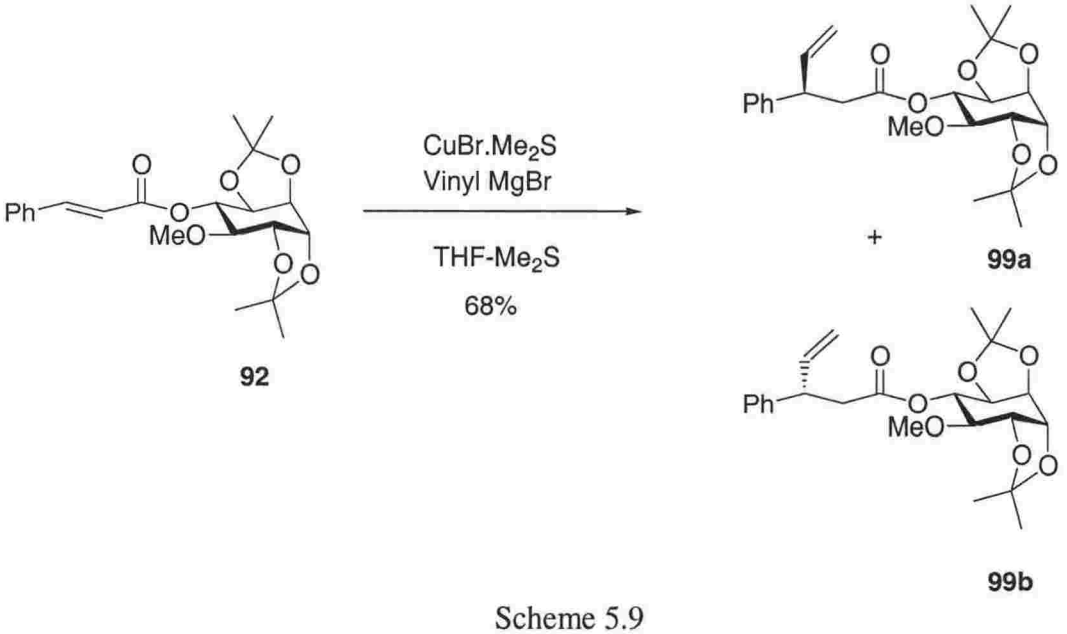
Scheme 5.8

The pathway via **96** is the most extensively studied with **96** being formed by oxidative addition then followed by a reductive elimination to give **98**. It should be noted that the CuIII species is an intermediate where a formal oxidation state of +3 has been given to the copper. Theoretical calculations have indicated that it is actually the organic ligands that are oxidized and reduced so the actual species resembles $CuI(R)(R^{+})(R^{-})$, however CuIII $(alkyl)_3$ is used for convenience. While there is evidence for this pathway, the second route, where **97** is formed by a 1,2-migratory insertion followed by rearrangement to **98**, is also viable and there is evidence in some cases to support this mechanism.[97] Franz and co-workers attempted to distinguish between the two pathways by studying ^{13}C kinetic isotope effects. Their results support the first pathway, however, they have not yet studied the system that is most likely to go via a carbocupration mechanism.

5.3 Copper Mediated Michael Reactions on the inositol system

Initial investigations into this system focused on the same copper mediated Michael reaction carried out by Tadano and his colleagues. For this reaction, highly pure $CuBr{\cdot}Me_2S$ was prepared by the method published by Theis and Townsend.[8] This reagent retained its reactivity when stored in a vacuum dessicator for many months. The organocuprate species was prepared by mixing five equivalents of the $CuBr{\cdot}Me_2S$ with ten equivalents of the chosen Grignard reagent at –78 °C under an inert atmosphere for one hour, the solvent system for this was a 2:1 (V:V) mixture of $THF:Me_2S$. The Michael acceptor was then added to this black mixture, and maintained at –78 °C until the reaction was judged complete. At this stage, the reaction was quenched with saturated ammonium chloride, warmed and the product extracted with EtOAc.

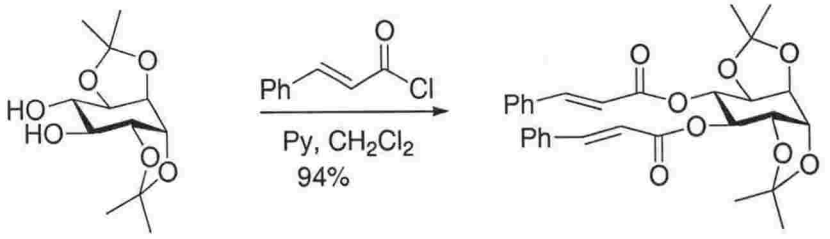
Initially, **92** was used with an organocuprate prepared from vinylmagnesium bromide. This system demonstrated the potential for the use of inositols as auxiliaries in the Michael reaction. The methoxy group, however did not provide the necessary steric bulk to be an effective chiral auxiliary, as examination of the ^{13}C NMR of the crude product showed doubling of the peaks in an almost 1:1 ratio, scheme 5.9. This was attributed to the formation of the two diastereomers, **99a** and **99b**, in equal amounts. Intuition leads to the believe that a methoxy group would not effectively block one face of the Michael acceptor and thus give poor selectivity. This was further confirmed by Tadanos' results where an analogous system containing a methoxy group gave a selectivity of 56:44. Thus **92** and **93**, figure 5.5 were not taken any further in these investigations.



Scheme 5.9

Although this result was successful obviously the investigation of other substrates was necessary to increase the selectivity of the reaction. Given the ease of formation of diol **21**, conversion of it into a diacceptor such as **100**, scheme 5.10, would produce a

facile synthesis of a potential selective substrate. Furthermore each acceptor would serve as a blocking group of the other and a 2 for 1 reaction would be possible, i.e. two active sites on one auxiliary. Thus the conditions used above to synthesize **93** were applied to **21**, and the diester was generated in excellent yield.



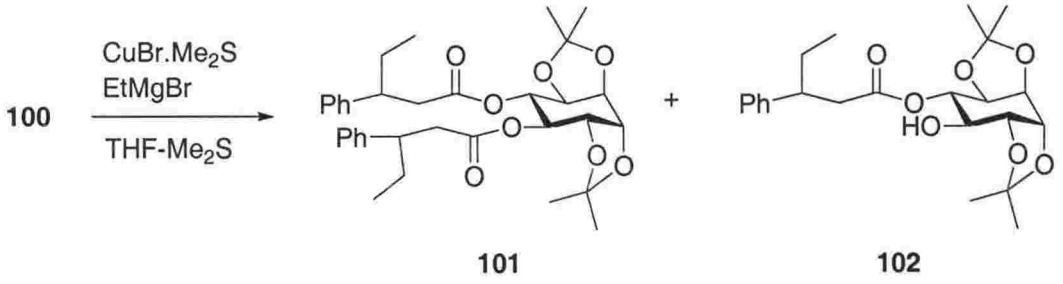
21 **100**

Scheme 5.10

The work on the aldol reaction showed that the isopropylidene groups were large enough to hinder this system therefore the cyclohexylidene moieties were not synthesized for this study. The corresponding dicrotonic acceptor was also synthesized although not fully investigated.

Diester **100** was then subjected to the reaction detailed above with organocuprates prepared from three different Grignard reagents-vinylmagnesium bromide, allylmagnesium chloride and ethylmagnesium chloride. With **100,** the reaction proved to be highly temperature dependant and optimal results were attained with addition of the inositol at –78 °C then warming to –23 °C. The best results using this reaction were attained with ethylmagnesium bromide, scheme 5.11, however severe limitations were discovered. It was not reliably repeatable and when a reaction did occur a complex mixture of products was formed. This mixture often proved impossible to separate and thus isolation of the desired product was not achieved. Using EtMgCl, allowed the by-product **102** to be identified. It was unable to be determined if the cleavage leading to

102 had occurred before or after the Michael addition however examination of the NMR spectra indicated the selectivity was excellent as it appeared only one isomer was obtained.



101 **102**

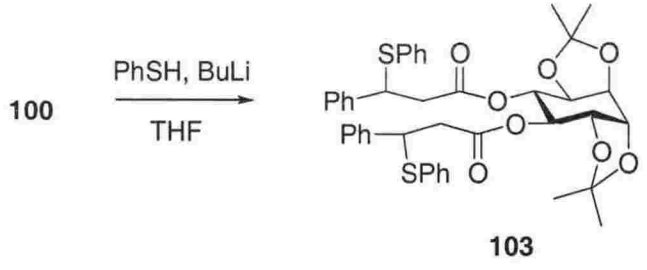
Scheme 5.11

As stated previously hard nucleophiles such as Grignard reagents will add in a 1,2-fashion rather than a 1,4, like softer organocuparates. As discussed in section 5.2 these organocuprates can be formed by the transmetallation of an organometallic reagent with a copper salt. In the above reaction, the copper salt is used in five equivalents with respect to the inositol, while there is 10 equivalents of the Grignard reagent. It is highly likely that the excess Grignard reagent led to a 1,2- reaction, thus causing the cleavage. Varying the quantities of both the Grignard and the copper complex was attempted, however as stated this reaction was not reliable and under any of the conditions tested only unreacted starting material was recovered.

These results did show that this system has potential as an auxiliary, however the cuprate reaction has too many limitations to be of value so other reactions were surveyed for potential application to this system.

5.4 Conjugate Addition Using Thiols as Nucleophiles

Thiols have been used as nucleophiles in conjugate addition reactions with great success.[99] An example of the use of this reaction was reported by Naito and co-workers in their complete synthesis of (+)-Diltiazem, a clinically useful cardiac drug.[100] In this reaction, BuLi is added to a thiol forming a catalytic amount of lithium thiolate in the presence of excess thiol. Nucleophilic addition of the thiolate to the alkene forms a transient enolate that is readily protonated from the excess thiol and thus forms another thiolate ion. These conditions were applied to **100** using thiophenol and gratifyingly gave **103**, scheme 5.12.

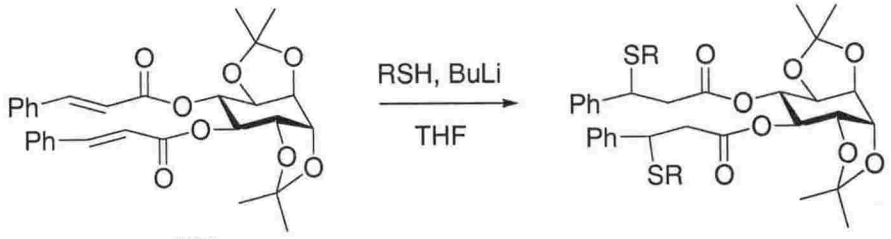


103

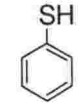
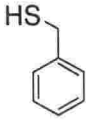
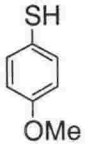
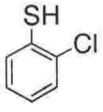
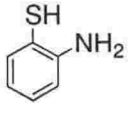
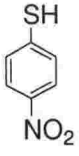
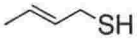
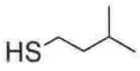
Scheme 5.12

Unlike copper catalyzed conjugate addition reactions, which usually require temperatures below –20 °C, these reactions will occur at 0 °C or even room temperatue.[99] Reaction of **100** at 0 °C gave a mixture of products that proved to be inseparable, however lowering the temperature in an ice-salt bath to just –10 °C gave a clean reaction without the formation of impurities. This reaction was carried out on **100** with a range of thiols and the results of this are shown in table 5.1.

Table 5.1- Conjugate addition of thiols to **100**



100

Entry	Thiol (RSH)	Product	Yield (%)
1		**103**	75
2		**104**	59
3		**105**	67
4		**106**	59
5		**107**	61
6		—	
7		**108**	31
8		**109**	53

As seen with entry six, electron withdrawing thiols are poor nucleophiles for this reaction, with 4-nitrothiophenol not reacting at all. In contrast 2-aminothiophenol, entry five worked reasonably well, however the product decomposed rapidly presumably due to reaction between the amine and the ester linkage of the inositol ring, therefore this is reported as a crude yield. Entry four also decomposed rapidly. With crotonic thiol, entry seven, crude thiol was used in the reaction, prepared by the manufacturers of skunk shot, and the purity of the thiol could not be guaranteed.

With these systems, diastereomers were formed, and evidence for this can be seen by examining the ^{1}H NMR, figure 5.4. The figure shows the protons attached to C-3 and C-4 on the inositol ring which are equivalent protons. By comparing the doublet of doublets at 5.2 ppm with the doublet of doublets at 5.0 ppm an approximate 1:1 ratio of diastereomers is clearly obvious.

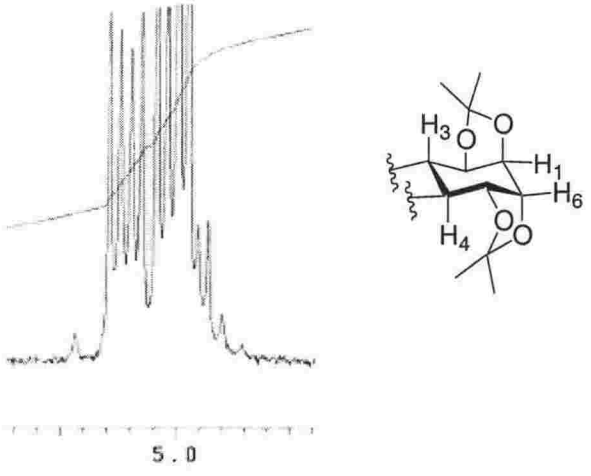


Figure 5.4 – H-3 and H-4 of **103** showing diastereomers

These molecules proved too large to be able to generate any useful data via GC analysis and thus exact d.e.'s were not determined. Conjugate addition to **100** will lead to four possible products, figure 5.5, however **103a** and **103b** are equivalent. This means there are three possible diastereomers that will lead to the two possible enantiomers after removal of the auxiliary. Therefore determining the de was not a priority as figure 5.4 could potentially be displaying a diastereomeric ratio that is not indicative of the final e.e.

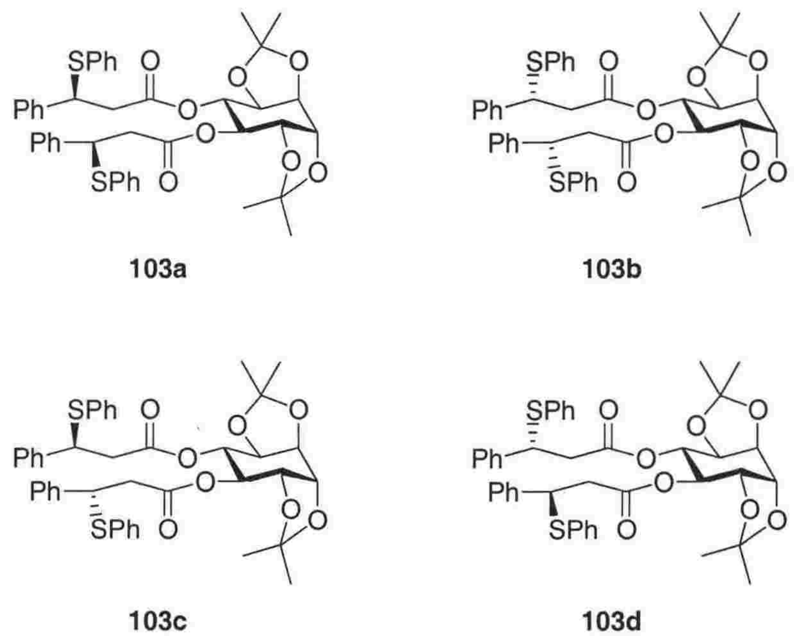
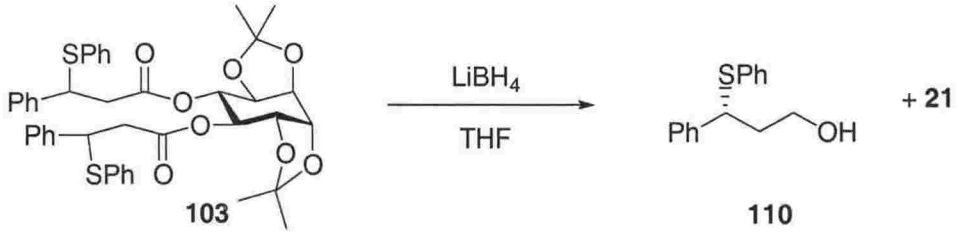


Figure 5.5 - Diastereomers of **103**

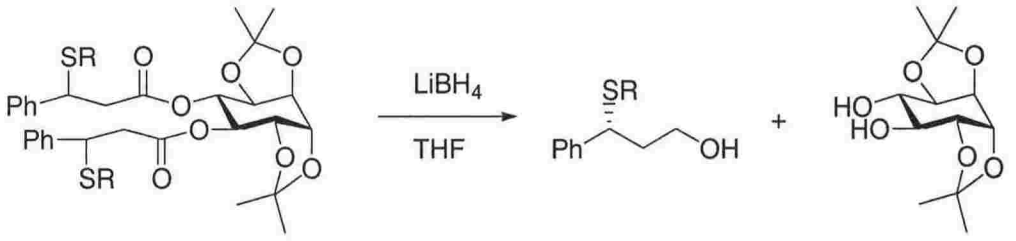
Cleavage of the inositol auxiliary would produce a chiral thiol derivative with an unknown degree of optical activity. Initially LAH was trialed, however this proved to be unsuccessful, with no reaction observed. $LiBH_4$ in THF proved to work very well giving a clean conversion to the thiol alcohol **110**, scheme 5.13.

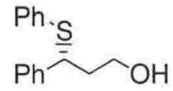
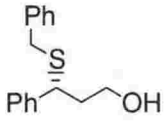
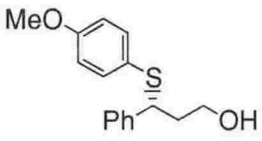
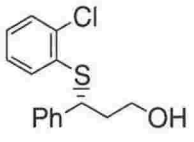
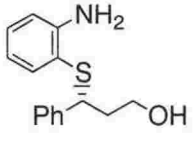
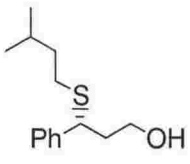


Scheme 5.13

The remaining thiol derivatives were treated with $LiBH_4$, the results of this reaction are summarized in table 5.2. The figures are percentage yields with respect to the theoretical yield assuming two equivalents of product result from each equivalent of adduct. After aqueous work up, diol **21** was found to reside in the aqueous layer due to the effect of the THF solvent. It was recovered by removing the water under reduced pressure, dissolving the resulting white solid in CH_2Cl_2 and washing with water. In all cases the recovery of **21** was between 84% and 96%, and with no further purification was treated with cinnamic chloride to regenerate the starting Michael acceptor. This meets a key requirement of an auxiliary, the ability to be recycled. The absolute configuration of the thiol products was determined by comparison of the optical rotation of compounds **110-114** to known literature values.[101] Enantiomeric selectivity was determined by GC analysis using a chiral HP cyclodexB column. The only unusual result was with *p*-methoxythio phenol, entry three, where the molecule appeared to decompose and no evidence of product or **105** was evident.

Table 5.2- Removal of Auxiliary from **103-109**



Entry	Thiol	Product	Yield (%)	e.e.(%)
1		**110**	69	50
2		**111**	65	47
3		—	0	
4		**112**	55	46
5		**113**	69	26
6		**114**	73	42

While this system allowed the optimal conditions for this type of Michael reaction to be determined, the selectivity was quite poor. Obviously the two acceptors are not

producing the extent of facial hindrance hoped for. This can be rationalized by the conformation the molecule is adopting, as shown by molecular modeling, figure 5.6.

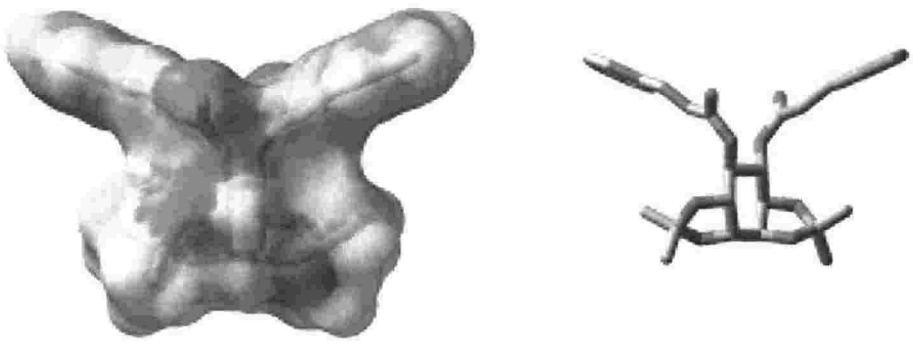


Figure 5.6 - Conformation of **100**

As can be clearly seen in the above view, the two Michael acceptors form a large 'bowl' at the top of the molecule, with the easiest access to the Michael acceptors being from the top face. An incoming nucleophile approaching this has equal access to either acceptor, with the carbonyl groups aligning to opposite sides this gives access to diasterotopic faces that will lead to diasteromers **103a** and **103b** and hence poor overall selectivity.

To increase selectivity a group needs to be placed at C-4 to block one face of the Michael acceptor at C-3. In the work carried out by Tadano with mannose derivatives the acceptor was in an environment analogous to the C-3 position of **21**. It was found that optimal selectivity was attained when there was a pivaloyl group at the C-4 position. This dependence on protecting group was rationalized by a proposed conformational analysis. If the Michael acceptor is sitting in the conformation depicted above (drawn this way for clarity) there will be unfavorable interaction between the metallic species

and the carbonyl. This leads to the molecule adopting a new conformation as shown in figure 5.7.

