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Recoverable Ligands for the Sharpless Asymmetric Epoxidation

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By

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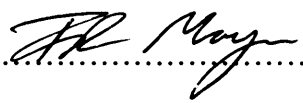
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Serendipity/luck.......

Discovery/accident......

The genius/intelligence is when these are noticed

And their significance appreciated......

William S. Knowles,

Ryoji Noyori and

K. B. Sharpless, 2001.

Abstract

The aim of this work was to synthesise a polymer supported ligand for the Sharpless Asymmetric Epoxidation, which could be recovered with ease and then reused without significant reduction in the enantiomeric excess in the epoxy-alcohol product. A *bis*-dihydroxy ester model system was synthesised that featured the removal of the "redundant esters" as present in the tartrate system and successful epoxidations led to this system being incorporated into a polymer supported ligand. A polymer supported system was synthesised but the showed low selectivity in asymmetric epoxidations. The model system was further investigated and it yielded highly selective ligands for the Sharpless Asymmetric epoxidations and in optimal cases was directly comparable to the Sharpless tartrate system. After practical obstacles had been overcome, a ligand was formulated that could be recovered post-epoxidation in good yield by relatively simple solvent manipulations. This recovered ligand could then be re-used without significant loss in enantioselectivity and represented the synthesis of a recoverable ligand for the Sharpless asymmetric epoxidation, a leader in the field. The ligand was further tested in the kinetic resolutions of secondary allylic alcohols and this novel ligand system equalled the tartrate system and in optimal cases the enantiomeric excess of the secondary allylic alcohols were higher than the tartrate system.

Serendipitously, the most tested ligand in the asymmetric epoxidations performed the phenomena of gelation, the spontaneous self organisation of the ligand/gelator solution, forming a supramolecular molecular structure that exhibited no flow, a gel. Derivatives of this "gelator" were synthesised in the search for further examples and in order to determine the origin of this phenomenon. Further gelators were discovered and these all contained a distinct functional similarity to the original discovery and these gelators were capable of gelling a wide range of solvents. The apparent gel-forming functionality was incorporated into a *bis*-acetylene moiety in an attempt to create a conducting material and this *bis*-acetylene was subsequently polymerised to form a coloured gel containing the poly(eneyne) moiety.

Acknowledgements

Abbreviations

Abbreviations used in this text:

AD	Asymmetric Dihydroxylation
AE	Asymmetric Epoxidation
^{i}Am	*iso*-Amyl
APCI	Atmospheric Pressure Chemical Ionisation
^{i}Bu	*iso*-Butyl
^{t}Bu	*tert*-Butyl
bp	Boiling point
15-c-5	15-crown-5
CC	Column Chromatography using silica gel
CHP	Cumene hydroperoxide
CI	Chemical Ionisation
Cy	Cyclohexyl
DCM	Dichloromethane
DET	Diethyl tartrate
DMF	Dimethylformamide
DMT	Dimethyl tartrate
DIPT	Diisopropyl tartrate
ee(s)	Enantiomeric excess(es)
EI	Electron Ionisation
eq	Equivalents
ES	Electrospray Ionisation
FTIR	Fourier Transform Infra-Red
GC	Gas Chromatography
h	Hours
HPLC	High Pressure Liquid Chromatography
KR	Kinetic Resolution
LMOG	Low Molecular Mass Organogelator
M	Molar (moles L^{-1})
MeCN	Acetonitrile
MeI	Methyl Iodide

mins	Minutes
mp	Melting Point
MPEG	Poly(ethylene glycol) monomethyl ether
ms	Mass Spectrometry
NaH	Sodium Hydride
NaIO$_4$	Sodium metaperiodate
NMR	Nuclear Magnetic Resonance
o/n	Over Night
PEG	Poly(ethylene glycol)
^{i}Pr	*iso*-Propyl
Rf	Relative front
RT	Room Temperature
SAE	Sharpless Asymmetric Epoxidation
SiO$_2$	Silica gel
TBAF	Tetrabutyl ammonium fluoride
TBAI	Tetrabutyl ammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TBDMS	*tert*-Butyldimethylsilyl
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid
pTSA	*para*-Toluenesulphonic acid

To my parents, without their encouragement
And financial contributions,
This work would not have been possible.

Contents

Chapter 1

Introduction to the Sharpless Asymmetric Epoxidation Methodology.

Introduction

The word chiral comes from the Greek word *cheir*, which means hand. Our hands are chiral, our right hand is a mirror image of our left hand and therfore our hands are non-superimposable but otherwise identical. Therefore, the definition of chirality is when two molecules are related by object and mirror image, that is they are identical chemically and physically but they cannot be superimposed. The Dutch chemist J. H. van't Hoff and the French chemist J. A. Le Bel, independently of each other in 1874, discovered that when the four substituents of a tetrahedrally arranged carbon atom are different, an effect known as "chirality" arises due to this asymmetric arrangement of groups around the central carbon atom.

It is often necessary to obtain pure enantiomers of a given substrate, especially in the field of pharmaceuticals and pest controlling substances (*e.g.* pheromones). When the "effecting" chemical elicits its influence by an interaction with a biological system, such as an enzyme, which is a large pool of chirality, only one enantiomer exerts the desired effect and the other could exert an undesired effect, (*e.g.* thalidomide). The chiral pool of nature provides a number of optically pure compounds, which supply starting materials for product or reagent synthesis. Nevertheless, some natural products are not easily isolated or are not available in useful quantities, for example anti-cancer compounds are isolated in milligram quantities from biological sources such as sea sponges. Such compounds can show phenomenal biological activity and warrant synthesis which, in turn, requires the use of optically pure reagents.

Separation of enantiomers is always an option but resolution of a racemate immediately reduces the yield to at most 50%. Such separations can be achieved by diastereoisomer formation and fractional crystallisation or chromatography. However, if the compound in question has many stereogenic centres, the number of possible stereoisomers can be immense (2^n). Therefore, it is significantly more elegant and economical to prepare the single enantiomer needed with efficient asymmetric reactions and Table 1.1 highlights the fundamental methods for obtaining single enantiomers.

Table 1.1: Methods for obtaining single enantiomers.

Method	Resolution	Chiral Pool	Chiral Auxiliary	Chiral reagent	Asymmetric Catalyst
Advantage	Both enantiomers usually available.	Usually 100 % ee guaranteed.	Often excellent de can recrystallise to purify to high de.	Often excellent ee, can recrystallise to achieve high ee.	Economical; only small amounts of potentially recyclable material used. Very high ee obtainable.
Disadvantage	Max 50 % yield, only one enantiomer may be needed.	Often only 1 enantiomer available.	Extra steps to introduce and remove auxiliary.	Only few reagents are successful and often for few substances.	Only a few reactions are successful.

During the past few decades, there has been intensive research into developing methods for the synthesis of one enantiomer rather than the other, asymmetric synthesis:

"Asymmetric synthesis: A traditional term used for stereoselective synthesis of chiral compounds". [1]

In an asymmetric synthesis prochiral starting molecules (substrate molecules) are used to synthesise new chiral molecules (products) by means of various asymmetric chemical reactions.[2] Synthesis of optically pure organic compounds is a challenging task for chemists, for which reason the use of catalysts is very important: By definition, a catalyst is a substance that increases the rate of a reaction by providing an alternative reaction profile with lower activation energy, without being consumed itself. There are only a limited number of synthetic procedures that allow the transformation of a prochiral substrate into an optically pure substrate. In 2001, K.Barry Sharpless was jointly awarded the Nobel Prize for such work: The Sharpless asymmetric epoxidation, SAE and the Sharpless Asymmetric Dihydroxylation, AD, both of which are capable of yielding products in exceedingly good enantiomeric excesses.[3,4] Enantiomerically pure epoxides are essential synthetic intermediates in organic syntheses, the associated ring strain of the epoxide heterocycle (*ca.* 114 kJ mol^{-1}) making the moiety reactive and accessible to a wide variety of usually nucleophilic reagents. Many products can be obtained from such reactions with epoxides and any high enantiopurity of these is transferred into the products. Epoxides thus constitute electrophilic chiral building blocks with an "unnatural" 1,2-functional group relationship. Additionally, elimination processes on small rings can be stereoelectronically disfavoured in some situations, thereby rendering epoxides more useful than their acyclic equivalents. Thus, the use of enantiomerically pure epoxides is an efficient way of introducing asymmetry into a target molecule. The following illustration (Scheme 1.1) shows the some of the synthetic transformations of an epoxide:
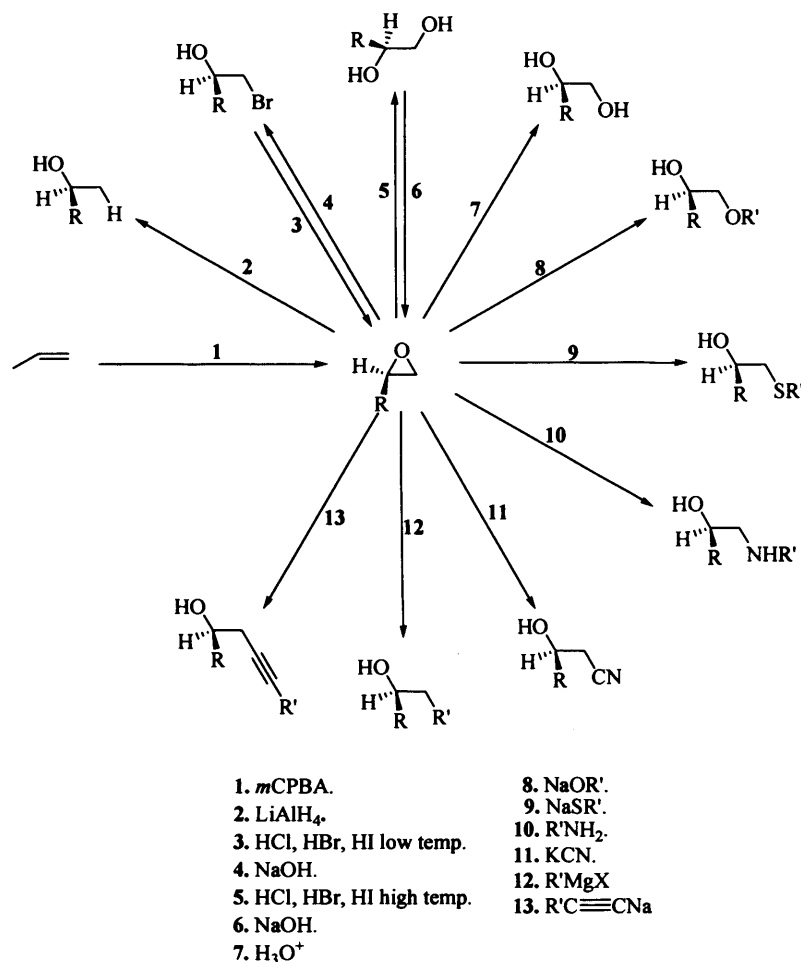
Scheme 1.1: Synthetic transformations of an epoxide.

1. *m*CPBA.
2. LiAlH₄.
3. HCl, HBr, HI low temp.
4. NaOH.
5. HCl, HBr, HI high temp.
6. NaOH.
7. H₃O⁺

8. NaOR'.
9. NaSR'.
10. R'NH₂.
11. KCN.
12. R'MgX
13. R'C≡CNa

There are only a handful of ways in which enantiopure epoxides can be synthesised. A little known method is Schurig's oxidative kinetic resolution of racemic epoxides.[5] This catalytic method utilises a chiral molybdenum-(VI)-(oxodiperoxo)hydroxyl-acid/amide/diol catalyst with oxygen as the re-oxidant and affects the kinetic resolution (KR) of certain *trans*-disubstituted epoxides (Scheme 1.2). This reaction is of great interest given, the limited alternative methods that currently exist for accessing these epoxides with this substitution pattern in enantiopure form.
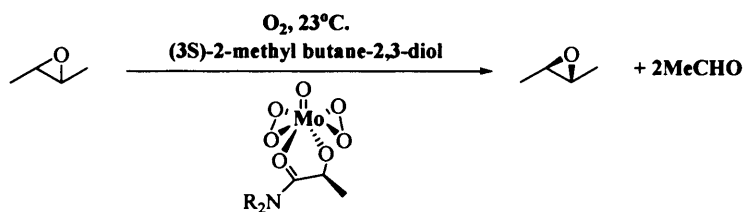
Scheme 1.2: Schurig kinetic resolution.

The Shi epoxidation has a wider synthetic utility, as it is useful for the epoxidation of terminal, *trans*-disubstituted, trisubstituted, conjugated *cis*-disubstituted olefins and styrenes (Scheme 1.3).[6] The oxidant is a chiral dioxirane intermediate which stereoselectivly epoxidises the olefin, *via* a spiro-transition state.[7,8]
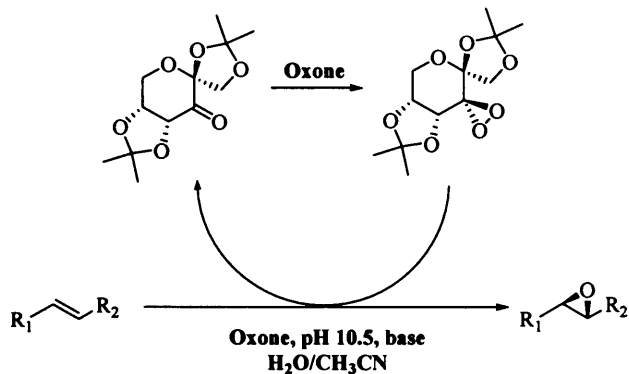
Scheme 1.3: Example of Shi Epoxidation.

In 1980,[3] K.B. Sharpless published an initial report of the titanium/tartrate-catalysed asymmetric epoxidation which will be discussed later. Sharpless has also been the pioneer of another asymmetric reaction, the Sharpless Asymmetric Dihydroxylation or AD reaction. This has been thoroughly investigated and an excellent review has been written which includes some very smart chemistry.[9] This represents an excellent example of how, with a little imagination, a seemingly and relatively simple transformation, (here alkene *bis*-hydroxylation) can have a major impact on synthetic design in general. An example of the application of the Sharpless AD is in the synthesis of 1,2-cyclic sulphates, (Scheme 1.4).
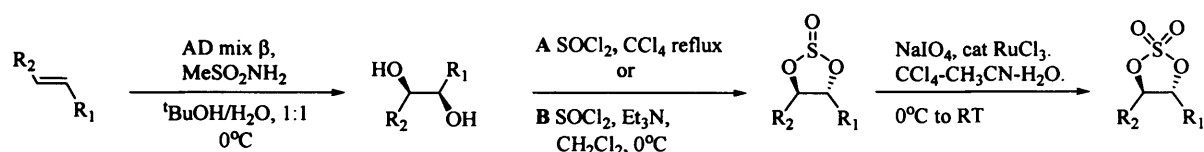
Scheme 1.4: Cyclic sulphate synthesis.

Many of the beneficial properties of epoxides are shared by cyclic sulphates and sulphites, with the often useful distinction that cyclic sulphates are more reactive than the commoner epoxides. Consequently, these compounds can be regarded as synthetic equivalents of epoxides, (Scheme 1.5).[10,11,12]
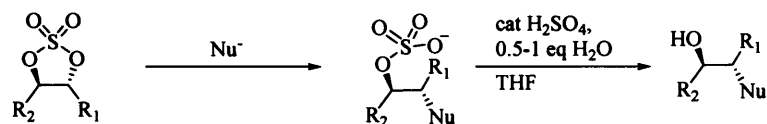
Scheme 1.5: Nucleophilic opening of a cyclic sulphate.

A further application of the AD is in the synthesis of epoxides. Regioselective arenesulphonation of a 1,2-diol and subsequent elimination leads to the epoxide and an arenesulphonic acid (Scheme 1.6).
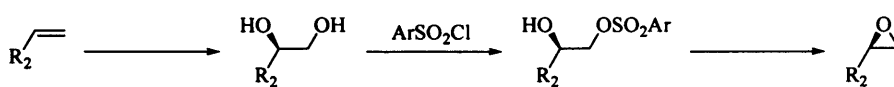
Scheme 1.6: Epoxide formation from a 1,2-diol.

In order for the above strategy to be successful, it is important to realise that a high selectivity in the initial sulphonation step is required, since the cyclisation of the regioisomeric sulphonates **1**, **2** leads to opposite enantiomers, **3**, **4** and consequently a loss in optical purity:
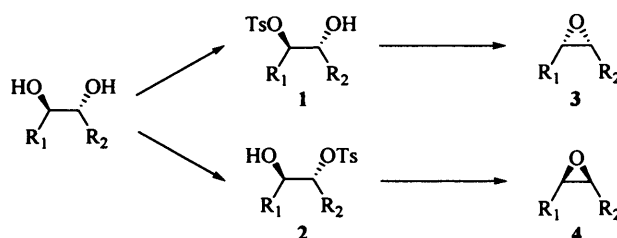
A high yielding and convenient 'one-pot' method for the stereospecific conversion of 1,2-diols into epoxides superseded the previous method, (Scheme 1.7).[13] This process is based on the acetoxonium ion-mediated formation of acetate esters of halohydrins and proceeds with inversion at the halide receiving stereocentre. Subsequent ester saponification and cyclisation with a second inversion at the halide centre gives the epoxide. Thus, the transformation results in overall retention of configuration and therefore the regioselectivity of the initial acetoxy halide formation is inconsequential, *cf.* regioselectivity in arenesulphonation. Therefore, the foregoing method has a distinct advantage over the sulphonation route when applied to 1,2-disubstituted diols.
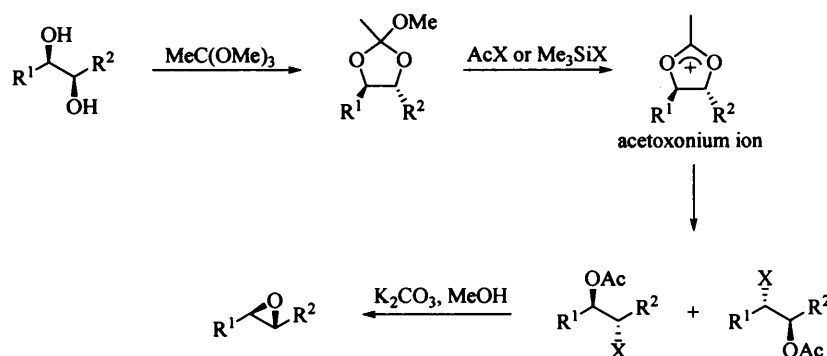
Scheme 1.7: One pot epoxide synthesis

One can never forget that Nature, the mother of asymmetric synthesis, provides us with many tools for synthesis. Enzymatic resolution of terminal epoxides is also possible with epoxide hydrolase enzymes such as *Aspergillus niger* epoxide hydrolase with the Furstoss group leading the way in such investigations.[14] Furstoss and Archelas dub their epoxide hydrolases "new enzymes," due to chemists now finding them increasingly in micro-organisms, whereas until recently, knowledge of them was limited to mammalian sources. The availability of such a hydrolase from *Aspergillus niger* means that the gene can be cloned and over expressed for production in commercial amounts. An example of its utilisation is the kinetic resolution of racemic 2-(2-pyridyl)oxirane **6**, synthesised by epoxidation of 2-vinylpyridine **5**. Subsequent resolution resulted in a 43% yield (of a possible 50%) of the (*S*)-epoxide **7** in greater than 97% ee and a 43% yield of diol **8** with 62% ee (Scheme 1.8). The enantiomeric excess of either the epoxide or diol can be optimised by running the reaction short of, or past the 50% mark.
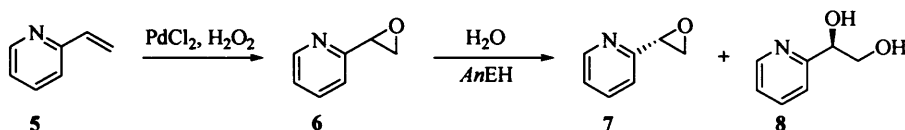
Scheme 1.8

In 1990, Jacobsen reported that manganese complexes of chiral Schiff bases (*e.g.* **9**) catalysed the epoxidation of alkyl- and aryl-substituted olefins with the highest enantioselectivities at the time for a non-enzymatic catalyst.[15]

9
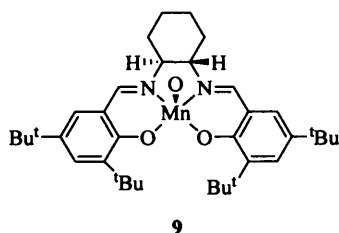
The Jacobsen catalysts are highly selective for the epoxidation of *cis*-disubstituted olefins but *trans*-disubstituted olefins react more slowly and with diminished selectivity, juxtaposed to the SAE where the opposite selectivity is the case.[16] As these methodologies have evolved further, the catalysts have been tuned to encompass a wider range of substrates. Given the correct choice of catalyst, tri- and tetra-substituted olefins can also be epoxidised with high enantioselectivities and yields. The selectivity of the epoxidations is determined through non-bonded interactions and the observed selectivities are explained by a side-on approach of the olefin. The exact mechanism of the oxygen transfer is still a point of contention.

The Jacobsen catalysts are also amenable to mediation of kinetic resolution; racemic epoxides can be selectively hydrolysed and this is commonly referred to as the Jacobsen hydrolytic kinetic resolution (HKR), (Scheme 1.9). Racemic epichlorohydrin **11**, a highly versatile C-3 building block, can be resolved using the cobalt-salen catalyst **10** with excellent selectivity and in good yield.[17] A further advantage of this process is that both products are exceptionally useful in general synthesis.

11	(R,R)-**10**, 2 mol %	**12**	**13**	**10**
0.50 eq H$_2$O, 4°C		96% ee, 44% y	96% ee, 50% y	
0.55 eq H$_2$O, 4°C		>99% ee, 42% y	89% ee, 52% y	
0.30 eq H$_2$O, -10°C		63% ee	98.7% ee, 27% y	
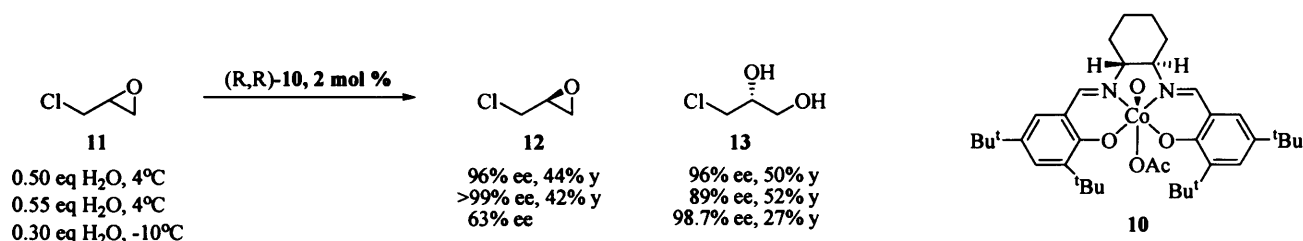
Scheme 1.9: Jacobsen HKR

From its discovery in 1980, the Sharpless asymmetric epoxidation (SAE), although only twenty five years old, represents a truly classical reaction and as the research performed over the duration of my PhD is based on these methodologies, the topic requires a thorough review.

It is important to note that the high selectivity observed in the SAE is restricted to allylic alcohols but nonetheless, this orthogonal epoxidation is also an advantage, as other olefins will be unaffected (Scheme 1.10).

The tartrate esters [C_2 symmetric 1,2-diols, dialkyl (D)- or (L)-tartrates] provide the source of chirality in the reaction, indeed the first reported reaction had an optical induction >90% ee.

Prior to this, the best method of induction gave 80% ee using a vanadium catalyst bearing a proline derivative as the chiral ligand.[19] Therefore, in the SAE, the high optical purity of the tartrate esters is transformed, *via* a transition state, into the final product with great selectivity. Optically pure epoxy-alcohols are also very useful chiral building blocks and shown below is an illustration of many possible transformations:

Synthetic transformations of 2,3-epoxy-alcohols.

An intriguing aspect of the SAE is that the epoxidation system is more selective toward (*E*)-olefins. (*Z*)-Olefins are epoxidised with lower enantioselctivities (*ca.* 5-10 % lower ee for aliphatic disubstituted olefins) supposedly arising from the structure of the catalyst, an aspect that will be discussed later. Homoallylic alcohols are epoxidised with even lower enantioselectivities with some of the more successful substrates only giving enantiomeric excesses in the region of 50 %.[20]

The synthesis of 2,3-epoxy alcohols is commonly achieved using L-(+) and D-(-)-DET/DIPT/DMT, titanium(IV) tetraisopropoxide and *t*-butyl hydroperoxide (oxidant) as shown in Scheme 1.10.

Scheme 1.10: Sharpless asymmetric epoxidation mnemonic.

An attractive aspect of this system is that the necessary components are all commercially available at low to moderate cost. The epoxidation system possesses two especially striking features: uniformly high asymmetric inductions throughout a range of substitution patterns in allylic alcohols and an apparent obligation (no exception known) to deliver the oxidant to the same enantioface of the olefin regardless of the substitution pattern, upon use of a given tartrate enantiomer, as represented in Scheme 1.10.