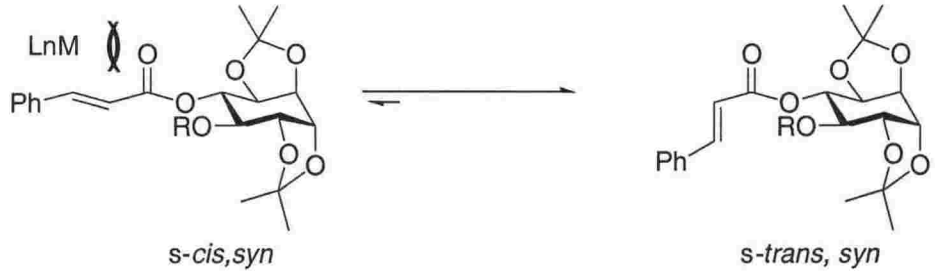


Figure 5.7 - Conformation of acceptor

When the unsaturated system is sitting in the s-*trans*, syn conformation, the protecting group on the C-4 carbon can effectively shield the front face of the molecule forcing the organocuprate to attack from the back face. Thus, increased steric size at this site will give increased selectivity. The pivaloyl group has been shown to give high selectivity compared to a benzyl group as the three methyl groups are sitting at a more optimal position to shield a face of the π-system. With the flat aromatic ring rotation can expose both sides of the acceptor π-system, figure 5.8.

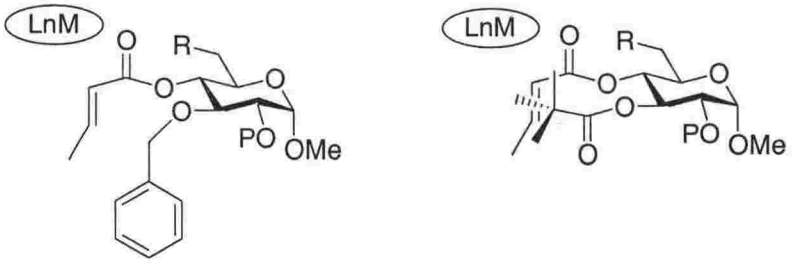
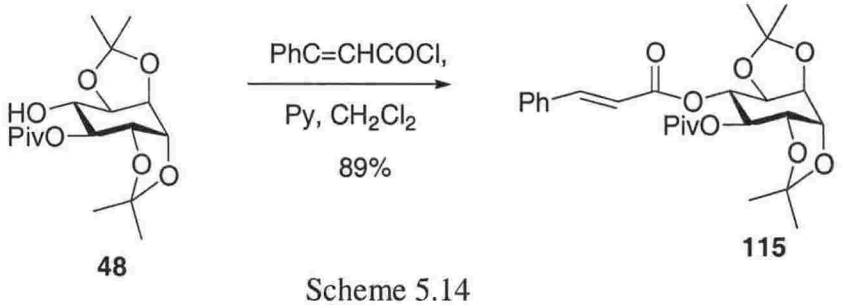


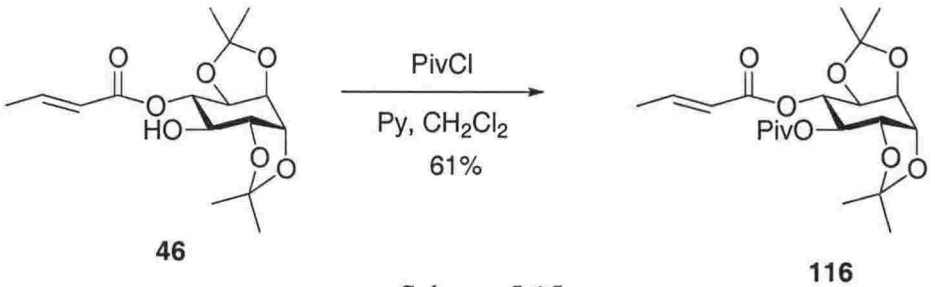
Figure 5.8 - Bn versus Piv for blocking ability

Using these concepts **115** was synthesized in an 89% yield as shown in scheme 5.14. Alternatively, the corresponding crotonate **116** was synthesized by treating **46** with pivoyl chloride, scheme 5.15.



48 **115**

Scheme 5.14

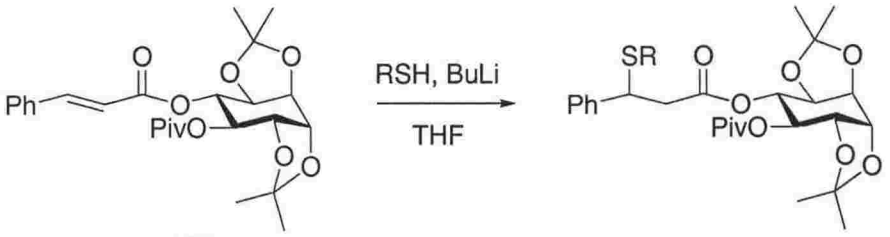


46 **116**

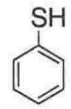
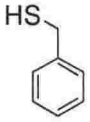
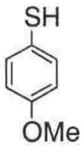
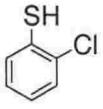
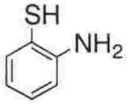
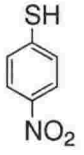
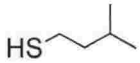
Scheme 5.15

Initially, the conjugate addition was carried out on the D and in some cases the L isomers of **115,** with the results being summarized in table 5.3. These results are consistent with those for **100**, in which electron deficient thiols failed to give conjugate addition, as in entry six. In entry four the acceptor was cleaved to give **48**. For entry five the product proved to be less stable than the corresponding di- species, and was cleaved in situ. Thus it is apparent that only certain thiols can be effectively used.

Table 5.3- Conjugate addition of thiols with **115**

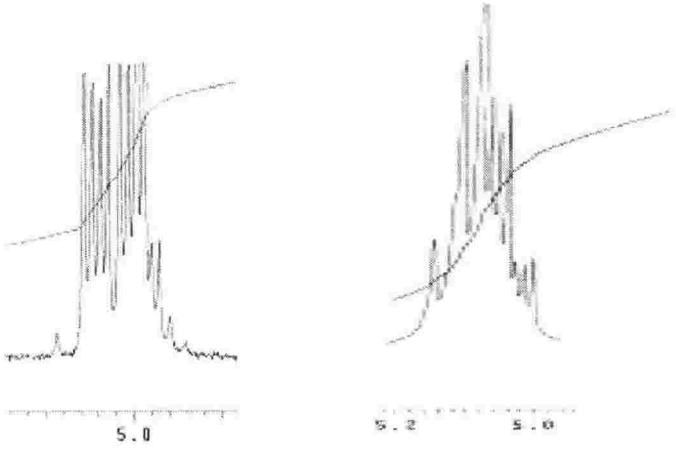


115

Entry	Thiol (RSH)	Product	Yield D (%)	Yield L (%)
1		**117**	79	75
2		**118**	74	72
3		**119**	76	n.a
4		**48**	—	n.a.
5		**120**	n.a	68
6		—	—	n.a.
7		**121**	71	73

n.a. indicates reaction not attempted.

However, examination of the ^{1}H NMR shows no indication of diasteromers in the product, figure 5.9. This figure compares the difference between the H-3 and H-4 protons of **103** and the corresponding proton on **117**.



103 **117**

Figure 5.9 – Comparison of ^{1}H NMR of **103** and **117**.

The full ^{1}H NMR spectrum for **117** is shown in figure 5.10, in this the methyl groups from the isopropylidene and piv groups can be seen between 1.0 ppm and 1.6 ppm. The multiplets between 2.3 ppm and 2.8 ppm are from the CH_2 adjacent to the ester linkage, C-7. The multiplet at 3.6 ppm, integrating for one proton, is the H atom on C-8. The two peaks between four ppm and five ppm are for the H-2/H-5 and H-1/H-6 protons of the inositol ring with the multiplet at 5.1 ppm from the H-3 and H-4 protons of the inositol. Remarkably, no diastereomeric peaks are observed in this spectrua. Finally, the multiple peaks between 7.2 ppm and 7.5 ppm are due to the 10 aromatic protons in this molecule.

Thus it appears the initial and overall goal, a chemical transformation with high selectivity brought about by an inositol has been successfully achieved.

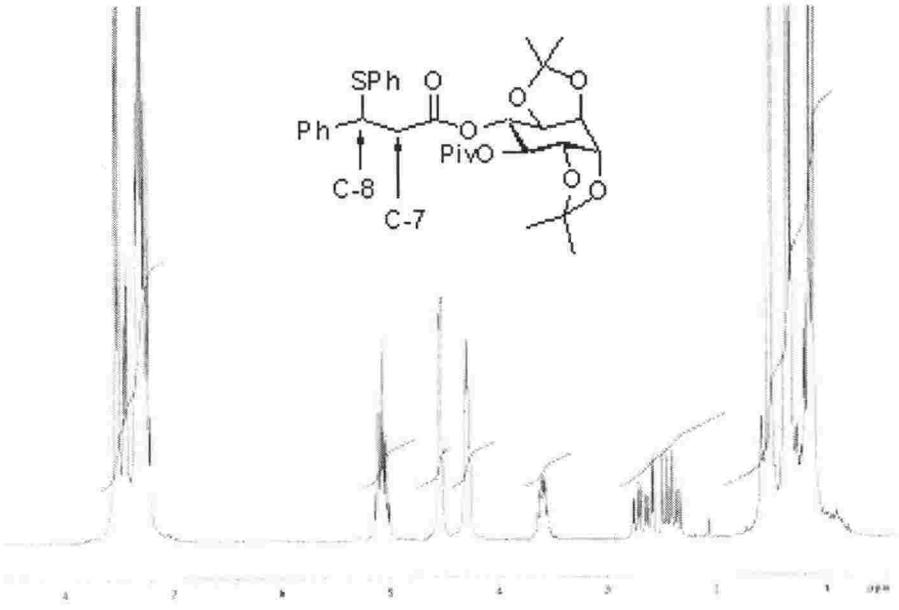
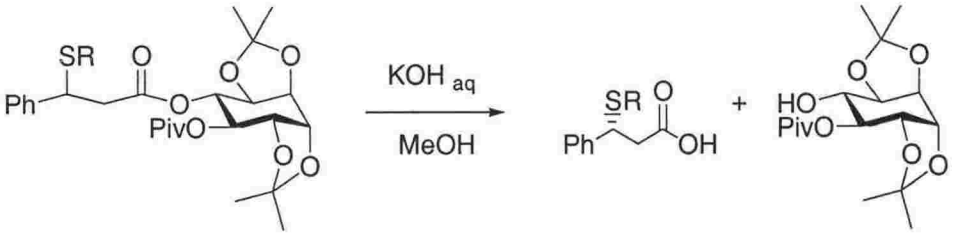
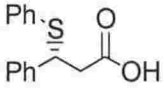
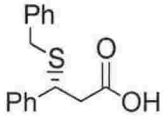
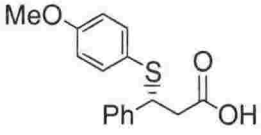
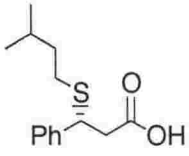


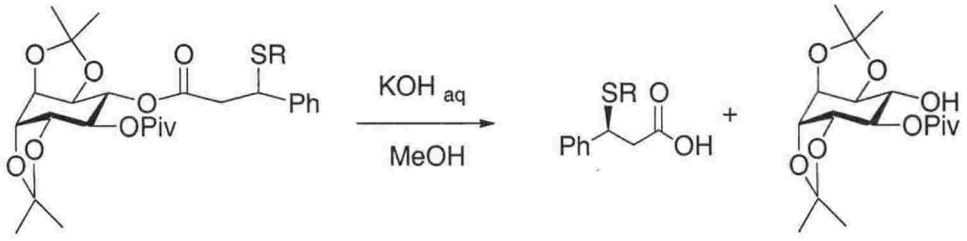
Figure 5.10 – ^{1}H NMR of **117**

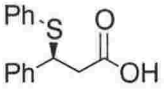
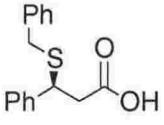
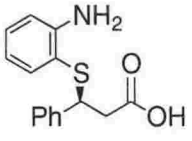
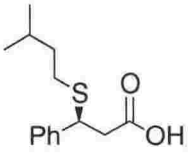
Removal of the auxiliary from these compounds was a delicate step, as selectively cleaving the acceptor at C-3 without removal of the piv group at C-4 was desired. This was achieved by careful and selective base hydrolysis and the results of this are summarized in table 5.4.

Table 5.4- Removal of Addition Product from Inositol Auxiliary



Entry	Thiol	Product	Yield (%)	ee (%)
1		**122a**	76	>95
2		**123a**	75	>95
3		—	—	
4		**125a**	72	>95



Entry	Thiol	Product	Yield (%)	ee (%)
1		**122b**	74	>95
2		**123b**	72	>95
3		**124b**	59	>95
4		**125b**	67	>95

In this system, **48** was recovered from the first aqueous extraction in 84-91% yield, was filtered through a silica gel plug with hexanes and EtOAc (5:1) and treated with cinnamic chloride to regenerate the reactive species in comparable yield.

Although the yields for this system are not as high as compared to the diacceptor system (**100**) the ee's are excellent. By carrying out molecular modeling on this system, it can be seen that the pivaloyl group does indeed block the front face of the Michael acceptor thus forcing the nucleophile to attack from the back face, figure 5.11.

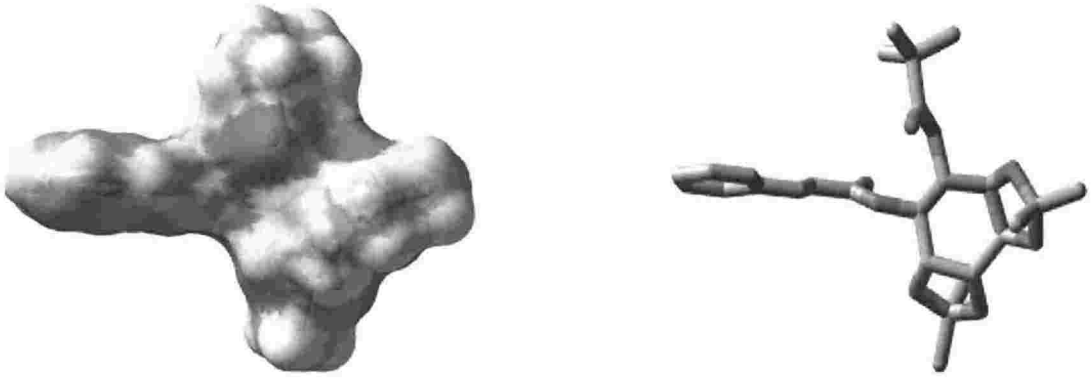
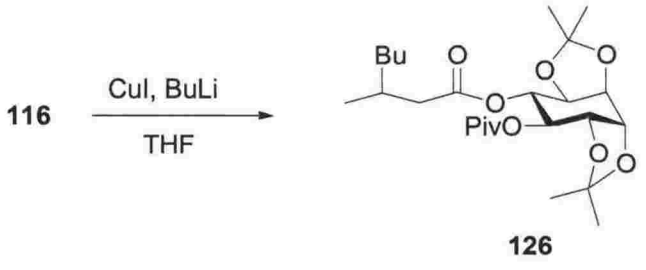


Figure 5.11 – Conformation of **115**

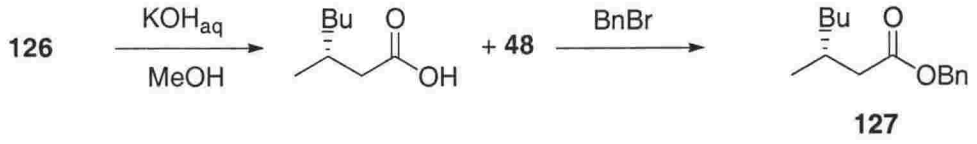
An alternate copper catalyzed reaction was also carried out, using inositol **116**. The method used was reported by Schneider and Reese as a part of their investigations into diastereoselective conjugate additions to *t*-leucine derived *N*-enoyl-1,3-oxazolidin-2-ones.[14] In this procedure, the organocuprate was formed by the addition of an alkyl lithium reagent to a suspension of CuI in THF, a Lewis acid was then added followed by the Michael acceptor. On this system, BuLi was added to the CuI and stirred for 30 minutes at –30 °C after which, the mixture was cooled to –78 °C and $BF_3{\cdot}OEt_2$ was added. Following this **116** was cannulated in and the reaction was warmed slowly to –40 °C. This reaction occurred successfully in a yield of 43% to give **126**, scheme 5.16.



126

Scheme 5.16

Again the selectivity appears to be excellent with no evidence of diasteromers in the NMR spectra. The adduct was then cleaved, however in this case base hydrolysis followed by a benzylation was used to give **127** as shown in scheme 5.17.



127

Scheme 5.17

While this reaction was more successful than using a Grignard reagent, the yield was low with a bigger problem being the availability of appropriate alkyl lithium reagents, thus this reaction was not investigated further. However it has been shown that *chiro*-inositols work extremely well as auxiliaries in the asymmetric Michael reaction. Not only were excellent ee's attained but the auxiliary was able to be successfully recycled.

Chapter Six – Inositols as Chiral Ligands for Metal Catalyzed Asymmetric Synthesis.

Substantial work has gone into developing new ligands for metal catalyzed stereoselective synthesis in recent times, and an important class of these contain nitrogen.[102] Unlike many types of ligands that contain multiple bonds, nitrogen ligands do not tend to have any π bond character. Thus, the metal-ligand bond strength in these ligands is dependant on the electron density at the metal center as there can be no π back-bonding. While nitrogen containing ligands are less common, they have many advantages over the often more favored phosphorous ligands. For example, many nitrogen ligands are derived from natural sources such as amino acids, thus there is a readily available, enantiopure source. Generally, the chirality on these ligands tends to be on the carbon backbone, as epimerisation occurs readily at nitrogen atoms leading to racemization. Another advantage to using nitrogen is the chemistry of this element is well understood so adaptations and optimization of ligand properties can be achieved with relative ease. Nitrogen also has the ability to act as a strong base or strong nucleophile and thus can form complexes with a wide variety of metals across the periodic table.

An example of carbohydrate derived nitrogen containing ligands was reported by Ruffo and co-workers.[103] They successfully synthesized the diimino and diamino ligands shown in figure 6.1. These were used for the copper catalyzed cyclopropanation of styrene giving yields of 75% to 90% with ee's of 0 to 55%.

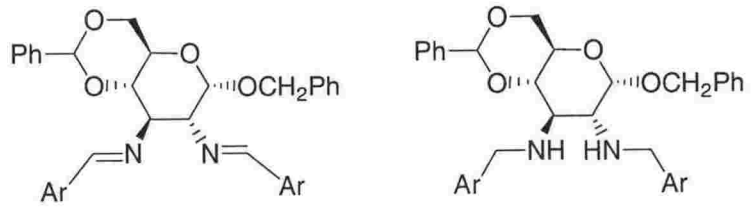
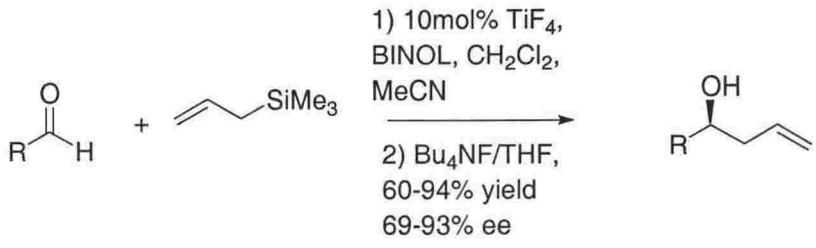


Figure 6.1 - Nitrogen containing ligands from carbohydrates

Inositols have also been investigated as ligands, for example Holmes synthesised a poly(pentylmethacrylate) from a *scyllo*-inositol derivative.[104] However, the use of this polymer as a metal-chelating ligand is yet to be reported. As with other areas of inositol chemistry, most of the work into the use of inositols as ligands has focused on *myo*-inositol. The *chiro*-inositols however have C–2 symmetry, the advantage of this symmetry element in ligand design was noted in the introduction. Ongoing work is being carried out at IRL into the use of *chiro*-inositols as phosphorous containing ligands, this part of the project is to develop a diamino, amino alcohol or diol ligand from *chiro*-inositol that can be used in asymmetric catalysis.

6.1 Use of diol **21**.

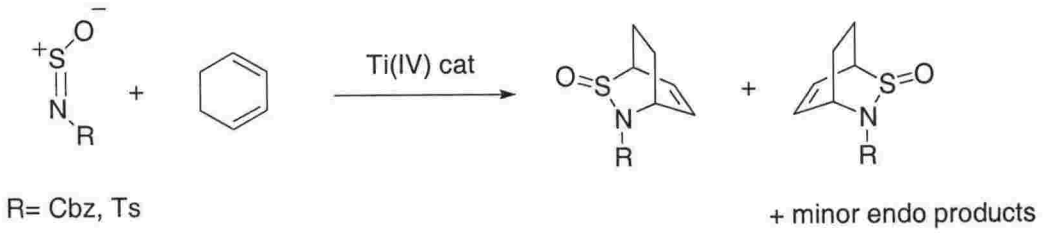
Initially a diol ligand was investigated for use in asymmetric catalysis. As mentioned in the introduction, oxygen containing molecules are often used as ligands with titanium due to the high affinity between titanium and oxygen. Thus it seems somewhat of an oversight that diol **21** has not been used as a ligand. Therefore some known metal catalyzed transformations that used chiral diols as ligands were screened. Initial attempts used a procedure of Carreira and Gauthier in which BINOL and TiF_4 catalyzed the enantioselective addition of allylsilanes to aldehydes, scheme 6.1.[105]



Scheme 6.1

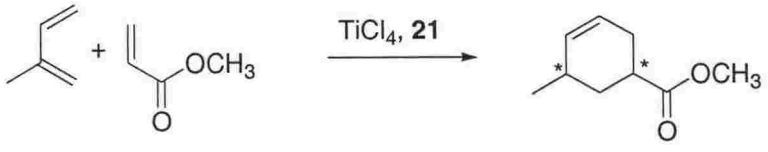
Solid TiF_4 is commercially available, unfortunately it has very limited solubility, being soluble in MeCN but not Et_2O, THF, CH_2Cl_2 or benzene. As reported when a solution of BINOL in MeCN was added to a solution of TiF_4 in MeCN, a deep red solution resulted. After drying under reduced pressure, the residue was suspended in CH_2Cl_2, and TMS allyl and a small amount of MeCN were added followed by the aldehyde. Repeating this with diol D-**21** and TiF_4 gave a suspension in MeCN, thus a MeCN/CH_2Cl_2 mixture was used. Stirring at room temperature gave no color change, therefore the mixture was refluxed overnight giving a pale orange colored solution. This was dried and treated with TMSallyl and benzaldehyde. Unfortunately, the only compounds isolated were benzaldehyde and D-**21**. Generally it has been found that for the allylation of carbonyls, allytrialkyl silanes are less reactive nucleophiles than the corresponding, but more toxic, stannanes. This is attributed to the lack of Lewis acidity needed to activate the carbonyl group allowing nucleophilic attack to occur. TiF_4 was initially used in this reaction as it was hoped the increased electronegativity of fluorine would be enough to activate this reaction where chloride and bromide complexes had not worked. Obviously, this has no effect when using the non-aromatic diol **21**. This reaction was not investigated further.