The same epoxidation system is also amenable to kinetic resolution experiments. A wide variety of racemic allylic alcohols can be resolved into a single enantiomer of the allylic alcohol and the corresponding 2,3-epoxyalcohol.[18] To obtain good resolution one requires a relative epoxidation rate difference greater than 5-10 (k_{rel} > 5-10), an example of which being the epoxidation of (*E*)-1-cyclohexylbut-2-en-1-ol **14**, shown below (Scheme 1.11). A further insight from the studies is that a relative rate difference of only 100 is nearly as effective as a relative rate difference of infinity.
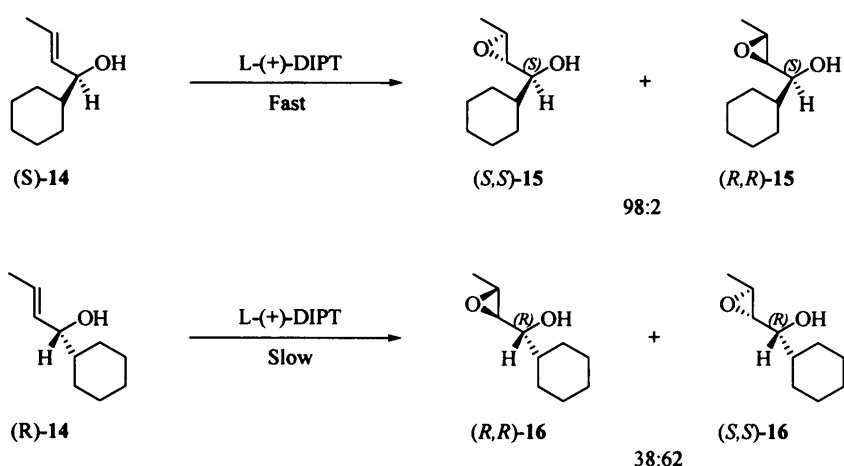
Scheme 1.11: Kinetic resolution using SAE.

The occurrence of kinetic resolution can be explained simplistically by the use of the concept of matched and mis-matched pairs. From Scheme 1.11; a matched pair is demonstrated by (*S*)-14

and the catalyst derived from (L)-DIPT, as this allylic alcohol epoxidises at a fast rate consuming the (S)-**14** enantiomer. On the other hand, a mis-matched pair is demonstrated by (R)-**14** and the catalyst derived from (L)-DIPT resulting in very slow epoxidation of this enantiomer. Effectively, the result of these matched and mis-matched pairs is that the (S)-**14** enantiomer is consumed whilst the (R)-**14** enantiomer remains, resulting in the phenomenon that is kinetic resolution.

In the example above, the kinetic resolution studies revealed that the titanium alkoxide/(L)-tartrate catalyst strongly favours the formation of (S,S)-**15**.[18] Note that with (E)-1-cyclohexylbut-2-en-1-ol **14**, the two effects (the preference for α attack and formation of (S,S)-**15**) are consonant for the (S)-enantiomer but are dissonant for the (R)-enantiomer [formation of (R,R)-**16**]. Using (L)-DIPT, experimentally, the (S)-enantiomer is observed to react 104 times faster than the (R)-enantiomer, however the (R)-enantiomer preferentially gives the (S,S) product. The preference for α attack in this case is marginally favoured over the tendency toward forming the (R,R)-**16**. Subsequent studies showed that the degree of selectivity in the kinetic resolution experiments increased in the order DMT<DET<DIPT. Reactions using more sterically demanding tartrate analogues DCHT (dicyclohexyl tartrate) and DCDT (dicyclododecyl tartrate) resulted in a further increase in selectivity.[22]

In the original report,[3] the general procedure called for a stoichiometric amount of the titanium tartrate catalyst unless substrates were highly reactive. This meant that post-epoxidation, the tartrate and titanium species (derived from catalyst destruction) were present in stoichiometric quantities and complicated purification procedures, which could even cause unwanted side reactions such as epoxide ring opening. One of the most common methods employed to remove the excess tartrate was the addition of 1M sodium hydroxide saturated with brine; this hydrolysed the reactive tartrate esters so that they could be removed by standard aqueous extraction techniques. Nonetheless, the large quantities of base required would still reduce yields due to unwanted side reactions such as the Payne rearrangement.

A general method for the catalytic procedure was published in 1986, the key modification being the addition of activated 3Å or 4Å molecular sieves to the reaction.[21] The sieves simply scavenge any adventitious water present in the reaction that would otherwise destroy the catalyst; further discussions can be found in the Results and Discussion section. The advantages of this modification included economy, mildness of conditions, ease of isolation, increased yields and the potential for *in situ* derivatisation of the product. In the absence of molecular sieves, employing sub-stoichiometric amounts of the catalyst (10 mol%) yields products with low optical purity and the reaction stops after 50-60 % conversion. In contrast, the catalytic procedure enables the reaction to be carried out with only 5-10 mol % of titanium alkoxide in the

best cases, furnishing the product with high enantioselectivity at rates comparable to the stoichiometric system. Another advantage of the catalytic system is that the upper concentration limit can be raised to 0.5 M-1.0 M, as opposed to the stoichiometric reaction where substrate concentrations must be kept relatively low (0.1 M-0.3 M) in order to avoid side reactions (such as epoxide opening), due to the large amount of titanium tartrate species and isopropyl alcohol [from Ti(O^{i}Pr)$_4$] present in solution. The catalytic procedure is also amenable to kinetic resolution experiments.[22]

The question remains: how does such a selective process occur? Considering the nature of titanium alkoxide systems in general, they have several properties crucial to the success of the SAE reaction: exchange of monodentate alkoxide ligands is rapid in solution; the titanium(IV) participates in four covalent bonds, which is exactly the number required for this reaction (two for the divalent chiral auxiliary, tartrate and one each for the TBHP and the allylic alcohol); d^0 Alkoxide systems display a range of coordination numbers and geometries hence their chemistry is presumed to be flexible and, finally, titanium(IV) alkoxides are weak Lewis acids and thus serve to activate a coordinated alkyl peroxide toward nucleophilic attack by the olefin of the bound allylic alcohol. Obviously other d^0 transition metals posses the same propensities, but they fail to give high enantiomeric excess when used with tartrate and TBHP in the standard fashion. Therefore, Ti(IV) possesses a unique confluence of properties that permits the formation of an effective catalyst structure with tartrate and:

"allows the reactants to interact efficiently in compliance with what we believe are strict molecular orbital requirements" K. B. Sharpless.[22]

The active catalyst is achieved when equimolar amounts of titanium tetra-alkoxide (usually titanium tetraisopropoxide) and a single isomer of tartrate [*e.g.* (L)- or (D)-diethyl tartrate] release two equivalents of alcohol into solution forming a dominant species of stoichiometry [Ti(OR)$_2$(tartrate)]$_x$.[24] Scheme 1.12 illustrates these mechanistic aspects of the SAE.

$$\text{Ti(OR)}_4 + \text{tartrate} \xrightarrow{\;-2\text{ROH}\;} \underset{17}{[\text{Ti(OR)}_2(\text{tartrate})]} \;\underset{\text{ROH}}{\overset{\text{TBHP}}{\rightleftharpoons}}\; [\text{Ti(OR)(tartrate)(OO}^t\text{Bu)]}$$

AOH = allylic alcohol
OA = allylic alkoxide
OE = epoxy alcohol

K_1

$\text{ROH} \;\Vert\; \text{AOH} \quad \text{K}_2{}'$

$\text{K}_2 \quad \text{AOH} \;\Vert\; \text{ROH}$

$\text{K}_1{}'$

$$[\text{Ti(tartrate)(OA)(OR)}] \;\underset{\text{ROH}}{\overset{\text{TBHP}}{\rightleftharpoons}}\; \underset{18}{[\text{Ti(OA)(tartrate)(OO}^t\text{Bu)]}}$$

oxygen transfer $\;\Big|\; \text{k}_e$

$$\underset{19}{[\text{Ti(OE)(tartrate)(O}^t\text{Bu)]}}$$

Scheme 1.12: Ligand exchange pathway in SAE.

After formation of the titanium tartrate complex **17**, the two remaining alkoxides are replaced in reversible exchange reactions with TBHP and the allylic alcohol to give the "loaded" complex **18**. The reaction is independent of which of the two pathways is used to reach complex **18**. Oxygen transfer can then occur to give the coordinated epoxy alkoxide and *t*-butoxide in complex **19**. These product alkoxides re-equilibrate with more allylic alcohol and TBHP to regenerate **18** and complete the catalytic cycle. Thus, the inverse squared relationship between the rate and the inhibitor alcohol (equation 1) is due to the necessary replacement of the two alkoxide ligands in the initial complex **17** with hydroperoxide and the allylic alcohol.

A mechanism in which transesterification of the tartrate with the allylic alcohol, followed by the epoxidation of the allyl tartrate, was excluded by the observation that the geranyl diester of (+)-tartaric acid was epoxidised much more slowly itself in the presence of diethyl tartrate under otherwise identical conditions. Furthermore, geraniol was not released from the tartrate by transesterification, as would be required in this alternative mechanism.

In full accord with Scheme 1.12, the experimental rate equation was determined under pseudo-first order conditions to be given as:

$$rate = \frac{k[TBHP][Ti(OR)_2\,(tartrate)][allylic.alcohol]}{[inhib.alcohol]^2}$$

Equation 1.

The above rate expression has been found to apply to several different substrates and tartrate esters and extends over a 10 fold concentration range in the Ti-DIPT complex.[24] Note that the observed rate constant k is actually the product of the rate of epoxidation k_e and the equilibrium constants K_1 and K_2 (or K_1' and K_2'). To the extent that $K_1K_2 = 1$, the observed reaction rate is approximately equal to the rate of oxygen transfer k_e.

During early investigations into the structure of the catalytic species, it was found that the Ti-tartrate species existed as a dimer in solution (deduced by differential vapour phase osometry and Rayleigh light scattering).[23] Indeed, the electron impact mass spectrum was in full accord with a dimeric structure and gave no evidence for either monomer or any species larger than a dimer. It has been concluded that within the typical concentration range (0.34 M- 4.4 M), the Ti-tartrate catalyst does not undergo a change in molecularity, nevertheless the catalyst structure remained unclear due to the highly fluxional nature and high reactivity of the complex complicating structure elucidation. An X-ray crystal structure of a complex of tartaric acid and vanadium(IV), [(VO)$_2$(tart)$_2$], found by Tapscott and coworkers,[25,26] was used as a model for the SAE catalyst structure due to latter's IR and NMR (^{13}C and ^{1}H) spectra being consistent with the vanadium-tartrate structure. The Ti-tartrate showed both free (1738 cm^{-1}) and co-ordinated (1635 cm^{-1}) carbonyl stretching bands leading to the publication of the dimer structure **17a** for the unloaded structure (comparative proton and carbon-13 NMR spectra of a number of complexes with chiral 1,2-diols supported this assignment). It can be clearly seen that the Ti centres possesses penta-coordinate geometry and are in accordance to the available NMR and IR data and with the crystal structures of various tartrate transition metal complexes. A mechanism was proposed in order to satisfactorily account for the remarkable enantioselectivity shown.[27,28]


17a
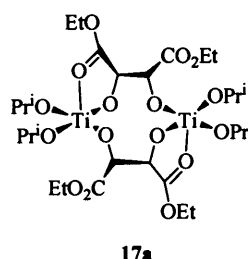
Postulating that the titanium-tartrate structure **17a** would resemble vanadium-tartrate proved to be of false logic however as, in 1984, Sharpless and co-workers, no doubt after many attempts, resolved X-ray crystal structures for two titanium-tartrate complexes **20, 21** and thus proving the previously published structure to be erroneous (Scheme 1.13).[29]

R = Pr^i
X = NCH$_2$Ph

20

R = Et

21
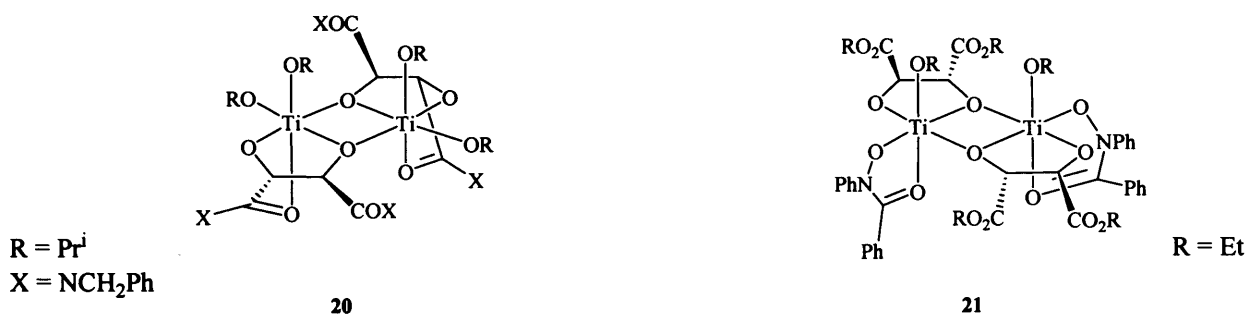
Scheme 1.13: Hexacoordinate titanium-tartrate.

To assume that the pre-loaded catalyst structure had the same structure in the solid state as well as the solution phase is also not necessarily prudent. Therefore, one could still argue that in the solution phase, the pre-loaded catalyst structure is different; this aspect will be discussed later. Evidence of the dimeric nature of the above tartrate-derived complexes in solution was further provided by the use of the Signer method for molecular mass determination in the solution phase.[29]

Upon addition of the titanium tetraisopropoxide and tartrate ester, alkoxide exchange occurs resulting in the liberation of two molecules of isopropanol per titanium centre, forming the pre-loaded binuclear complex **22** (Scheme 1.14). This complex is highly fluxional, hence the reaction is run at -20°C to reduce such fluxional effects and any associated loss in enantioselectivity.


Allylic alcohol
TBHP

R = Pr^i
X = OR

22

R = Pr^i

24

X = OR

+2 ROH

23
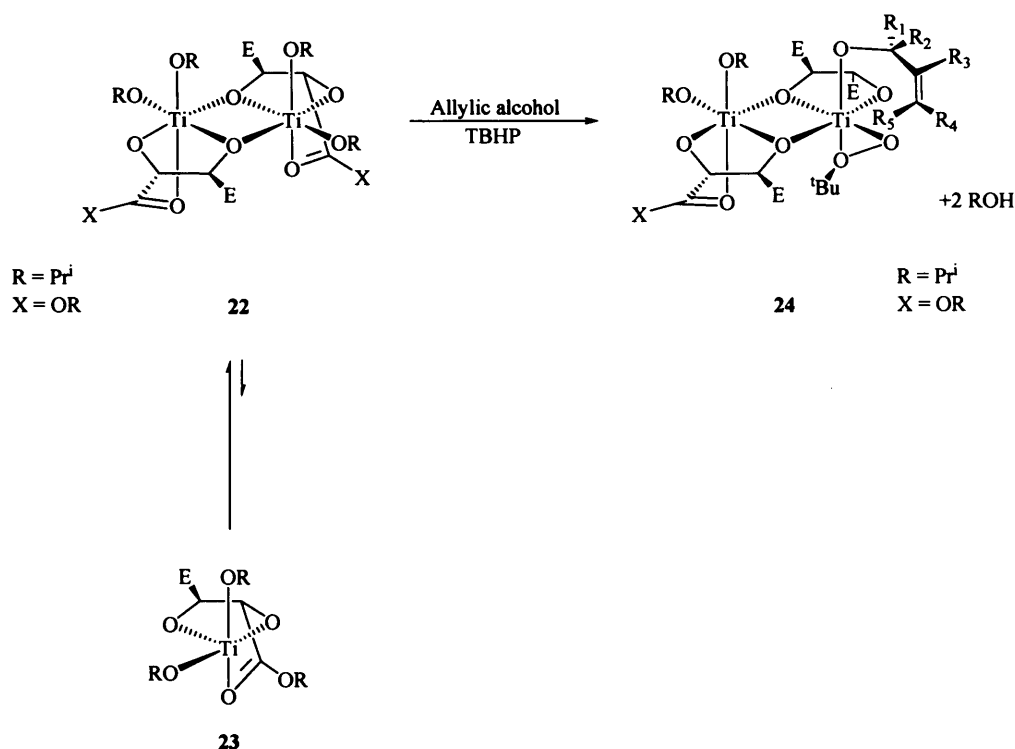
Scheme 1.14

The two monodentate isopropoxide ligands on each titanium atom in structure **22** occupy axial and equatorial ligand sites. The replacement of these non-reactive ligands by the epoxidation reactants can place either the allylic alkoxide or the alkyl peroxide in an axial position.[31] Sterically encumbered hydroperoxides are necessary, since non-bulky hydroperoxides do not mediate high levels of enantioselective epoxidation. Since the alkyl peroxide is thought to bind in a bidentate fashion (as in the ground state vanadium-TBHP complex), a great deal of space is required at the alkyl peroxide ligand site. Space filling molecular models indicates that O^1 of the alkyl peroxide [$^tBu-O^2-O^1-Ti$] should occupy the equatorial position for this requirement to be satisfied. The ground state complex **22** has one carbonyl per tartrate bound to a metal and is in a state of flux such that there exists dynamic equilibria between all of the components and a monomeric species **23**. Addition of the allylic alcohol and TBHP results in further alkoxide exchange and the formation of the active catalyst **24**. It is believed that for both steric and electronic reasons, the bound carbonyl is released from the metal centre in the transition state. As a consequence, the model assumes a six coordinate arrangement of ligands about the reactive titanium atom in the transition state.

Allyl alcohol is epoxidised in 95 % ee at -20°C representing a value of 1.83 Kcal mol^{-1} for the difference in energies of the two possible diastereomeric transition states. Placing alkyl groups at four of the possible five positions of the allyl alcohol results in little or no loss in enantioselectivity; this suggests that allylic alcohol is subject to a set of enantioselective interactions that are not substantially perturbed by substitution on the carbon skeleton. This strongly suggests that at least some of these controlling interactions cannot be steric in nature.

Identification of this putative stereoelectronic effect was an important goal in the mechanistic investigation. A simple geometric difference may be responsible: the required S_N2-type approach of olefin to peroxide can be reached more easily by the allylic alkoxide conformation wherein the transfer of oxygen proceeds *via* a *spiro*-transition state rather than a planar one (Scheme 1.15). The enantioselectivity can only be rationalised when this *spiro*-transition state is considered.

spiro   planar
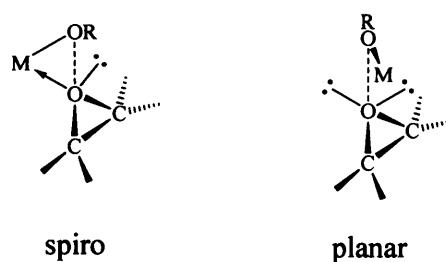
Scheme 1.15: Oxygen transfer.

Yet another simple and attractive suggestion was put forward by Eschenmoser, based on the reasonable assumption that the initial product of oxygen transfer is an epoxy-alkoxide with the epoxide oxygen atom bound to titanium in a dative fashion (Scheme 1.16). Oxygen transfer from a *spiro*-geometry yields a lone pair already directed toward the titanium atom, perfectly disposed for dative coordination. The direct product of the planar orientation involves a titanium atom that lies well away from the epoxide oxygen lone pairs, so that the incipient epoxy alkoxide moiety can only be envisioned as bound to the metal in a badly distorted fashion, thus disfavouring such a planar transition state. To the extent that the transition state resembles the bound epoxy-alkoxide product, this difference provides a compelling rationale for oxygen transfer through a *spiro*-geometry in the metal-catalysed case.
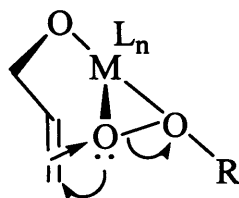

Scheme 1.16: General transition state structure.

Substitution (R_2) at the pro-S position at C-1 in complex **24**, (Scheme 1.14) produces a major change in the course of the asymmetric epoxidation, giving rise to a substrate that is reactive with only the (L)-tartrate catalyst. Hence a combination of the (D)-tartrate catalyst and complex [**24**, $R_2 \neq$ H] represents mis-matched pairs. Thus, it is this position on an allylic alcohol that must experience the greatest steric crowding, consequently giving rise to the phenomenon of kinetic resolution. Relative rates of kinetic resolution increase dramatically with increased size of the tartrate ester group, therefore steric crowding at C-1 probably involves the tartrate ligand.

In an attempt to rule out the likelihood that the asymmetric epoxidation proceeds *via* a small concentration of monomeric titanium-tartrate complex **23** (Scheme 1.14), Sharpless and co-workers synthesised a series of *bis*-tartrate ligands **27a-c** for use in epoxidation studies.[32] The fact that the reaction is first order with respect to titanium tartrate catalyst over a 10 fold concentration range poses a strong argument against the sole intermediacy of a monomeric titanium tartrate. Nonetheless, the solution equilibria may be quite complex and hence the failure to observe deviation from first order behaviour is less than definitive evidence. Given this, it was believed that using the ligands **27a-c** would allow experimental discrimination between epoxidation by monomer and dimer. The linked *bis*-tartrate ligands were synthesised by

alkylation of monobenzyl tartaric acid, **25** with the corresponding α,ω-diiodoalkane **26** (Scheme 1.17).
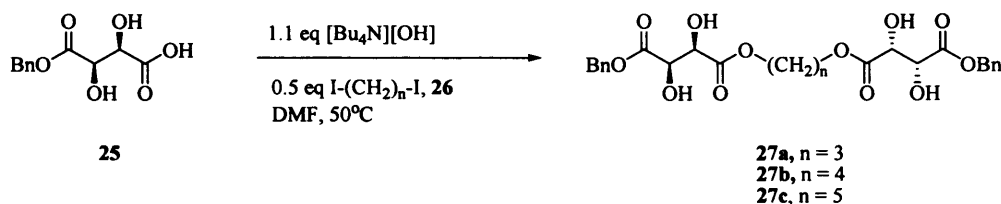
Scheme 1.17: Bis-tartrate synthesis.

Due to the nature of the ester linkage, the ligands **27** proved labile to transesterification at room temperature in the presence of Ti(O^{i}Pr)$_4$, but showed no sign of this after 24 h at room temperature in the presence of Ti(O^{t}Bu)$_4$. Therefore, in order to ensure absolute integrity of the ligands, the epoxidation was carried out with Ti(O^{t}Bu)$_4$ even though the rate of epoxidation at -20°C is faster than transesterification. Following the reaction, the ligands were recovered in >90% yield, lending credence to this hypothesis. The molecularity of the Ti(O^{t}Bu)$_4$ complex was determined by the isopiestic Signer method,[30] and the results were consistent with a predominance of 2:1 Ti:ligand species, reinforcing the evidence for the presumed catalytic species (Scheme 1.18).

The titanium complexes **29a-c** mediated high levels of asymmetric induction (88-94% ee), though these were not as high as when using the parent catalyst (Scheme 1.18). As such, it appeared that the active catalytic species in the *bis*-tartrate manifold was strikingly similar structurally to that in the parent system, thus lending further ammunition for the argument for a *bi*-nuclear catalyst structure.

Surprisingly, the linked *bis*-tartrate system did not mediate kinetic resolution of racemic secondary allylic alcohols. Prior to this, no tartrate catalytic system had been found that did not mediate both kinetic resolution and asymmetric epoxidation. Therefore, the decoupling of asymmetric epoxidation and kinetic resolution was unprecedented and quite significant. It was argued that this decoupling of the kinetic resolution was due to the steric disposition of the tartrate ligand around each titanium centre, while inclusion of the link did not compromise the fundamental recognition characteristics of the catalyst but did diminish its tolerance for substrate variation (primary *vs* secondary allylic alcohols). However, the decoupling of kinetic resolution was additional evidence for the *bi*-nuclear epoxidation because if the titanium-tartrate epoxidation was proceeding *via* a monomer (or the *bis*-tartrate forming *bi*-nuclear structure with

another *bis*-tartrate moiety), there seemed to be no reason why the system could not mediate kinetic resolution.

R = Bu^t	28a, n = 3	29a, n = 3	R = Bu^t
X = OBn	28b, n = 4	29b, n = 4	X = OBn
	28c, n = 5	29c, n = 5	
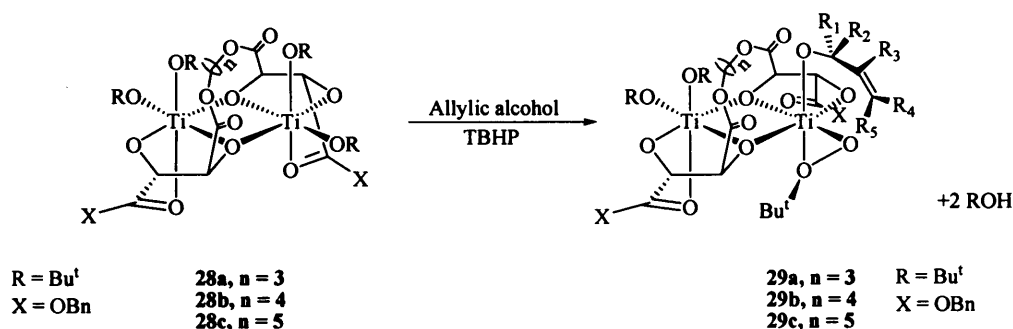
Scheme 1.18: *Bis*-tartrate ligands.

Significantly, a key control experiment was overlooked in the original report[32] and, as a result, subsequent work revealed that the forgoing conclusion regarding the decoupling of the kinetic resolution was inaccurate, the control experiment being kinetic resolution using Ti(O^{t}Bu)$_4$ and a standard tartrate ester. These later studies[33] revealed that simply changing the alkoxide from isopropoxide to *t*-butoxide greatly reduced the ability of the complex to perform efficient kinetic resolutions which was therefore not solely due to the *bis*-tartrate linker. It has been argued that this "ligand bystander effect" is the cause of this diminished kinetic resolution efficacy. The results of this study also supported the belief in a *bi*-nuclear catalyst, due to the difficulty in envisaging how the experimentally observed effect of the bystander alkoxides could exist if the active catalyst was monomeric **23**.

In 1990, Corey submitted his controversial "logical mechanistic explanation for the stereoselectivity in the Katsuki-Sharpless epoxidation".[34] In this proposal, the catalytic complex, more accurately "complexes" **30**, exist as an ion pair, shown in Scheme 1.19. Therein, Corey presented his putative conclusions based purely on the evidence and results provided by Sharpless; no novel work was carried out by Corey.

30
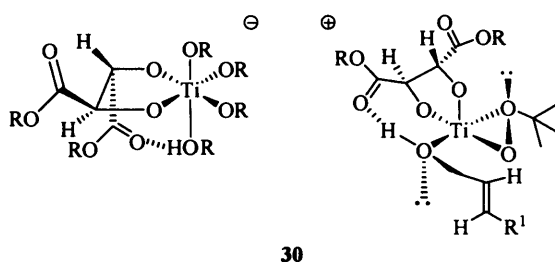
Scheme 1.19: Corey's proposed transition state.

In an attempt to settle the dispute over the catalyst structure and epoxidation mechanism, Sharpless and co-workers published two back-to-back papers concerning kinetics and catalyst structure.[24] The proposal by Corey featuring the ion-pair transition state was inconsistent with observed kinetic data:

"The putative ion-pair transition state (**30**) contains four equivalents of spectator alcohol in addition to the substrate and the oxidant. Such a mechanism would not be expected to show the inverse squared dependence of rate on inhibitor alcohol concentration that is *observed* under pseudo-first-order conditions" K. B. Sharpless, equation 1.[24]

For the following reasons the catalyst structure is believed to be *bi*-nuclear:[24]

A. The average molecularity of the [Ti(tartrate)(OR)$_2$]$_x$ in solution is 2 (Signer method).[31]

B. NMR (^{17}O, ^{1}H, ^{13}C) measurements in different solvents yielded data that at least 80% of the total mixture in solution was due to a single structure. Therefore, with the evidence presented above, this major structure must be a dimer.

C. NMR spectra also identify at least one of the minor species in solution as the 2:1 Ti-tartrate complex. This material has been shown to be a much more sluggish epoxidation catalyst than the 2:2 complex. Species containing more tartrate than titanium have also been shown to be poor catalysts for epoxidation of allylic alcohols (1:2 Ti:tartrate is an inactive catalyst).

D. The pseudo first order rate varies linearly with Ti-tartrate over a 10-fold concentration range, suggesting that the active catalyst does not participate in a bi-molecular equilibrium reaction with species of a different aggregation state as proposed by Corey. The only way for a non-dimeric species to be the epoxidation catalyst is for it to be present in trace amounts and for it to be inert to association-dissociation equilibria, an uncharacteristic property of titanium d^0 chemistry, thus making the existence of such a substitutionally moribund Ti-tartrate complex highly unlikely.

Concordantly, there is an abundance of evidence to support the catalyst structure, **22**, in solution:

A. ^{1}H, ^{13}C and IR spectra are consistent with such a structure.

B. ^{17}O NMR spectra show resonances of two different tartrate alkoxide oxygens and only one type of monodentate alkoxide, consistent with the tartrate-bridged dimer structure **22** and inconsistent with the 10 membered ring structure **17a**, which has only terminal tartrate alkoxides.

C. Difference FTIR spectra of deuterium-labelled alkoxide complexes show the presence of only terminal isopropoxides in [Ti(DIPT)(O^{i}Pr)$_2$]$_2$, ruling out an isopropoxide-bridged structure.
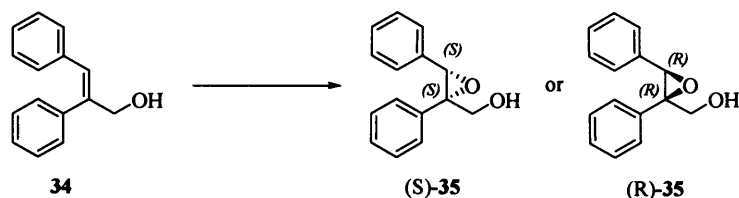
During the course of these studies, different ligands for the SAE were also synthesised and investigated; the first of these new systems being tartramides.[35] Initially, erratic results were obtained but careful investigation resulted in the discovery of an efficient epoxidation catalyst based on a tartramide **31** (Scheme 1.20).
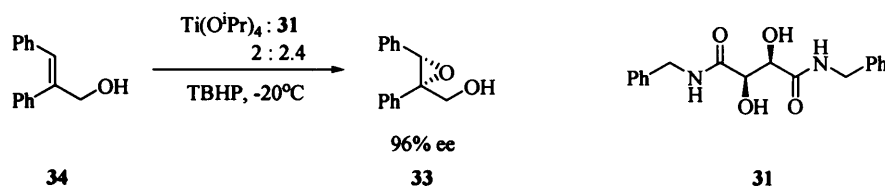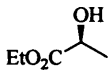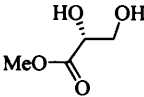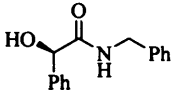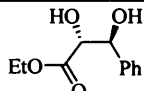

Scheme 19: Tartramide epoxidation.
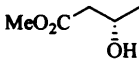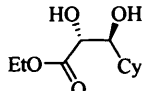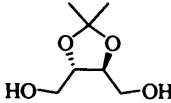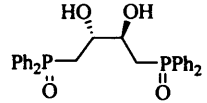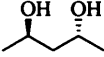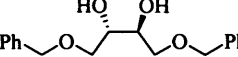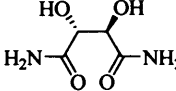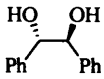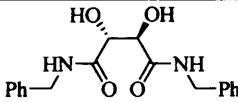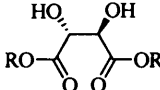
During these investigations the standard ratio of Ti:tartrate, 2:2.4, was varied and it was discovered that at an optimal ratio of 2:1, inverse enantiofacial selection was observed. However, this inverse selection was not as selective as the standard ratio and was substrate specific. The enantiomeric excess of the corresponding enantiomer of epoxide **33** was 82%.

More thorough investigations studied more than fifty different potential ligands[31] including tartrate and binol derivatives, 1,2-diols and 1,3-diols.[36] These studies revealed that ester or amide groups are necessary at both ends of a 1,2-diol ligand for good selectivity in both AE and KR. Substitution of methyl groups for C-2 and C-3 hydrogen substituents of tartrate severely reduces catalyst selectivity. Table 1 shows a selection of ligands tested in the SAE, for the epoxidation of (*E*)-2,3-diphenyl-2-propenol **34** by Ti(O^{i}Pr)$_4$ and TBHP at 0°C leading to this formation of *S*-**35** *R*-**35** (Scheme 1.21).

Scheme 1.21

Table 1.2: Potential ligands for SAE

entry		% ee	entry		% ee
1	EtO$_2$C—CH(OH)—CH$_3$	0	8	MeO—C(O)—CH(OH)—CH$_2$OH	35 (S)
2	HO—CH(Ph)—C(O)—NH—CH$_2$Ph	4 (S)	9	EtO—C(O)—CH(OH)—CH(OH)—Ph	80 (S)
3	MeO$_2$C—CH$_2$—CH(OH)—CH$_3$	5 (R)	10	EtO—C(O)—CH(OH)—CH(OH)—Cy	>98 (S)
4	(acetonide) HO—CH$_2$—...—CH$_2$—OH	23 (S)	11	Ph$_2$P(O)—CH(OH)—CH(OH)—P(O)Ph$_2$	0
5	CH$_3$—CH(OH)—CH(OH)—CH$_3$	13 (S)	12	Ph—CH$_2$O—CH(OH)—CH(OH)—CH$_2$O—Ph	12 (R)
6	(CH$_3$)$_2$CH—CH(OH)—CH$_2$OH	5 (R)	13	H$_2$N—C(O)—CH(OH)—CH(OH)—C(O)—NH$_2$	19 (R)
7	Ph—CH(OH)—CH(OH)—Ph	0	14	PhCH$_2$—NH—C(O)—CH(OH)—CH(OH)—C(O)—NH—CH$_2$Ph	96 (S)
			15	RO—C(O)—CH(OH)—CH(OH)—C(O)—OR	>98 (S)

Simple homochiral α-hydroxy esters and amides (entries 1,2) and β-hydroxy esters (entry 3) gave very low stereoselection, demonstrating that one ester and one carbinol are not sufficient to generate an enantioselective catalyst. Homochiral 1,4-, 1,3- and 1,2-diols (entries 4-7) are also poor ligands in the epoxidation, suggesting that diolate alone is also not sufficient. Incorporating three of the four functional groups into the ligand (entries 8-10) does give an enantioselective catalyst, particularly when the "fourth" slot is taken up by more sterically demanding groups, but results in less effective kinetic resolution of racemic secondary allylic alcohols.

Clearly, both a 1,2-diol and at least one ester or amide carbonyl are essential for obtaining high enantioselectivity in the reaction. This is consistent with the ground state model **24**, which suggests that only tridentate coordination of the tartrate ligand is required and that the unbound carbonyl is not essential for formation of an active species.

"Still, the uncoupling of face selectivity in kinetic resolution (entries 9 and 10) suggests that *all four* tartrate functional groups may be playing a role in the latter process" K. B. Sharpless.[36]

The progress of computer technology has also aided in the debate on the mechanism of the SAE. DFT (Density functional Theory) studies were undertaken in the mid-90s using Gaussian 92/DFT program and the B3LYP/3-21G basis sets (at the time was a very powerful method although nowadays the method has been updated to the more accurate Gaussian 03 and increasingly powerful computer processors).[37-39] Several conclusions were reached: there is a significance preference for a *spiro* transition structure over a planar transition structure; this conformational preference is rationalised by a more favourable interaction between the HOMO of the alkene and the LUMO of TiOOR. The *spiro*-transition structure for the epoxidation is nearly symmetrical with the two C-O bonds forming to a similar extent whereas in the planar transition structure, the outer C-O bond forms to a much larger extent than the inner C-O bond (Scheme 1.15). There is a η_2 structure for the Ti-O-O unit in the transition structure. Consequently the Sharpless proposal, Scheme 1.14, was further reinforced by these computational studies and Corey's ion pair transition state "theory" was deemed highly unlikely.

The application of the SAE has been widespread and this aspect has been thoroughly reviewed elsewhere.[40-42] The reaction has been applied in complex natural product syntheses such as resiniferatoxin, swinholide A[43] and used to synthesise the key starting material in the synthesis of the β-blocker propanolol.[45,45]

As with many other synthetic transformations, the SAE is not without experimental drawbacks. For example, due to the highly fluxional nature of the active catalyst, there is a need to conduct the experiment at low temperatures (typically -20°C). After the reaction is complete, a relatively complicated reaction work-up is required to dispose of any excess hydroperoxide and remove the catalyst system (tartrate ester and titanium salts), which can complicate purification and/or destroy the precious epoxy alcohol. Further details of the experimental procedures can be found in the practical considerations section (Chapter 2, pages 63-70). On large industrial scales, these experimental subtleties become much more deleterious and further complications arise such as the disposal of the catalyst components. A ton of tartrate ester/tartaric acid cannot be disposed of into the local river or sewage system and as the process has contact with chlorinated media (reaction solvent dichloromethane), the by-products need to be processed in a suitable manner (afterburner incineration), avoiding the production of any toxic compounds such as dioxins (formed by or due low temperature incineration).

Given these significant limitations, it seems a logical and straightforward conclusion that if one could immobilise and/or recycle the tartrate catalyst, then some of these experimental drawbacks could be overcome. Tartrate esters are not easily separated from precious epoxy alcohol products

in the relatively complex epoxidation brew, which can sometimes be simplified by the correct choice of tartrate ester but if the product is novel, a certain amount of guess work is needed. Moreover, during aqueous work-up, tartrate has the undesirable characteristic of forming emulsions leading to separation problems. If a suitable tartrate ester is used that leads to its re-isolation and re-use, it is a mandatory requirement that the tartrate has remained optically pure or else re-use will result in loss of enantioselectivity in the epoxidations. Tartrates are relatively reactive moieties due to the presence of the labile CHs at C-2 and C-3. The addition of acid or base to tartrates can result in epimerisation of these stereogenic centres and hence loss in selectivity in any subsequent epoxidations. More catastrophically, results obtained by the Knight group have shown that tartrate can polymerise, leading to complete loss of the chiral source required for the subsequent epoxidation.

Immobilisation of tartrate seems to be a very logical remedy for these conundra and this aspect has been subject of thorough research. The first example of such an approach was published in 1983, by Farrall and co-workers: polystyrene-benzyl bromide resin **36** was derivatised by lithium-halogen exchange and quenching with epoxy-ethane. The resulting alcohol **37** was transesterified with DMT in the presence of catalytic acid giving a solid-supported tartrate source **38** (Scheme 1.22).[46] Epoxidation of geraniol was used as a model reaction: the highest enantiomeric excess obtained was 66% ee, compared to 95% ee in the standard SAE. The polymer was simply recovered by filtration and reused in subsequent runs, however after five cycles, the ee of the product had fallen by a third. Clearly, this heterogeneous support although easy to recover, was inefficient from the outset and subsequent cycles reduced the selectivity even further.
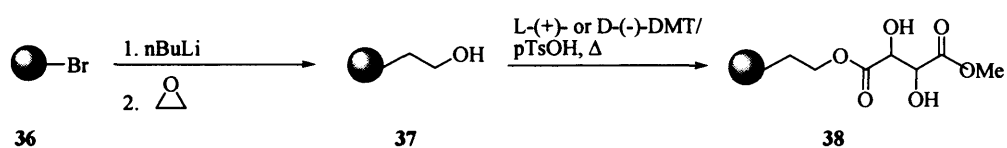

Scheme 1.22: First tartrate immobilisation.

Some years later, Sherrington published one of a series of papers describing an attempt to synthesise an efficient and recoverable tartrate source for the SAE.[47-50] Linear poly(tartrate)s **39a-d** and **40a-b** were synthesised and their induction in the epoxidation of *trans*-2-hexene-1-ol, **41** was determined (Scheme 1.23, 1.24).

24
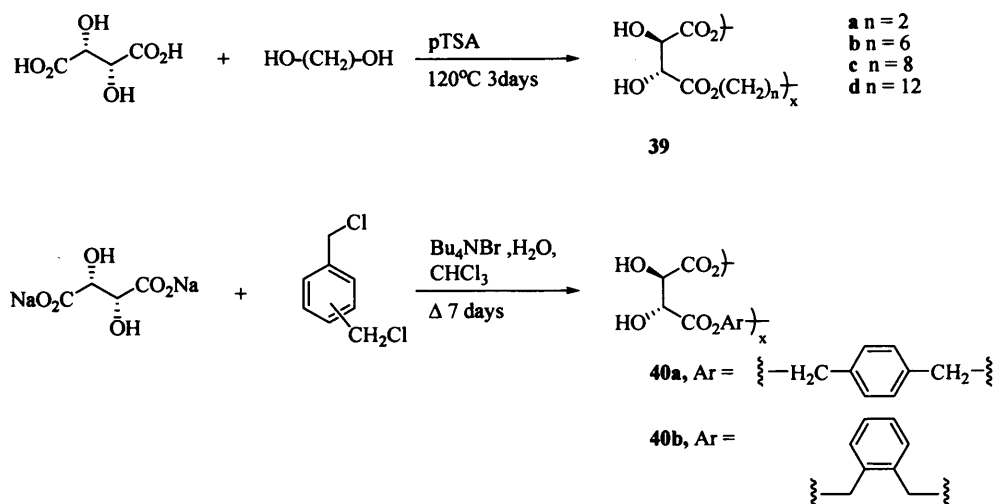
Scheme 1.23: Linear poly(tartrate)s syntheses.

The screening process entailed substitution of tartrate esters with the poly(tartrate) analogues in the asymmetric epoxidation brew, with the conditions of the reaction being otherwise unchanged. As the exact amount of "available tartrate" in the polymer was not accurately known in the study, the ratio of the poly(tartrate):Ti(O^{i}Pr$_4$) was varied to determine the optimum ratio. The yield of epoxy-alcohol product **42**, Scheme 1.24, ranged from 20-90% depending on the polymer ligand and ratio used. The best enantiomeric excess of epoxy-alcohol product **42** obtained was 79% ee using poly(tartrate) **39c**, significantly less than DET (>98% ee). There was seemingly no attempt at re-use of the ligands which arguably negates the whole point of immobilising the tartrate. As previously mentioned, tartrate is prone to epimerisation and the conditions in which the poly(tartrate)s were synthesised may have caused some "scrambling" of the stereocentres and hence loss of enantioselectivity in the epoxidation.
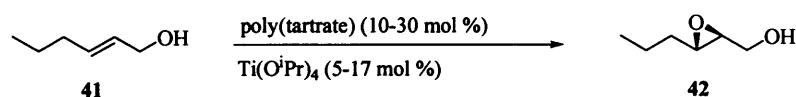
Scheme 1.24: Poly(tartrate) epoxidation.

Sherrington *et al* expanded the foregoing methodology with the more successful poly(tartrate) **39c**. The polymer was re-synthesised under harsher conditions (130°C) in order to increase the amount of crosslinking/branching, giving a series of polymers (3 - >15% crosslinking).[49] In the epoxidation of *trans*-2-hexene-1-ol **41**, the most successful poly(tartrate) was **39c** with 3% crosslinking, furnishing the epoxy alcohol **42** in 87% ee. The optimum results collected for each substrate are illustrated in Table 1.2.

Table 1.2:Optimum results from poly(tartrate)s

Entry	Substrate	Molar ratio (substrate:Ti:"tartrate")	% crosslinking	Epoxide Yield / %	ee / %
1	*trans*-2-hexene-1-ol	100:25:50	3	87	87
2	*trans*-2-undecene-1-ol	100:20:60	6	54	98
3	*trans*-cinnamyl alcohol	100:25:50	6	38	89
4	geraniol	100:25:50	6	66	72

The screening yielded some potential significant results, although on closer examination, the amount of polymer needed was >50 mol % in order to obtain enantioselectivities comparable to tartrate-mediated asymmetric epoxidation. Perhaps this is reflected in the isolated yields of entries 2 and 3: inclusion of the epoxy alcohol products (*N.B.* low solubility in dichloromethane in these two cases) in the polymer matrix may be a problem, thereby reducing the yield. Again, no attempt was made at re-using the polymers and testing their asymmetric induction in "recycle runs".

The initial studies by Farrall and co-workers were revisited by Suresh: Tartrate functionalised polystyrene co-polymers were prepared with divinyl benzene and tetraethyleneglycol diacrylate as the crosslinking agent, then chloromethylated and finally functionalised with tartaric acid.[51] In a separate experiment, diallyl tartrate was co-polymerised with divinylbenzene and the resulting resins used in the asymmetric epoxidation under otherwise standard SAE conditions. The yields were reasonably good with high enantiomeric excess of the epoxy alcohols; the most selective results are given in Table 1.3.

Table 1.3

Entry	Substrate	Resin	Epoxide Yield /%	ee / %
1	*trans*-2-hexene-1-ol	A	73	89
3	*trans*-cinnamyl alcohol	A	66	91
4	geraniol	A	55	76

Resin A = 0.78 mmol of tartrate/g of polystyrene

The group managed to modify Farrall's initial work and improve the selectivity with some very promising results and some excellent enantiomeric excesses. The recycling of the polymer-bound tartrate and re-use was again not reported in the communication, which was disappointing. The diallyl tartrate-divinyl benzene co-polymer did not provide high induction in epoxidations; the maximum enantiomeric excess was 77% in the epoxidation of *trans*-2-hexene-1-ol. There have been reports in the literature of other co-polymerisations yielding some constructive conclusions:[52] When co-polymerising two chemically inequivalent olefins, the relative stability of the corresponding olefin radical and hence rate of polymerisation, needs to be taken into

account; for example comparing the rate of polymerisation between allyl acetate (k_a) and styrene (k_b), k_a ~0 and k_b~90, this essentially represents a relative rate difference of infinity and the allyl acetate will no co-polymerise with the styrene. Diallyl tartrate and allyl acetate are very similar in functionality, therefore the styrene will react and form a homopolymer(s) ahead of the formation of allyl-ester-styrene polymer(s), and hence, diallyl tartrate will not be incorporated into the polymer(s). The most probable reason for the "co-polymer"-mediated epoxidation is that the diallyl tartrate is likely to be in the form of an inclusion complex in the polymer matrix; as such the active catalytic complex can still form.

A different approach was adopted by Li and co-workers;[53] their work involved the synthesis of an organic-inorganic hybrid material. A chiral tartaric acid derivative **43** was grafted onto the surface of silica and mesoporous Zeolite MCM-41, giving the two supports **44a** and **44b** respectively (Scheme 1.25).
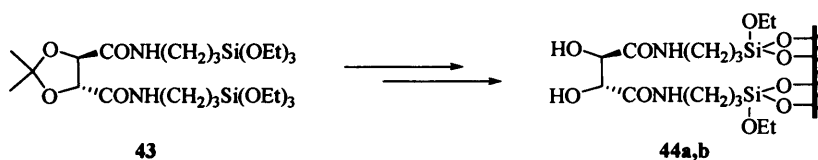
Scheme 1.25: Organic-inorganic hybrid catalyst.

These synthetic catalysts showed enantioselectivities up to 86% (support **44a** was most efficient) for the asymmetric epoxidation of allyl alcohol. The enantioselectivity was comparable to the standard SAE as was the turn-over number for the catalysts and therefore it was assumed that the active catalyst in this heterogeneous case was similar to the homogeneous Sharpless catalyst, **22**. Although an inorganic hybrid is easy to separate from the epoxidation reaction, again no re-use was reported in this case.

The reduction in reaction rate in the majority of heterogeneous supports/catalysts is an inherent disadvantage of such systems. Homogeneous supports, or heterogeneous-homogeneous hybrids (*e.g.* Janda gel) logically overcome this disadvantage.[54] PEG (polyethylene glycol) is a versatile polymer for use in certain homogeneous chemical reactions where PEG is soluble (*e.g.* reactions in dichloromethane). The synthesis and testing of MPEG-tartrate (monomethyl polyethylene glycol) analogues was investigated by Wang and co-workers;[55] high chemical yields and good enantiomeric excesses were obtained using such polymers (Scheme 1.26). The associated advantage of this system is that the scaffold is homogeneous under the epoxidation conditions but the polymer can be recovered post-reaction simply by adding an appropriate solvent (*e.g.* ether or hexane) to induce precipitation of the MPEG-tartrate ligand.
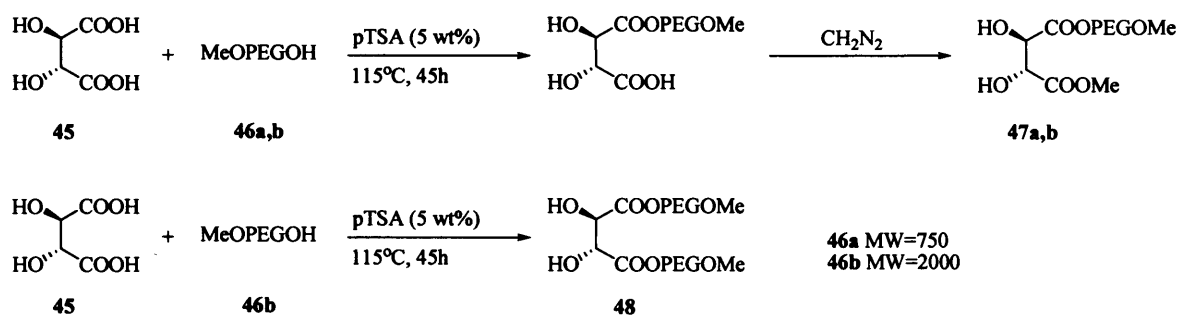
Scheme 1.26: Soluble polymer tartrate scaffold

The enantioselectivities varied significantly with different ligand:Ti ratios. With **47a**, **47b** and **48** up to 93, 93 and 90% ees were obtained respectively. Surprisingly, in the epoxidation of *trans*-2-hexene-1-ol, (-)-(2S,3S)-*trans*-propyloxiranemethanol **42** was obtained with ligand **47a**, yet (+)-(2R,3R)-*trans*-propyloxiranemethanol was obtained using ligand **47b**. The unprecedented difference in absolute configuration was believed to be due to contributions from molecular weight variations (750 *vs* 2000) and conformational factors, but see below.