Another catalytic reaction where a 1,2-diol has been successfully used as a ligand is in the asymmetric Diels-Alder reaction. Devine and Oh used a catalyst derived from an optically active hydrobenzoin and $TiCl_4$, reporting yields of 68-91% and ee's between 16% and 92%.[106] A further example is the catalyzed reaction of N-sulfinyl dienophiles with 1,3-cyclohexadiene.[107] Yields of 29-85% and ee's of 13-76% were achieved with a variety of chiral diols as catalysts, scheme 6.2.



Scheme 6.2

Thus, the use of **21** in conjunction with titanium reagents to promote an asymmetric Diels-Alder reaction between isoprene and methylacrylate was attempted, scheme 6.3.



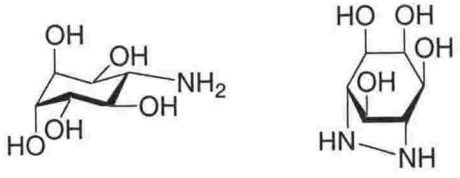
Scheme 6.3

Initially, the method used was as outlined in the Oh paper,[106] in which BuLi and **21** were combined followed by $TiCl_4$ and then methyl acrylate and isoprene. This reaction was trialed at a range of temperatures and in each case a dark brown mixture rapidly resulted from which nothing discreet could be extracted. The reaction was repeated with TiO^iPr_4, but only unreacted starting materials were isolated. It should be noted that in the absence

of **21** a racemic Diels-Alder product was formed. It appears that **21** is interacting with the Lewis acid, as its presence stops the known reaction from occurring. However, it is not forming a stable complex that will catalyze the reaction. Thus **21** is not performing as an effective ligand and other areas were investigated.

6.2 Development of a chiral diamine.

Given the lack of success with a diol ligand the next step was to generate a diamine that could be used as a C-2 symmetric ligand. The synthesis of nitrogen containing inositol derivatives such as inosamines has received attention in the past as they are important components of many antibiotics.[108] These include fortamine **128**, figure 6.2.

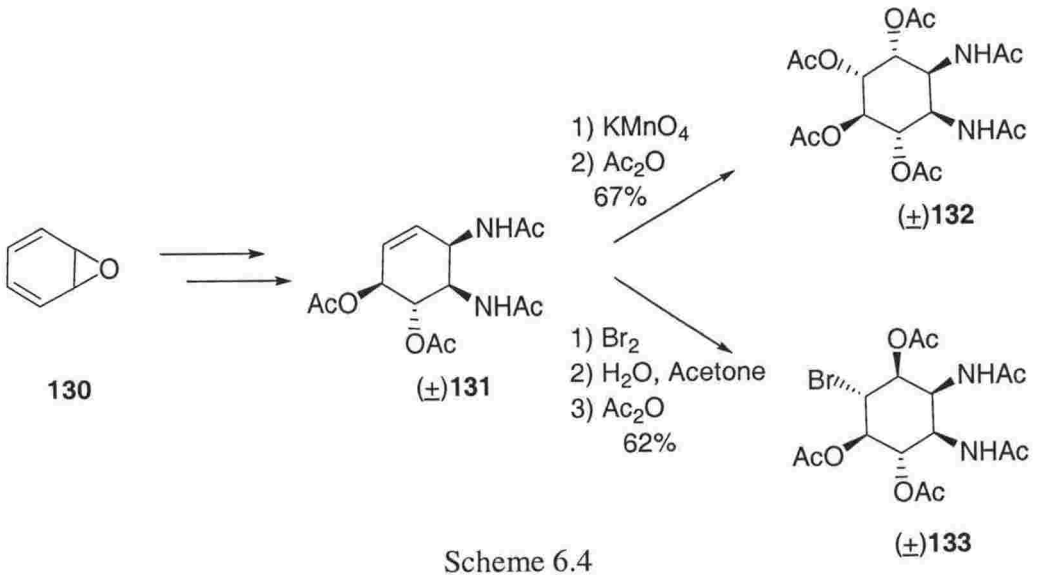


128 **129**

Figure 6.2 - Inosamine derivatives

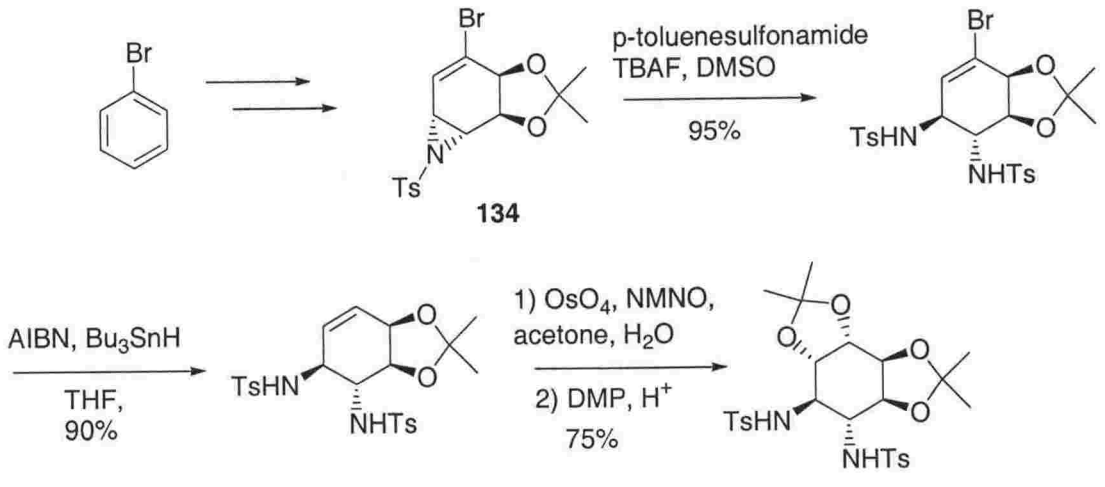
A wide variety of modifications have been carried out on these inosamines as part of structure activity relationship studies.[109] Amino cyclitols were studied extensively in the 1960's by Ogawa and co-workers.[110] These investigations included studies into the synthesis of streptamine and the formation of some very interesting polycyclic amino structures such as **129,** which was subsequently hydrogenated and acetylated to give 4,6-dideoxy-4,6-diacetamido-1,2,3,5-tetra-*O*-acetyl-*myo*-inositol. Other similar molecules have been prepared by Schwesinger, Fritsche and Prinzbach.[111]

Diamino inositol derivatives with the *chiro* configuration are less common, Kresze, Weiβ and Dittel generated a diamino cyclitol with the *chiro* congfiguration in 1984.[112] This synthesis began with *meso*-epoxide **130**, which was transferred in five steps and 21% overall yield into the racemic alkene (±)**131**. Alkene (±)**131** was then converted into both the *chiro*- ((±)**132**) and the *myo*- ((±)**133**) inosamines, scheme 6.4.



Scheme 6.4

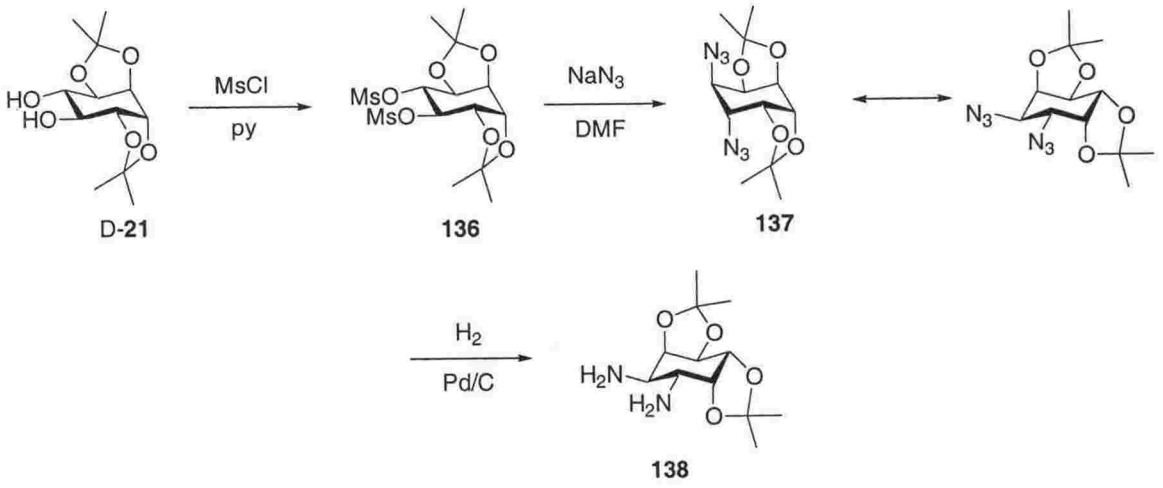
Another example of a diamine with the *chiro*-configuration was synthesized by Hudlicky and co-workers.[113] The synthesis began with bromobenzene, which was converted enzymatically into bromocyclohexadiene-*cis*-diol. This was converted into enantiopure vinyl aziridine **134** that was opened with p-toluenesulfonamide and TBAF as a catalyst to give the chiral diamine **135**, scheme 6.5. Hudlicky incorporated **135** into salen type complexes which were inactive.[113b]



Scheme 6.5

These two examples show it is possible to generate C-2 symmetric diamines that have inositol structures, however, in both cases they did not begin with inositols and the stereochemistry was in part determined by the use of enzymes.

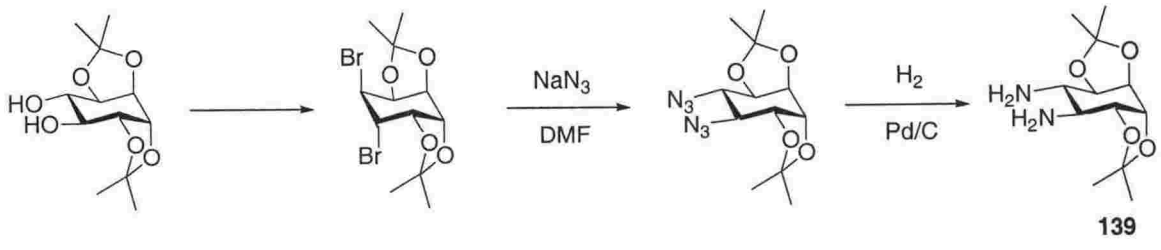
The desired diamine was 1,6-diamino-1,6-dideoxy-2,3;4,5-diisopropylidene-*neo*-inositol **138**, scheme 6.6. With a proposed synthesis based on the synthesis of (±)-1,2-dideoxy-1,2-diamino-*myo*-inositol reported by Schlewer and co-workers.[114] Diol **21** would be converted into dimesylate **136**, followed by displacement with azide to give the diazide **137**. Subsequent hydrogenation would provide the diamine **138**.



D-21 136 137 138

Scheme 6.6

This synthesis would give a product with a *neo-* configuration, which modeling indicated was ideal for binding a metal cation as a bidentate ligand. Alternately, the *chiro-* configuration could be attained by double displacement to give **139**, scheme 6.7.



139

Scheme 6.7

This latter route was not investigated extensively as initial attempts at generating a dihalide with both chloride and bromide were unsuccessful.

Inositol **136** was synthesized in 89% yield by treating diol D-**21** with MsCl in pyridine at 0 °C under an inert atmosphere. This molecule proved to be very insoluble, being only sparingly soluble in solvents such as CH_2Cl_2 or ethanol. The lack of solubility meant displacement of the mesylates by azide proved impossible, as **136** would not

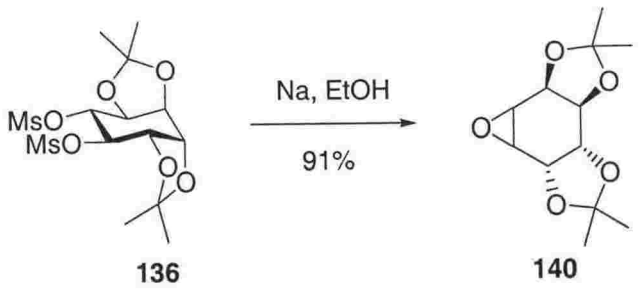
dissolve in DMF or DMAC. Treatment of **136** with azide in CH_2Cl_2, DMSO, 2-methoxy ethanol and refluxing DMF also gave unreacted starting material, table 6.1.

Table 6.1 – Reaction conditions of attempted conversions on **136** to **137**

Nucleophile	Solvent	Temperature
NaN_3	DMF	0 °C → reflux
	DMAC	0 °C → reflux
	CH_2Cl_2	0 °C → reflux
	DMSO	R.T. → reflux
	$MeOCH_2CH_2OH$	reflux
Urea	H_2O/KOH	reflux
$NaN(CHO)_2$	DMF	0 °C → reflux

As shown, other strategies involved treatment with urea and sodium diformyl amide. Yinglin and Hongwen used sodium diformyl amide as an alternate reagent in the Gabriel synthesis.[115] While the classic Gabriel synthesis is a method of generating primary amines, it does involve the displacement of an oxygen leaving group by a substituted amine. Unfortunately neither of these strategies worked on this system.

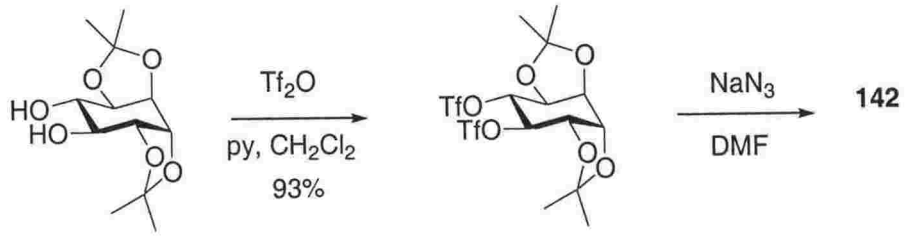
Dimesylate **136** was then treated with metallic sodium in ethanol by the method of Angyal.[116] This generated the epoxide **140** as shown in scheme 6.8, which in theory could be opened with a nitrogen nucleophile to give an amino alcohol, this will be discussed in section 6.3.



136 **140**

Scheme 6.8

Given the solubility problems with **136,** a more reactive leaving group was tested in the hope it would be successfully dislpaced by a nitrogen containg group. The ditriflate **141** was synthesized in 93% yield by reacting diol **21** with triflic anhydride in a mixture of pyridine and CH_2Cl_2, scheme 6.9. **141** proved to be more soluble than **136** being soluble in a range of organic solvents including CH_2Cl_2.

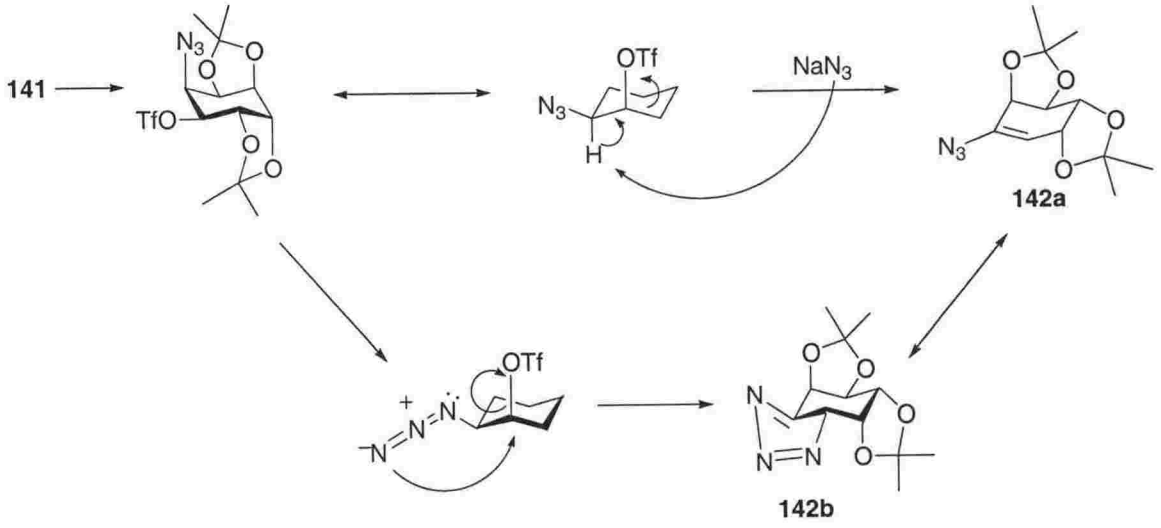


D-**21** **141**

Scheme 6.9

Ditriflate **141** is a white solid that is stable in air and can be purified by silica gel chromatography. The ditriflate **141** was reacted with NaN_3 in DMF to give a product that was subsequently found not to be the desired diazide **137**. The same product, **142** was formed over a range of temperatures from 0 °C to refluxing DMF. When only one equivalent of NaN_3 was used then the isolated products were a mixture of **142** and ditriflate **141**. Initially the proposed structure for this unknown product was triazole

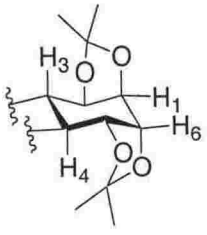
142b. This could be formed by the displacement of one triflate by an azide anion and subsequent elimination of the other triflate leading to a tautomeric structure as shown in scheme 6.10.



Scheme 6.10

This tautomeric structure was consistent with NMR data and most importantly the IR spectrum had an azide peak at 2112 cm^{-1}, table 6.2. Unfortunately, the unknown product would not ionize and mass spectral analysis could not be obtained.

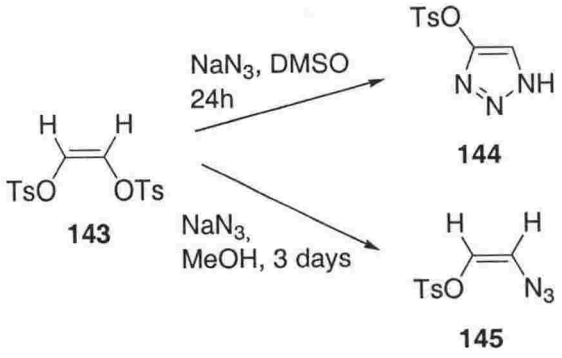
Table 6.2 – Analytical Data for unknown **142**



Assinment	^{1}H NMR Shift/ppm	^{13}C NMR Shift/ppm	^{19}F NMR Shift/ppm
Isopropylidenes	1.35, 1.39 (12H)	26.5, 26.7, 27.9,	

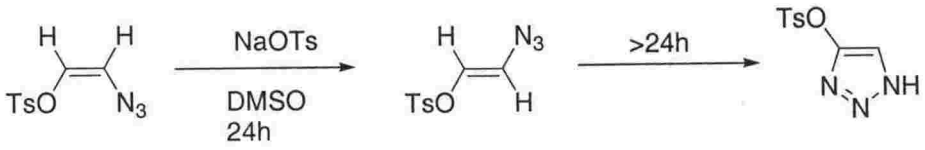
		28.2, 109.7, 110.5	
H-1, H-6	4.54 (m) (2H)	70.7	
H-2, H-5	4.67 (m) (2H)	71.4, 72.0	
H-3, H-4	5.26 (m) (2H)	74.1	
Triflates		136.2	– 73.72, –75.00
IR	2986.5, 2116.6, 1688.8 cm^{-1}		

Substitution by azide groups is a standard method in synthetic chemistry and hence is well understood.[117] Azides can be regarded as moderately strong nucleophiles and the azide ion is border line between a hard and a soft base.[118] The ambiguity with this ion comes from its high solvation energy and electron affinity in protic solvents, which are usually associated with weak nucleophiles. However, the strength of the C–N_3 bond is closer to that of a strong nucleophile. The idea of an azide isomerizing to give a triazole is not new, attempts at this conversion were carried out as early as 1910.[119] In 1967 Fowler and Meek isolated triazole **144** from the addition of NaN_3 to 1,2-di-*p*-toluenesulfonylethylene **143** in DMSO. When this reaction was carried out in aqueous methanol, the expected azide **145** was formed via addition-elimination, scheme 6.11.



Scheme 6.11

Thus, they proposed the azide was displacing an OTs group followed by isomerism to give the triazole **144**. This was further supported by the reaction shown in scheme 6.12.