The methodologies were further extended, in a later publication, to include recovery and recycling of a MPEG supported tartrate **49**:[56]
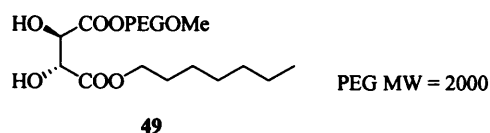
Using *trans*-2-hexene-1-ol **41** as the epoxidation substrate, the ligand **49** was recycled three times but only moderate ees were obtained (Table 4). Over four runs, the ee dropped from 85% to 66% and thus the enantioselectivity of the catalyst in the recycle experiments could not maintain an invariable value. ^{1}H NMR spectroscopic analysis showed that the recovered MPEG-tartrate had significant differences from the starting materials. The ratio of the number of hydrogens in high field positions to low field varied relative to the MPEG-tartrate before the reaction. A sensible explanation was that partial degradation of the polymer had occurred under the oxidation conditions of the epoxidation.

Table 1.4: MPEG-tartrate recycling

Entry	Times Recycled	Molar ratio (substrate:Ti:ligand)	Time (h)	Epoxide Yield / %	ee / %
1	nil	100:5:10	8	80	92
2	First	100:5:10	8	66	85
3	Second	100:5:10	8	62	77
4	Third	100:5:10	8	67	66

The unprecedented reverse in enantioselectivity discussed previously was subsequently re-investigated by Janda and co-workers[57] when, in the second publication by Wang and co-workers, this unprecedented reversal in enantioselectivity was confusingly retracted.[56] A larger series of MPEG-grafted tartrate ligands were synthesised with molecular weights up to 2000. These smaller MPEGs were monoglyme, diglyme, triglyme, and tetraglyme. The lower molecular weight PEG-tartrates **50d-i** furnished the epoxy alcohol product as the (2S,3S)-enantiomer, the same enantioselectivity as the corresponding tartrate ester provides (Table 5, entry 11). Increasing the molecular weight yet further, resulted in reversal (or onset) of the enantioselectivity, furnishing the (2R,3R) epoxy-alcohol, **50a-c**, entries 1-3 (Table 5).
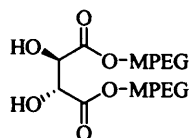
50a MPEG = MW 2000
50b MPEG = MW 750
50c MPEG = MW 550
50d MPEG = MW 350
50e MPEG = $CH_3O(CH_2CH_2O)_4$
50f MPEG = $CH_3O(CH_2CH_2O)_3$
50g MPEG = $CH_3O(CH_2CH_2O)_2$
50h MPEG = $CH_3OCH_2CH_2O$
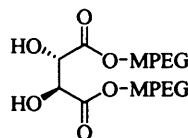
50i MPEG = MW 2000

Isopiestic methods (Signer) revealed that the major species in solutions containing Ti(O^{i}Pr)$_4$ and (L)-DIPT or ligand **50h** were dimeric, 2:2 Ti:ligand (*cf.* **22** standard SAE), whereas mixtures of **50a,c,e,f,g** and Ti(O^{i}Pr)$_4$ comprised mainly of a monomeric species. A plausible explanation for this change in molecularity observed after the addition of only three extra atoms (contrast **50g** with **50h**), is that ligand **50h** cannot chelate to the metal due to the presence of only a single ethylene oxide unit, while **50g** is of suitable length to complex the metal and favour formation of a 2:1 Ti:ligand complex. As the MPEG length increases, a statistically greater number of oxygen atoms are present that can interact with the metal, thereby increasing the relative proportion of monomeric species. Thus, the observation of inversion in enantioselectivity is explained by the

fact that the molecularity of the active catalytic varies (*cf.* enantioreversal in Scheme 1.20) with molecular mass of MPEG. A control experiment was carried out (entry 10, Table 1.5) where PEG dimethyl ether (MW 2000) was added to a standard SAE; the addition had no effect on the enantioselectivity of the reaction, indicating that simple coordination of metal and MPEG is not important in establishing a monomeric species.

Table 1.5: MPEG-tartrate enantioreversal studies.

Entry	Ligand	MPEG MW	Yield/%	ee/ %	Product
1	**50a**	2000	54	75	(2R,3R)
2	**50b**	750	66	67	(2R,3R)
3	**50c**	550	89	8	(2R,3R)
4	**50d**	350	95	75	(2S,3S)
5	**50e**	207	93	80	(2S,3S)
6	**50f**	163	83	89	(2S,3S)
7	**50g**	119	72	85	(2S,3S)
8	**50h**	75	75	93	(2S,3S)
9	**50i**	2000	63	78	(2S,3S)
10	**L-DIPT**[a]	-	96	87	(2S,3S)
11	**L-DIPT**	-	96	96	(2S,3S)

a control experiment

The loss in enantioselectivity with re-use of the MPEG-tartrates employed by Wang was also explained by Janda: MPEG has the propensity to form peroxy ethers in the presence of peroxides, therefore *t*-butyl hydroperoxide will react with PEG thereby changing the structure and leading to destruction of the polymer in an unpredictable and detrimental fashion.[58] As a result, one can conclude that MPEG scaffolds are unsuitable for the synthesis of recoverable ligands for the Sharpless Asymmetric Epoxidation.

In summary: A significant amount of work has been undertaken to produce a tartrate analogue that is easy to separate from the epoxidation mixture and has been met with success in a number of cases. Nonetheless, one can question the logical use of these polymers since the correct choice of tartrate ester can obviate many associated problems of the SAE work up, unless one wishes to re-use the polymer in question to circumvent disposal of tartrate. As reviewed in this Chapter the recycling of tartrate catalysts has met with sparse success, arguably the best result being obtained with the MPEG scaffold tartrate, **49**, but as cited earlier the use of MPEG in recoverable ligands for asymmetric epoxidations with alkyl hydroperoxides is not recommended.

Chapter 2

Results & Discussion.

Results and Discussion.

In the search for a recoverable ligand for the Sharpless Asymmetric Epoxidation (SAE), two aspects from Sharpless's original studies were used in the present project: the linking of two tartrate moieties and elimination of the "redundant ester" (Scheme 1.17 and Table 1.2 entry 10).[32,36] Conglomeration of these two concepts and addition of a means to immobilise the novel ligand system led to the logical design of the generic system **51** (Scheme 2.1):
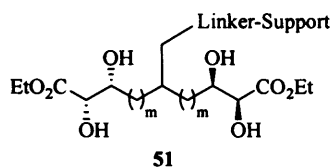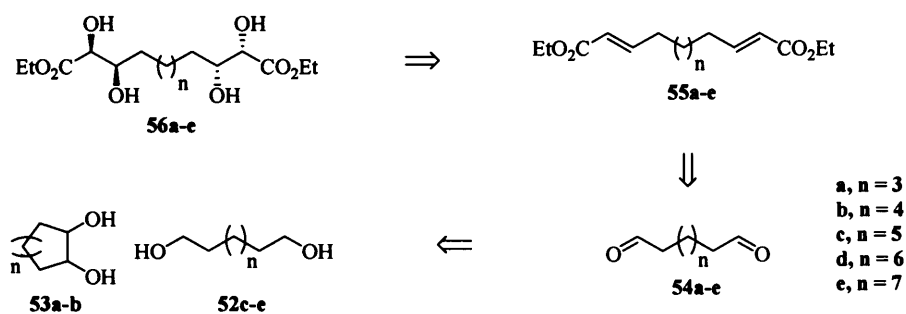

Scheme 2.1

The system has the necessary means to mediate SAE and the linker on the hydrocarbon backbone provides the means to tether the ligand to an appropriate support. The C_2 symmetry (*cf.* tartrate) is preserved, the linker is positioned equidistant from each dihydroxy ester terminus because it was thought that if the linker was placed in a position that created an additional asymmetric centre, the fundamental recognition characteristics of the catalyst system would be perturbed.

Initially, the correct choice in length of the hydrocarbon backbone was uncertain, but comparison with Sharpless's most successful *bis*-tartrate **27c** (Scheme 1.18) yielded a possible solution; m = 4, nine methylene units between the dihydroxy ester termini. The proposed catalyst system was still fundamentally different from any previous examples, therefore it was concluded that it would be prudent to model the system and, more specifically, investigate the effect of backbone length in such epoxidation reactions. This led to the design of the homologous ligand series **56a-e** shown below:
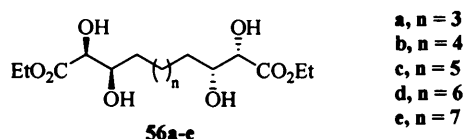

Initial retrosynthetic analysis of this model ligand series showed that the synthesis should be relatively straightforward and had the possibility of being efficient and expedient (Scheme 2.2).

**Scheme 2.2: Retrosynthetic analysis of ligand model.**

The synthesis begins with the oxidation of the diols **52c-e** or oxidative cleavage of the 1,2-dihydroxy cycloalkanes **53a-b** to obtain the α,ω-dialdehydes **54a-e**. The oxidation of α,ω-diols **52a-e** was undertaken using the Swern oxidation[59] or pyridinium chlorochromate (PCC) oxidation[60] furnishing the α,ω-dialdehydes **54c-e** in 34-70% yields and *ca* 80% yields respectively. Where possible, the oxidative cleavage of the 1,2-cyclodiols **53a-b** with a heterogeneous $NaIO_4$-SiO_2 system[61] proved to be more efficient, providing the dialdehydes **54a-b** in higher yields (89% and 95%) and purities, obviating any need for chromatography (Scheme 2.3). Ozonolysis of cycloalkenes could also have been used to form the dialdehydes **54a-b**, however ozonolysis is far messier than the method employed above, furnishing a mixture, containing unwanted α-oxidation products also.

The formation of the *bis*-α,β-unsaturated esters **55a-e** *via* double olefination is an important step in the synthesis because the final step, ironically the Sharpless asymmetric dihyroxylation (AD), requires that the olefin is predominantly *E*, so that the enantioselectivity in the AD is the highest possible.[9] Contamination with (*Z*)-olefin would reduce the selectivity in the AD and when such ligands were used in the SAE they would, concordantly, result in diminished epoxy-alcohol enantiomeric excess. The most popular reaction methods for this olefination are the Horner-Wittig (Wittig),[62] Horner-Wadsworth-Emmons (HWE)[63] and Masamune-Rousch (MR-HWE) modification of the HWE.[64] In test experiments it was discovered that the Wittig, although an efficient reaction gave, an unsatisfactory mixture of geometrical isomers, (*E,E*)/(*E,Z*) of **55** which were difficult to separate by standard column chromatography (*ca* 20% *Z*). On the other hand, the MR-HWE furnished the *bis*-α,β-unsaturated esters with more than satisfactory *E,E:E,Z* ratios of >95% by ^{1}H-NMR. Another advantage of the MR-HWE is that the products **55a-e** can be extracted from the reaction mixture (impurities remain in acetonitrile and water layers) with a very non-polar solvent system (1-10% ether/hexane) eliminating the need for further purification (Scheme 2.3).
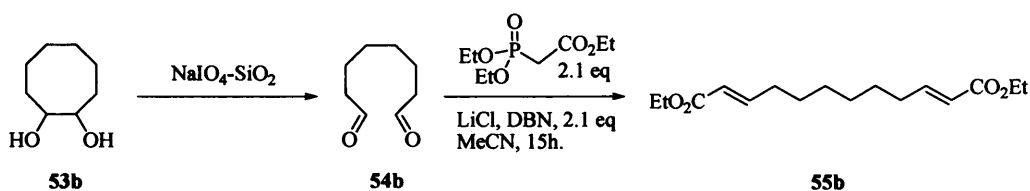
Scheme 2.3: MR-HWE

The literature[9,65] showed that the most selective ligands for AD of *bis*-α,β-unsaturated esters are the *Cinchona*-phthalazine class, second generation dimeric ligands, (DHQD)₂PHAL and (DHQ)₂PHAL, providing enantiomeric excesses in the range 96-98% ee for the corresponding dihydroxy ester products (Scheme 2.4).

Alk* = DHQD, Dihydroquinidine   Alk* = DHQ, Dihydroquinine   PHAL, Phthalazine
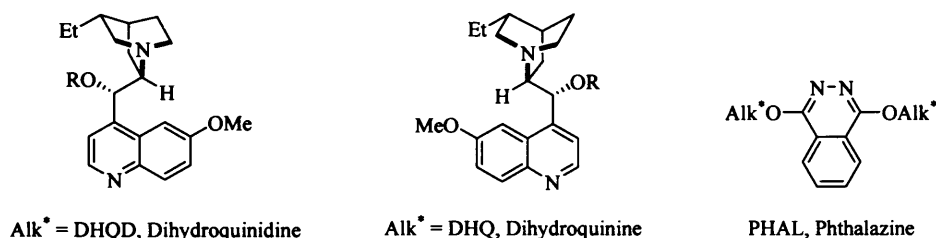
Scheme 2.4: Phthalazine ligands for AD.

There was literature precedence for the (DHQD)₂PHAL mediating AD with slightly higher selectivities than the (DHQ)₂PHAL ligand, 98% ee *versus* 96% ee and therefore, in all subsequent experiments, this ligand was used.[9,65] The *bis*-asymmetric dihydroxylation reactions proceeded smoothly, supplying the potential ligands **56a-e** in good yields as crispy, colourless solids (Scheme 2.5). The physical state of the products gave a simple means of purification by crystallisation, in all cases from chloroform/hexane. The optical purity of these ligands is pursed in Chapter 4, page 100-105.

AD mix β: K₃Fe(CN)₆, K₂CO₃,
K₂OsO₂(OH)₄, (DHQD)₂PHAL.
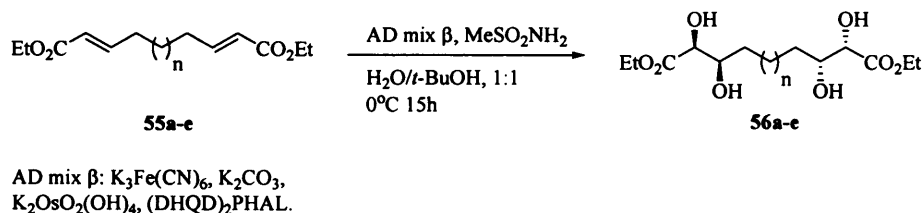
Scheme 2.5

Screening of these initial ligands in an SAE reaction was the next course of action (Scheme 2.6). The SAE has many practical subtleties of paramount importance that were taken into account before the testing of ligands **56a-e** and these will be discussed in depth later.
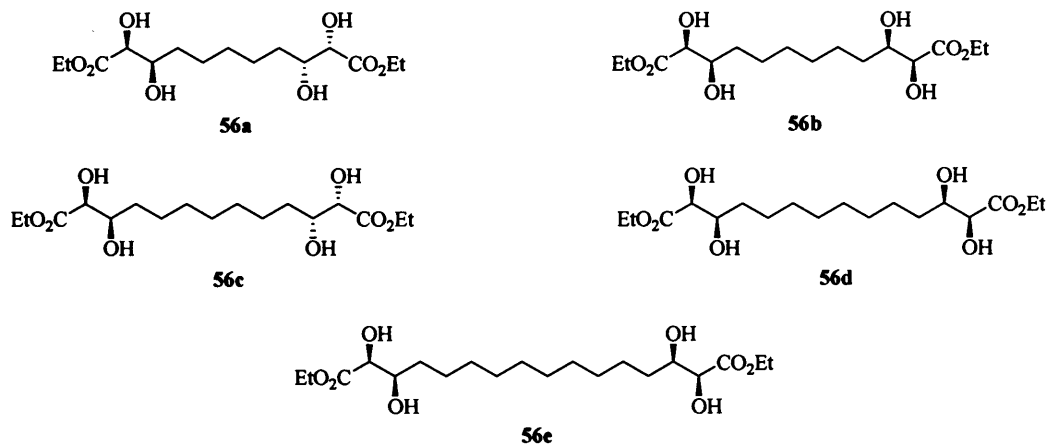
Scheme 2.6: Model ligands.

A suitable substrate was required to assay the asymmetric induction of the model ligands: (*E*)-Cinnamyl alcohol **57** was chosen because the product **58** had literature precedence for being sensitive but owing to the electron rich nature of the olefin, cinnamyl alcohol would provide a satisfactory reaction rate and therefore, cinnamyl alcohol would provide a "testing" but fair substrate assay. A further advantage was that, due to the nature of the substrate, the enantiomeric excess of the epoxy alcohol product (epoxy cinnamyl alcohol **58**) could be determined by HPLC, GC and optical rotation without the need for further derivatisation (intermediate b.p, chromophore present, large optical rotation). The following table summarises the results obtained from this initial ligand screening (Table 2.1).

Table 2.1: Model ligand screening.

Ligand No.	n	Complex / mol %	Temp / °C	ee after 20 h / %	Complete consumption of S.M.
56a	3	15	-20	12	N
56b	4	17	-20	92	Y
56c	5	21	-20	95	Y
56d	6	21	-20	96	Y
56g	8	21	-20	96	Y
D-DIPT	-	21	-20	99	Y
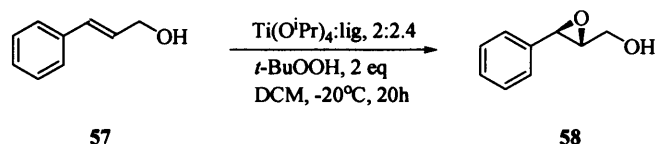
The asymmetric induction of D-DIPT mediated epoxidation was also determined so that a true comparison could be formulated; all experimental procedures were constant such that any experimental inadequacies/errors were reproduced in the tartrate mediated epoxidation, thus acting as a control.

One can clearly see the effect of the chain length on the induction in the epoxidation; the shortest chain length, n = 3 **56a**, the induction was a meagre 12% ee. Upon increasing the chain length by one methylene unit, **56b**, there was an exponential increase in the enantiomeric excess to 92%, further increase in the chain length resulted in only slight increases in the asymmetric induction up to a maximum of 96% ee when using **56d** and **56e**. It seems there is a minimal chain length, which once overcome, **56a** to **56b**, results in the formation of an efficient catalytic complex providing a high enantiomeric excess of the epoxy alcohol product and further increases beyond n = 6 do not result in higher enantiomeric excess in the epoxy alcohol product. The best examples namely **56d-e** are, arguably, directly comparable to tartrate mediated epoxidation. Therefore the model ligand screening provided precedence for our potential immobilised novel ligand system **51** and the design of the system commenced (Scheme 2.1).

The screening demanded that the alkyl chain length (backbone) have at least eight methylene units between the two dihydroxy ester termini, as previously mentioned, thus avoiding the formation of a further stereocentre and therefore required a backbone chain length of nine methylene units, m = 4. From the model system, this chain length was expected to provide high asymmetric induction. The next main obstacle was the choice of linker; upon careful consideration, an alkyl phenol moiety was chosen. The phenol provided a flexible means by which the ligand could be immobilised; ether formation (for immobilisation on a polymer) is straightforward and can be undertaken under relatively mild conditions that should not affect the dihydroxy ester functionalities and also the phenol could be functionalised giving the option of forming a co-polymer. The following structure **64** was the target of subsequent syntheses, where R is a suitable protecting group (*e.g.* benzyl):

64
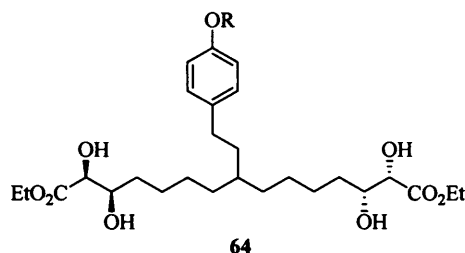
A synthetic strategy was designed and the retrosynthetic analysis overleaf illustrates the resulting postulated transformations (Scheme 2.8). The projected synthesis was five steps to the target molecule **64**, which could be regarded as somewhat pedestrian. However, it was brought to our attention by Dr Tomkinson that the transformation of **61** to **63** could be undertaken in one step by alkene cross metathesis, thereby removing a potentially low yielding and tedious *bis*-oxidative cleavage (**61** to **62**).[66] The feasibility of metathesis was examined on a test substrate, 1,11-dodecadiene **65** in a *bis*-cross metathesis with ethyl acrylate mediated by Grubb's second generation catalyst **66** (Scheme 2.7).
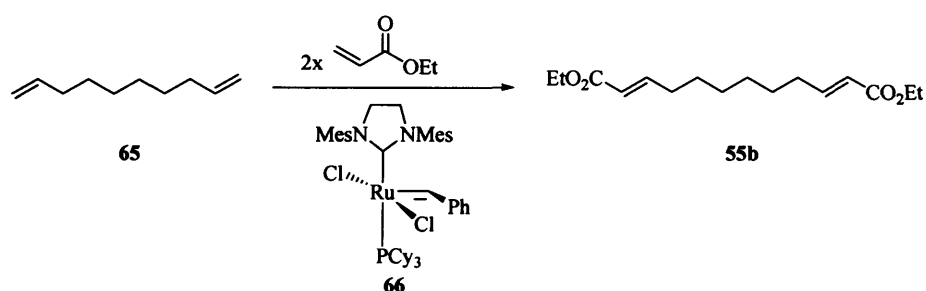
Scheme 2.7: Alkene cross-metathesis

The result was spectacular: 1 mol% of Grubb's second generation catalyst **66** resulted in complete conversion of the diene **65** into the *bis*-α,β-unsaturated ester **55b**, exclusively (>99%) as the (*E,E*)-geometrical isomer in excellent yield (>85%) and represented a paradigm shift in the method for making conjugated esters. The represented an improvement on the MR-HWE approach and even a even greater improvement on the Wittig approach; The MR-HWE provides an (*E,E*)/(*E,Z*) ratio greater than 95% and the Wittig in approximately 80%.
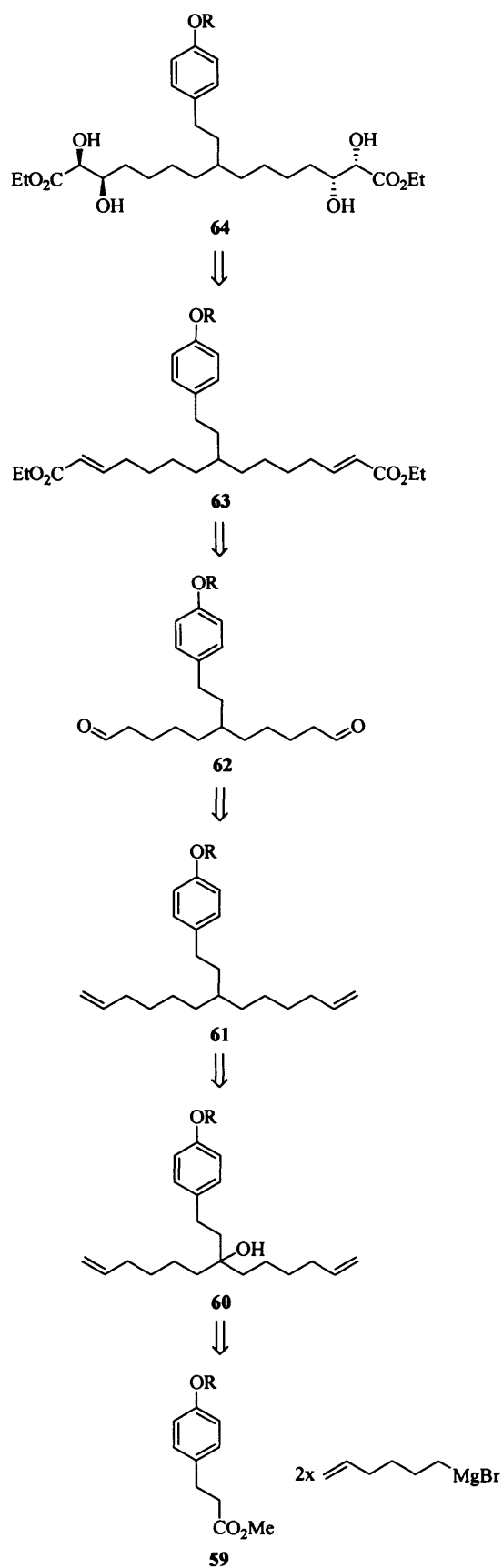
Scheme 2.8

38

The synthesis of the ligand **64** commenced with the double Grignard addition of 5-hexenylmagnesium bromide which proceeded smoothly, providing the tertiary alcohol **63** in good yield (Scheme 2.9).
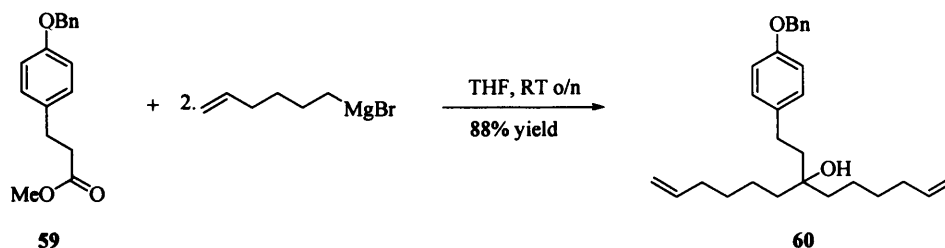
Scheme 2.9

The next step was the reduction of the tertiary alcohol to yield **61**. There are seemingly adequate numbers of methods for the direct reduction of alcohols to the corresponding alkanes including Barton-McCrombie radical de-oxygenation and alkylsilane-acid mediated reduction.[67,68] Radical de-oxygenation was discounted as a feasible method because a tertiary free radical would be created at the 7-position on the alkyl backbone of **60** and this would set up a possibility of a competing reaction, 6-*exo*-trig cyclisation between the terminal alkene and the radical. Therefore, the alkylsilane route was chosen (Scheme 2.10).
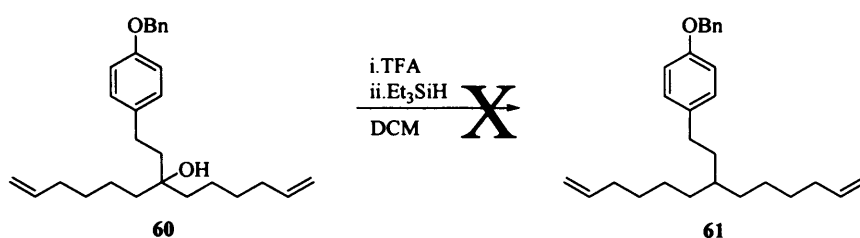
Scheme 2.10

The reduction of the tertiary alcohol **60** was unsuccessful, no reduction whatsoever was observed by ^{1}H and ^{13}C-NMR analysis of the reaction products, despite many attempts (Table 2.2).

Table 2.2: Alcohol reduction attempts

Entry	Equivalents Et₃SiH	TFA /eq	Conditions	Result
1	1.2	6.5	DCM, 0C to RT, 24 h	No reduction
2	2	6.5	DCM, 0C to RT, 24 h	No reduction
3	3	6.5	DCM, 0C to RT, 24 h	No reduction

The synthesis could not continue, alternative reaction routes were hypothesised but seemed more complicated in comparison and therefore it was decided to modify the current synthetic route and the tertiary alcohol **60**, instead of being reduced, was to be blocked by methylation (Scheme 2.11). The methylation would result in the final ligand possessing a pseudo-quaternary position at the centre of the alkyl backbone of **70**, thereby changing the fundamental characteristics of any resulting catalytic complex. However, this Thorpe-Ingold effect (geminal dimethyl effect) was hoped to increase the propensity of the ligand system to form a chelate in the catalytic complex (*cf.* Scheme 1.18), thereby diminishing the fluxional nature associated with these titanium systems and perhaps making the catalyst more selective.
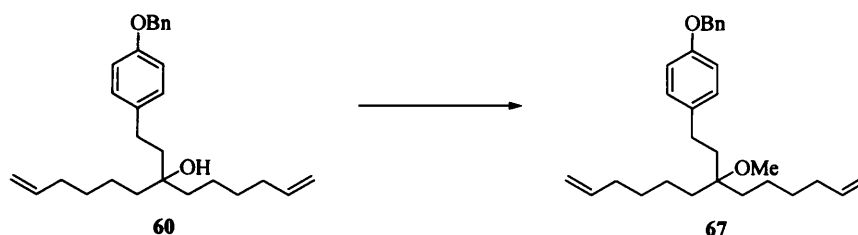
Scheme 2.11

Methylation also proved to be troublesome, numerous attempts finally resulted in a suitable reagent combination as summarised in Table 2.3. Entry 7, the most successful, yielded the alcohol in 77%. The difficulty in methylation was believed to be due to the nature of the molecule and the solvents employed in the transformation. The alcohol **60** as a whole is non-polar and therefore when placed in a polar solvent such as tetrahydrofuran or dimethylformamide will adopt a conformation that will maximise more favourable intramolecular Van der Waals interactions (*i.e.* coil up). This probably results in the tertiary alcohol of **60** being more sterically encumbered than an analogous tertiary alcohol such as *t*-BuOH, thereby reducing the efficiency of the deprotonating reagents and preventing any subsequent methylation.

Table 2.3: Methylation procedures.

Entry	Reagents	Conditions	Result
1	Dimethyl sulphate, KOH (15 wt% H$_2$O)	1,4-Dioxane, 65°C o/n.	No methylation
2	NaH, MeI, TBAI	THF, 0°C to RT o/n.	**67**, < 50% yield
3	NaH, MeI, TBAI, 15-C-5	DMF, 50°C, 48 h	No methylation
4	MeI added prior to Grignard work-up	RT o/n	No methylation
5	AgBF$_4$, Ag$_2$CO$_3$, MeI	RT 48 h, MeCN	No methylation
6	Ag$_2$O, MeI	RT 48 h, MeCN	No methylation
7	nBuLi, MeI	RT, 72h	**67**, 77% yield

Application of alkene cross metathesis for the formation of the *bis*-α,β-unsaturated ester **68** proceeded smoothly, furnishing the *bis*-α,β-unsaturated ester **68** in 86% yield with exclusive (>99%) (*E*)-geometry;
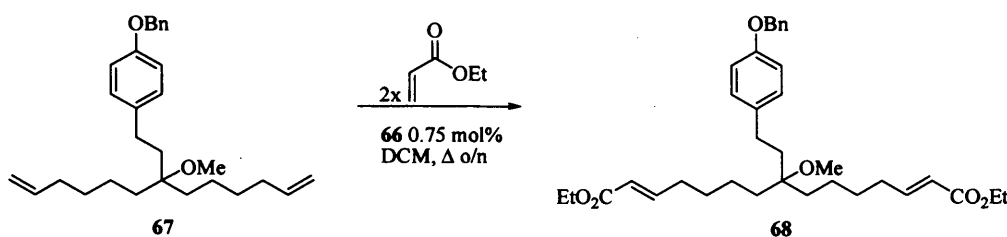
The tetra-ol **69** was obtained by bis-asymmetric dihydroxylation of the *bis*-α,β-unsaturated ester **68** under standard AD conditions yielding the tetra-ol **69** in an excellent yield of 96%.[9,65] Subsequent deprotection of the tetra-ol phenol moiety **69** by hydrogenolysis yielded the penta-ol **70** in good yield, ready to be immobilised on a suitable support (Scheme 2.12).

AD mix β: $K_3Fe(CN)_6$, K_2CO_3,
$K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$.
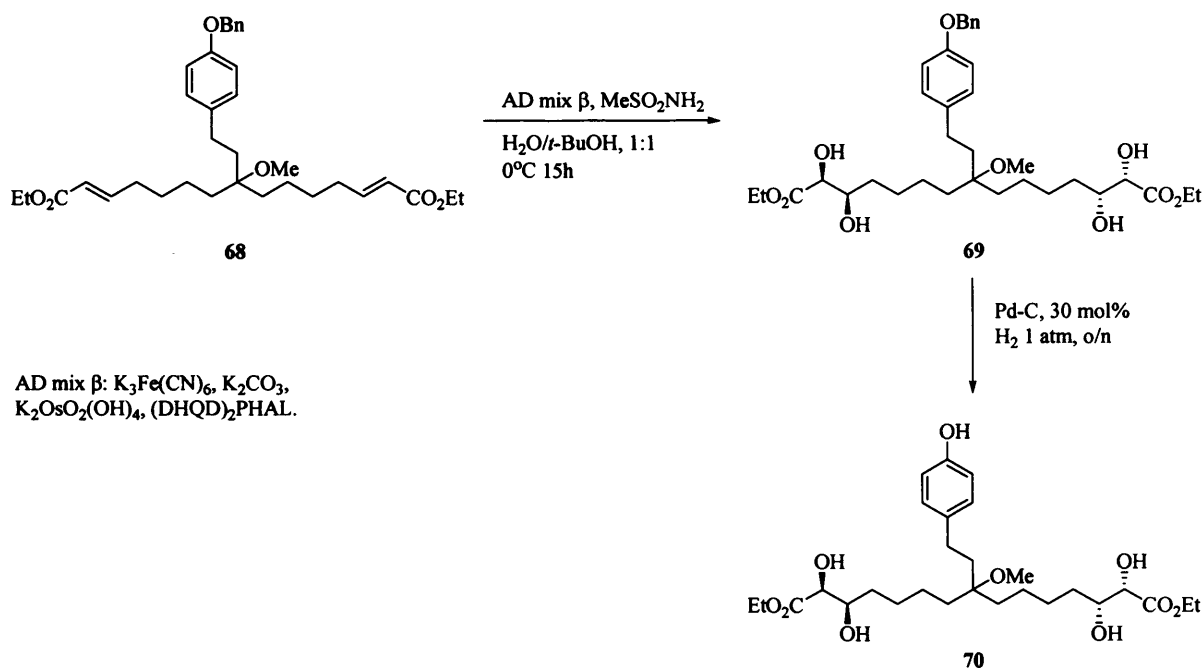
Scheme 2.12

There are a plethora of heterogeneous and homogeneous polymers and inorganic supports and previous tartrate immobilisation studies, reviewed in Chapter 1, led us to choose a polystyrene resin, because it is stable to the oxidative conditions of epoxidation (*cf.* MPEG) and the immobilisation of the ligand *via* the phenol could be established under relatively mild conditions.[69] Polystyrene supports in previous tartrate immobilisation studies had also supplied high epoxy-alcohol enantiomeric excesses and therefore, Merrifield benzyl chloride polystyrene resin, 1% cross linked with divinylbenzene, was chosen as the support. The immobilisation was undertaken under a standard literature procedure, heating the reagents in dimethylformamide at 80°C with the base caesium carbonate and a catalytic amount of TBAI as a phase transfer catalyst (Scheme 2.13).[69] Considering the *bis*-dihydroxy ester **70** and in the reaction conditions used, it was expected the phenoxide anion made *in-situ* by deprotonation with caesium carbonate would be selectively alkylated in preference to the secondary alcohols, thereby obviating the need for their protection.
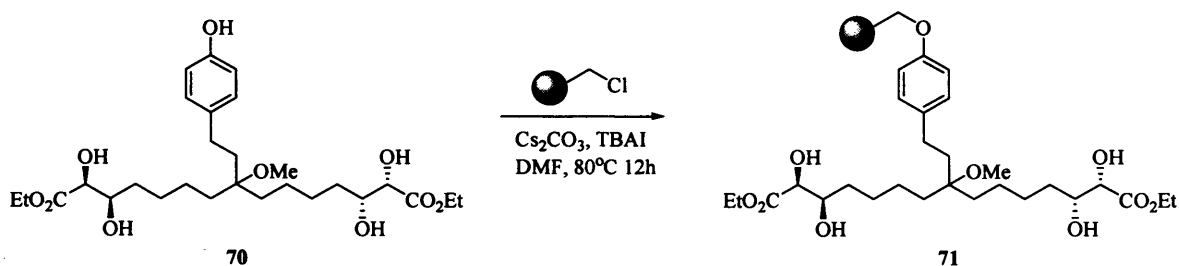
Scheme 2.13

Upon reaction completion, the resin was filtered and extensively washed (see Experimental section) to remove excess reagents and finally subjected to high vacuum to remove any trace amount of solvents. Upon weighing, the polymer did not show the expected increase in mass and FTIR analysis revealed the absence of a carbonyl stretching signal, thus it was concluded that the reaction had not been successful, an unexpected result. The only explanation was that the four secondary alcohols of the *bis*-dihydroxy esters **70** were "interfering" with the reaction in some way and therefore the synthesis was modified to include protection of these alcohols prior to phenol deprotection. A possible explanation is that the caesium ion may have been forming a chelate with the free secondary alcohols, preventing any deprotonation.

t-Butyldimethylsilyl (TBDMS) was chosen because of the associated orthogonal deprotection strategy offered, an anticipated stability to the immobilisation procedure and the mild method of deprotection offered (TBAF).[70] The "*tetra*" protection proceeded smoothly yielding the tetra-TBDMS protected ligand **72** in 71% yield and a subsequent hydrogenolysis of the protected phenol gave a quantitative yield of the tetra-TBDMS phenol **73** (Scheme 2.14).
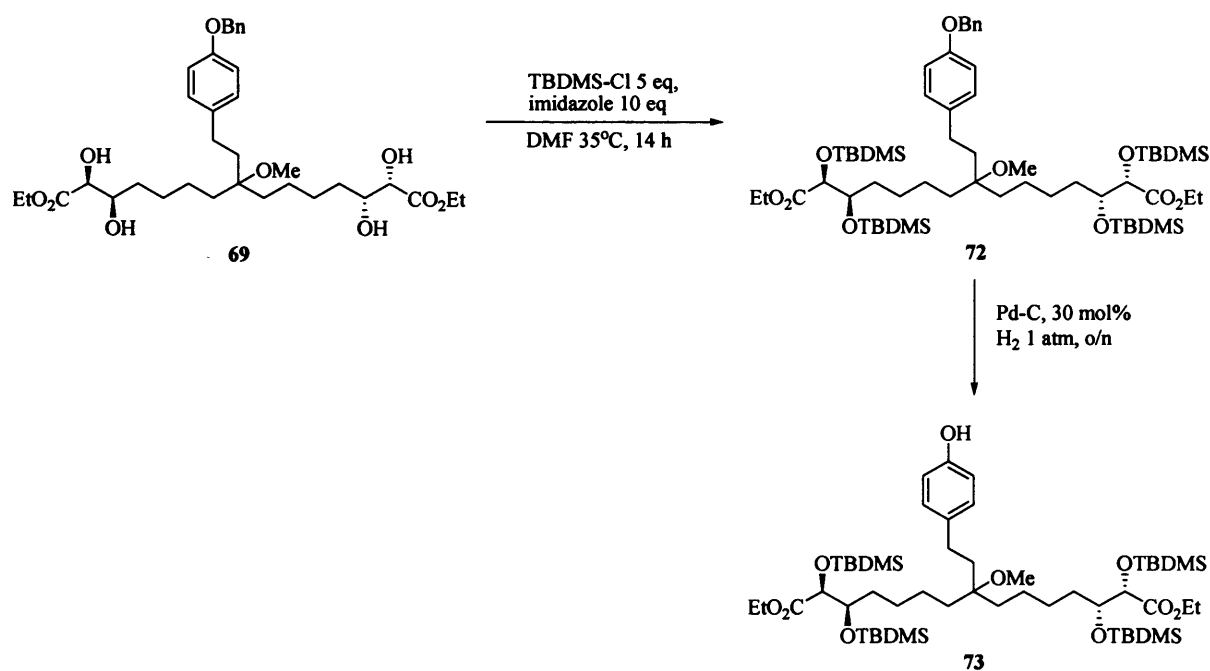
Scheme 2.14

Optimisation studies, for a phenol immobilisation (4-benzyloxyphenol), yielded slightly different reaction conditions than those used previously and these were subsequently used for the immobilisation of the tetra-TBDMS phenol **73** (Scheme 2.15). The reaction success was confirmed by mass analysis, microanalysis and FTIR which showed the presence of a carbonyl stretching frequency. De-silylation was mediated using six equivalents of TBAF and again the reaction completion was confirmed by microanalysis, mass change and FT-IR.
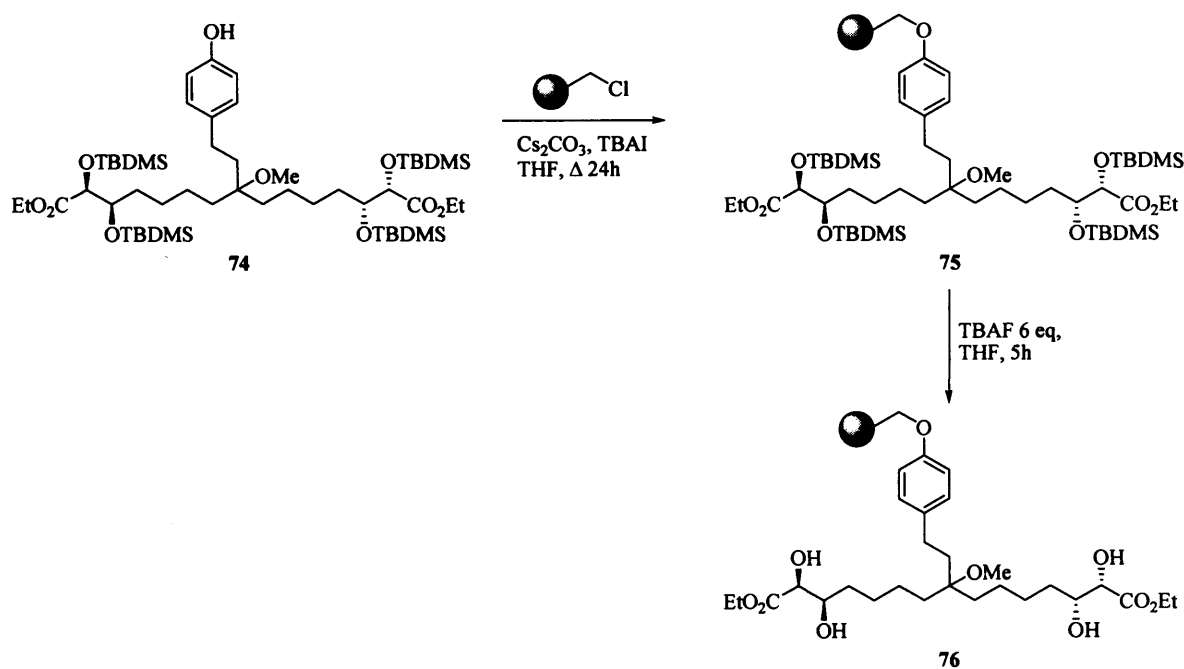
Scheme 2.15

Testing of the new ligand **76** was warranted after its successful synthesis and, as in previous assays, (*E*)-cinnamyl alcohol was chosen as the epoxidation substrate (Scheme 2.16).
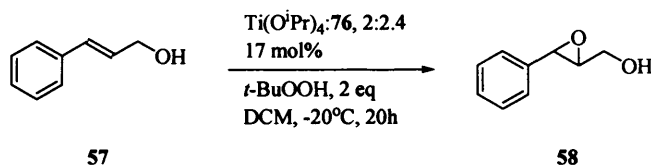
Scheme 2.16: Immobilised ligand test.

Gas chromatographic analysis of the epoxidation mixture after 20 hours showed consumption of the cinnamyl alcohol **57** but the synthesised epoxy cinnamyl alcohol **58** was racemic. This represented a major setback, as the bound catalyst system thus seemed to have fundamental flaws. Experimental observations provided a possible answer to the problem: when the polystyrene resins came into contact with dichloromethane significant swelling of the polymer occurred (>3 x original volume). One can postulate that this swelling of the resin resulted in the ligand **76** being "obscured" from epoxidation reagents Ti(O^{i}Pr)$_4$, *t*-BuOOH and cinnamyl alcohol and hence the catalytic complex did not form and therefore non-enantioselective epoxidation was mediated by the free Ti(O^{i}Pr)$_4$. The length of the linker was probably an additional contributing factor to this too; the link between the polymer matrix and the active ligand centres was approximately seven chemical bonds and this is arguably insufficient to accommodate the

sterically encumbered catalytic complex. Therefore it is highly likely that the catalytic complex never formed resulting in non-stereoselective asymmetric epoxidation.

At this stage in the research a pause for contemplation was required. The ligand system **51** still remained viable but it seemed that the synthesis required to produce a functional system would be too convoluted in comparison to the simplicity and low cost of the standard SAE. The answer to the conundrum had actually presented itself in the model ligand studies, not previously mentioned: the ligands **56a-e** could be recovered post-epoxidation. These ligands proved to be chemically robust and tolerated the epoxidation conditions therefore further studies using these ligands was undertaken to determine whether their recovery and recycling was feasible (*cf.* tartrate polymerisation, epimerisation). Initial ideas were to take advantage of the associated high polarity of the tetra-ol ligands and recover them by simple solvent extraction/precipitation techniques nonetheless, the efficacy of the ligand system had to be further probed and therefore the study was expanded to include reaction condition effects, different ligands **56f,g** and different allylic alcohol substrates.

Further epoxidations using the ligand series **56a-e** were carried out using (*E*)-cinnamyl alcohol as the substrate, in order to determine the effect of catalyst loading and reaction temperature dependence (Table 2.4).

Table 2.4: Further epoxidation screening

Entry	Ligand No.	R	n	Complex / mol %	Temp / °C	ee after 20 h / %	Complete consumption of S.M.
1	**56b**	Et	4	21	0	88	N
2	**56d**	Et	6	21	-20	96	Y
3	**56d**	Et	6	21	-10	99	Y
4	**56d**	Et	6	21	0	96	Y
5	**56d**	Et	6	21	RT	76	Y
6	**56d**	Et	6	10	-20	98	Y
7	**56d**	Et	6	5	-20	89	N
8	**56e**	Et	8	21	-20	96	Y
9	**56e**	Et	8	21	RT	77	Y
10	**DIPT**	-	-	21	-20	99	Y

Ti(OⁱPr)₄:lig, 2:2.4
t-BuOOH, 2 eq
DCM, 20h

57   **58**
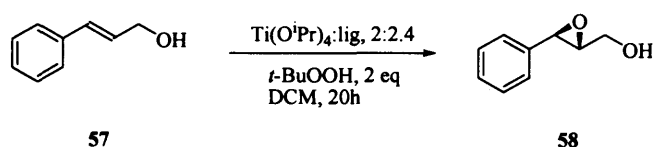
No chemical yields were obtained because the study was used as a screening procedure; the complete consumption of starting material (S.M.) was deemed to be sufficient. The majority of

SAEs are run at -20°C and so a series of experiments were undertaken to determine the effect of temperature on our novel epoxidation system (Entries 1,3,4,5 and 9). Increasing the epoxidation temperature to -10°C, entry 3, had no detrimental effect on the selectivity of the epoxidation, in fact a slight increase in epoxide ee was observed. Further increase in temperature, entry 4, with the same ligand **56d** led to an epoxide ee of 96%, identical to that observed at -20°C, contradicting the expected drop in ee due to the increase fluxionality at higher temperatures. As expected, epoxidation at room temperature, entry 5 and 9 resulted in a significant drop in epoxide enantiomeric excess by approximately 20%). Epoxidation at 0°C using **56b** resulted in a drop in ee of the epoxide product (4%) but as shown, epoxidation with ligand **56d** at 0°C did not lower the epoxy-alcohol ee. The shorter chain length of **56b** may infer a greater temperature dependence in the resulting catalytic complex formed and therefore, furnishing the epoxy-alcohol **58** with the lower ee observed.

The effect of ester variation was also investigated. The methyl ester **56f** was synthesised by oxidation of 1,10-decanediol **52d**, *bis*-MR-HWE of the dial **54d** and, finally, *bis*-AD of the *bis*-α,β-unsaturated ester **77** furnishing the ligand **56f** in moderate overall yield (Scheme 2.17).
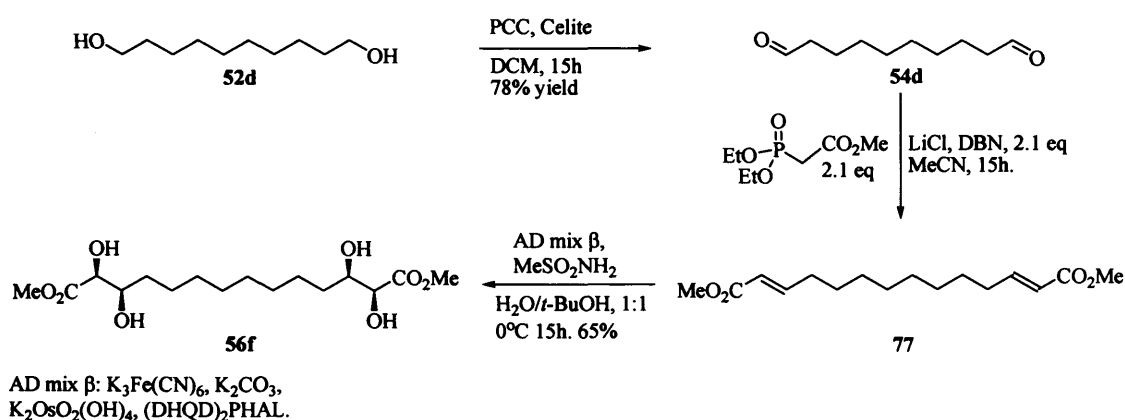
Scheme 2.17

The appeal, simplicity and expedience of alkene cross metathesis was irresistible and the vast majority of subsequent syntheses were to use this method. The selectivity in the production of exclusively (*E*) olefin (*cf.* 95% with MR-HWE, by ^{1}H NMR) was a further advantage in the ligand syntheses inferring higher selectivity in subsequent asymmetric dihydroxylation. Thus, the isopropyl ligand **56g** was synthesised by *bis*-cross metathesis between 1,11-dodecadiene **78** and isopropyl acrylate **79** furnishing the *bis*-α,β-unsaturated ester **80** in excellent yield. The ensuing *bis*-AD yielded some interesting results: during the AD reaction the heterogeneous slurry gelled. The reaction had to be shaken vigorously to break up this gel to ensure complete

dihydroxylation. The reaction work up proceeded as normal for these types of ligands yielding the crude ligand **56f** in good yield of 90%. However, attempts at recrystallisation proved to be cumbersome; the usual solvent system, chloroform/hexane, was employed and upon addition of sufficient hexane to prompt crystallisation, instead the compound formed an optically clear gel. This was unprecedented and practically challenging because the gel was most difficult to handle, but the gel was filtered and the solid washed with hexane yielding the pure ligand **56g** (Scheme 2.18). Further examples and an in-depth discussion can be found in Chapter 4.
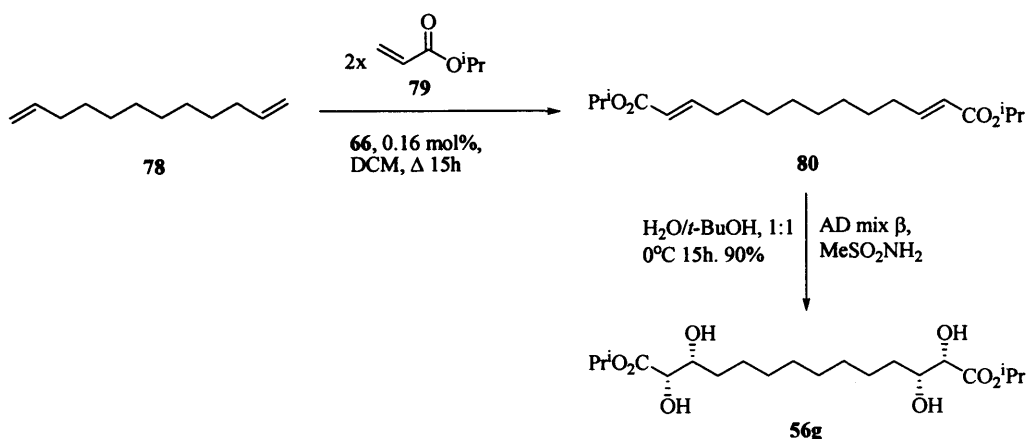
Scheme 2.18

The new ligands **56f-g** were tested in an identical manner as in previous screenings. The methyl ester **56f** derivative did not mediate epoxidation as effectively as the ethyl ester **56d** yielding the epoxy-cinnamyl alcohol in 78% ee (*ca* 20% less). The increased polarity of the methyl ester **56f** may have been a contributing factor, its solubility in dichloromethane was low and this could have resulted in the catalytic complex not forming to completeness. Therefore this could have resulted in non-enantioselective epoxidation with the remaining, free, Ti(O^{i}Pr)$_4$ thereby reducing the enantiomeric excess of the epoxy cinnamyl alcohol **58**. Conversely, the isopropyl ester **56g** provided the epoxy-cinnamyl alcohol **58** with slightly greater enantiomeric excess at -10°C and -20°C, 99% and 98% ee respectively (Table 2.5).