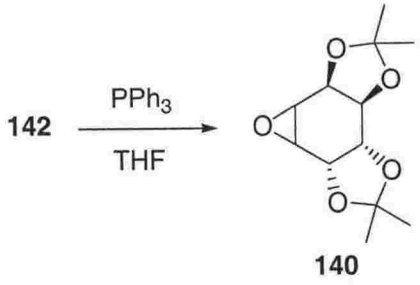


Scheme 6.12

There have been two mechanisms postulated for this cyclization, the first involves the formation of an intermediate triazoline which tautomerises to gain aromatic stabilization. The other possibility for this system is that due to the acidity of the vinyl proton that is α to the tosyl group a carbanion may be formed and this induces the cyclization. A similar rearrangement was used by Marco-Contelles and Rodriguez-Fernandez to build a variety of substituted 1,2,3-triazoles on sugar scaffolds.[120]

A series of reactions were carried out on **142** in order to establish its structure by chemical means. As indicated above, it was proposed that the triazole could exist in tautomeric forms. Given the strong azide peak in the IR, it was likely that the vinyl azide **142a** was the predominant form. When azides are reacted with alkynes, 1,3-dipolar cycloadditions can occur leading to a triazole.[121] We therefore treated **142** with an alkyne in an attempt to form a triazole, however no reaction was observed. A further test was performed using reducing conditions, in which three types of reductions were attempted. Treatment with hydrogen gas at 100 psi in methanol with Adams catalyst or palladium on activated charcoal surprisingly gave ditriflate **141** in 62% recovered yield over 2 steps, thus disproving the triazole structure. The final reduction used PPh_3 in wet THF and

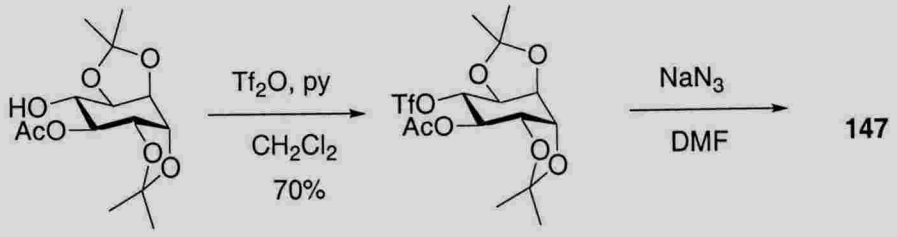
interestingly gave epoxide **140**, in 63% yield over the two steps, scheme 6.13. Unknown **142** proved to be very susceptible to attack by water forming epoxide **140** very rapidly. Unfortunately, it was not similarly reactive with nitrogen nucleophiles as attempts to form corresponding aziridines were unsuccessful.



140

Scheme 6.13

Given the difficulties of reacting the ditriflate inositol **141**, the next logical step was to use a monotriflate. Thus, inositol **44** was converted into the corresponding triflate **146,** which was then treated with azide under the same conditions as were used to generate **142**, scheme 6.14.

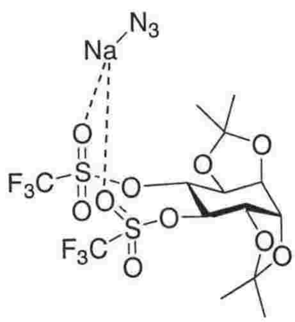


44 **146**

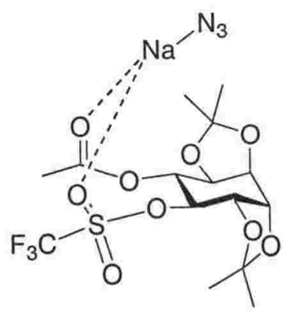
Scheme 6.14

Again a reaction occurred to give an unknown product **147** with properties similar to **142**, an azide peak evident in the IR at 2115 cm^{-1}. When **147** was treated with H_2 and Pd/C, the triflate **146** was recovered in a 68% yield over the two steps. As with **142,** this molecule (**147**) would not ionize and give useful mass spectral data. Given the similar

results in both cases the proposed structure is where the azide ion is not displacing the triflate but is coordinating to the sp^2 oxygens of the sulphonates, through the sodium ion giving a complex similar to those formed by crown ethers, figure 6.3.



142



147

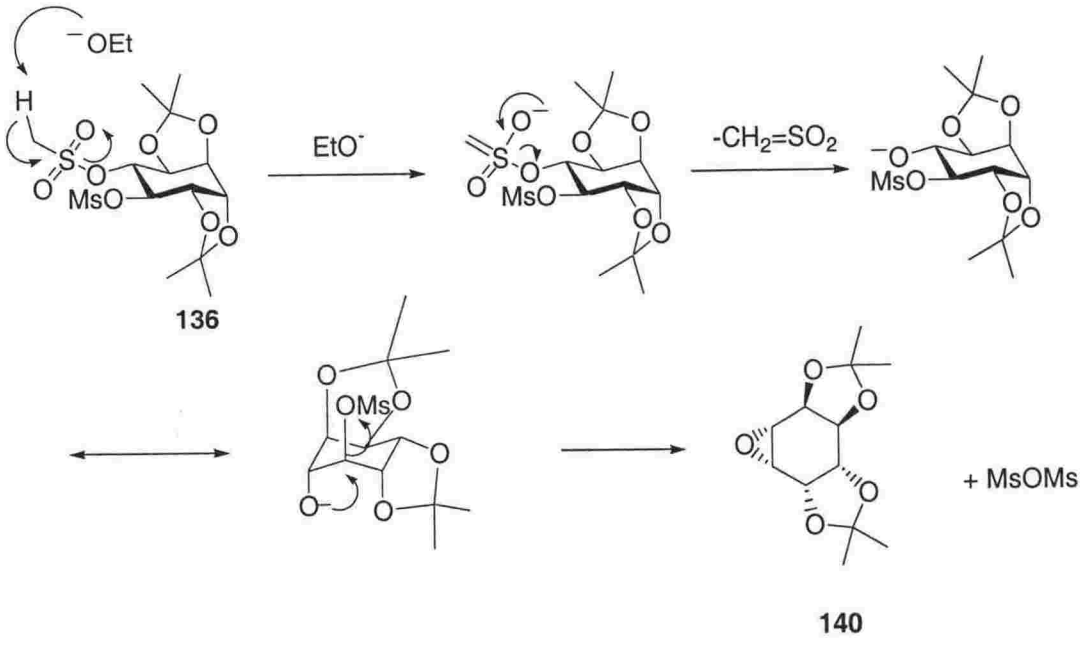
Figure 6.3 - Proposed crown ether like structures

This fits with NMR and IR data, although definitive proof would require X-ray data which unfortunately was not able to be obtained. ^{19}F NMR of **142** had intense peaks at –73.72 and –75.00 ppm which correspond to what would be expected from triflate fluorines. A sample of **142** was sent for elemental analysis, however the results received did not match what would be expected for complex **142** as depicted in figure 6.3. This is not entirely surprising as it is highly likely that **142** decomposed while en-route for analysis as it is temperature sensitive. What is more concerning is that atomic absorption spectroscopy gave no evidence of sodium in either **142** or **147**. However at present, the formation of these complexes is the theory that best agrees with spectral and chemical results. In both instances, azide would not displace the triflate despite prolonged heating. As with dimesylate **136**, ditriflate **141** was unsuccessfully treated with sodium diformyl amide.

A Mitsunobu reaction converts an alcohol into an azide without the initial need to convert the alcohol into a leaving group.[122] As a final attempt, a Mitsunobu displacement was attempted on diol D-**21**, involving the addition of PPh_3 to a cooled solution of diethyldicarboxylate (DEAD) in anhydrous THF. Sodium azide was added to this followed by **21**, however only unreacted **21** was recovered. An alternate to the Mitsunobu is the zinc azide mediated reaction.[123] This uses a $Zn(N_3)_2.2py$ reagent that is prepared from $Zn(NO_3)_2$, NaN_3 and pyridine. In this reaction the zinc reagent was prepared and placed in anhydrous toluene with **21** and PPh_3 under argon. DEAD was added dropwise and the reaction monitored, again unreacted **21** was recovered with no trace of any reaction product.

6.3 Development of a chiral amino alcohol

As mentioned in section 6.2 we were able to form epoxide **140** by treating dimesylate **136** with metallic sodium in ethanol, see scheme 6.8. Mechanistically, this can be viewed as removal of an acidic mesylate proton followed by displacement of the remaining OMs by the resulting oxyanion as shown in scheme 6.15.



Scheme 6.15

This transformation was initially viewed as a negative result when it occurred through decomposition of **142**. However, opening of the epoxide with a nitrogen nucleophile would lead to an amino alcohol, although cyclohexane epoxides which cannot be opened trans diaxially, can be difficult to open.[124] The difficulty opening this epoxide is supported by previous work by Angyal, in which epoxide **140** was originally synthesized as part of a study on epoxide migration. They found this particular epoxide was stable enough to remove the isopropylidene groups via treatment with acid yet leave the epoxide ring intact. Despite this, we attempted to open **140** using various nitrogen nucleophiles and new methods developed since 1957.[125] A range of nucleophiles and conditions were used in attempts to open epoxide **140**, these are summarized in figure 6.4, with conditions as listed in table 6.3.

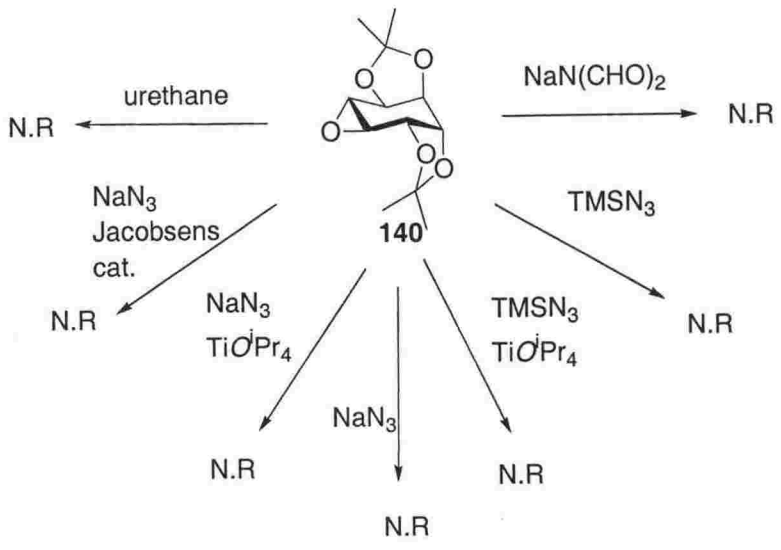


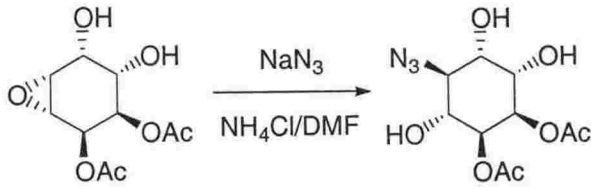
Figure 6.4 - Attempted methods of epoxide opening

Table 6.3 – Epoxide openings attempted on **140**

Nucleophile	Catalyst	Solvent	Temperature
$NaN(CHO)_2$	—	DMF	0 °C- reflux
$TMSN_3$	—	Et_2O	0 °C- R.T.
	$Ti(O^iPr)_4$	Et_2O	0 °C- R.T.
	$Ti(O^iPr)_4$	CH_2Cl_2	reflux
NaN_3	—	Et_2O	R.T.
	Jacobsens cat.	CH_2Cl_2	0 °C- reflux
	$Ti(O^iPr)_4$	Toluene	0 °C- reflux
Urethane	—	Et_2O	R.T.

The unusual stability of this epoxide can be attributed to the isopropylidene groups and the effect they have on the conformation of this system. Cyclohexane epoxides will open *trans* diaxially, however with **140** it is likely the isopropylidene groups are not allowing the inositol to undergo a ring flip into a conformation where the epoxide can be opened. These results are especially in agreement with work done by Nicolosi and co-workers, who synthesized azido and amino inositols via a chemoenzymatic route. In their studies,

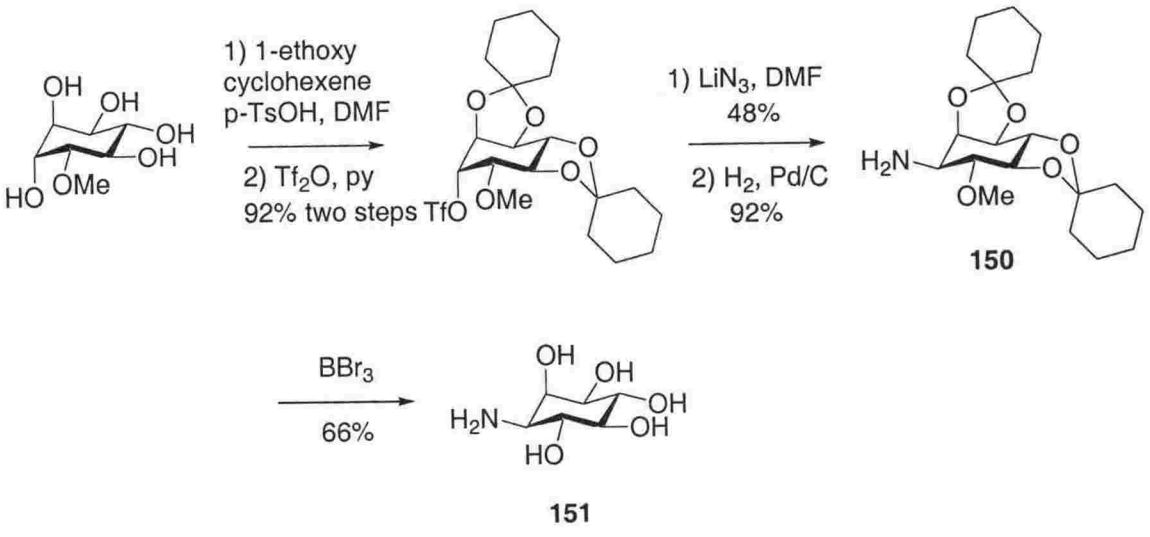
they opened epoxide **148**, which can ring flip, with NaN_3 and NH_4Cl in DMF at room temperature to give azido alcohol **149** in 79% yield, scheme 6.16.[126] The lack of success in opening epoxide **140** led to the decision to synthesize amino alcohols by an alternate route. This decision was also based on the length of the synthesis, as five steps were required to form **140** from pinitol and a further three were envisioned to deprotect, ring open and re-protect the epoxide.



148 **149**

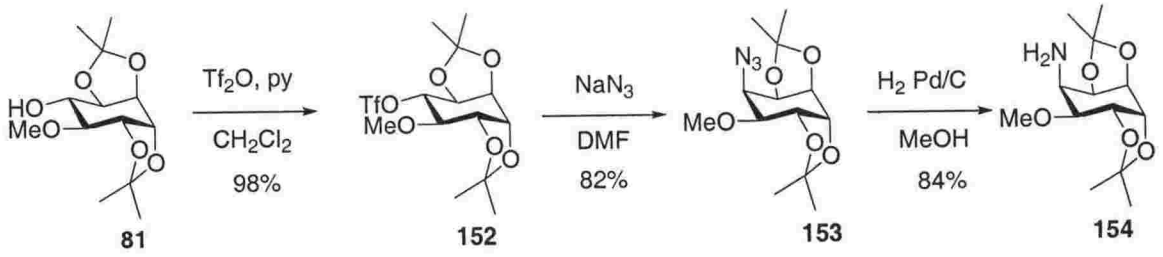
Scheme 6.16

As discussed in the introduction, amino alcohols have also been successfully used as ligands. Using both pinitol or quebrachitol, amino ethers have successfully been synthesized. Baker and co-workers began with quebrachitol in the synthesis of 1-D-3-amino-1,2;5,6-di-*O*-cyclohexylidene-3-deoxy-4-*O*-methyl-*myo*-inositol.[56] The route they used is similar to the one attempted in section 6.2, with the only difference being the use of LiN_3 to generate the azide en-route to **150**, scheme 6.17.



Scheme 6.17

The corresponding azide with isopropylidene protecting groups has also been synthesized by Ogawa and co-workers.[108] Using the strategy followed in section 6.2 1-L-2-amino-1-*O*-methyl-3,4;5,6-diisopropylidene-2-deoxy-*allo*-inositol **154** was synthesized from pinitol derivative **81**, scheme 6.18.

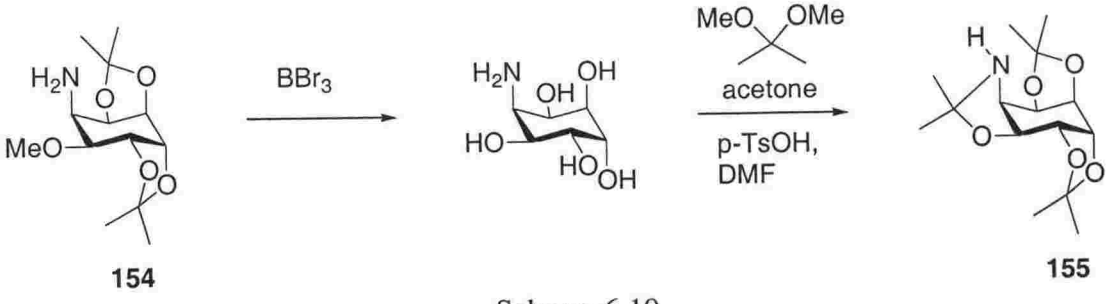


Scheme 6.18

The final step required demethylation of **154** to give the amino alcohol. The first demethylation attempted was an $AlCl_3$-*n*-Bu_4NI mediated demethylation using the procedure of Akiyama and Ozaki.[127] This procedure enables the demethylation of α-

hydroxy methylethers while preserving the cyclohexylidene protecting groups of the inositol. A requirement of the reaction is an OH vicinal to the methoxy, in order to complex the $AlCl_3$ and direct it to the methyl ether. It was hoped the vicinal amine in this system would perform the required complexation in a similar manner. Unfortunately, this assumption proved incorrect as this reaction was unsuccessful under a range of conditions.

In the work carried out by Baker, complete deprotection of **150** was accomplished with BBr_3 resulting in the formation of **151** in a 66% yield, scheme 6.16. When the same conditions were applied to **154,** all the protecting groups were indeed removed as evident by treatment of the product with acetone, 2,2-dimethoxypropane and p-TsOH in DMF to give a very low yield (<8%) of triacetonide **155**, scheme 6.19. Given the very low yield of **155** it was decided to not pursue this area.

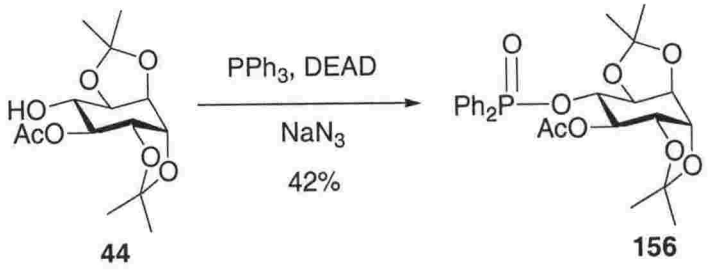


154 **155**

Scheme 6.19

In an alternative to this strategy, investigations moved to **44** as an acetate group is much easier to remove than a methyl ether. As discussed in the previous section, the strategy outlined above will not work with **44**, as we generate **147**. Thus the next logical step was to use a Mitsunobu reaction. Initially, **44** was treated with PPh_3 and DEAD in the presence of NaN_3 following a procedure that has proven to work in our lab. In section

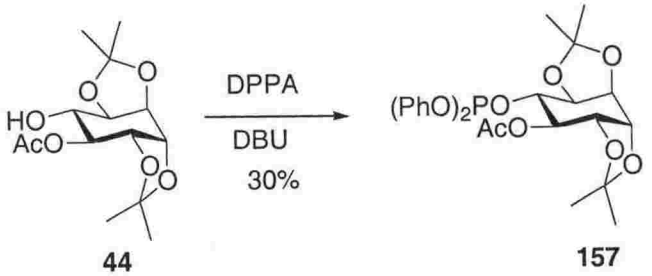
6.2 when **21** was subjected to these conditions no reaction occurred, in this example the activated phosphine reacted with the alcohol, however this was not displaced with azide and the phosphinic ester **156** was isolated, scheme 6.20.



44 **156**

Scheme 6.20

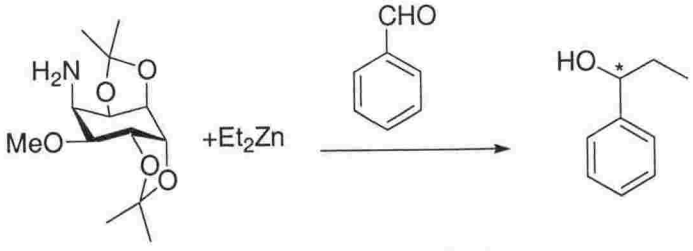
The use of prolonged heating and a stronger nucleophile, $TMSN_3$, also gave **156**. An alternate to the Mitsunobu was reported by Thompson and co-workers.[128] This involved the use of diphenyl phosphorazidate (DPPA) in the presence of a strong base such as DBU. This method gets around one of the major problems with a Mitsunbou reaction which is the formation of up to 6 equivalents of by-products. Applying these conditions to **44** resulted in the formation of a phosphate, in this case heating improved the yield of **157**, scheme 6.21.



44 **157**

Scheme 6.21

The final investigations that we carried out on this system involved the use of amino ether **154,** as this was routinely formed in good yield. One of the reactions discussed in the introduction is the asymmetric alkylation of carbonyls by dialkyl zinc reagents. While this is routinely catalyzed by amino alcohol containing catalysts, amino ethers have occasionally been successfully used. As amino ethers form less stable complexes than amino alcohols we did not extensively investigate this area, however we did attempt the alkylation of benzaldehyde. This involved treating **154** with diethyl zinc and subsequently adding benzaldehyde, scheme 6.22. We did not see any evidence of alkylation using this system.



154

Scheme 6.22

Conclusion

Chiro-inositols are a readily available and inexpensive source of chiral molecules in both enantiomeric forms that have had only limited use. The aim of this project was to investigate the use of these molecules in asymmetric synthesis protected primarily by di-isopropylidenes; to this end some success has been achieved. It became rapidly apparent that the system chosen to work with was a difficult one, this is shown by compounds very similar to the ones aimed for being reported in the literature. However, these were made by other synthetic or enzymatic methods and were not from inositol starting materials. One of the reasons for this was the choice of protecting groups, these led to a decrease in reactivity as the isopropylidenes skewed the conformation of the central inositol ring. This was highlighted by the stability of epoxide **140**, especially when compared to the ease with which epoxide **148** was opened. Despite these difficulties some very useful and interesting chemistry was carried out.

While possibly appearing insignificant, the application of Clarkes method of mono-esterifying C-2 symmetric 1,2 diols to this inositol system proved invaluable to this project. It proved especially useful in the development of Michael acceptors. Chemistry on these monoesterified moieties also gave valuable insights into chemistry that was occurring in other areas of work.