Table 2.5: Summary of ester variation

| Ligand No.	R	n	Complex / mol %	Temp / °C	ee after 20 h / %	Complete consumption of S.M
56d	Et	6	21	-20	96	Y
56f	Me	6	21	-20	78	N
56g	^{i}Pr	6	21	-20	98	Y
56g	^{i}Pr	6	21	-10	99	Y

An unanswered, but highly important question remained at this stage of the research and this was; what was the enantiomeric purity of the synthesised ligands? This avenue of research is pursued in Chapter 4, pages 100-105.

Initial re-isolation trials of the ligands after the epoxidation showed that the ethyl ester **56d** was prone to transesterification, forming the isopropyl ester, the isopropyl alcohol/alkoxide present in the epoxidation mixture thus results in the formation of a mixture of esters in the recovered ligand. Ti(O^{i}Pr)$_4$ is in fact documented as a catalyst for transesterification (due to its Lewis acidic nature) explaining the observed transesterification.[71] A solution to this problem was obviously to use the isopropyl ester ligand **56g**, the associated higher steric encumberment would hopefully prevent any transesterification or if this still occurred the ligand would remain the same (isopropoxide exchange). As hoped, a significant advantage associated with the highly polar ligand **56g** was the ease with which it could be separated from the epoxidation reaction by column chromatography. Therefore, the isopropyl ester **56g** was chosen for subsequent studies to determine the feasibility of recycling and re-using the ligand.

Thus far, the novel ligands performed well in the epoxidation of cinnamyl alcohol nevertheless, other allylic alcohol substrates had to be assayed to ensure that this result was not just a "one off" example. The new substrates **41, 82-83** had different olefin substitution patterns and electronic characteristics that would test the ligand **56g** in a more complete manner. In each substrate epoxidation, a tartrate mediated epoxidation was run simultaneously, using the same reagents and protocols ensuring a more accurate comparison (Table 2.6).

Table 2.6: Allylic alcohol variation.

Entry	Ligand No.	R	n	Complex / mol %	Temp / °C	Allylic Alcohol	ee after 20 h / %	Complete consumption of S.M	Isolated Yield / %
1	56g	^{i}Pr	6	21	-20	41	88	Y	41
2	56g	^{i}Pr	6	21	0	41	79	Y	58
3	*D*-DIPT	-		21	-20	41	88	Y	51
4	56g	^{i}Pr	6	21	-20	82	72	Y	52
5	*D*-DIPT	-		21	-20	82	83	Y	51
6	56g	^{i}Pr	6	21	-20	83	70	Y	34
7	*D*-DIPT			21	-20	83	87	Y	38
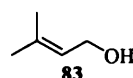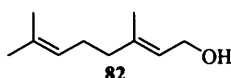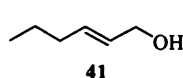
The induction on *trans*-2-hexene-1-ol **41** (another 2,3-disubstituted allylic alcohol) using ligand **56g** was directly comparable to tartrate mediated epoxidation as was the yield (Entries 1 and 2).

The asymmetric inductions using ligand **56g** on 2,3,3-trisubstitued allylic alcohols **82,83** were not as high as tartrate mediated epoxidation; the induction was 11% less with geraniol, **82**, and 17% less with 3-methylbut-2-en-1-ol **83**, although the isolated yields were still comparable. Thus further substitution at the 3 position resulted in the decrease in the corresponding epoxy alcohol enantiomeric excess. However, an advantage of the ligand system was observed during purification by column chromatography, the ligand **56g** having high polarity meant that the epoxy alcohols could be separated by flash chromatography (*cf.* tartrate where careful chromatography is warranted). The R_f of **56g** was less than 0.1 compared to values of around 0.4 for the epoxy alcohols in the typical solvent system (20% ether/petrol).

On the study of the *bis*-tartrate esters undertaken by Sharpless and co-workers only a 2,2,3-trisubstituted allylic alcohol was investigated and the ees achieved were very similar to tartrate.[32] Therefore, an extra substitution at the 3-position has a more pronounced effect than further substitution at the 2 position.

$$R = {}^iPr \qquad \textbf{56g, y = 4} \qquad \qquad \textbf{84}$$
$$X = O^iPr$$
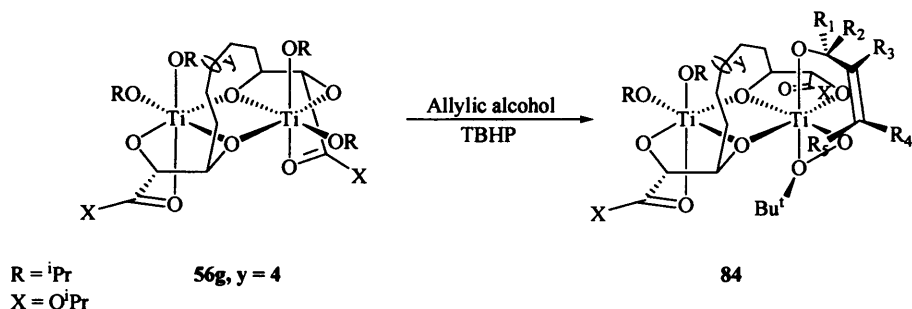
Scheme 2.19:

Assuming the ligand **56g** forms the catalytic complex in a similar manner to that from tartrate, the complex **84** could be a reasonable illustration of the active catalyst structure (Scheme 2.19). The alkyl backbone increases the steric crowding of this complex compared to the complex derived from tartrate **24** (Scheme 1.14) and it is conceivable that this "strap" may modify recognition characteristics of the enantioselective system in question.

Consider the co-ordination of the allylic alcohol at the right hand side titanium on the active complex, **84**: One can postulate that the extra substitution of a 2,2,3-trisubstituted substrate would not affect the "business" end of the epoxidation as much as the extra substitution on a 2,3,3-trisubstitued substrate. In the tartrate derived complex this effect is less significant, however, in the catalyst **84**, the alkyl "strap" yields a more sterically encumbered oxygen transfer site and the substitution change of R^5 = H to a larger moiety such as methyl would have a greater effect on the adopted conformation of the catalytic system. Therefore, it is plausible

that the asymmetric induction is affected to a greater extent in this case of 2,3,3-trisubstituted allylic alcohols, leading to the observed reduction in epoxide excess. Nevertheless, in optimum cases, the ligand **56g** was directly comparable to tartrate mediated epoxidation in both enantiomeric excess and yield of the epoxide and further strategies were developed.

A series of experiments were devised to investigate the viability of ligand recycling. The most important aspect of this study was to recover the ligand and determine its induction in subsequent epoxidations and therefore, only the recovery of the ligand was optimised during the work-up procedures utilised. The practical implications of destroying the catalytic species in solution to maximise the ligand recovery were not trivial; initial attempts at efficient recovery of the ligands proved unsuccessful in that the yield of the recovered ligands used was low. These methods included column chromatography of the complete epoxidation mixture and removal of the epoxy-alcohol by selective precipitation of the ligand complex. However, the ligands could not be recovered in satisfactory yields (<40%) and the recovery required intense research into the nature and more important the co-ordination chemistry of the catalyst system. These initial studies had overlooked the "chemistry" of titanium alkoxide; titanium salts of chelates such as the ligands **56a-h** have the propensity to form stable insoluble poly-oxo materials. It was concluded that the ligands were remaining in the insoluble titanium salts as some unknown complex, preventing their extraction and therefore, methods were sought to destroy these complexes without detrimentally affecting the ligand.

The majority of methods used post epoxidation are designed to not only break down the catalyst complex but to hydrolyse, thus destroy, the tartrate ester used, nonetheless appropriate methods were found that circumvented ester hydrolysis but still resulted in efficient destruction of the titanium salts. (see Practical Considerations, pages 63 to 70). The high polarity of the ligands **56a-g** presented an auxiliary method for their purification and removing non-polar media from the post-epoxidation mixture by means of solvent protocols such as selective precipitation of the ligands, (*cf.* MPEG precipitation). A typical solvent precipitation procedure was to dissolve the epoxidation mixture in the minimum amount of chloroform (1 vol) and add to vigorously stirred pentane or hexane (*ca* 10 vol).

In a preliminary recycle run attempt (Table 2.7) the following work-ups were utilised:

i. Epoxidation reaction evaporated. The remaining residue was extracted with 20% ether/petrol and columned to obtain the epoxy alcohol. Residues from extraction treated with aqueous citric acid to destroy the insoluble titanium species added, then the ligand was extracted with ethyl acetate and finally washed with aqueous potassium carbonate. No ligand purification.

ii. Aqueous citric acid added at -20°C, ligand and epoxy alcohol was extracted with ethyl acetate and after an aqueous potassium carbonate wash the Epoxy-alcohol and ligand were purified by CC.

iii. Entire reaction mixture quenched with citric acid solution and ferrous sulphate then extracted with ethyl acetate and evaporated. The Ligand and epoxy-alcohol were subsequently purified by column chromatography.

Table 2.7: Initial ligand recycling

Recycle Run	Allylic Alcohol	Epoxide Yield / %	ee / %	Ligand Yield / %	Workup
0	41	81	89	90	I
1	41	80	82	84	Ii
2	41	57	73	83 (>99%ee)	Iii
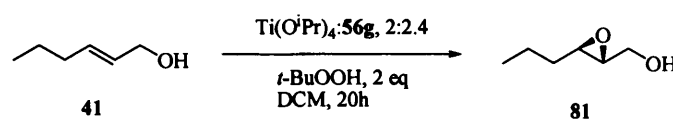
It was found that the ligand **56g** could be isolated in good yields and appeared sufficiently pure by ^{1}H NMR. However, the induction in subsequent runs was reduced by 16% ee over the three runs, although the reduction was not drastic it still represented a significant decline in selectivity. It was concluded that slight impurities in the ligand must be affecting the epoxidation in the later runs. Closer examination of the ^{13}C NMR spectrum of the ligand retrieved from run 1 showed a peak at 30.2 ppm (Spectra 2.1). This corresponds to the methyl groups of *t*-butanol and rough integration showed that it constituted *ca* 10 mol%. Therefore the mass of the ligand added was inaccurate, leading to imprecise addition of $Ti(O^iPr)_4$ and this overestimate of $Ti(O^iPr)_4$ would have resulted in non-enantioselective epoxidation by free "Ti". On a more promising note, these studies also revealed that after Run 2, the ligand had not lost any optical purity. The optical purity (see Chapter 4, pages 100 to 105) of the original ligand **56g** sample was >99% ee and this was retained after the three epoxidations therefore, this result led credence to the hypothesis that impurities were having a detrimental effect on the enantioselectivity.

Spectra 2.1

With the optical purity "guaranteed" this provided the vigour to prove the potential of the ligand **56g** and efforts concentrated on a method for purifying the ligand; it was found that a majority of the impurities post epoxidation, *t*-BuOOH, titanium salts, trace amounts of peroxide could be destroyed with sequential washing protocols (Table 2.8), which are summarised below:

Workup A: Aqueous citric acid added at -20°C, extract ethyl acetate, aqueous potassium carbonate wash, precipitate ligand in pentane. Epoxide purified by CC. Ligand purification; 2M sodium hydroxide wash, 2M hydrochloric acid wash, and potassium carbonate wash.

Workup B: Aqueous citric acid added at -20°C, extract ethyl acetate, aqueous potassium carbonate wash, purify epoxide and ligand by CC. Ligand further purified; 2M sodium hydroxide wash, 2M hydrochloric acid wash, and potassium carbonate wash.

Workup C: Acid sensitive protocol; Add 1 ml water per mmol epoxy alcohol, dry with magnesium sulphate, filter epoxidation mixture through Celite®, purify CC. Titanium-sieves-magnesium sulphate residue treated with aqueous citric acid and extracted with ethyl acetate to recover any ligand complexed with titanium.

The aim of this second study was to purify the ligand ensuring that the ligand added was free of any *t*-butanol and inorganic titanium residues that could falsify any mass measurements; the success of this study is shown in Table 2.8.

Table 2.8: Ligand recycling

| Recycle Run	Allylic Alcohol	Epoxide Yield / %	ee / %	Ligand Yield / %	Workup	Melting point/°C
0	41	63	86	82	A	100-102
1	41	47	84	77	A	100-101
2	41	50	82	52	B	99-101
3	57	26	97	81	C	98-100
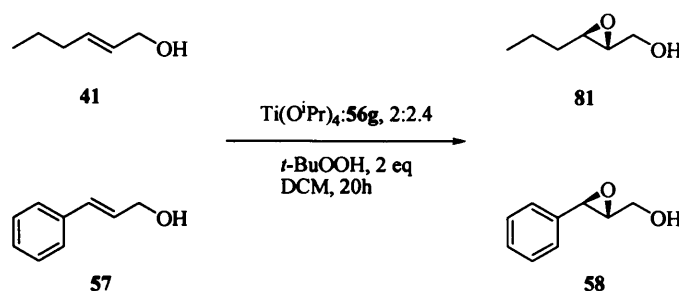
From Table 2.8 it can be seen that in recycle run 1 and 2 the epoxide ee was only slightly reduced (2–4 %) and the recycling of the ligand was consistent for run 0 and 1 using work up procedure **A**. A reduced ligand yield of 52 % after run 2 can be attributed to the different workup procedure, **B**. In the final run a different substrate was chosen to prove the flexibility of the ligand **56g**, cinnamyl alcohol was chosen and the corresponding epoxy alcohol was produced in a highly selective manner 97% ee and good yield of ligand 81 %. The low yield of the epoxy alcohol are attributed to the lack of optimisation in recovery, indeed the relative volatility of propyloxiranemethanol **81** was also an attributing factor as is the high reactivity of epoxy-cinnamyl alcohol. Work up procedure **A** was the most efficient and more importantly the most simple, involving simple solvent extraction/precipitation techniques and avoiding column chromatography.

The melting point of the recovered ligand provides an insight into the purity; unsurprisingly authentic material had the marginally higher melting point of 100-102°C nonetheless, the melting point of the ligand **56g** after subsequent recycle runs remained relatively constant and indicates the presence of slight impurities. Therefore, the "clean up" procedures used yielded the ligand **56g** sufficiently pure and no degradation of the ligand occurred. This supposition is reinforced by the ^{1}H and ^{13}C NMR of the recycled catalysts, samples of these spectra after Run 1 (Spectra 2.2 and 2.3) and 3 (Spectra 2.4 and 2.5) are shown below.
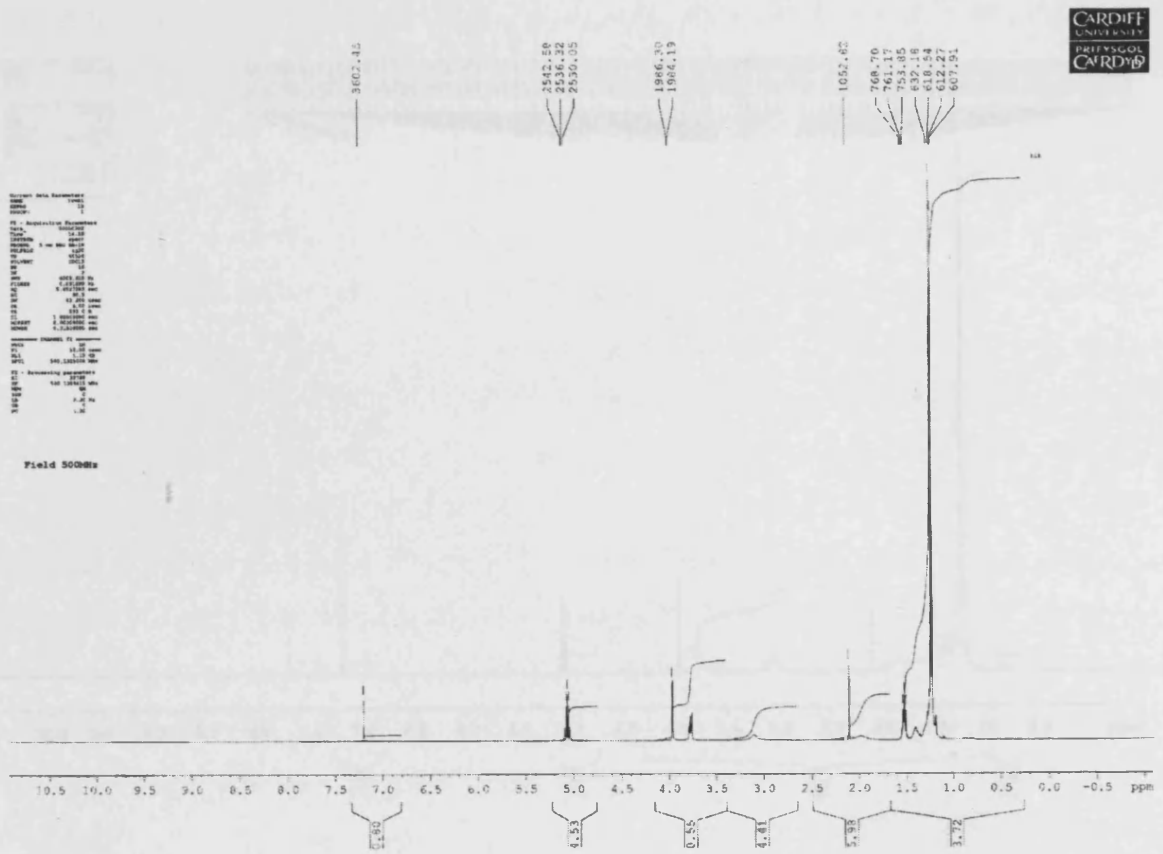
Spectra 2.2

Spectra 2.3
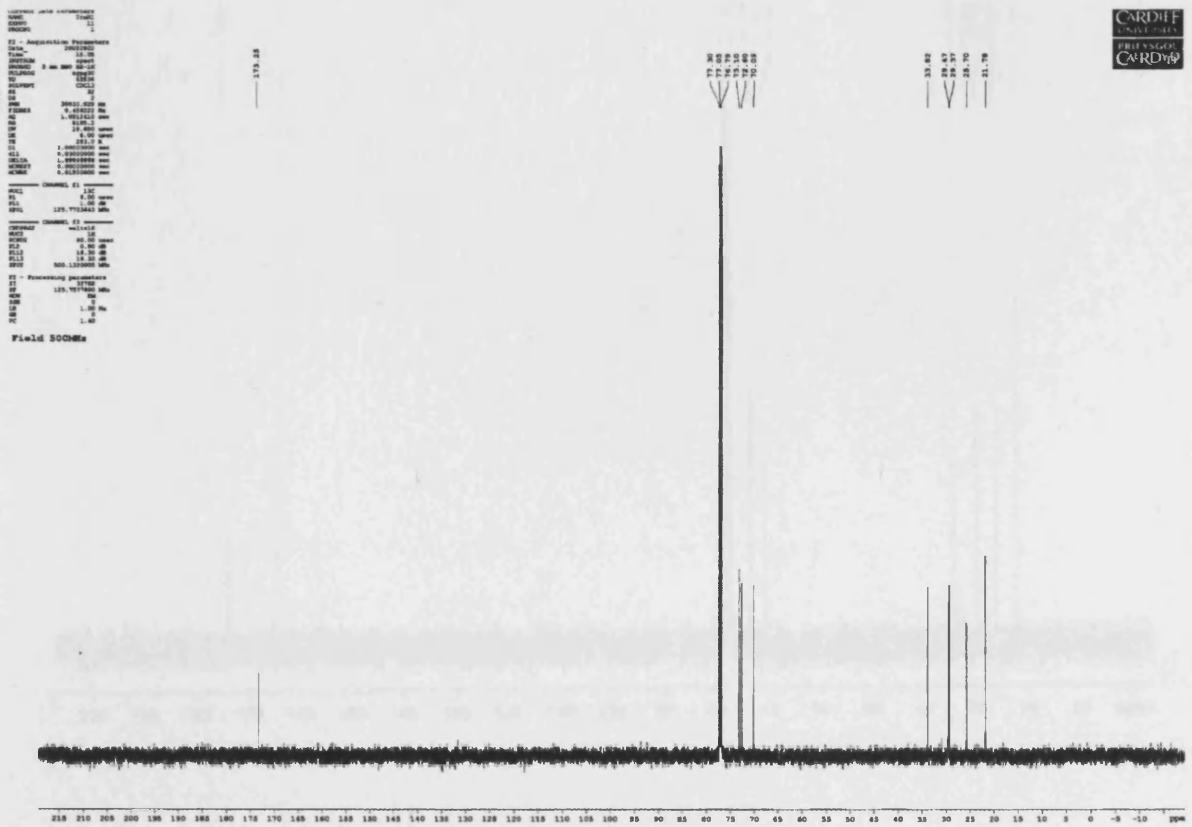
Spectra 2.4

Spectra 2.5

These results symbolise the design and development to what is a novel, recoverable and in optimal cases a highly efficient ligand **56g** for Sharpless asymmetric epoxidations and represents the leader in the field in such research.

The main objective of the project had been completed but nonetheless, further avenues of investigation still remained: the only reactions undertaken with novel ligands to date was the enantioselective epoxidation of (*E*)-allylic alcohols. Therefore, the scope of the study was expanded to include a (*Z*)-allylic alcohol **85**, homoallyic alcohols **87a-b** and, more contentious, the kinetic resolution of racemic (*E*)-allylic alcohols was to be studied (Schemes 2.21 and 2.22). Previous studies by Sharpless and co-workers, as reviewed earlier, had concluded that for kinetic resolution, the redundant ester *did* play a subtle enabling role in this process, although the phenomena had not been explained, (Scheme 1.20, Table 1.2).[36] Therefore, there existed literature precedence that our ligand system (*e.g.* **56g**) would not mediate kinetic resolution of racemic allylic alcohols to the required degree of diastereoselectivity and the experiments were only carried out as a matter of completeness.