The use of diol **21** as a precursor to a chiral reagent had some limited success. An asymmetric hydroboration was never attempted, the use of protecting groups that are not acid labile would solve the problems with this reaction although that could make the cost of the reagent prohibitive. The attempted allylation of benzadehyde was unfortunately unsuccessful, however given the low yield in forming the silane, especially when the cost

of the allyltrichlorosilane is taken into account, could also make this economically unviable.

The application of these inositols as chiral auxiliaries was the most successful part of this project. Initial investigations into the aldol reaction were again hindered by the choice of protecting group. The removal of the reactive site further from the inositol ring led to Michael acceptors that could be used very successfully for both the copper catalyzed reaction and the addition of a thio nucleophile. The stability of diol **21** proved useful in this area as it could be successfully recycled, which is an important property for a successful chiral auxiliary.

Attempts to carry out asymmetric catalysis while not successful did lead to some interesting chemistry. The use of diol **21** or amino ether **154** as ligands showed no catalytic activity. Attempts to synthesize a diamine or amino ether were also unsuccessful. Given other results it is probable that if these molecules had been generated there may have been problems complexing them to a metal cation, although the diamine would have had the *neo-* configuration so may have had more promise. The formation of the (proposed) crown ether was another indication of the difficulties in carrying out chemistry on this system. A good understanding of this system has been gained which can be applied to future work. The biggest hindrance to this project was the choice of protecting groups. In some instances the steric bulk of the isopropylidenes proved to be too much, this problem could be over come by the use of a system such as that shown below, figure 7.1.

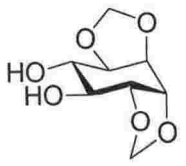


Figure 7.1 - Alternate system

However, this will not negate the larger problem with this system which is the conformation of the central inositol ring. To negate this problem systems such as those in figure 7.2 may prove successful.

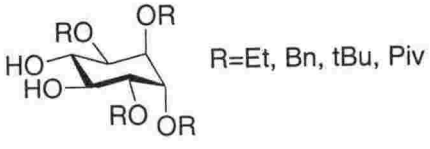


Figure 7.2 - Alternate diols

The use of larger groups should provide enough steric hindrance to provide selectivity. The trade off will be the ease of synthesis, diol **21** is easily formed from commercially available DCI in two steps in 87% overall yield. The diols shown in figure 7.2 will require protection/deprotection strategies reminiscent of other areas of carbohydrate chemistry.

In summary this project has shown *chiro*-inositols can be successfully used in asymmetric synthesis.

Experimental

General. All melting points are uncorrected. Optical rotations were measured with w Perkin-Elmer 241 polarimeter using a 10cm cell at ambient temperature in CH_2Cl_2, with concentration measured in gmL^{-1}. Reaction progress was monitored using aluminium backed TLC plates pre-coated with silica UV 254 and visualised by either UV radiation (254 nm) or ceric ammonium molybdate dip [$(NH_4)_2Mo(VI)\cdot 4H_2O$, 12.5 g; $Ce(SO_4)_2\cdot 4H_2O$, 5 g; 10% aqueous H_2SO_4 in H_2O (v:v) 500 mL] followed by heating. Flash column chromatography was performed using silica gel 60 (220-240 mesh) with the solvent systems as indicated. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova at 300 and 75 MHz, respectively; and referenced to solvent peaks (^1H – residual $CHCl_3$; ^{13}C –$CDCl_3$). Accurate masses were recorded on a Mariner time of flight spectrometer using positive ionization techniques. Elemental analyses were performed at the University of Otago, Dunedin, New Zealand. GC analyses of e.e.'s were carried out on a Hewlett-Packard 6890 series instrument using a J&W Scientific 60m, 0.25 mm narrowbore, cyclodex B column. Conditions for ee determination were an injection temperature of 60 °C held for one minute followed by a temperature ramp of 1 °C per minute with retention times as indicated. Pinitol was obtained from New Zealand Pharmaceuticals and demethylated according to literature procedures.[42] Solvents and reagents from stock were dried and purified by standard methods.[129] Gry THF and Ether were freshly distilled from Sodium under argon with benzophenone added as an indicator of dryness. LDA was prepared by cooling a solution of diisopropyl amine (1.1 eq) in THF to –78 °C to this was added BuLi (1.1 eq), after stirring for 5 min the solution was warmed to 0 °C and stirred for a further 0.5 h. Reactions involving the use of air-sensitive materials were performed in sealed reaction vessels under zero grade Argon gas. Moisture sensitive liquid reagents were

transferred by syringe through rubber septa. Cold baths were generated by the use of dry ice (or liquid nitrogen in the absence of dry ice) slurries with appropriate solvents to generate the required temperature.[129]

1-D-1,2:5,6-Di-*O*-isopropylidene-*chiro*-inositol 21: To a solution of 1D-*chiro*-inositol (2.00 g, 11.1 mmol) in DMF (11 mL), acetone (12.0 mL, 166.5 mmol) and 2,2-dimethoxypropane (10.0 mL, 77.7 mmol) was added p-TsOH (200 mg, 10mol%). The mixture was stirred overnight at room temperature under air then neutralized with Et_3N and concentrated. Filtration of the resulting syrup through silica gel using hexanes:EtOAc (1:1) gave the tris-acetonide (3.17 g, 95 %) as a white solid. Selective hydrolysis following the procedure of Paulsen[54b] gives **21** in 88-93 % yield.

General Procedure for the $YBCl_3$ and $CeCl_3$ catalysed monoesterification of 21 and 22 with anhydrides: The anhydride (5 mmol) was added to a stirred solution of diol **21** or **22** (1 mmol) and metal salt ($YbCl_3.6H_2O$ or $CeCl_3.7H_2O$) (0.1 mmol, 10 mol%) in THF (5 ml). The reaction was stirred at room temperature and monitored by TLC (hexanes-EtOAc, 5:1). Upon completion, EtOAc (10 mL) was added, the organic layer was washed with satd. Aq. $NaHCO_3$ (3 x 10 mL), once with brine (10 mL) and dried over $MgSO_4$. Filtration, concentration and purification via flash chromatography (hexanes-EtOAc mixtures) gave pure **43-50**.

1-D-3-*O*-chloroacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol D-43: Eluted with 5:1 hexanes:EtOAc (R_f = 0.15) to give a white solid, mp 109 °C, $[\alpha]^{21}_D$ +50.2° (c $1.86x10^{-2}$, CH_2Cl_2). ^1H NMR: (300MHz $CDCl_3$): δ 1.37 (s, 3H, CMe_2), 1.39 (s, 3H, CMe_2), 1.53 (s, 6H, CMe_2), 2.24 (brs, 1H, OH), 3.64 (dd, 1H, *J*= 8.1, 11.5Hz, H-4),

4.19 (s, 2H, CH_2Cl), 4.24 (m, 2H, H-2, H-5), 4.5 (m, 2H, H-1, H-6), 5.03 (dd, 1H, *J*=8.3, 11.5Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 25.7, 25.8, 27.8, 28.1, 41.1, 71.6, 75.2, 75.3, 75.5, 76.2, 79.0, 109.1, 110.0, 167.4; IR (neat): 3463, 2987, 1764 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{22}{}^{35}ClO_7$ [M + H] 337.1054, found 337.1049.

1-D-3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 44: Eluted with 5:1 hexanes:EtOAc (R*f* = 0.10) to give a colourless oil, $[\alpha]^{21}{}_D$ +41.1° (c $1.97x10^{-2}$, CH_2Cl_2). ^1H NMR: (300MHz $CDCl_3$): δ 1.36 (s, 3H, CMe_2), 1.38 (s, 3H, CMe_2), 1.51 (s, 6H, CMe_2), 2.17 (s, 3H, Ac), 2.60 (brs, 1H, OH), 3.60 (dd, 1H, *J*= 8.1, 11.2Hz, H-4), 4.24 (m, 2H, H-2, H-5), 4.46 (m, 2H, H-1, H-6), 4.95 (dd, 1H, *J*=8.3, 11.5Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 21.3, 25.6, 25.8, 27.8, 28.1, 71.9, 75.5, 75.4, 75.7, 76.5, 79.2, 109.1, 109.5, 170.9; IR (neat): 3468, 2987, 1764 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{23}O_7$ [M + H] 303.1440, found 303.1438.

1-D-3-*O*-propanoyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 45: Eluted with 5:1 hexanes:EtOAc (R*f* = 0.18) to give a colourless oil, $[\alpha]^{21}{}_D$ +44.9° (c $9.0x10^{-3}$, CH_2Cl_2) ^1H NMR: (300MHz $CDCl_3$): δ 1.18 (t, 3H, J= 7.5 Hz, CH_3), 1.35 (s, 3H, CMe_2), 1.37 (s, 3H, CMe_2), 1.51 (s, 6H, CMe_2), 2.45 (q, 2H, *J*=7.5 Hz, CH_2), 3.41 (brs, 1H, OH), 3.59 (dd, 1H, *J*= 8.1, 11.4Hz, H-4), 4.23 (m, 2H, H-2, H-5), 4.45 (m, 2H, H-1, H-6), 4.96 (dd, 1H, *J*=8.2, 11.4Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 9.4, 25.7, 25.9, 27.9 (2C), 28.2, 72.1, 72.8, 73.6, 75.9, 76.7, 79.4, 109.9, 110.0, 178.4; IR (neat): 3466, 2987, 1741 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{25}O_7$ [M + H] 317.1597, found 317.1595.

1-D-3-*O*-[(*E*)-but-2-enoyl]-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 46: Eluted with 5:1 hexanes:EtOAc (R*f* = 0.21) to give a colourless oil, $[\alpha]^{21}{}_D$ +58.1° (c $7.3x10^{-3}$,

CH_2Cl_2); ^1H NMR: (300MHz $CDCl_3$): δ 1.35 (s, 3H, CMe_2), 1.37 (s, 3H, CMe_2). 1.52 (s, 6H, CMe_2), 1.91 (dd, 3H, *J*=1.7, 6.9 Hz, CH_2), 3.64 (dd, 1H, *J*= 8.0, 11.3Hz, H-4), 4.27 (m, 2H, H-2, H-5), 4.46 (m, 2H, H-1, H-6), 5.01 (dd, 1H, *J*=8.2, 11.4Hz, H-3), 5.93 (dd, 1H, *J*= 1.7, 15.6Hz, vinylCH), 7.06 (m, 1H, vinylCH); ^{13}C (75 MHz $CDCl_3$): 18.4, 25.7, 25.9, 27.9, 28.2, 31.2, 72.2, 73.6, 75.8, 76.0, 76.8, 79.4, 109.9, 110.0, 122.5, 146.6, 166.7; IR (neat): 3469, 2989, 1724 cm^{-1}; HRMS *m/z* calcd for $C_{16}H_{25}O_7$ [M + H] 329.1600, found 329.1595.

1-D-3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 47: Eluted with 5:1 hexanes:EtOAc (R*f* = 0.25) to give a white solid mp 81 °C, $[\alpha]^{21}_D$ +47.4° (c $1.4x10^{-2}$, CH_2Cl_2); ^1H NMR: (300MHz $CDCl_3$): δ 1.36 (s, 3H, CMe_2), 1.38 (s, 3H, CMe_2), 1.54 (s, 6H, CMe_2), 3.6 (dd, 1H, *J*= 8.1, 11.5Hz, H-4), 4.31 (dd, 1H, *J*=6.1, 8.1Hz, H-5), 4.4 (dd, 1H, *J*=5.7, 8.1Hz, H-2), 4.5 (m, 2H, H-1, H-6), 5.24 (dd, 1H, *J*=8.1, 11.5Hz, H-3), 7.45 (m, 2H, Bz), 7.55 (m, 1H, Bz), 8.08 (m, 2H, Bz); ^{13}C (75 MHz $CDCl_3$): 25.7, 25.9, 27.9, 28.1, 72.1, 74.2, 75.6, 75.9, 76.7, 79.3, 109.6, 109.9, 128.6, 130.2, 133.6, 166.7; IR (neat): 3465, 2987, 1723 cm^{-1}; HRMS *m/z* calcd for $C_{19}H_{25}O_7$ [M + H] 365.1595, found 365.1595. Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 62.80; H, 6.61.

1-D-3-*O*-pivaloyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 48: Eluted with 5:1 hexanes:EtOAc (R*f* = 0.15) to give a white solid, mp 88 °C ; ^1H NMR: (300MHz $CDCl_3$): δ 1.25 (s, 9H, piv), 1.26 (s, 3H, CMe_2), 1.27 (s, 3H, CMe_2), 1.50 (s, 3H, CMe_2), 1.51 (s, 3H, CMe_2), 3.60 (dd, 1H, *J*= 8.3, 11.5Hz, H-4), 4.23 (m, 2H, H-2,H-5), 4.46 (m, 2H, H-1, H-6), 4.92 (dd, 1H, *J*=8.3, 11.5Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 25.6, 25.9, 27.4, 27.8, 28.1, 72.1. 73.3, 75.5, 75.7, 76.6, 79.3, 109.7, 178.9; IR (neat):

3468, 2983, 1733 cm^{-1}; HRMS *m/z* calcd for $C_{17}H_{29}O_7$ [M + H] 345.1907, found 345.1908

1-L-3-*O*-chloroacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol L-43: Eluted with 5:1 hexanes:EtOAc (R*f* = 0.15) to give a white solid, mp 108.5 °C, $[\alpha]^{21}_D$ –51.5° (c $1.3x10^{-2}$, CH_2Cl_2) HRMS *m/z* calcd for $C_{14}H_{22}{}^{35}ClO_7$ [M + H] 337.1054, found 337.1049.

1-D-3-*O*-chloroacetyl-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol 49: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.21) to give a colourless oil, $[\alpha]^{21}_D$ +25.9° (c $9.7x10^{-3}$, CH_2Cl_2), ^1H NMR: (300MHz $CDCl_3$): δ 1.39-1.68 (m, 20H, Cy), 3.61 (dd, 1H, *J*= 8.3, 11.2Hz, H-4), 4.14 (s, 2H, CH_2Cl), 4.24 (m, 2H, H-2, H-5), 4.53 (m, 2H, H-1, H-6), 4.99 (dd, 1H, *J*=8.5, 11.5Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 22.6, 23.6, 23.8, 23.9, 24.8, 34.6, 34.8, 37.3, 37.7, 40.9, 71.6, 74.5, 74.8, 75.4, 78.3, 110.2, 110.4, 167.2; IR (neat): 3437, 2937, 1732 cm^{-1}; HRMS *m/z* calcd for $C_{20}H_{30}{}^{35}ClO_7$ [M + H] 417.1680, found 417.1675.

1-D-3-*O*-acetyl-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol 50: Eluted with 5:1 hexanes:EtOAc (R*f* = 0.16) to give a colourless oil, $[\alpha]^{21}_D$ +27.0° (c $1.49x10^{-2}$, CH_2Cl_2), ^1H NMR: (300MHz $CDCl_3$): δ 1.36-1.56 (m, 20H, Cy), 2.14 (s, 3H, Ac), 2.62 (brs, 1H, OH), 3.54 (dd, 1H, *J*= 8.3, 11.2Hz, H-4), 4.20 (m, 2H, H-2, H-5), 4.49 (m, 2H, H-1, H-6), 4.91 (dd, 1H, *J*=8.5, 11.5Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 21.3, 23.8, 23.9, 24.1, 24.2, 25.1, 25.2, 34.9, 35.1, 37.6, 38.0, 72.1, 73.8, 75.0, 75.3, 76.0, 78.8, 110.2, 110.3, 171.2; IR (neat): 3466, 2934, 2859, 1749 cm^{-1}; HRMS *m/z* calcd for $C_{20}H_{31}O_7$ [M + H] 383.2070, found 383.2064.

1L-1,2:3,4-diisopropylidene-cyclohex-5-ene-1,2,3,4-tetrol 55: To a solution of D-**21** (610 mg, 2.34 mmol) in anhydrous toluene (20 mL) was added PPh_3 (6.14 g, 23.4 mmol) and imidazole (1.58 g, 23.4 mmol). Iodine (5.92 g, 23.4 mmol) was added portionwise over 15 min and the reaction was refluxed for 5 h. A further batch of iodine (5.92 g, 23.4 mmol) was added followed by NaOH (1M, 15 mL) and the mixture was stirred for 30 min at ambient temperature. The toluene phase was separated and washed with water (15 mL), 5 % sodium thiosulphate (15 mL), $NaHCO_3$ (15 mL) and water (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography, hexanes:EtOAc 10:1 (R_f= 0.43) afforded 0.194 g (0.43 mmol, 37 %) of a white solid, mp 54 °C; ^{1}H NMR: (300MHz $CDCl_3$): δ 1.38 (s, 12H, CMe_2), 4.45 (m, 4H, H-3, H-4, H-5, H-6), 5.3 (s, 2H, H-1, H-2); ^{13}C (75 MHz $CDCl_3$): 26.7, 28.0, 70.5, 73.4, 109.4, 127.2; IR (neat): 2986, 2362, 1366cm^{-1}.

Procedure for the formation of boron triflate from 55: To a solution of **55** (110 mg, 0.49 mmol) in anhydrous Et_2O (15 mL) in an oven dried flask was added borane-dimethylsufide complex (0.2 mL, 0.25 mmol) dropwise over 30 min. The reaction was stirred for 4 h at 0 °C and the resulting white solid was then allowed to settle with out stirring. The supernatant organic solution was removed as much as possible by syringe and the residual solid was dried under reduced pressure. To this solid was added anhydrous hexane (15 mL), then triflic acid (380 mg, 0.25 mmol) was added dropwise over 30 min with stirring. The mixture was stirred for 1 h over which time gas was evolved. The mixture was allowed to stand for a further 2 h and a white solid separated out, the supernatant solvent was cannulated into an oven dried flask and kept

at –40 °C for 36 h over which time no further product solidified. The white solid was dried under reduced pressure.

Allylchloro(3,4-[1D-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol]di-yl)silane 60: To a solution of allyltrichlorosilane (0.28 mL, 1.84 mmol 95% soln) in CH_2Cl_2 (8 mL) at 0 °C was added DBU (0.5 mL, 2.4 mmol) followed by a solution of D-**21** (436 mg, 1.68 mmol) in CH_2Cl_2 (2.5 mL) added dropwise. The solution was stirred at 0 °C for 2 h and then at ambient temperature for a further 16 h. The solution was concentrated, Et_2O (10 mL) was added, and stirred for 3 h before being filtered and concentrated. The resulting white solid was dissolved in CH_2Cl_2 and washed with H_2O before being dried, concentrated and purified by flash chromatography hexanes:EtOAc 10:1 (neutralized with Et_3N R*f*=0.2, 0.1) to give 0.16 g (0.35 mmol, 21 %) of a colourless oil; ^{1}H NMR:(300MHz $CDCl_3$): 1.36 (s, 3H, CMe_2), 1.46 (s, 3H, CMe_2), 1.47 (s, 3H, CMe_2), 1.57(s, 3H, CMe_2), 1.68 (bs, 2H, silane), 3.68 (m, 1H, alkene), 3.84 (bs, 2H, H-2, H-5), 4.38 (bs, 2H, H-1, H-6), 4.41 (m, 2H, H-3, H-4), 5.00 (bs, 2H, alkene CH_2); ^{13}C (75 MHz $CDCl_3$): 24.7, 27.3, 27.4, 76.6, 78.3, 79.6, 111.1, 113.9; IR (neat): 2987, 2935, 1382, 1061, 732cm^{-1};

Procedure for the allylation of benzaldehyde: To a solution of silane **60** (220 mg, 0.33 mmol) in toluene (1.5 mL) was added benzaldehyde (37 μL, 0.36 mmol). The reaction was stirred at 0 °C for 4 h then heated at reflux for 48 h before TLC and ^{1}H NMR indicated decomposition of the silane.

1-D-3-*O*-acetyl-4-*O*-methyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 83: To a solution of **81** (500 mg, 1.92 mmol) in pyridine (5 mL) and CH_2Cl_2 (10 mL) under

argon at 0 °C was added dropwise acetic anhydride (0.27 mL, 2.88 mmol). The solution was stirred at 0 °C overnight, concentrated, then dissolved in CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (3 x 10 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography, hexanes:EtOAc 10:1 (R*f*= 0.39) afforded 0.57g (1.80 mmol, 94%) of a colourless oil; ^1H NMR: (300MHz $CDCl_3$): δ 1.26 (s, 3H, CMe_2), 1.28 (s, 3H, CMe_2), 1.41 (s, 3H, CMe_2), 1.44 (s, 3H, CMe_2), 2.05 (s, 3H, OAc), 3.15 (dd, 1H, *J*=7.3, 11.5Hz, H-4), 3.43 (s, 3H, OMe), 4.18 (m, 2H, H-2, H-5), 4.29 (m, 2H, H-1, H-6), 4.94 (dd, 1H, *J*=8.3, 11.2Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 21.2, 25.6, 25.7, 27.6, 28.1, 59.9, 72.3, 75.8, 75.9, 76.5, 78.9, 80.2, 109.4, 109.8, 170.1; IR (neat): 2984, 2937, 1749cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{25}O_7$ 317.1597 found 317.1595.

1-D-3-*O*-acetyl-4-*O*-methyl-1,2:5,6-di-*O*-cyclohexylidene-*chiro*-inositol 84: To a solution of **82** (1.05 g, 2.9 mmol) in pyridine (10 mL) and CH_2Cl_2 (20 mL) under argon at 0 °C was added dropwise acetic anhydride (0.45 mL, 4.8 mmol). The solution was stirred at ambient temperature overnight, concentrated, dissolved in CH_2Cl_2 (15 mL) and washed with $NaHCO_3$ (3 x 10 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography, hexanes:EtOAc 10:1 (R*f*=0.34) afforded 1.03g (2.6mmol, 90%) of a colourless oil; ^1H NMR: (300MHz $CDCl_3$): δ 1.39-1.68 (m, 20H, Cy), 2.13 (s, 3H, OAc), 3.18 (dd, 1H, *J*=7.8, 11.5Hz, H-4), 3.51 (s, 3H, OMe), 4.27 (m, 2H, H-2, H-5), 4.42 (m, 2H, H-1, H-6), 4.97 (dd, 1H, *J*=8.5, 11.3Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 21.3, 23.8, 23.9, 24.1, 24.2, 25.1, 25.2, 34.9, 35.1, 37.5, 38.0, 60.1, 72.8, 75.4, 75.5, 76.1, 78.5, 80.6, 110.0, 110.4, 170.3; IR (neat): 2935, 1749cm^{-1}; HRMS *m/z* calcd for $C_{21}H_{33}O_7$ [M+H] 397.2242 found 397.2221.

1-D-3*O*-(trimethylsilylacetyl)-4-*O*-methyl-1,2:5,6-diisopropylidene-*chiro*-inositol

85: A solution of diisopropylamine (122 μL, 0.87 mmol) in THF (5 mL) under argon was cooled to –78 °C and BuLi (0.5 mL, 1.6M soln in THF) was added. This was stirred for 5 minutes at –78 °C then the solution was warmed to 0 °C and stirred for 0.5 h. The solution was re-cooled to –78 °C and **83** (250 mg, 0.79 mmol) in THF (3 mL) was added. The mixture was stirred for 1 h then HMPA (75 μL) was added, after stirring for 10 min TMSCl (150 μL, 1.19 mmol) was added and the mixture stirred for 2.5 h. The mixture was warmed to ambient temperature, Et_2O (15 mL) was added and the resulting solution was washed with H_2O (3 x 5 mL). The organic fraction was dried over $MgSO_4$, filtered and purified by flash chromatography hexanes:EtOAc 50:1 (R*f*=0.48) to give 210 mg (0.55 mmol, 69%) of a colourless oil; ^{1}H NMR: (300MHz $CDCl_3$): δ 0.29 (s, 9H, TMS), 1.32 (s, 3H, CMe_2), 1.35 (s, 3H, CMe_2), 1.48 (s, 3H, CMe_2), 1.50 (s, 3H, CMe_2), 1.96 (s, 2H, alkene), 3.25 (dd, 1H, *J*=6.8, 11.6Hz, H-4), 3.48 (s, 3H, OMe), 4.28 (m, 4H, H-1, H-2, H-5, H-6), 5.04 (dd, 1H, *J*=8.1, 11.2Hz, H-3); ^{13}C (75 MHz $CDCl_3$): -1.3, 25.7, 27.3, 27.8, 28.1, 59.4, 71.4, 76.1, 76.1, 76.9, 79.2, 80.0, 109.7, 110.0, 172.1; IR (neat): 2986, 2937, 1732cm^{-1}; HRMS *m/z* calcd for $C_{18}H_{33}O_7Si$ [M+H] 389.1990 found 389.1973.

1-D-3*O*-(trimethylsilylscetyl)-4-*O*-methyl-1,2:5,6-dicyclohexylidene-*chiro*-inositol

86: A solution of diisopropylamine (0.4 mL, 2.63 mmol) in THF (15 mL) under argon was cooled to –78 °C and BuLi (1.65 mL, 1.6M soln in THF) was added. This was stirred for 5 minutes at –78 °C then the solution was warmed to 0 °C and stirred for 0.5 h. The solution was re-cooled to –78 °C and **84** (974 mg, 2.39 mmol) in THF (10 mL) was added. This was stirred for 1 h then HMPA (0.2 mL) was added, after stirring for

10 min TMSCl (0.46 mL, 3.59 mmol) was added and the mixture was stirred for 4 h. The mixture was warmed to ambient temperature, Et_2O (20mL) was added, and the resulting solution was washed with H_2O (3 x 10 mL). The fraction was dried over $MgSO_4$, filtered and purified by flash chromatography hexanes:EtOAc 50:1 (R*f*=0.43) to give 784 mg (1.67 mmol, 63 %) of a colourless oil; ^{1}H NMR: (300MHz $CDCl_3$): δ 0.14 (s, 9H, TMS), 1.48 (m, 20H, Cy), 1.98 (s, 1H, alkene), 2.19 (s, 1H, alkene), 3.18 (dd, 1H, *J*= 7.1, 11.5 Hz, H-4), 3.48, s, 3H, OMe), 4.20 (m, 2H, H-2, H-5), 4.36 (m, 2H, H-1, H-6), 4.97 (dd, 1H, *J*=8.3, 11.2 Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 0.7, 23.8, 23.9, 24.2, 24.3, 25.3, 34.7, 34.9, 38.0, 38.1, 60.5, 74.6, 76.3, 76.5, 78.6, 79.8, 82.3, 110.13, 172.06; IR (neat): 2936, 1733 HRMS *m/z* calcd for $C_{24}H_{40}O_7Si$ [M+H] 469.2613 found 469.2616.

1-D-3-*O*-(triisopropylacetyl)-4-*O*-methyl-1,2:5,6-diisopropylidene-*chiro*-inositol

87: A solution of diisopropyl amine (77 μL, 0.55 mmol) in THF (3 mL) under argon was cooled to –78 °C and BuLi (0.34 mL, 1.6M soln in THF) was added. This was stirred for 10 minutes at –78 °C then the solution was warmed to 0 °C and stirred for 0.5 h. The solution was re-cooled to –78 °C and **83** (160 mg, 0.5 mmol) in THF (2 mL) was added. This was stirred for 1 h then HMPA (50 μL) was added after stirring for 10 min TIPSCl (0.16 mL, 0.75 mmol) was added and the mixture was stirred for 3 h. The mixture was warmed to ambient temperature, Et_2O (10 mL) was added, and the resulting solution was washed with H_2O (3 x 5 mL). The organic fraction was dried over $MgSO_4$, filtered and purified by flash chromatography hexanes:EtOAc 50:1 (R*f*=0.25) to give 0.13 g (0.27 mmol, 54 %) of a colourless oil; ^{1}H NMR: (300MHz $CDCl_3$): δ 1.09 (s, 9H, TIPS), 1.11 (s, 9H, TIPS) 1.32 (s, 3H, CMe_2), 1.37 (s, 3H, CMe_2), 1.48 (s, 3H, CMe_2), 1.53 (s, 3H, CMe_2), 2.09 (s, 2H, alkene), 2.19 (s, 3H,

TIPS), 3.27 (dd, 1H, *J*=6.6, 11.5Hz, H-4), 3.49 (s, 3H, OMe), 4.28 (m, 4H, H-1, H-2, H-5, H-6), 5.06 (dd, 1H, *J*=7.8, 11.5 Hz, H-3); ^{13}C (75 MHz $CDCl_3$):11.5, 18.7, 19.3, 25.6, 25.7, 27.8, 59.3, 71.6, 76.3, 76.4, 76.7, 79.3, 80.1, 109.7, 110.0, 173.0; IR (neat): 2940, 2867, 1731cm^{-1}; HRMS *m/z* calcd for $C_{24}H_{45}O_7Si$ [M+H] 473.2926 found 473.2929.

1-D-3*O*-(triisopropylacetyl)-4-*O*-methyl-1,2:5,6-dicyclohexylidene-*chiro*-inositol 78: A solution of diisopropylamine (0.32 mL, 2.29 mmol) in THF (15 mL) under argon was cooled to –78 °C and BuLi (1.4 mL, 1.6M soln) was added. This was stirred for 10 min at –78 °C then the solution was warmed to 0 °C and stirred 0.5 h. The solution was re-cooled to –78 °C and **84** (826 mg, 2.08 mmol) in THF (9 mL) was added. This was stirred for 1 h then HMPA (0.2 mL) was added after stirring for 10 min TIPSCl (3.12 mL, 0.67 mmol) was added and the mixture was stirred for 5 h. The mixture was warmed to ambient temperature, Et_2O (10 mL) was added, and the resulting solution was washed with H_2O (3 x 5 mL). The organic fraction was dried over $MgSO_4$, filtered and purified by flash chromatography hexanes:EtOAc 100:1 (R*f*=0.12) to give 0.646 g (1.17 mmol, 51 %) of a colourless oil; ^1H NMR: (300MHz $CDCl_3$): δ 1.06 (s, 18H, TIPS), 1.49 (m, 20H, Cy), 2.10 (s, 2H, alkene), 2.14 (s, 3H, TIPS), 3.19 (dd, 1H, *J*=7.8, 11.2 Hz, H-4), 3.52 (s, 3H, OMe), 4.24 (m, 2H, H-2, H-5), 4.43 (m, 2H, H-1, H-6), 4.98 (dd, 1H, *J*=8.5, 11.5 Hz, H-3); ^{13}C (75 MHz $CDCl_3$):12.5, 17.9, 23.9, 23.9, 24.1, 24.2, 25.2, 25.2, 35.0, 35.1, 37.6, 38.1, 60.2, 72.8, 75.4, 75.5, 76.2, 78.5, 80.7, 110.5, 110.0, 170.4; IR (neat): 2940, 2866, 1729cm^{-1}; HRMS *m/z* calcd for $C_{30}H_{52}O_7Si$ [M+H] 553.3546 found 553.3555.

Representative Procedure for the Mukiyama aldol reaction:

A solution of 10 mol% of $TiCl_4$ in CH_2Cl_2 under argon was cooled to –78 °C and 1.5 eq of benzaldehyde was added dropwise. To this was added 1eq of the silylenol ether and the reaction was warmed to the required temperature.

1-D-3-*O*-[(E)-3-phenyl-prop-2-enoyl]-4-*O*-methyl-1,2:5,6-diisopropylidene-*chiro*-inositol 92: To a stirred solution of **81** (0.52 g, 1.89 mmol) and DMAP (20 mg, 0.19 mmol) in pyridine (4 mL) and CH_2Cl_2 (15 mL) at 0 °C was added cinnamoyl chloride (340 mg, 2.08 mmol). The mixture was stirred overnight at ambient temperature. When TLC, hexanes:EtOAc 10:1, indicated no starting material the solution was added to EtOAc (10 mL) and washed with $NaHCO_3$ (3x 5 mL). The organic fractions were combined and dried over $MgSO_4$. Concentration and purification by column chromatography, hexanes:EtOAc 5:1 (R*f*=0.37) afforded 650 mg (1.61 mmol, 85%) of a white solid, mpt 112 °C; ^{1}H NMR: (300MHz $CDCl_3$): δ 1.37 (s, 3H, CMe_2), 1.40 (s, 3H,CMe_2), 1.55 (s, 3H, CMe_2), 1.56 (s, 3H, CMe_2), 3.34 (dd, 1H, *J*=7.3, 11.2Hz, H-4), 3.53 (s, 3H, OMe), 4.42 (m, 2H, H-1, H-6), 4.43 (m, 2H, H-2, H-5), 5.19 (dd, 1H, *J*=7.8, 11.2Hz, H-3), 6.51 (d, 1H, *J*=15.9Hz, vinylH), 7.41 (m, 3H, Ph), 7.52 (m, 2H, Ph), 7.77 (d, 1H, *J*=15.9Hz, vinylH); ^{13}C (75 MHz $CDCl_3$): 25.67, 25.78, 27.80, 28.12, 60.19, 72.64, 75.98, 76.02, 76.79, 78.98, 80.53, 109.64, 110.08, 117.95, 128.38, 129.14, 130.63, 145.78, 166.31; IR (KBr): 2988, 2937, 1708, 1633cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{29}O_7$ [M+H] 405.1898 found 405.1908.

1-D-3-*O*-[(E)-but-2-enoyl]-4-*O*-methyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 93: To a stirred solution of **81** (0.35 g, 1.28 mmol) and DMAP (20 mg, 0.128 mmol) in pyridine (2 mL) and CH_2Cl_2 (10 mL) at 0 °C was added crotonic anhydride (0.21 mL, 1.4 mmol). The mixture was stirred overnight at ambient temperature. When

TLC, hexanes:EtOAc 10:1, indicated no starting material the solution was added to EtOAc (10 mL) and washed with $NaHCO_3$ (3x 5 mL). The organic fractions were combined and dried over $MgSO_4$. Concentration and purification by column chromatography, hexanes:EtOAc 5:1 (R*f*=0.36) afforded 260 mg (0.76 mmol, 59 %) of a colourless oil; ^1H NMR: (300MHz $CDCl_3$): δ 1.31 (s, 3H, CMe_2), 1.33 (s, 3H,CMe_2), 1.47 (s, 3H, CMe_2), 1.49 (s, 3H,CMe_2), 2.10 (s, 3H, crotonyl Me), 3.20 (dd, 1H, *J*=7.3, 11.2Hz, H-4), 3.48 (s, 3H, OMe), 4.23 (t, 2H, *J*=6.3Hz, H-1 , H-6), 4.34 (m, 2H, H-2, H-5), 4.99 (dd, 1H, *J*=8.1, 11.5Hz, H-3), + 2 more H's; ^{13}C (75 MHz $CDCl_3$): 18.30, 25.62, 25.73, 27.75, 28.07, 60.15, 72.24, 75.94, 76.00, 76.79, 78.89, 80.48, 109.60, 110.02, 122.58, 145.82, 165.79;

General procedure for the copper catalyzed Grignard reagent to a Michael Acceptor: To a solution of CuBr.Me_2S (5 mmol) in THF-Me_2S 2:1 (V:V, 15 mL) at –78 °C was added the alkylmagnesium halide solution (10 mmol). The resulting dark black/brown solution was stirred at –78 °C for 1 h, a solution of **92** or **100** (1 mmol) in THF (5 mL) was then added. The mixture was warmed to –43 °C and stirred until TLC hexanes:EtOAc (10:1) indicated the reaction was complete. The mixture was quenched with saturated $NH_4Cl_{(aq)}$ and stirred for 10 min at ambient temperature. EtOAc (15 mL) was added, the organic layer washed with $NH_4Cl_{(aq)}$, dried and concentrated.

1-D-3-*O*-(3-phenylpent-4-enoyl)-4-*O*-methyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 99: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.21) to give a crude yield of 300 mg, (68 %). ^1H NMR: (300MHz $CDCl_3$): δ 1.28 (s, 3H, Me), 1.35 (s, 3H, CMe_2), 1.40 (s, 3H, CMe_2) 1.43 (s, 3H, CMe_2), 2.31 (m, 6H, CH_2), 2.6 (d, 2H, *J*=7.5 Hz, CH_2), 3.17

(m, 2H, CH), 4.18 (m, 2H, H-2, H-5), 4.42 (m, 2H, H-1, H-6), 4.95 (m, 6H, H-3, H-4, vinyl CH_2), 5.61 (m, 2H, vinyl CH), 7.19 (m, 5H, Ph);^{13}C (75 MHz $CDCl_3$): 25.7, 27.7, 27.8, 28.1, 49.4, 61.5, 76.4, 79.3, 72.2, 75.9, 76.4, 79.3, 79.6, 79.9, 109.7, 109.9

1-D-3:4-di-*O*-[(E)-3-phenyl-prop-2-enoyl]-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 100: To a stirred solution of D-**21** (670 mg, 2.57 mmol) in pyridine (5 mL) and CH_2Cl_2 (20 mL) at 0 °C was added cinnamoyl chloride (1.07 g, 6.4 mmol). The mixture was stirred overnight at ambient temperature. When TLC, hexanes:EtOAc 5:1, indicated no starting material the solution was added to EtOAc (15 mL) and washed with $NaHCO_3$ (3x 8 mL). The organic fractions were combined and dried over $MgSO_4$. Concentration and purification by recrystalization from hexanes afforded 1.27 g (2.44 mmol, 94%) of a white solid, mpt 162 °C; ^{1}H NMR: (300MHz $CDCl_3$): δ 1.41 (s, 6H, CMe_2), 1.59 (s, 6H,CMe_2), 4.48 (m, 2H, H-1, H-6), 4.62 (d, 2H, J=6.8Hz, H-2, H-5), 5.30 (dd, 2H, *J*=2.7, 5.9Hz, H-3, H-4), 6.38 (d, 2H, *J*=15.9Hz, alkeneH), 7.35 (m, 6H, Ph), 7.44 (m, 4H, Ph), 7.65 (d, 2H, *J*=15.9Hz, alkeneH); ^{13}C (75 MHz $CDCl_3$): 26.01, 27.86, 71.42, 75.27, 76.62, 110.02, 117.37, 128.43, 129.05, 130.64, 134.42, 146.18, 166.33; IR (KBr): 2998, 2891, 1711, 1636cm^{-1}; HRMS *m/z* calcd for $C_{30}H_{33}O_8$ [M+H] 521.2164 found 521.2170.

1-D-3:4-di-*O*-(3-phenylpentanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 101: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.29) to give a crude yield of 110 mg, (0.19 mmol, 32 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 0.86 (s, 3H, Me), 1.26 (s, 3H, CMe_2), 1.35 (s, 3H, CMe_2) 1.40 (s, 3H, CMe_2), 1.43 (s, 3H, CMe_2), 1.69 (m, 4H, CH_2), 2.58 (m, 4H, CH_2), 3.01 (m, 2H, CH), 4.18 (m, 2H, H-2-, H-5), 4.46 (m, 2H, H-1, H-6), 4.98 (m, 2H, H-3, H-4), 7.20 (m, 10 H, Ph); ^{13}C (75 MHz $CDCl_3$): 12.2, 25.8, 27.7,

28.0, 29.7, 41.3, 43.4, 71.6, 73.5, 75.6, 75.9, 76.5, 78.8, 109.8, 109.9, 127.0, 127.6, 128.9, 144.2, 172.1.

1-D-3-*O*-(3-phenylpentanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 102: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.15) to give a colourless oil 80 mg, (19 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 0.8 (s, 3H, Me), 1.30 (s, 3H, CMe_2), 1.38 (s, 3H, CMe_2) 1.42 (s, 3H, CMe_2), 1.49 (s, 3H, CMe_2), 1.65 (m, 1H, Et-CH_2), 1.71 (m, 1H, Et-CH_2), 2.78 (m, 2H, CH_2), 3.02 (m, 1H, CH), 3.42 (dd, 1H, *J*= Hz, H-4), 4.13 (m, 2H, H-, H-5), 4.39 (m, 2H, H-1, H-6), 4.87 (dd, 1H, *J*= Hz, H-3), 7.14 (m, 5H, Ph); ^{13}C (75 MHz $CDCl_3$) 12.11, 25.5, 27.7, 27.8, 28.0, 41.3, 43.9, 71.9, 73.5, 75.6, 75.9, 76.5, 78.8, 109.7, 109.8, 126.9, 127.6, 128.8, 172.1: IR (neat): 3468, 2984, 2934, 1742 cm^{-1};

General procedure for the Michael addition of thiols to 100 and 116: Thiol (10 mmol) was added with stirring in an ice or ice/salt bath as indicated to a solution of 1.6 M n-butyllithium in hexane (0.1 mmol) to give a solution of 100:1 mixture of thiol and lithium thiophenoxide. To the resulting solution was added a solution of chiral ester (1mmol) in THF (5mL). The reaction was stirred at –10 °C for 18-24 h. Upon TLC indicating no more starting material the mixture was made alkaline by the addition of 5% $NaOH_{(aq)}$ and extracted with CH_2Cl_2. Filtration, concentration and purification via flash chromatography (hexanes-EtOAc mixtures) gave pure **103-109** or **117-121**.

1-D-3:4-di-*O*-(3-phenyl-3-phenylthiopropanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 103: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.16) to give a colourless oil (75 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 1.30 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2)

1.37 (s, 3H, CMe_2), 1.39 (s, 3H, CMe_2), 1.52 (m, 2H, CH_2), 2.96 (m, 2H, CH_2), 4.19 (m, 2H, H-2, H-5), 4.53, (m, 4H, H-1, H-6, CH), 5.02 (m, 2H, H-3, H-4), 7.32 (m, 20H, Ph); ^{13}C (75 MHz $CDCl_3$) 25.7, 27.3, 40.3, 48.9, 71.1, 74.6, 76.2, 109.5, 127.3, 127.4, 125.7, 127.6, 127.7, 127.8, 128.2, 128.3, 128.7, 128.8, 133.2, 133.6, 140.5, 170.1: IR (neat): 3060, 2986, 2936, 1747 cm^{-1}.

1-D-3:4-di-*O*-(3-phenyl-3-benzylthiopropanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 104: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.17) to give a colourless oil (59 %). ^1H NMR: (300MHz $CDCl_3$): δ 1.30 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2) 1.39 (s, 3H, CMe_2), 1.44 (s, 3H, CMe_2), 1.59 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 3.48 (m, 4H, CH_2), 4.13 (m, 4H, H-2, H-5, CH), 4.44, (d, 2H, J= 2.9 Hz, H-1, H-6), 4.95 (m, 2H, H-3, H-4), 7.32 (m, 20H, Ph); ^{13}C (75 MHz $CDCl_3$) 25.9, 27.6, 27.7, 29.2, 36.0, 41.3, 44.9, 76.4, 75.0, 71.2, 109.7, 128.1, 128.3, 128.7, 128.9, 137.9, 141.4, 169.9: IR (neat): 3061, 2985, 1748 cm^{-1};

1-D-3:4-di-*O*-(3-phenyl-3-*p*-methoxyphenylthiopropanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 105: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.29) to give a white solid (67 %) mpt 145 °C. ^1H NMR: (300MHz $CDCl_3$): δ 1.29 (s, 3H, CMe_2), 1.32 (s, 3H, CMe_2) 1.36 (s, 3H, CMe_2), 1.44 (s, 3H, CMe_2), 2.73 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 3.77 (s, 6H, OMe), 4.20 (m, 2H, H-2, H-5), 4.24 (m, 4H, H-1, H-6, CH), 5.00 (m, 2H, H-3, H-4), 6.98 (m, 4H, Ph), 7.32 (m, 20H, Ph); ^{13}C (75 MHz $CDCl_3$) 25.9, 27.6, 40.1, 49.9, 55.5, 71.3, 74.9, 76.4, 109.7, 114.5, 127.4, 127.9, 128.4, 137.1, 170.4: IR (neat): 2987, 2938, 1748 cm^{-1}; Anal. Calcd for $C_{44}H_{48}O_{10}S_2$: C, 65.97; H, 6.04; S, 8.01: Found: C, 65.72; H, 6.07; S,8.19.