The (*Z*)-allylic alcohol **85** was epoxidised using cumene hydroperoxide (CHP) as the oxidant because this peroxide mediates the epoxidation at a faster rate and was used as a precaution just in case the (*Z*)-substrate was more sluggish (Scheme 2.21). The epoxidation proceeded smoothly, yielding the epoxy-alcohol **86** in 63% yield and with an enantiomeric excess of 67%. Tartrate-mediated epoxidation furnishes the epoxy-alcohol **86** with *ca* 80% ee. Therefore, the complex(es) derived from ligand **56g** was not quite as selective as tartrate.[22]


$$\text{85} \xrightarrow[\substack{\text{DCM, 20h, -20°C} \\ \text{CHP, 2 eq}}]{\text{Ti(O}^i\text{Pr)}_4\text{:56g, 2:2.4}} \text{86}$$
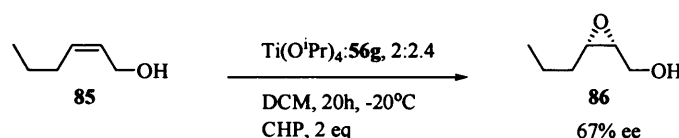
Scheme 2.21

Homoallylic alcohols[20] are renowned for being poor substrates in the SAE and the reactions carried out were in agreement: Attempted epoxidation of the homoallylic alcohols **87a-b** was unsuccessful; after 20 hours none of the corresponding epoxy-alcohol could be detected by ^{1}H-NMR (Scheme 2.22).
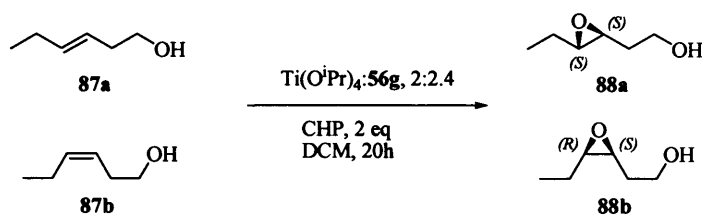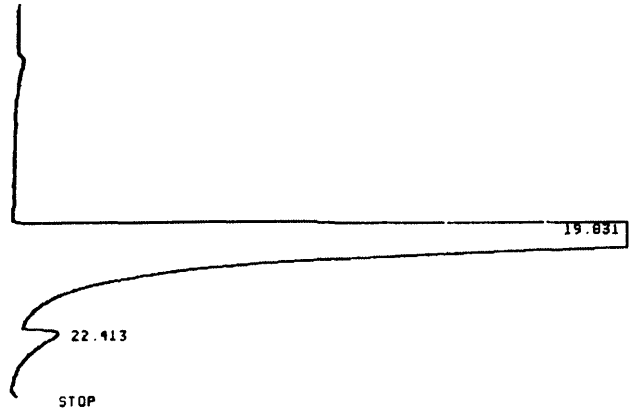
Scheme 2.22

Unperturbed, the next investigations were the kinetic resolution of the two racemic allylic alcohols **89** and **91**, having literature precedence for high reaction rates and excellent diastereoselectivty in "standard" SAE reactions. The substrate choice would also provide an insight into the effects of steric bulk at the catalyst complex: **89** encompassing a large steric bulk and the substrate **91** is comparatively much smaller (Scheme 2.23). The oxidant used was again cumene hydroperoxide to ensure a fast reaction rate and the amount added, 0.6 eq, ensured that reaction went to over 50% completion, and hence, if any significant resolution occurred, then the residual allylic alcohol would have the maximum enantiomeric excess, thus obviating the need to follow the reaction by gas chromatography.
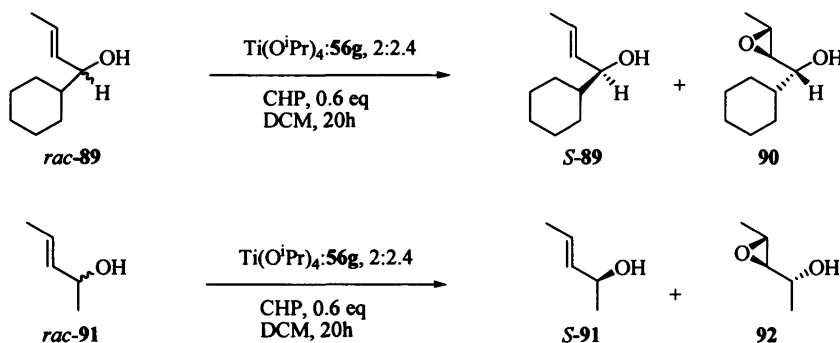
Scheme 2.23

Surprisingly, in view of Sharpless's previous results, the ligand **56g** did mediate the kinetic resolution (KR) of the racemic allylic alcohols **89** and **91**; the first substrate analysed, *rac*-**89**, showed an enantiomeric excess of 72% and 68% yield, compared to a tartrate-mediated resolution of >96% ee. The second substrate, *rac*-**91**, was resolved sufficiently to provide the allylic alcohol *S*-**91** with >99% ee (by GC, Trace 2.1); clearly the less sterically demanding allylic alcohol **91** was a more favourable substrate than the more sterically encumbered allylic alcohol **89**. To investigate the KR further, more allylic alcohols were synthesised and assayed and the experimental results for all kinetic resolutions examined are summarised in Table 2.9.
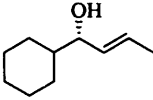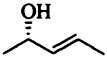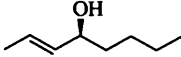
Trace 2.1

19.831

22.413

STOP
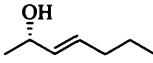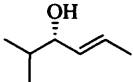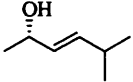
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AREA%
      RT      AREA TYPE  WIDTH    AREA%
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   3.049    78074   VV   .028    .10295
   3.130    56098   VH   .030    .07397
   3.182 50687008 >SHB   .098   66.83837
   3.775     6229   BH   .040    .00821
   3.885 13498416  SHB   .049   17.79967
   4.107    11842   BP   .072    .01562
   4.280  4856074  SPB   .076    6.40345
   5.048   122389   PB   .083    .16139
  12.994    39299   PV   .136    .05050
  19.831  6443059   BV   .590    8.49719
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MUL FACTOR=1.0000E+00
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Table 2.9: Kinetic resolution summary.
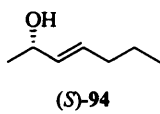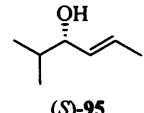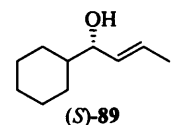
Entry	Allylic Alcohol	Enantiomeric Excess of (S)-Allylic Alcohol	Eq of Cumene hydroperoxide added
1	OH, (S)-89	72 %[a]	0.6
2	OH, (S)-91	>99 %	0.6
3	OH, (S)-93	90%	0.6
4	OH, (S)-94	>99 %	0.6
5	OH, (S)-95	95±3 %	0.6
6	OH, (S)-96	>99 %	0.6

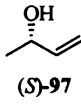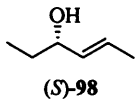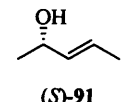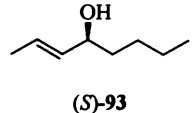a: Representative isolated yield of allylic alcohol **89** was 68% based on the reaction proceeding to completion (*i.e.* 60% conversion of allylic alcohol). On the same basis the epoxide **91** yield was 61%.

Removal of the β-branch (β to hydroxyl) but maintaining the high aliphatic nature (entry 3), the enantiomeric excess of the resolved allylic alcohol **93** was 90% ee. Another β-methyl substrate, **94**, but with a higher molecular mass, entry 4, was resolved to as high a degree as the allylic alcohol **91**. Clearly, the lack of steric bulk in this region of the allylic alcohols results in the most selective kinetic resolutions. Entry 5 represents another example of an β-branched substrate **95** directly comparable to the cyclohexyl substrate **89**. This allylic alcohol, **95**, was resolved selectively (*ca* 95% ee) but not to quite the spectacular extent as shown by other substrates. To further probe the effect of branching, one final substrate **96** was chosen, entry 6, wherein the branching was placed at the opposite side of the allylic alcohol. This substrate was resolved as selectively as racemates **91** and **94**, proving that branching and high a degree of steric encumberment alpha to the hydroxyl (**89** and **95**) had a deleterious effect on the fundamental recognition characteristics of the catalytic complex.

Of noteworthy interest is that, from literature examples,[33] in some cases (D)-DIPT did not mediate kinetic resolution as effectively as the ligand **56g**; and a comparison is shown in Table 2.10.

Table 2.10: Tartrate and ligand 56g mediated KR

Entry	Allylic Alcohol	56g mediated KR: ee of (S)-Allylic Alcohol	(D)-DIPT mediated KR: ee of (S)-Allylic Alcohol
1	OH (S)-97	-	88%
2	OH (S)-98	-	92%
3	OH (S)-91	>99 %	89%
4	OH (S)-93	90%	-
5	OH (S)-94	>99 %	-
6	OH (S)-95	95±3 %	90%
7	OH (S)-89	72 %	>96%

Entries 3 and 6 clearly show that the ligand **56g** mediates kinetic resolution to a higher degree of enantioselectivity than (D)-DIPT. However, it is documented that DIPT is not the most efficient kinetic resolution catalyst, the optimum is dicyclododecyl tartrate closely followed by dicyclohexyl tartrate nonetheless, these more efficient tartrates are not commercially available thus, their synthesis would be required.

The efficiency of the KR resolution depends on the relative rate difference of the two diastereomeric reaction pathways to be sufficient. Indeed to obtain good resolution results one requires a relative epoxidation rate difference greater than 5-10 (k_{rel} > 5-10). One can also use the analogy of matched and mis-matched pairs: A matched pair is exemplified by the catalytic complex formed from **56g** and the substrate (*R*)-**91** resulting in one diastereoselective pathway (epoxidation of *R*-**91**) being much more favoured, resulting in the very slow reaction of *S*-**91** and therefore yielding this residual epoxy-alcohol in a large enantiomeric excess, the mis-matched pair thus being the catalytic complex derived from **56g** and the allylic alcohol (*S*)-**91**. Considering the catalytic complex **84**:
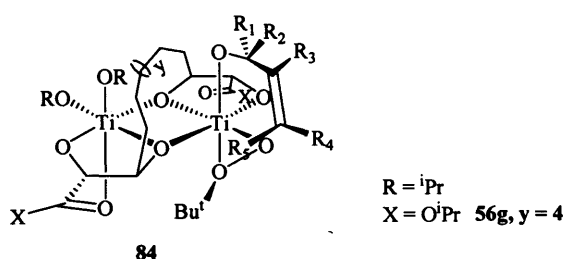
One can envisage that substitution at the methylene adjacent to the hydroxyl of the allylic alcohol (*i.e.* $R^1 \neq H$) would result in an increase in the steric repulsion with the hydrocarbon "strap" altering the ground state structure. Allylic alcohol **89** is the most sterically demanding at this position (substituted at R^1 = cyclohexyl) and this could result in a ground state that provides two diastereomeric reaction pathways of insufficient energy difference to mediate maximum resolution (*i.e.* k_{rel} < 10). Thus, concordantly by the Arhenius expression the rate constants of these two pathways will be closer, resulting in the observed lower enantiomeric excess of the allylic alcohol. The steric demand is less when allylic alcohols **93** (R^1 = *n*-hexyl) and **95** (R^1 = isopropyl) are the reactants and a drop in ee is observed but to a lesser extent, thus lending credence to the above hypothesis of the hydrocarbon strap affecting the magnitude of the kinetic resolution diasteroselectivity.

The observed increase in KR efficacy in some cases can most likely only be rationalised by invoking the phenomenon of the ligand by-stander effect,[33] the novel ligand **56g** exerting this effect that is, most probable, steric in nature. In the publication by Sharpless and co-workers in this area, a slight increase in ee (+3% ee) was observed when $Ti(O^tBu)_4$ was used instead of $Ti(O^iPr)_4$ in a tartrate mediated KR of alcohol **91**, the effect of the increase being smaller than observed in our system but this still adds credibility to the supposition of a ligand by-stander effect.

It is also not unreasonable to hypothesise that the novel catalyst system derived from the ligand **56g** has advantages over tartrate only in a certain "window" of substrate selection and that beyond this window, the tartrate-mediated KR is more selective and/or equally effective. From the present results, it is clear that this window was found in the substrates with small steric demand β-to the hydroxyl, [*e.g.* **91**, **94**] and less favourable, more sterically encumbered substrates were also found, such as **89**.

Practical Considerations[40-42]

Reagents:

Substrate. *Trans*-Cinnamyl alcohol was the allylic alcohol chosen to test the majority of the ligands synthesised. The reasons for choosing this allylic alcohol was that the epoxy-alcohol product is sensitive and not particularly volatile thereby allowing its isolation on a small scale and therefore, the substrate was a good and challenging assay choice. The liquid substrates (*e.g. trans*-2-hexen-1-ol **41**) can be pre-dried over 4Å molecular sieves prior to injection to ensure the absence of water.

Titanium alkoxide. Titanium tetraisopropoxide (titanate), $Ti(O^iPr)_4$, has been almost the only metal alkoxide used in asymmetric epoxidation and kinetic resolution reactions and was used as received from the supplier (Aldrich). When observed ees for a known reaction showed reduction, it can be a sign of impure titanate, in which case it can be purified by vacuum distillation (b.p 78-79°C/1.1 mm Hg) or alternatively and more preferable to purchase a new batch due to the low cost. $Ti(O^iPr)_4$ is moisture sensitive and is best transferred *via* syringe or cannula. $Ti(O^tBu)_4$ can also be used in the epoxidation of primary alcohols when epoxide ring opening is problematic or transesterification is likely. However, $Ti(O^tBu)_4$ is more expensive and not recommended when the substrate is a secondary allylic alcohol, because the relative rate constant obtained when using complexes derived larger alkoxide are lower than that with $Ti(O^iPr)_4$.

Dialkyl tartrates. DET and DIPT are the chiral auxiliaries most often used in either the stoichiometric or catalytic asymmetric epoxidation, the choice being irrelevant in terms of enantioselectivities except in the asymmetric epoxidation of allyl alcohol itself.[22] DMT is useful when a water-soluble tartrate is needed. Tartrate choice is much more critical in kinetic resolution reactions since k_{rel} increases in the order DMT < DET < DIPT. The highest

selectivities in kinetic resolutions have been obtained using dicyclododecyl tartrate, although DIPT has remained the tartrate of choice, because it is the most readily available and provides acceptable results. [22] Like $Ti(O^iPr)_4$, the tartrate ester can be used as received from commercial sources, but if sub-standard selectivities are obtained, the alkyl tartrate can be purified by distillation under high vacuum.

Organic peroxide. *t*-Butyl hydroperoxide, *t*-BuOOH (TBHP), is the most often used oxidant in asymmetric epoxidation and kinetic resolution reactions. It is available as a 70% solution in water, but preparation of anhydrous solutions is necessary. Anhydrous decane, nonane and isooctane solutions are commercially available (Aldrich Chemical Company). Sluggish epoxidations of some substrates were discovered, when using *t*-BuOOH in decane/nonane/isooctane.[22] This phenomenon has been attributed to the resulting change in solvent polarity due to the addition of such non-polar hydrocarbon solutions to polar dichloromethane reaction solution). It is well documented that dichloromethane is the solvent of choice as it provides enhanced reaction rates and enantioselectivities, therefore solutions of *t*-BuOOH in dichloromethane can be prepared to remedy this if required. However, it has been reported that storage of TBHP in halogenated solvents such as dichloromethane or 1,2-dichloromethane even at freezer temperatures result in oxygen release and the risk of explosion. Stable anhydrous TBHP in toluene/benzene solutions can be easily made and stored without decomposition, but there is an inherent danger when making anhydrous TBHP solutions of any nature.[72] Therefore, during all the present investigations, only commercially available anhydrous TBHP sources were used obviating any possible accidents and perceived dangers (TBHP 5.0-6.0M in decane).

Commercially available cumene hydroperoxide (80% or 88% solution in cumene) can be used too, as there is no reported loss in enantioselectivity and epoxidations are faster than when using TBHP. The only disadvantage of using cumene hydroperoxide is that the products are more difficult to isolate and careful chromatography of the reaction residue is required and is more troublesome.

To ensure the maximum epoxidation rate and enantioselectivity, it is generally desirable to pre-treat the desired quantity of hydroperoxide. Before each epoxidation, a sufficient quantity of the peroxide in question was dried with activated 4Å molecular sieve beads for approximately thirty minutes to remove any adventitious water that may be present due to natural decomposition of the hydroperoxide or absorbance from the surrounding air during manipulation.

Reaction solvent. Anhydrous dichloromethane is the solvent used in all epoxidation and kinetic resolution reactions, due to the associated high rate of epoxidations and enantioselectivities. Relative epoxidation rates using diethyl ether as the solvent are an order of magnitude less than dichloromethane, likewise epoxidation rates using pentane as the reaction medium results are decrease by around 70%.[24] It is supposed that these differences reflect the presence of a different aggregation state of the Ti-tartrate in the different solvents. However, the dichloromethane must be free of chelating solvents such as methanol, which decrease the rate by an inhibitory mechanism (Equation 1, page 13) and thus the yield and enantiomeric excess of the epoxy-alcohol product. The use of reagent grade dichloromethane usually results in roughly a 10 % reduction in rate while reactions in dried solvent or reagent grade solvent in the presence of 3Å or 4Å molecular sieves proceed at the same rate. Of noteworthy interest is that distillation from calcium hydride is ineffective at drying dichloromethane sufficiently, reactions using this source of solvent proceed at the same rate as reagent grade material.

Molecular sieves. The use of activated (Chapter 5, page 113) 3 or 4 Å molecular sieves (zeolites) is essential to accomplish both SAE and kinetic resolution in a catalytic manner. Their use in the stoichiometric reaction is also highly recommended. The amount added is not critical, so long as the peroxide and alcohol are pre-dried. Their role is to scavenge any water present in the solvent or which is produced during the SAE, which would otherwise hydrolyse the active complex, leading to a lower rate, yield and/or enantiomeric excess. In the absence of titanium, molecular sieves alone do not induce the disappearance of allylic alcohol at a significant rate. Therefore, and because of this, it is believed that the molecular sieves do not alter the catalyst structure and do not accelerate the reaction but serve only to remove moisture.

Reaction conditions:[41,22]

Asymmetric epoxidations can be run stoichiometrically (50% or more catalyst) or catalytically (5-10% catalyst). The use of the minimum amount of catalyst is recommended because the reaction products are more easily isolated. The catalytic complex is prepared *in situ* because it is unstable over long periods of time. Upon addition of the titanium tetraisopropoxide, chiral ligand and peroxide, aging of the active complex is required for the system to reach a stable equilibrium. This is very important and must be adhered to in catalytic SAEs. Also, the use of at least 10% excess tartrate over Ti(OiPr)$_4$ is essential in order to obtain optimal results (a ratio of 2.4:2 is recommended), ensuring no free titanium alkoxide is present that would otherwise reduce the enantiomeric excess by a non-enantioselective epoxidation pathway. Nonetheless, too large an excess of tartrate results in the formation of an inactive monomeric *bis*-tartrate

titanium complex [Ti(tart)$_2$], thereby reducing the epoxidation rate and therefore the optimal tartrate-Ti ratio must be adhered to ensure optimal epoxidations, clearly a narrow window.[24]

The low temperature of the reaction (*e.g.* -20°C) is essential due to a number of factors. The active complex is highly fluxional, which is of course proportional to temperature. Therefore, at lower temperatures, the active complex is in a lower state of flux and one would assume it is more selective in the SAE, *i.e.* can give higher enantiomeric excesses in the product. At increasing temperatures, the substrate molecules have sufficient kinetic energy (KE > E_a) for the competing diastereomeric reaction pathway, leading to a lower enantiomeric excess in the epoxy-alcohol. Side reactions are an issue at elevated temperatures due to the relatively reactive reagents used in SAEs; these including epoxide ring opening and transesterification of the tartrate/chiral ligand.

Substrate concentration is also an important aspect. In the epoxidation of cinnamyl alcohol, the product epoxy-cinnamyl alcohol is a relatively reactive compound and hence, the substrate concentration needs to be kept below 0.1M to minimise side reactions (mainly epoxide ring opening). When the tetra-ol ligands **56a-g** are used, the quantity of solvent needs to be adequate due to their low solubility in dichloromethane (0.1M is sufficient when using **56g**, others require slightly lower concentrations, *ca* 0.08M).

Finally as mentioned above, the SAE is sensitive to moisture and therefore these reactions must be run under anhydrous conditions using flame/oven-dried glassware and a dry nitrogen atmosphere.

Work up.[41] Alkyl hydroperoxides can be dangerous and must be treated with due respect especially when used on a large scale. If warranted, on safety grounds, excess hydroperoxide can be quenched before reaction work up and purification. The following methods can be used, but their compatibility with the epoxy-alcohol product must be considered carefully.

If the epoxy-alcohol has sufficient molecular mass and is therefore relatively involatile, excess TBHP can be removed by azeotropic evaporation with toluene, using a standard Büchi apparatus with a water bath at 50-60°C. This method has been successfully utilised on a mole scale. Chromatography can also be used with high efficiency to remove excess hydroperoxide. In order to destroy excess peroxide, many reagents can be used including aqueous ferrous sulphate, aqueous sodium sulphite, sodium hydrogen sulphite, sodium borohydride (which also forms water soluble borate esters with tartrate), dimethyl sulphide, trimethylphosphite and triphenylphosphine. Trimethylphosphite is the recommended reagent for reducing excess TBHP, because it reacts completely and rapidly at low temperature and because trimethylphosphite and trimethylphosphate are volatile and can be removed under high vacuum. On the scales used in

our studies, the dangers were deemed to be sufficiently low and the alkyl peroxides were removed during chromatographic purification. On the occasions where the organic peroxides were quenched, the organic extracts were washed with saturated aqueous ferrous sulphate.

Titanium removal.[31] It is often desirable to remove titanium species from the product because titanium tetraisopropoxide (a Lewis acid) has a tendency to increase the reactivity of the epoxide leading to side reactions. Aqueous methods include the addition of citric and tartaric acid solutions (10 %) resulting in a biphasic solution in which all the titanium is present in the aqueous layer as a titanium-acid complex. For acid sensitive substrates, saturated aqueous sodium sulphate can be added instead (1 ml per mmol), resulting in the formation of an insoluble titanium complex

Epoxy-alcohols are synthesised that have different properties and stabilities and therefore it necessary to treat them in the correct manner to avoid unwanted side reactions and/or loss of material.

With acid sensitive epoxy-alcohols such as epoxy-cinnamyl alcohol the work up must avoid any unnecessary exposure to acid. Therefore, the active complex and tartrate ligand are destroyed by addition of 1 – 2 ml per 1 mmol of tartrate of 10% sodium hydroxide saturated with sodium chloride.[41] The sodium hydroxide is saturated with brine to ensure that the organic phase remains free of base as this can also cause epoxide opening (*e.g.* Payne rearrangement). Addition of magnesium sulphate and celite®, to aid filtration, gives a solution containing the epoxy-alcohol, excess hydroperoxide and alcohol ready for further purification.

For relatively stable epoxy-alcohols (*e.g.* propyloxiranemethanol), as previously mentioned, aqueous citric/tartaric acid work up is appropriate, together with an aqueous or organic reducing agents to decompose the excess hydroperoxide. The preferred metod in our studies was the addition of a saturated aqueous citric acid solution (1 vol) to the epoxidation brew at -20°C and vigorous stirring was continued at room temperature for twenty minutes.

For non-aqueous methods and acid sensitive substrates, saturated sodium sulphate [1 ml/mmol Ti(O^{i}Pr)$_4$] is added to the reaction and allowed to stir for 2 hours at -20°C giving insoluble titanium species that are removed by filtration. Subsequently, this inorganic paste can be washed with hot ethyl acetate to sequest any lost product.

Water soluble epoxides demand careful treatment and there exists non-aqueous methods. For example, an ether/acetone solution of citric acid is added to the reaction resulting in the formation of an insoluble Ti-citrate complex (the use of 9:1 ether/acetone reduces the required solvent volume). This precipitate can then be filtered and digested with hot ethyl acetate (*c.f.* saturated sodium sulphate) to increase the yield of the epoxy alcohol product and dimethyl

sulphide can also be added with these non-aqueous methods to destroy any unwanted hydroperoxide.

In situ derivatisation:

This procedure is only really applicable to catalytic asymmetric epoxidations because the amounts of isopropyl alcohol and tartrate make *in situ* derivatisation impractical.[29] It is necessary to destroy excess TBHP because, unlike *t*-butyl alcohol, TBHP will react with most alkylating and acylating agents, due to the alpha effect making the peroxide hydroxyl relatively more nucleophilic.

Two important derivative classes are *para*-nitrobenzoates (PNB) and *para*-toluenesulphonates. Although both are useful synthetic intermediates, PNB derivatives are especially useful because these are easily isolated and usually crystalline, thereby providing an opportunity for further enhancement of optical purity by crystallisation.[45] In our studies no *in situ* derivatisation was used.

Enantiomeric excess determination:

There are a plethora of methods for enantiomeric excess determination, *e.g.* high performance liquid chromatography (HPLC), gas chromatography (GC), NMR and optical rotation. Each method has its own associated advantages and disadvantages and the choice of method is usually dictated by the substrate structure and functionality. HPLC is a very effective method and we have had success in the resolution of epoxy-cinnamyl alcohol using this method however the epoxide must be of high purity and there must be a chromophore present if one uses (as in most cases) a UV detector. Thus, for aliphatic epoxy-alcohols, HPLC is unsuitable unless the alcohol and/or epoxide are functionalised with a suitable chromophore (*e.g.* thiophenol, benzoyl chloride).