1-D-3:4-di-*O*-(3-phenyl-3-*o*-chlorophenylthiopropanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 106: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.34) to give a colourless oil (59 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 1.33 (s, 3H, CMe_2), 1.36 (s, 3H, CMe_2) 1.47 (s, 3H, CMe_2), 1.49 (s, 3H, CMe_2), 1.50 (bs, 4H, CH_2), 3.49 (m, 2H, CH), 4.17 (m, 2H, H-2, H-5), 4.40 (m, 2H, H-1, H-6), 4.86, (m, 2H, H-3, H-4), 7.26 (m, 18H, Ph); ^{13}C (75 MHz $CDCl_3$) 25.5, 25.8, 27.7, 28.0, 48.2, 71.5, 74.3, 75.5, 75.9, 76.3, 78.6, 109.8, 127.4, 127.8, 128.0, 128.5, 128.9, 129.0, 129.3, 130.3, 134.5, 139.5, 170.2: IR (neat): 3058, 2936, 1746 cm^{-1}.

1-D-3:4-di-*O*-(3-phenyl-3-*o*-aminophenylthiopropanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 107: Filtered through a silica plug, hexanes:EtOAc 10:1 to give a yellow oil (61 % crude yield). ^{1}H NMR: (300MHz $CDCl_3$): δ 1.32 (s, 3H, CMe_2), 1.34 (s, 3H, CMe_2) 1.43 (s, 3H, CMe_2), 1.48 (s, 3H, CMe_2), 2.93 (m, 4H, CH_2), 4.43 (m, 2H, CH), 3.85 (bs, 4H, NH_2), 4.25 (m, 2H, H-2, H-5), 4.49 (m, 2H, H-1, H-6), 5.06 (m, H,-3, H-4) 7.12 (m, 18H, Ph): ^{13}C (75 MHz $CDCl_3$) 25.4, 27.9, 38.4, 49.9, 60.8, 72.6, 76.4, 78.9, 109.9, 115.3, 118.7, 127.5, 127.9, 128.7, 130.6, 137.8, 142.1: IR (neat): 3330, 3062, 2944 cm^{-1};

1-D-3:4-di-*O*-(3-phenyl-3-crotonylthiopropanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 108: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.19) to give a colourless oil (31 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 1.29 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2) 1.36 (s, 3H, CMe_2), 1.39 (s, 3H, CMe_2), 1.46 (s, 3H, Me), 1.53 (s, 3H, Me), 2.19 (s, 8H, CH_2), 2.91 (m, 4H, alkene), 4.20 (m, 2H, H-2, H-5), 4.42 (m, 2H, H-1, H-6), 5.00 (m, 2H, CH), 5.42 (m, 2H, H-3, H-4) 7.25 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$) 18.0, 24.7,

26.0, 27.6, 31.2, 33.8, 41.4, 44.3, 71.2, 75.0, 76.5, 76.7, 78.4, 79.6, 109.7, 127.5, 128.1, 128.7, 141.7, 170.2: IR (neat): 2987, 1749 cm^{-1};

1-D-3:4-di-*O*-(3-phenyl-3-isobutylthiopropanoyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 109: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.21) to give a colourless oil (53 %). ^1H NMR: (300MHz $CDCl_3$): δ 0.78 (s, 3H, Me), 0.80 (s, 3H, Me), 0.82 (s, 3H, Me), 0.84 (s, 3H, Me), 1.30 (s, 3H, CMe_2), 1.33 (s, 3H, CMe_2) 1.39 (s, 3H, CMe_2), 1.40 (s, 3H, CMe_2), 1.43 (m, 4H, CH_2), 1.60 (s, 2H, CH_2), 2.29 (m, 4H, CH_2), 2.63 (m, 2H, CH_2), 2.95 (m, 2H, CH), 4.21 (m, 4H, H-2, H-5, CH), 4.45 (m, 2H, H-1, H-6), 4.99 (m, 2H, H-3, H-4), 7.28 (m, 20H, Ph); ^{13}C (75 MHz $CDCl_3$) 22.3, 22.6, 26.0 (2C), 27.7, 29.5, 38.4, 41.5, 45.2, 71.2, 75.0, 76.4, 109.7, 127.5, 127.9, 128.7, 141.8, 170.4: IR (neat): 2956, 1749 cm^{-1}; HRMS *m/z* calcd for $C_{40}H_{57}O_8S_2$ [M + H] 729.3494, found 729.3489.

General procedure for the removal of the inositol auxiliary with $LiBH_4$: To a solution of the inositol moiety (1 mmol), in THF (2.5 mL) at 0 °C was added $LiBH_4$ (1 mmol). This was warmed to ambient temperature and stirred for 12-16 h, the reaction was quenched by the addition of NH_4Cl (2 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL), the organic fractions were combined, concentrated and dried to give **110-114**. The aqueous layer was dried under reduced pressure, the resulting white solid was dissolved in CH_2Cl_2 (5 mL) and washed with H_2O (3 x 5 mL). The organic layers were combined, dried and concentrated to give **21**.

(-)-3-(phenylthio)-3-phenylpropan-1-ol 110: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.32) to give a white solid (69 %), mp 64 °C. ^1H NMR: (300MHz $CDCl_3$): δ 1.55 (bs,

1H, OH), 2.21 (m, 2H, H-2), 3.62 (m, 1H, H-1), 3.77 (m, 1H, H-1), 4.39 (t, 1H, *J*=7.8 Hz, H-3), 7.27 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$): 39.0, 50.4, 60.8, 127.4, 127.5, 128.0, 128.7, 130.0, 132.8; IR (neat): 3367, 3060, 2931 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{17}OS$ [M + H] 245.0984, found 245.0995. Retention times 14.7 min (minor isomer), 21.1 min (major isomer).

(-)-3-(benzylthio)-3-phenylpropan-1-ol 111: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.24) to give a colourless oil (65 %). ^1H NMR: (300MHz $CDCl_3$): δ 1.53 (bs, 1H, OH), 2.09 (m, 2H, H-7), 3.47 (s, 1H, H-2), 3.55 (m, 2H, benzyl CH_2), 3.68 (m, 1H, H-2), 3.86 (t, 1H, *J*=7.8 Hz, H-4), 7.31 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$): 35.6, 39.2, 46.2, 60.8, 127.2, 127.6, 128.2 (2C), 128.7 (2C), 128.9 (2C), 129.2 (2C), 138.5, 142.4; IR (neat): 3334, 3027, 2933 cm^{-1}. Retention times 14.9 min (minor isomer), 18.8 min (major isomer).

(+)-3-(*o*-chlorophenylthio)-3-phenylpropan-1-ol 112: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.28) to give a colourless oil (55 %). ^1H NMR: (300MHz $CDCl_3$): δ 1.61 (bs, 1H, OH), 2.23 (m, 2H, H-2), 3.65 (m, 1H, H-1), 3.81 (m, 1H, H-1), 4.54 (t, 1H, *J*=7.1 Hz, H-3), 7.22 (m, 9H, Ph); ^{13}C (75 MHz $CDCl_3$): 38.2, 48.7, 60.7, 127.2, 127.7, 128.0, 128.2, 128.8, 130.0, 133.0, 134.3, 141.3; IR (neat): 3364, 2937, 1492, 1035 cm^{-1}. Retention times 13.8 min (minor isomer), 16.9 min (major isomer).

(+)-3-(*o*-aminophenylthio)-3-phenylpropan-1-ol 113: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.23) to give a pale brown oil (69 %), $[\alpha]^{21}_D$ +54.2° (c 1.71×10^{-3}, CH_2Cl_2) ^1H NMR: (300MHz $CDCl_3$): δ 2.23 (m, 2H, H-3), 3.00 (bs, 3H, NH_2, OH), 3.62 (m, 1H, H-2), 4.18 (m, 1H, H-4), 6.60 (t, 1H, *J*=7.6 Hz, Ph), 6.69 (d, 1H,

J=7.8Hz, Ph), 7.20 (m, 7H, Ph); ^{13}C (75 MHz $CDCl_3$): 38.4, 49.9, 60.9, 118.7, 127.5 (2C), 127.9 (4C), 128.7 (3C), 130.6, 137.8; IR (neat): 3326, 3065, 2948 cm^{-1}. Retention times 13.4 min (minor isomer), 16.2 (major isomer).

(+)-3-isobutylthio-3-phenylpropan-1-ol 114: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.31) to give a colourless oil (114 %). ^1H NMR: (300MHz $CDCl_3$): δ 0.80 (d, 3H, *J*=6.6, Me), 0.83 (d, 3H, *J*=6.6, Me), 1.38 (m, 2H, H-6), 1.57 (m, 1H, H-7), 1.65 (bs, 1H, OH), 2.12 (m, 2H, H-3), 2.28 (m, 2H, H-5), 3.61 (m, 1H, H-2), 3.75 (m, 1H, H-2), 3.99 (t, 1H, *J*=7.3 Hz, H-4), 7.30 (m, 5H, Ph; ^{13}C (75 MHz $CDCl_3$): 22.3, 22.6, 27.6, 29.2, 38.5, 39.3, 46.7, 61.0, 127.4, 128.0, 128.0; IR (neat): 3346, 2954, 1453 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{13}OS$ [M + H] 235.1468, found 239.1464. Retention times 14.4 min (minor isomer), 17.5 min (major isomer).

1-D-3-*O*-[(E)-3-phenyl-prop-2-enoyl]-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 115: To a stirred solution of **48** (238 mg, 0.69 mmol) and DMAP (10 mg, 0.07 mmol) in pyridine (2 mL) and CH_2Cl_2 (4 mL) at 0 °C was added cinnamoyl chloride (180 mg, 1.04 mmol). The mixture was stirred 16 h at ambient temperature. When TLC, hexanes:EtOAc 10:1, indicated no starting material the solution was added to EtOAc (10 mL) and washed with $NaHCO_3$ (3x 5 mL). The organic fractions were combined and dried over $MgSO_4$. Concentration and purification by column chromatography, hexanes:EtOAc 5:1 (R*f*=0.29) afforded 290 mg (0.61 mmol, 89 %) of a white solid; ^1H NMR: (300MHz $CDCl_3$): δ 1.27 (s, 9H, Piv), 1.37 (s, 3H, CMe_2), 1.40 (s, 3H,CMe_2), 1.52 (s, 3H, CMe_2), 1.53 (s, 3H, CMe_2), 3.62 (dd, 1H, *J*=8.1, 11.2 Hz, H-4), 4.25 (m, 2H, H-1, H-6), 4.48 (m, 2H, H-2, H-5), 4.94 (dd, 1H, *J*=8.6, 11.5 Hz, H-3), 6.48 (d, 1H, *J*=15.9 Hz, alkeneH), 7.44 (m, 3H,

Ph), 7.58 (m, 2H, Ph), 7.82 (d, 1H, *J*=15.9 Hz, alkeneH); ^{13}C (75 MHz $CDCl_3$): 25.65, 25.93, 27.39 (3C), 27.86, 28.11, 72.14, 73.40, 75.51, 75.72, 76.63, 79.33, 109.77; IR (KBr): 2983, 2936, 1731, 1633cm^{-1};

1-D-3-*O*-[(E)-but-2-enoyl]-4-*O*-pivaloyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 116: To a stirred solution of **46** (810 mg, 2.4 mmol) in pyridine (2 mL) and CH_2Cl_2 (5 mL) at 0 °C was added pivaloyl chloride (0.45 mL, 3.65 mmol). The mixture was stirred 18 h at ambient temperature. When TLC, hexanes:EtOAc 10:1, indicated no starting material the solution was added to EtOAc (10 mL) and washed with $NaHCO_3$ (3x 5 mL). The organic fractions were combined and dried over $MgSO_4$. Concentration and purification by column chromatography, hexanes:EtOAc 5:1 (R*f*=0.28) afforded 620 mg (1.46 mmol, 61 %) of a colourless oil; ^1H NMR: (300MHz $CDCl_3$): δ 1.13 (s, 6H, CMe_2), 1.26 (s, 12H, Piv, CMe_2), 1.35 (s, 3H, CMe_2), 1.52 (d, 3H, *J*=5.8Hz, alkene Me), 4.32 (m, 2H, H-1, H-6), 4.53 (m, 2H, H-2, H-5), 5.11(m, 2H, H-3, H-4), 5.82(d, 1H, *J*=15.6Hz, alkeneH), 6.98 (m, 1H, alkeneH); ^{13}C (75 MHz $CDCl_3$): 18.27, 25.98, 26.08, 26.72, 27.23 (3C), 27.76, 70.79, 75.09, 76.65, 76.69, 109.76. 109.86, 122.13, 146.17, 165.55, 177.76; IR (neat): 2983, 1732, 1633cm^{-1}.

1-D-3-*O*-(3-phenyl-3-phenylthiopropanoyl)-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol D-117: Eluted with 10:1 hexanes:EtOAc (R*f* =0.13) to give a colourless oil (79 %). ^1H NMR: (300MHz $CDCl_3$): δ 1.12 (s, 3H, CMe_2), 1.16 (s, 3H, CMe_2) 1.36 (s, 9H, piv), 1.52 (s, 6H, CMe_2), 2.41 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 3.58 (m, 1H, CH), 4.28 (m, 2H, H-2, H-5), 4.54 (bs, 2H, H-1, H-6), 5.07 (m, 2H, H-3, H-4), 7.38 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$) 20.1, 26.1, 27.2, 27.3, 27.8,

39.4, 41.6, 70.7, 71.4, 74.9, 76.6, 109.8, 127.4, 127.7, 127.8, 129.3, 133.2, 137.3, 170.5, 177.7: IR (neat): 3065, 2948, 1738 cm^{-1};

1-D-3-*O*-(3-phenyl-3-benzylthiopropanoyl)-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol D-118: Eluted with 10:1 hexanes:EtOAc (R*f* =0.15) to give a colourless oil (74 %). ^1H NMR: (300MHz $CDCl_3$): δ 1.17 (s, 6H, CMe_2), 1.36 (s, 9H, piv), 1.47 (s, 3H, CMe_2), 1.50 (s, 3H, CMe_2), 1.53 (s, 2H, CH_2),2.85 (m, 2H, CH_2), 3.51 (m, 2H, H-4, CH), 4.19 (m, 2H, H-2, H-5), 4.45 (m, 2H, H-1, H-6), 5.00 (m, 1H, H-3), 7.28 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$) 27.3, 26.0, 27.1, 27.8, 36.0, 41.3, 44.7, 70.6, 71.5, 75.0, 76.5, 78.4, 79.6, 109.7, 109.8, 127.2, 128.2, 128.7, 128.8, 129.2, 138.0, 141.2, 169.8, 177.7: IR (neat): 2987, 2937, 1749 cm^{-1};

1-D-3-*O*-(3-phenyl-3-*p*-methoxyphenylthiopropanoyl)-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol D-119: Eluted with 10:1 hexanes :EtOAc (R*f*= 0.35) to give a colourless oil (76%). ^1H NMR: (300MHz $CDCl_3$): δ 1.15 (s, 6H, CMe_2), 1.32 (s, 9H, piv), 1.48 (s, 3H, CMe_2), 2.75m, 2H, CH_2), 3.69 (s, 3H, OMe), 3.88(m, 2H, CH) 4.21 (m, 2H, H-2, H-5), 4.27 (m, 2H, H-1, H-6), 5.09 (m, 2H, H-3, H-4), 7.26 (m, 9H, Ph): IR (neat): 2981, 1749 cm^{-1};

1-D-3-*O*-(3-phenyl-3-isobutylthiopropanoyl)-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 121: Eluted with 20:1 hexanes:EtOAc (R*f* = 0.16) to give a colourless oil (71 %). ^1H NMR: (300MHz $CDCl_3$): δ 0.80 (s, 3H, Me), 0.81 (s, 3H, Me), 1.01 (s, 3H, CMe_2), 1.21 (s, 9H, piv), 1.30 (s, 3H, CMe_2), 1.35 (s, 3H, CMe_2), 1.37 (s, 3H, CMe_2), 1.50 (s, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.87 (m, 3H, CH_2, CH), 4.19 (m, 1H, CH), 4.25 (m, 2H, H-2, H-5), 4.48 (m, 2H, H-1, H-6), 5.02 (m, 2H,

H-3, H-4), 7.28 (m, 5H, Ph); ^{13}C (75 MHz $CDCl_3$) 22.3, 22.6, 26.1, 27.4, 27.8, 29.5, 38.3, 41.3, 44.8, 71.4, 74.9, 76.9, 109.7, 109.8, 127.5, 128.0, 128.2, 128.7, 141.7, 170.1, 177.7: IR (neat): 2958, 1742 cm^{-1}.

1-L-3-*O*-(3-phenyl-3-phenylthiopropanoyl)-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol L-117: Eluted with 10:1 hexanes:EtOAc (R*f* =0.13) to give a colourless oil (75 %).

1-L-3-*O*-(3-phenyl-3-benzylthiopropanoyl)-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol L-118: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.15) to give a colourless oil (72 %).

1-L-3-*O*-(3-phenyl-3-*o*-aminophenylthiopropanoyl)-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol L-120: Eluted with 10:1 hexanes:EtOAc (R*f* = 0.22) to give a colourless oil (68 %). ^1H NMR: (300MHz $CDCl_3$): δ 1.25 (s, 3H, CMe_2), 1.29 (s, 9H, piv), 1.35 (s, 3H, CMe_2), 1.38 (s, 3H, CMe_2), 1.42 (s, 3H, CMe_2), 1.52 (s, 2H, CH_2), 3.42 (m, 1H, CH), 4.19 (m, 2H, H-2, H-5), 4.39 (m, 2H, H-1, H-6), 4.78 (m, 2H, H-3, H-4), 7.28 (m, 9H, Ph): IR (neat): 3064, 2938, 1748 cm^{-1}.

1-L-3-*O*-(3-phenyl-3-isobutylthiopropanoyl)-4-*O*-trimethylacetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 121: Eluted with 20:1 hexanes:EtOAc (R*f* = 0.16) to give a colourless oil (31 %).

General procedure for the removal of the inositol auxiliary with KOH: To a solution of **117-121** (1 mmol) in MeOH (10 mL) was added 4M $KOH_{(aq)}$ (5 mL).

This was refluxed for 12-18 h until TLC hexanes:EtOAc 3:1 indicated no starting material remained. H_2O (5 mL) was added and the solution was extracted with CH_2Cl_2. The organic layer was dried and concentrated to give **48**. The aqueous layer was acidified with HCl and extracted with with CH_2Cl_2, the organic layer was dried and concentrated to give **122-125**.

(–)-3-(phenylthio)-3-phenylpropionic acid 122a: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.19) to give a colourless oil (76 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 2.81 (d, 2H, *J*=7.6 Hz, H-2), 4.41 (t, 1H, *J*=7.2 Hz, H-3), 7.24 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$) 41.3, 59.8, 126.9, 127.1, 127.9(2C), 128.4 (2C), 128.8 (2C), 129.7, 131.3, 172.8: IR (neat): 3165, 3031, 1709 cm^{-1}. Retention times 15.3 min (minor isomer), 21.9 min (major isomer).

(–)-3-(benzylthio)-3-phenylpropionic acid 123a: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.19) to give a colourless oil (75 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 2.89 (d, 2H, *J*=7.4 Hz, H-2) 3.53 (m, 2H, benzyl CH_2), 4.29 (t, 1H, *J*=7.5 Hz, H-3), 7.29 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$) 38.9, 46.5, 61.2, 127.3, 127.6 (2C), 128.3 (2C), 128.5 (2C), 130.1 (2C), 129.1, 138.5, 142.4, 171.3; IR (neat): 3323, 3019, 2935, 1733 cm^{-1}. Retention times 15.5 min (minor isomer), 19.2 min (major isomer).

(+)-3-isobutylthio-3-phenylpropionic acid 125a: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.22) to give a colourless oil (72 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 0.81 (d, 3H, *J*=6.6 Hz, Me), 0.84 (d, 3H, J= 6.6 Hz, Me), 1.39 (dd, 2H, J= 8.1, 15.3 Hz, H-5) 1.59 (m, 1H, H-6), 2.35 (dd, 2H, *J*= 7.8, 13.7 Hz, H-4), 2.95 (d, 2H, *J*=7.8 Hz, H-2), 4.29 (t, 1H, *J*=7.1 Hz, H-3), 7.4 (m, 5H, Ph); ^{13}C (75 MHz $CDCl_3$) 22.3, 22.5, 27.6, 29.5,

38.3, 41.3, 45.0, 127.8, 127.9, 128.6, 128.8, 129.2, 131.1, 176.1: IR (neat): 3166, 3062, 3029, 1702 cm^{-1}. Retention times 14.9 min (minor isomer), 18.1 min (major isomer).

(+)-3-(phenylthio)-3-phenylpropionic acid 122b: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.19) to give a colourless oil (74 %). Retention times 15.3 min (major isomer), 21.9 min (minor isomer).

(+)-3-(benzylthio)-3-phenylpropionic acid 123b: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.19) to give a colourless oil (72 %). Retention times 15.5 min (major isomer), 19.2 min (minor isomer).

(+)-3-(*o*-aminothiophenyl)-3-phenylpropionic acid 124b: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.23) to give a colourless oil (59 %). ^{1}H NMR: (300MHz $CDCl_3$): δ 2.28 (d, 2H, *J*=7.7 Hz, H-2), 2.98 (bs, 2H, NH_2) 4.38 (t, 1H, *J*= 7.1 Hz, H-3), 6.71 (m, 2H, Ph), 7.18 (m, 7H, Ph); ^{13}C (75 MHz $CDCl_3$): 38.4, 46.2, 127.2, 127.8, 128.3, 129.6 (2C), 131.6, 172.3; IR (neat): 3326, 3065, 2948, 1738 cm^{-1}. Retention times 13.9 min (major isomer), 15.9 min (minor isomer)

(–)-3-isobutylthio-3-phenylpropionic acid 125b: Eluted with 3:1 hexanes:EtOAc (R*f* = 0.22) to give a colourless oil (67 %). Retention times 14.9 min (major isomer), 18.1 min (minor isomer).

1-D-3-*O*-(3-methyloctanoyl)-4-*O*-trimethylacetyl-1,2:5,6-diisopropylidene-*chiro*-inositol 126: To a stirred solution of CuI (330 mg, 1.71 mmol) in THF (5 mL) under argon at –30 °C was added BuLi (1.4 M soln in THF, 1.3 mL). The solution was stirred at –30 °C for 30 min before being cooled to –78 °C and $BF_3.OEt_2$ (0.21 mL, 1.71 mmol) was added followed by **116** (235 mg, 0.57 mmol) in THF (1 mL). The solution was slowly warmed to –40 °C and monitored by TLC, hexanes:EtOAc 5:1. After 6.5 h no starting material was visible, NaCl (5 mL) was added and the mixture was warmed to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$ concentrated and purified by column chromatography, hexanes:EtOAc 10:1 (R*f* = 0.18) to give 114 mg (0.242 mmol, 43 %) of a colourless oil ^1H NMR: (300MHz $CDCl_3$): δ 0.91(m, 6H, 2xMe), 1.19 (s, 6H, CMe_2), 1.26 (bs, 6H, CH_2), 1.44(s, 6H, CMe_2), 1.90 (m, 1H, CH), 2.18 (m, 2H, CH_2), 4.29 (m, 2H, H-2, H-5), 4.53 (d, 2H, *J*=5.1Hz, H-1, H-6), 5.08 (m, 2H, H-3, H-4); ^{13}C (75 MHz $CDCl_3$): 14.29, 19.76, 23.00, 26.10, 27.27, 27.78, 29.29, 30.48, 36.58, 41.87, 70.72, 74.96, 76.75, 76.81, 109.74, 172.46, 177.72; IR (neat): 2933, 1743cm^{-1}; HRMS *m/z* calcd for $C_{25}H_{43}O_8$ [M+H] 471.2937 found 471.2953.

(+)-3-methylheptanbenzoate 127: To a solution of **126** (86 mg, 0.183 mmol) in MeOH (1 mL) was added 4M $KOH_{(aq)}$ (1 mL). This was refluxed for 18 h until TLC hexanes:EtOAc 5:1 indicated no starting material remained. H_2O (2 mL) was added and the solution was extracted with CH_2Cl_2. The organic layer was dried and concentrated to give **48**. The aqueous layer was acidified with HCl and extracted with with CH_2Cl_2, the organic layer was dried and concentrated to give **127**.

Attempted addition of allylsilanes to carbonyls with TiF_4 and 21: To a solution of **21** (150 mg, 0.58 mmol) in anhydrous MeCN (1.5 mL) and anhydrous CH_2Cl_2 (1.5 mL) was added dropwise a solution of TiF_4 (0.04 g, 0.29 mmol) in anhydrous MeCN (1 mL). This mixture was heated at reflux overnight and a pale orange colour resulted. The solvent was removed under reduced pressure. The resulting solid was placed in CH_2Cl_2 (3 mL) with MeCN (0.1 mL) and allyltrimethylsilane (0.8 mL, 4.5 mmol) was added. This solution was stirred at 0 °C for 2 h whereupon benzaldehyde (0.3 mL, 3 mmol) was added. The reaction was monitored by TLC and ^{1}HNMR with no evidence of reaction being seen.

Attempted Diels-Alder reaction using 21: To a solution of $TiCl_4$ or $Ti(O^iPr)_4$ (1 eq) in anhydrous CH_2Cl_2 (0.1 M soln) was added BuLi (2 eq) and a solution of **21** (1 eq) in anhydrous CH_2Cl_2 (0.1 M soln). This mixture was stirred at 0 °C for 30 min whereupon the temperature was adjusted and the isoprene (10 eq) and methyl acrylate (10 eq) were added.

1-D-3:4-di-*O*-(methanesulfonyl)-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 136: To a solution of D-**21** (1.59 g, 6.14 mmol) in pyridine (15 mL) under argon at 0 °C was added dropwise methanesulfonyl chloride (3 ml, 38 mmol). The solution was stirred at 0 °C overnight. The resulting brown solution was concentrated to dryness then filtered through a silica gel plug with hexanes:EtOAc (1:1). Recrystalization in acetone gave 2.27 g (5.46 mmol, 89 %) of a white solid, mp (decomposed) 261 °C $[\alpha]^{21}_D$ +111.5° (c $1.5x10^{-2}$, CH_2Cl_2) ^{1}H NMR: (300MHz $CDCl_3$): δ 1.40 (s, 6H, CMe_2), 1.56 (s, 6H, CMe_2), 3.21 (s, 6H, Ms), 4.37 (m, 2H, H-3, H-4), 4.60 (m, 4H, H-1, H-2, H-3, H-4);

^{13}C (75 MHz $CDCl_3$): 25.9, 27.7, 39.8, 74.6, 76.7, 79.3, 110.5; IR (KBr): 3449, 1358, 1176 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{25}O_{10}S_2$ [M+H] 417.0882 found 417.0884.

1-D-3:4-di-*O*-(*O*-trifluoromethanesulfonyl)-1,2;5,6-di-*O*-isopropylidene-*chiro*-inositol 141: To a solution of D-**21** (426 mg, 1.64 mmol) in pyridine (5 mL) and CH_2Cl_2 (5 mL) under argon at 0 °C was added dropwise Tf_2O (0.5 mL, 3 mmol). The solution was stirred at 0 °C overnight. The resulting dark red solution was concentrated to dryness then filtered through a silica gel plug, hexanes:EtOAc (3:1). Purification by flash chromatography hexanes:EtOAc 5:1 (R*f* = 0.47) gave 705 mg (1.52 mmol, 93 %) of a white solid, mp 117 °C; ^1H NMR: (300MHz $CDCl_3$): δ 1.40 (s, 6H, CMe_2), 1.52 (s, 6H, CMe_2), 4.44 (m, 2H, H-1, H-6), 4.64 (d, 2H, *J*=5.1Hz, H-2, H-5), 4.69 (m, 2H, H-3, H-4); ^{13}C (75 MHz $CDCl_3$): 25.70, 27.40, 74.38, 75.75, 83.12, 116.47, 120.70; ^{19}F (282 MHz $CDCl_3$) –73.69; IR (KBr): 2995, 1420, 1384, 1219, 1133 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{22}NO_{10}S_2F_6$ [M+NH_4] 542.0574 found 542.0584

Reaction of 1-D-3:4-di-*O*-(*O*-trifluoromethanesulfonyl)-1,2;5,6-di-*O*-isopropylidene-*chiro*-inositol with NaN_3 142: To a solution of **141** (500 mg, 0.95 mnol) in DMF (10 mL) under argon at 0 °C was added NaN_3 (600 mg, 9.54 mmol). The mixture was stirred overnight at ambient temperature, the resulting yellow solution was dried under reduced pressure and filtered through a silica gel plug, hexanes:EOAc (10:1) to give 440 mg of a white solid. mp 40 °C; ^1H NMR: (300MHz $CDCl_3$): δ 1.35 (s, 6H, CMe_2), 1.39 (s, 6H, CMe_2), 4.54 (m, 2H, H-1, H-6), 4.67 (m, 2H, H-2, H-5), 5.26 (m, 2H, H-3, H-4) ; ^{13}C (75 MHz $CDCl_3$): 26.5, 26.7, 27.9, 28.2, 70.7, 71.4, 72.9, 74.1, 109.7, 110.5, 111.3, 136.2; ^{19}F (282 MHz $CDCl_3$): –73.72, –75.00; IR (neat): 2985, 2116, 1688cm^{-1}.

Reaction of 142 with H_2: A solution of **142** (340 mg) in MeOH (10 mL) with either Adams catalyst (10 mol%) or Pd/C (10 mol%) was placed in a Fischer-Porter bottle and purged with argon. The solution was then frozen and the bottle evacuated by vacuum. The bottle was then purged to 100 psi, evacuated and refilled with H_2 three times. The reaction was allowed to warm to ambient temperature and was stirred overnight (with pressure rising to 110 psi). The solution was filtered, concentrated and purified by flash chromatography to give 240 mg (0.46 mmol, 62 %) of **141, 141→142→141**.

Reaction of 142 with PPh_3: To a solution of **142** (500 mg) in THF (5 mL) was added in small portions PPh_3 (530 mg, 2.05 mmol). After stirring 3 h at ambient temperature water (2 mL) was added and the solution was stirred vigorously overnight. The phases were separated, the organic layer was filtered and concentrated to give **140** (160 mg, 0.68 mmol, 63 %) over two steps **141→142→140**.

1-D-3-*O*-trifluoromethanesulfonyl-4-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 146: To a solution of **44** (326 mg, 1.13 mmol) in pyridine (1 mL) and CH_2Cl_2 (2 mL) under argon at 0 °C was added dropwise Tf_2O (0.3 mL, 1.7 mmol). The solution was stirred at 0 °C overnight. The resulting dark red solution was concentrated then filtered through a silica gel plug, hexanes:EtOAc (5:1). Purification by flash chromatography hexanes:EtOAc 10:1 (Rf = 0.15) gave 343 mg (0.79 mmol, 70%) of a white solid, mp 108 °C ; ^{1}H NMR: (300MHz $CDCl_3$): δ 1.38 (s, 3H, CMe_2), 1.41 (s, 3H, CMe_2), 1.53 (s, 3H, CMe_2), 1.54 (s, 3H, CMe_2), 2.18 (s, 3H, OAc), 4.30 (dd, 1H, J=5.4, 8.6Hz, H-6), 4.44 (dd, 1H, J= 5.6, 8.3Hz, H-1), 4.57 (d, 1H, J=5.4Hz, H-2), 4.64 (dd, 1H, J=4.9Hz, H-5), 4.70 (T, 1H, J=8.6Hz, H-3), 5.21 (dd, 1H, J=8.3,

11.2Hz, H-4); ^{13}C (75 MHz $CDCl_3$): 20.9, 25.9, 26.0, 27.6, 27.7, 69.6, 74.4, 75.0, 75.5, 76.4, 85.6, 110.3, 110.5, 169.9; IR (neat): 2992, 1759, 1414cm^{-1};

Reaction of 1-D-3-*O*-trifluoromethanesulfonyl-4-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol with NaN_3 147: To a solution of **146** (320 mg, 0.85 mmol) in DMF (7.3 mL) under argon at 0 °C was added NaN_3 (0.24 g, 3.65 mmol). This was stirred overnight at ambient temperature. The resulting yellow solution was dried under reduced pressure and filtered through a silica gel plug, hexanes:EOAc (10:1) to give 0.34 g of a white solid.; ^1H NMR: (300MHz $CDCl_3$): 1.34 (s, 3H, CMe_2), 1.37 (s, 3H, CMe_2), 1.46 (s, 3H, CMe_2), 1.59 (s, 3H, CMe_2), 2.18 (s, 3H, OAc), 4.04 (m, 1H, H-6), 4.36 (m, 1H, H-1), 4.46 (d, 1H, *J*= 7.1 Hz, H-5), 4.55 (m, 2H, H-2, H-3), 4.78 (d, 1H *J*= 7.0 Hz, H-4); ^{13}C (75 MHz $CDCl_3$): 21.4, 24.5, 24.8, 26.2, 27.4, 60.2, 72.4, 74.4, 74.7, 76.6, 77.7, 109.6, 110.6, 170.7; IR (neat): 3005, 2115, 1743 cm^{-1}.

Reaction of 147 with H_2: A solution of **147** (100 mg) in MeOH (3 mL) with either Adams catalyst (10 mol%) or Pd/C (10 mol%) was placed in a Fischer-Porter bottle and purged with argon. The solution was then frozen and the bottle evacuated by vacuum. The bottle was then purged to 100 psi, evacuated and refilled with H_2 three times. The reaction was allowed to warm to ambient temperature and was stirred overnight (with pressure rising to 110 psi). The solution was filtered, concentrated and purified by flash chromatography to give 63 mg (0.17 mmol, 68%) of **146**, over two steps **146→147→146**.

1-D-3-*O*-trifluoromethanesulfonyl-4-*O*-methyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 152: To a solution of **81** (223 mg, 0.738 mmol) in pyridine (1 mL) and CH_2Cl_2 (5 mL) under argon at 0 °C was added dropwise Tf_2O (0.2 mL, 1.1 mmol). The solution was stirred at 0 °C overnight. Resulting in a dark red solution, which was concentrated then filtered through a silica gel plug, hexanes:EtOAc (5:1). Purification by flash chromatography hexanes:EtOAc 3:1 (R*f* = 0.65) gave 318 mg (0.723 mmol, 98%) of a white solid, mp (decomposed) 103 °C; ^{1}H NMR: (300MHz $CDCl_3$): δ 1.39 (s, 6H, CMe_2), 1.51 (s, 6H, CMe_2), 1.55 (s, 6H, CMe_2), 3.31 (dd, 1H, *J*=7.5, 11.0Hz, H-4), 3.62 (s, 3H, OMe), 4.28 (T, 1H, *J*=7.6Hz, H-2), 4.37 (dd, 1H, *J*= 6.1, 8.5Hz, H-5), 4.48 (dd, 1H, *J*=2.4, 6.1Hz, H-1), 4.53 (dd, 1H, *J*=2.4, 5.9Hz, H-6), 4.60 (dd, 1H, *J*=8.3, 11.0Hz, H-3); ^{13}C (75 MHz $CDCl_3$): 25.75, 25.77, 27.67, 28.06, 60.75, 74.91, 75.49, 75.55, 79.06, 79.58, 87.30, 109.79, 110.43, 120.86; IR (neat): 2940, 1415, 1375, 1214 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{22}O_8F_3S$ [M+H] 407.0974 found 407.0982.

1-L-2-azido-2-deoxy-1-*O*-methyl-3,4:5,6-di-*O*-isopropylidene-*allo*-inositol 153: To a solution of **152** (888 mg, 2.2 mmol) in DMF (20 mL) under argon at 0 °C was added NaN_3. After stirring for 12 h at ambient temperature the solution was concentrated and filtered through a silica plug, hexanes:EtOAc 10:1 to give 541 mg (1.8 mmol, 82%) of a colourless oil; ^{1}H NMR: (300MHz $CDCl_3$): δ 1.32 (s, 6H, CMe_2), 1.45 (s, 3H, CMe_2), 1.55 (s, 3H, CMe_2), 3.226 (d, 1H, *J*=7.1 Hz, H-4), 3.487 (s, 3H, OMe), 4.10 (m, 1H, H-2), 4.18 (m, 1H, H-5), 4.33 (m, 1H, H-1), 4.39 (m, 1H, H-6), 4.44 (m, 1H, H-3); ^{13}C (75 MHz $CDCl_3$): 24.6, 24.8, 26.3, 27.5, 57.9, 59.9, 75.1, 77.2, 77.5, 78.0, 80.0, 109.6, 110.6; IR (neat): 2988, 2937, 2111 cm^{-1}

1-L-2-amino-2-deoxy-1-*O*-methyl-3,4:5,6-di-*O*-isopropylidene-*allo*-inositol 154: To a solution of **153** (450 mg, 1.50 mmol) in MeOH (10 mL) with either Adams catalyst (10 mol%) or Pd/C (10 mol%) was placed in a Fischer-Porter bottle and purged with argon. The solution was then frozen and the bottle evacuated by vacuum. The bottle was then purged to 100 psi, evacuated and refilled with H_2 three times. The reaction was allowed to warm to ambient temperature and was stirred overnight (with pressure rising to 110 psi). The solution was filtered, concentrated and purified by flash chromatography to give 340 g of a colourless oil (1.26 mmol, 84 %) ^{1}H NMR: (300MHz $CDCl_3$): δ 1.30 (s, 6H, CMe_2), 1.37 (s, 3H, CMe_2), 1.46 (s, 3H, CMe_2), 3.20 (dd, 1H, *J*= 1.95, 5.62 Hz, H-1), 3.43 (s, 3H, OMe), 3.65 (dd, 1H, *J*=1.95, 4.89 Hz, H-6), 4.10 (m, 1H, H-5), 4.23 (m, 1H, H-4), 4.42 (m, 1H, H-3), 4.6 (m, 1H, H-2); ^{13}C (75 MHz $CDCl_3$): 24.5, 24.8, 26.5, 27.6, 49.2, 57.5, 75.1, 77.7, 77.8, 78.1, 78.4, 83.0, 108.8, 109.7; IR (neat): 3396, 2987cm^{-1};

Attempted de-methylation of 154 via $AlCl_3$: To a solution of **154** (121 mg, 0.41 mmol) in MeCN (4 mL) under argon was n-Bu_4NI (1.51 g, 4.1 mmol), $AlCl_3$ (550 mg, 4.1 mmol) and pyridine (0.33 mL). This was stirred for 6 h at ambient temperature before being heated at reflux until streaking on the TLC plate indicated decomposition was occurring. The reaction was quenched by the addition of water (10 mL) and the aqueous layers were extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were successively washed with 10 % Na_2SO_3 solution (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give a dark brown oil from which nothing of value was extracted.

1-D-3-amino-3-deoxy-1,2:3,4:5,6-tri-*O*-isopropylidene-*allo*-inositol 155: To a solution of **154** (540 mg, 1.98 mmol) in anhydrous CH_2Cl_2 (10 mL) was added BBr_3 (10 mL, 1M soln in CH_2Cl_2), this solution was stirred overnight. The resulting dark brown solution was concentrated and dissolved in MeOH and concentrated four times (4x10 mL) to remove most of the boron by-products. The solid was then placed in H_2O and washed with CH_2Cl_2, the organic layer was concentrated to dryness with no product being found. The aqueous layer was freeze dried to give 20 mg of a pale brown solid. This was placed in DMF (1mL), acetone (1.5 mL) and 2,2-dimethoxypropane (1.5 mL) with p-TsOH (40 mg). The mixture was stirred overnight at room temperature under air then neutralized with Et_3N and concentrated. Filtration of the resulting syrup through silica gel using hexanes:EtOAc (1:1) gave 51 mg of the tris-acetonide (0.16 mmol, 8 % from **154**) as a pale brown solid. ^{1}H NMR: (300MHz $CDCl_3$): δ 1.36 (s, 6H, CMe_2), 1.47 (s, 6H, CMe_2), 1.54 (s, 6H, CMe_2), 3.68 (dd, 2H, *J*=2.9, 5.1 Hz, H-3, H-4), 4.40 (m, 4H, H-1, H-2, H-5, H-6); ^{13}C (75 MHz $CDCl_3$): 24.7, 27.3, 27.4, 29.9, 76.7, 78.4, 79.6, 111.1, 113.9; IR (neat): 2922, 2834 cm^{-1};.

1-D-3-*O*-diphenylphosphinoyl-4-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 156: A solution of **44** (130 mg, 0.44 mmol) in THF (4.4 mL) was treated with PPh_3 (171 mg, 0.66 mmol) in THF (1 mL) followed by DEAD (124 mg, 0.66 mmol) in THF (1 mL). This solution was stirred at 0 °C for 30 min then NaN_3 (86 mg, 1.32 mmol) was added and the reaction stirred at ambient temperature overnight. This was placed in Et_2O (10 mL) and washed with $NaHCO_{3\,(aq)}$ (5 mL) and brine (3x 10 mL), the organic layer was dried over $MgSO_4$ and concentrated. Purification by flash chromatography hexanes:EtOAc 10:1 (Rf = 0.32) gave 88 mg (0.18 mmol, 42%) of a colourless oil; ^{1}H NMR: (300MHz $CDCl_3$): δ 1.36 (s, 6H, CMe_2), 1.56 (s, 6H, CMe_2),

1.91 (s, 3H, OAc), 4.35 (m, 2H, H-1, H-6), 4.59 (m, 3H, H-2, H-5), 5.21 (m, 1H, H-4), 7.28 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$): 21.1, 26.0, 27.7, 27.8, 71.0, 74.8, 74.9, 76.5, 77.1, 78.7, 109.0, 110.0, 120.3, 125.9, 130.1, 170.5; IR (neat): 2987, 1753, 1487 cm^{-1};.

1-D-3-*O*-diphenylphosphoryl-4-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol 157: To a solution of **44** (275 mg, 0.91mmol) in toluene (2 mL) under argon at 0 °C was added diphenylphosphorazide (0.3 mL, 1.1 mmol) and DBU (0.2 mL, 1.09 mmol). The solution was heated to reflux overnight. The solution was washed with H_2O (10 mL) and 5% HCL (10 mL), the organic layer was dried over $MgSO_4$ and concentrated. Purification by flash chromatography hexanes:EtOAc 10:1 (R*f* = 0.24) gave 146 mg (0.27 mmol, 30%) of a colourless oil; ^1H NMR:(300MHz $CDCl_3$):δ 1.34 (s, 3H, CMe_2), 1.36 (s, 3H, CMe_2), 1.48 (s, H, CMe_2), 1.53 (s, 3H, CMe_2), 1.91 (s, 3H, OAc), 4.3 (dd, 1H, *J*=5.4, 8.3 Hz, H-1), 4.37 (dd, 1H, *J*= 5.4, 8.3 Hz, H-6), 4.54 (m, 2H, H-2, H-5), 4.63 (m, 1H, H-4), 5.19 (dd, 1H, *J*=8.5, 11.4Hz, H-3), 7.27 (m, 10H, Ph); ^{13}C (75 MHz $CDCl_3$): 21.0, 26.0, 27.7, 27.8, 70.9, 74.8, 75.0, 76.5, 77.1, 78.7, 110.0, 120.3, 120.4, 125.4, 129.7, 130.1, 170.5; IR (neat): 2987, 1753, 1590, 1488cm^{-1}.

Attempted use of 154 as a chiral ligand: A solution of **154** (0.30 g, 1.1 mmol) was placed in toluene (1.5 mL) under argon and cooled to 0 °C, Et_2Zn (1.2 mL, 1.2 mmol) was added this was stirred at 0 °C for 30 min, benzaldehyde (0.12 mL, 1.2 mmol) and warmed to ambient temperature. The reaction was monitored by both TLC and ^{1}HNMR with no reaction being observed.

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