Optical rotation (specific rotation) is a very useful technique, nevertheless, in calculating optical purity one must assume a linear relationship between specific rotation and enantiomeric excess. Therefore, if such a non-linear relationship exists, this technique may have an unquantifiable error associated with it and on the occasions where specific rotations are small, the errors associated with the technique are increased, arguably, to unacceptably high levels. Furthermore, it is of paramount importance that the analyte is free of any impurities especially if chiral and non-racemic as they will influence the rotation of plane polarised light (*e.g.* a chiral ligand used in an asymmetric synthesis), if an impurity's rotation is high, the results will be erroneous.

The use of chiral shift reagents in conjunction with NMR is another method for ee determination. The substrate must have functionality that will coordinate with the chiral lanthanide complex, hence one supposes that this is indeed a suitable method for epoxy-alcohols and asymmetric allylic alcohols. All attempts utilising this method to resolve *rac*-(3*E*)-4-phenylbut-3-en-2-ol **99** proved fruitless and one has come to the conclusion that this method is indeed a "black art" (Scheme 2.24). When shift reagents are successful, one "simply" determines the ratio of the appropriate diastereomeric NMR signals by integration to determine the enantiomeric excess of the substrate. During the Fourier Transform, errors are introduced into the processed data which can be significant and for this reason, the precision of NMR-derived ees are believed to be approximately ± 5 %.
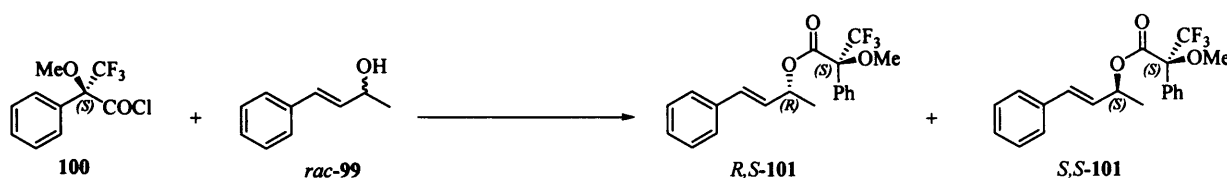
Scheme 2.24

Mosher's acid chloride **100** can be used with chiral substrates (alcohols, amines) such as the alcohol *rac*-**99** resulting in the transformation of the two enantiomers into diastereoisomers, for example *S,S*-**101** and *R,S*-**101** (Scheme 2.24). These derivatives can then be analysed by standard techniques including ^{1}H NMR, ^{19}F NMR, standard HPLC and standard GC. Mosher's acid chloride is usually purchased from a suitable supplier, thus the limit of precision is determined mainly by the enantiomeric purity of the reagent. There are two grades available from the Sigma-Aldrich group, 98 % ee and ≥99 % ee (≥99.5 : 0.5), *i.e.* limits of precision of ±2 % and ±1% respectively. Also, these ees were determined by GC and the degree of accuracy and precision of this technique is a contentious debate that will be pursed later.

Gas chromatography was by far the best method found for ee determination of the epoxy-alcohols and secondary allylic alcohols (KR). There are a wide range of chiral stationary phases available and the most commonly used are cyclodextrin-based. The simplest and cheapest are non-bonded permethylated cyclodextrins (α, β and γ). These readily available stationary phases were used to in the quest for means to resolve the racemates of epoxy-alcohols used in our studies, but only the permethylated α-cyclodextrin was found to be of use, in the resolution of epoxy-cinnamyl alcohol. In the quest for other stationary phases we found a company (Astec[73]) that made a wide range of functionalised bonded cyclodextrin columns and upon consulting

their UK representative, we purchased the adeptly named GTA column (2,6-di-O-pentyl-3-trifluoroacetyl-γ-cyclodextrin). This column has proven its worth on many occasions and is capable of resolving all but a few of the substrates (derivatised with TFAA or underivatised) and the only special treatment is that water must be excluded to prevent the hydrolysis of the trifluoroacetyl functionality on the bonded stationary phase.

The accuracy and precision of GC has been subject to continual debate. Some individuals quote enantiomeric excesses to a very high level, of precision (2 d.p in some cases) and we are of the opinion that this is too precise. Therefore, to add credit to this humble opinion, a simple statistical analysis was undertaken on data from the GC traces of racemic epoxy-alcohol and allylic alcohols, for the GTA column. When synthesising the racemic epoxy-alcohols, the amount of molecules synthesised, for example on a one millimole scale 6.023×10^{20}, is enormous and therefore statistically speaking, the two enantiomers present will be exactly a 50:50 mixture. In an ideal situation, the GC trace data of these racemates would be representative of this statistical probability. However, no instrument is free from errors and thus the data for each enantiomer of a racemate on a trace will not be precisely equal and this difference needs to be quantified from a sample of racemate traces (Table 2.11). The table consists of random traces of racemic epoxy alcohols/secondary allylic alcohols at random conditions because this provides a better average of any results obtained.

Table 2.11: Statistical analysis

| Entry	First Peak/counts	Second Peak/counts	% difference
1	901109	901889	0.043
2	184761	186375	0.435
3	478454	477848	0.063
4	1319719	1309228	0.400
5	631733	646700	1.171
6	240161	237749	5.060
7	637403	649265	9.220
8	1710152	16666482	1.290
9	808514	826751	1.120
10	2361008	2350666	0.220
		Average	**1.9%**

Therefore, this statistical analysis shows that there is an average error of 1.9% between the peak data of the two enantiomers, which represents a significant difference. Therefore, any recorded enantiomeric excess may have an associated error (1.9% in this case) and to quote enantiomeric excesses to greater than two significant figures would seem to be considerably overstating the accuracy and precision of the equipment.

Catalytic Complex Modelling:

During the course of the project, efforts were made to characterise the species that formed from the addition of two equivalents of titanium tetraisopropoxide and one equivalent of a ligand in question **56a-g** by NMR and X-ray crystallography. Initially, the NMR spectra of these species were complicated by the excess isopropanol liberated from the titanium during the chelation and thus the exact experimental details used by Sharpless and co-workers on analogous systems was used. The Sharpless protocol required that after the ligand/titanate species had equilibrated, the liberated isopropanol was removed *in vacuo* under standard air-sensitive conditions. Further to this, two portions of anhydrous ether were added to dissolve the complex and the solvent removal was also repeated. Finally, the remaining titanium/ligand species was suitable for NMR experiments. The protocol did not proceed in the same manner as the Sharpless tartrate system; upon removal of the isopropanol in the first pump cycle, the remaining white powder proved to be insoluble in all solvents tried. This phenomenon prevented further characterisation because the same protocol is used to derive a crystal of the catalytic complex for X-ray crystallography and therefore, an alternative method was sought for the elucidation of the catalytic species.

Density functional study on the nature of the original Sharpless asymmetric epoxidation species has been undertaken previously yielding results that were in agreement with experimentally recorded data for the catalytic species.[38,39] Therefore, there was literature precedent for the DFT techniques yielding at least a qualitative answer, thus models were constructed and analysed with Gaussian 03 using the BLYP non-local density functional approximation and the 3-21G* basis set which are the same level of theory used in the afore mentioned analysis.

The scope of the molecular modelling was relatively simple, the jobs were constructed to run and yield the molecular structures in their minimised energy geometries. However, it is unwise to believe that the geometries given are completely representative of our new ligand system. What the information does provide is comparative geometries that allow reasonable discussions and conclusions to be formulated.


R = Pr^i
X = NCH$_2$Ph
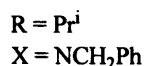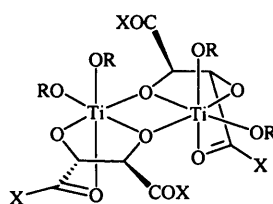
20

The foregoing structure **20** was resolved by the Sharpless group using X-ray crystallography and these data provided the decisive evidence for the structure of the SAE catalyst and valuable physical measurements for comparison with computational methods.[38,39] Although **20** is dimeric, its two halves are related by a two-fold axis, one diolate oxygen of each tartramide ligand bridges two titanium atoms producing six coordinate, pseudo-octahedral coordination. The Ti-Ti inter-nuclear separation is 3.35Å. The planar Ti$_2$O$_2$ core is an asymmetric rhombus, with Ti-O bond distances of 2.16Å and 1.97Å, the longer distance being the result of the ring strain. The Ti-carbonyl bond is 2.20Å which indicates a weak bond, a necessary requirement for the catalytic nature of the complex:- facilitating the exchange of the carbonyl with the substrate molecules, allylic alcohol and TBHP *via* a presumed penta-coordinate Ti intermediate.

The first structure modelled was the Ti-tartrate system **102** because the results of this simulation could be compared to known data of the above analogous complexes, therefore indicating the accuracy of the technique (Scheme 2.24).


R = Me
X = OMe
E = CO$_2$Me

102
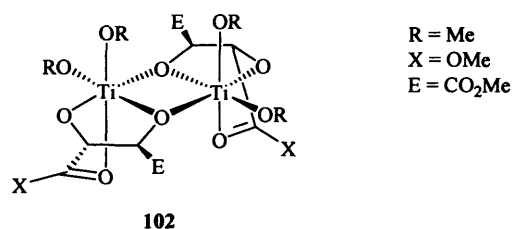
Scheme 2.24

The model was directly comparable to the X-ray data (Picture 2.1): an asymmetric rhomboid core with Ti-O bond lengths of 2.17Å and 1.99Å; Ti-carbonyl 2.49Å; Ti-Ti 3.38Å and Ti-OMe 1.79Å. The Ti-carbonyl bond length is larger, presumably due to the difference in Lewis basicity between an amide carbonyl **20** and an ester carbonyl **102**; an amide carbonyl having the larger magnitude of basicity (due to the greater mesomeric effect of nitrogen) resulting in a more efficient ligand for bonding. These data represented justification for the modelling of analogues of the ligands **56a-g**.


R = Me   y = 1-4 and 6
X = OMe

Scheme 2.25

72
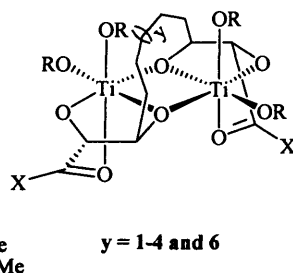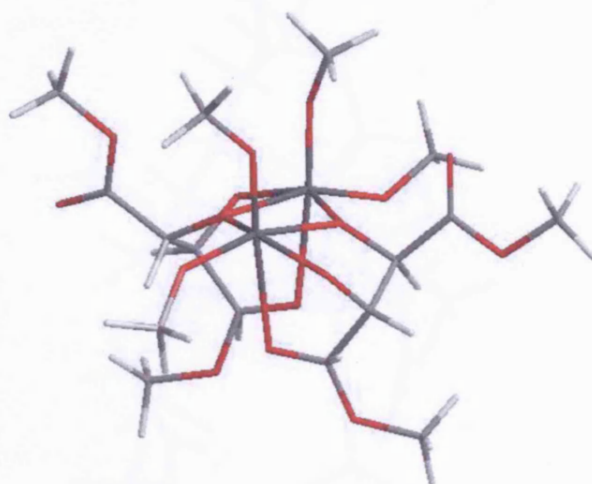
Picture 2.1

The complexes modelled are shown in Scheme 2.25. The methyl esters and methoxide ligands were used to aid in the expedience of the simulations because these simpler functionalities (*cf.* isopropyl) would reduce the degrees of freedom in the complex hastening the calculations, hopefully without adversely affecting the outcome. The study concentrated on deducing the effect of varying the alkyl chain length on the shape/geometry. In all the simulations performed, upon reaching a minima threshold in the RMS (root mean square) force and maximum force, the calculations were deemed satisfactorily complete.

For all the complexes modelled, it was found that the illustration in Scheme 2.25 was not a true representation; in the minimised geometries obtained from the calculations, the carbonyl oxygens dissocoiated from the titanium centres during the course of the calculations resulting in the final structure bearing two five-coordinate titanium moieties (Scheme 2.26). Each titanium centre bore a pseudo-trigonal bipyramidal geometry (*e.g.* Picture 2.2).

R = Me
X = OMe

103, y = 1 **106**, y = 4
104, y = 2 **107**, y = 6
105, y = 3
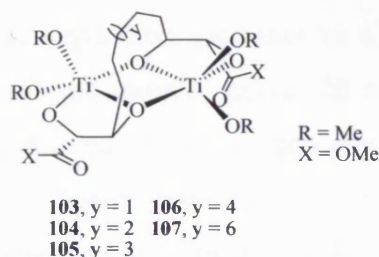
Scheme 2.26
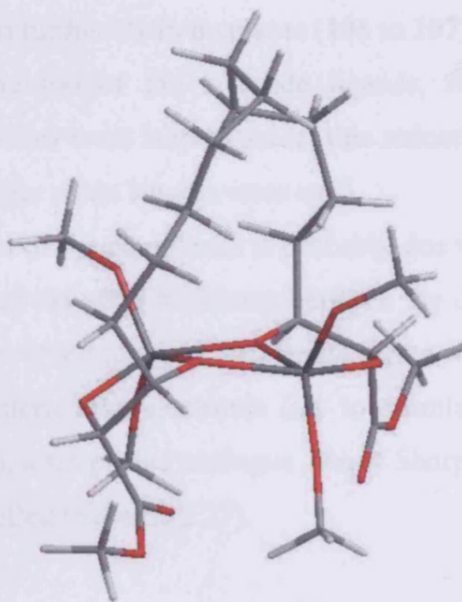
Picture 2.2

Data from the simulations are summarises in the following table (Table 2.12):

Table 2.12: Simulation measurements

Complex	Ti-Ti/Å	Ti-O (bridged) /Å	Ti-O=C/Å	Ti-OR/Å	Ti-O-Ti/Å	Rhomboid Dihedral/°
20 (X-ray)	3.35	2.16 and 1.97	2.20	-	-	-
102	3.38	2.17 and 1.99	2.49	1.79	107	10.6
103	3.27	2.08 and 2.02	-	1.80	105.2	19.7
104	3.26	2.09 and 2.03	-	1.77	104.0	22.1
105	3.30	2.08 and 2.01	-	1.78	107.2	23.1
106	3.29	2.09 and 2.03	-	1.79	105.9	26.6
107	3.32	2.07 and 2.02	-	1.80	109.9	14.0

The "physical" measurements and structures do provide a valuable insight into the structure of our ligand system during catalysis. The minimum energy conformation of the preloaded catalyst **103-107** is fundamentally different from the tartrate derived binuclear species **102** and **20**. Upon increasing the chain length of the alkyl backbone, the following putative generalisations can be made. Generally, the inter-nuclear separation increases to a maximum for **107**, a trend that shows increasing character towards the tartrate species **20** and **102**; The bridged Ti-O bond lengths are shorter for the ligand-derived complexes and this may be due to the higher Lewis acidity associated with penta-coordinate titanium. The alkoxide-Ti bond lengths remain relatively constant. Upon increasing the chain length the Ti-O-Ti bond angle of the rhomboid core increases to a value more characteristic of tartrate, and the rhomboid dihedral angle increases to a maximum for **106** then drastically falls for **107**. This observation may be due to the steric repulsion of the alkyl chain and the alkoxides reaching a peak, resulting in a more

skewed complex and then further chain increases (**106** to **107**) remove this repulsion because the chain can loop over the top of the alkoxide ligands, reducing the repulsion drastically. Nevertheless if the alkoxides were isopropoxide, this reduction is steric strain would probably not occur until much greater chain lengths were used.

The carbonyl dissociation of the complexes is probably due to the associated steric strain of the complex; incorporation of the alkyl backbone between the dihydroxy ester moieties obviously adds a significant amount of strain when the chelate forms with the titanium alkoxide. To prove that this effect is more steric than electronic (*i.e.* to examine if the removal of the redundant ester was a causal effect), a simplified analogue **28a** of Sharpless's *bis*-tartrate complexes **28a-c** (Scheme 1.18) was modelled (Scheme 2.27).


R = Me   **28a, n = 3**
X = OMe
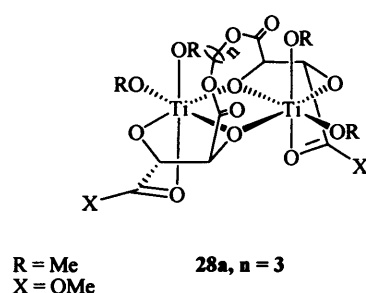
Scheme 2.27

The spacing between the mandatory dihydroxy ester moieties was comparable to the modelling of our ligand system with seven methylene units between these two moieties. The minimisation, Picture 2.3, provided a different structure to that shown in Picture 2.2; the geometry of one titanium atom was pseudo-trigonal bipyramidal due to the dissociation of one of the two carbonyl oxygens and the other titanium centre was pseudo-octahedral just like the tartrate complex **102**. Therefore, in both cases, it has been shown that the hydrocarbon backbone/linker does change the geometry of the preloaded catalyst structure. Nevertheless, both systems are still efficient at mediating asymmetric epoxidations so if the penta-coordinate species is present in solution, upon addition of TBHP and the allylic alcohol, the titanium centre still has the capability to form the six-coordinate catalytically active complex. The only difference would be that the carbonyl oxygen would no longer be in competition with *t*-BuO⁻/*t*-BuOO⁻ and the catalytically active titanium centre would have a higher Lewis acidity. The result of this change could affect the rate of the epoxidation reaction because the dissociation of the *t*-BuO⁻ from the titanium would be limited by the diffusion/collision (including large steric repulsion between two *t*-butyl species) of fresh oxidant rather than the more rapid intramolecular carbonyl

dissociation pathway (steric repulsion between two *t*-butyl moieties obviated). The increase in Lewis acidity of the titanium centre could result in the bond strength of the bystander alkoxide ligands and reacted substrates to the titanium being greater and this could result in a lower reaction rate because the alkoxides need to dissociate so that fresh substrates can undergo the subsequent epoxidation steps.

The molecular modelling does provide valuable information on the nature of our new catalyst system, most importantly the modelling showed that the linker has a significant effect on the structure of the active catalyst species.
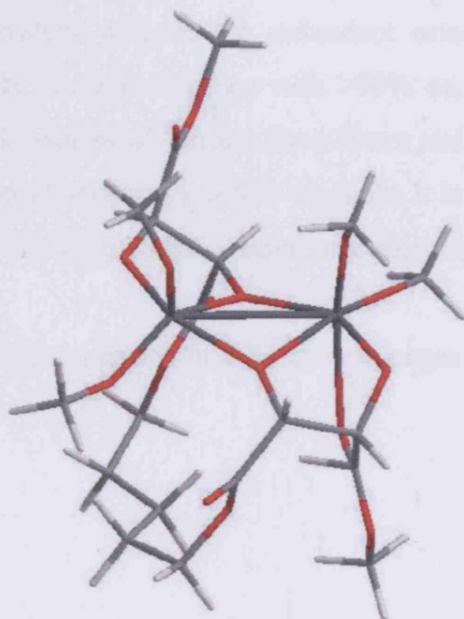
Picture 2.3

Conclusion

The synthesis and screening of the ligands **56a-g** led to the discovery of suitable ligands for use in the Sharpless Asymmetric Epoxidation the optimum ligand being **56g**. This ligand, in optimal cases, furnished epoxy-alcohols with exceedingly high enantiomeric excesses and yields that are directly comparable to the original tartrate-mediated epoxidation. The ligand **56g** (others would show similar efficacy also) could be recovered and cleaned by simple processes post-epoxidation and then re-used in further epoxidations with little or no loss in the enantioselectivity in these subsequent epoxidations. Importantly, this represents the lead in efforts made to synthesise a recoverable source of "tartrate" for the SAE.

Curiously, this ligand system without the redundant esters mediates kinetic resolution of secondary allylic alcohols, in optimal cases with >99% ee, the surprise being that Sharpless stated that all four functionalities of tartrate (two esters and two hydroxyls) are necessary for efficient kinetic resolution of secondary allylic alcohols. It is now clear that the redundant ester does not mediate a subtle effect in kinetic resolution experiments and the statement by Sharpless is somewhat erroneous.

A further mechanistic insight is discussed in Chapter 4, pages 113-114.

Chapter 3

Introduction to Organogels.

Gelators

The recent years have been witness to a rapidly growing interest in the self-assembly phenomenon of low molecular mass organogelators (LMOGS); small molecules that spontaneously self-assemble to create a three-dimensional network capable of entrapping the solvent and creating gels.[75-77] Molecular self-assembly and network-formation by gelators has stimulated much recent research attempting to answer the fundamental questions as to the nature of this fascinating phenomenon. Due to their applications in templated materials synthesis,[78] drug delivery,[79] separations[80] and biomimetics,[81] gels formed by molecular agents constitute an important class of functional materials. The self-assembly of low molecular weight gelators to form fibre-like structures, which entangle to form a three-dimensional 3D network, has the result of immobilising organic fluids, giving rise to the phenomenon that is known as gelation.

In contrast to their gel-forming macromolecular and inorganic counterparts, such as diluted solutions of polymers, proteins and silica or clays in organic solvents and water, the gelation of solvents through the self-assembly of small molecules into networks is solely mediated by physical interactions, including hydrogen bonding, stacking and solvophobic effects. The nature of the interactions responsible for self assembly can be used to classify the structurally diverse organogelators. The majority of gelators are covered by classification into non-hydrogen bond-based gelators and hydrogen bond-based gelators. Anthracene, anthraquinone, tetralin and steroid-based organogelators are well studied and constitute the family of non-hydrogen bond-based gelators as their aggregation is driven by π-π-stacking and solvophobic effects.[82]

The molecular interactions can be classified into three types: dipole-dipole, Van der Waals and hydrogen bonding interactions. The hydrogen bonding interaction(s) generally takes place when a hydrogen atom locates between two oxygen atoms and these three atoms then align linearly. This strict unidirectional orientation leads the molecules to align in a specific manner, which is the major cause of highly organized supramolecular structures.[87]

Thermally reversible viscoelastic liquid-like or solid-like materials (*i.e.* organogels) are comprised of an organic liquid and low concentrations (typically <2 wt %) of relatively low molecular mass molecules (*i.e.* gelators). The physical characteristics of organogels can range from those of surfactants in solution (*e.g.* micellisation, lyotropism and crystallization) to those of polymer solutions (*e.g.* swelling and microscopic mass motion); gels are at the interface between "complex fluids" and phase-separated states of matter.[83] In addition to being thermally reversible, some organogels with low molecular mass gelators are also thixotropic: when

sufficient mechanical stress is applied isothermally, they form a solution that reverts, at rest, to the gel state. An example of this is a simple *N*-hydroxyalkyl amide.[84]

As noted prophetically by Dr. Dorothy Jordon Lloyd nearly 70 years ago, "....the colloid condition, the gel, is easier to recognize than to define".[85] This and other empirical definitions of the gelled state, including the first by Thomas Graham in 1861, relied on the qualitative macroscopic observations that were available and, in fact, not all gels are colloidal![86] The first attempt to link macroscopic and microscopic properties to define a gel served as the basis for what is, perhaps, the most comprehensive (and cumbersome to apply) definition advanced more than 20 years ago by Flory.[87] Thus, a substance is a gel if it (1) has a continuous structure with macroscopic dimensions that is permanent on the time scale of an analytical experiment and (2) is solid-like in its rheological behaviour. For screening purposes, the motto of Jordon Lloyd is still useful and preferred: if it looks like "jelly", it must be a gel. The simplest and most widely accepted experimental technique for determining whether a system is a gel is the "stable to inversion technique": the sample is merely inverted in a suitable vessel such as a vial or test tube and if it remains in the same, now metastable, position, the sample is deemed to be a gel. Therefore two loosely defined criteria, one rheological and one structural can be used to define the gel condition; The materials return to their original form when relieved of an applied stress (below a certain limit) and the materials appear solid-like and yet are composed predominantly of a liquid at the macroscopic scale.

Typically, an organogel is usually prepared by warming a gelator in an organic liquid until the solid dissolves and then cooling the solution (or sol). When the temperature of an organogel is increased, at a certain temperature, the viscoelastic material suddenly changes to liquid. This thermal transition can be explained by a lowering of the network density which finally becomes unable to support the gel phase and the supramolecular structure deliquesces. This phase transition temperature is called T_{gel}. Another preparative method is the use of a two solvent mixture. Initially the gelator is dissolved in an appropriate solvent and then a second solvent is added in which the gelator is less soluble, thereby facilitating the self assembly mechanism leading to the gelation. The resulting material is a gel or jelly, depending upon its hardening or thickening ability; the formal description and classification is based upon rheological properties. Colloidal aggregates (*i.e.* whose typical dimensions fall between 20 and 2000 Å) in the gel are linked in complex, three-dimensional networks that immobilise the liquid component to a variable extent (principally) by surface tension. In spite of the many chemical compositions and physical properties of gels that are known, several important questions remain to be answered. Among these are:[88]

(1) How and why organogels composed of low concentration LMOGS and an organic fluid form?

(2) What molecular and bulk factors affect gel stability?

(3) Which structural features of LMOGs are most important to their successful applications?

(4) Is there a relationship between the mode of molecular packing of the gelator molecules in the gel state and in their neat crystalline phases?

(5) What is the simplest type of molecule that can be a LMOG?

Point (5) has been answered with the discovery that long chain *n*-alkanes have the ability to form organogels.[89] Point (4) has been answered in part by the discovery of which morphology is responsible for the solid component of organogels derived from the LMOG hexatriacontane.

Points (1)-(3) have partial answers only because complete elucidation requires an understanding of the nascent stages of gelation. Learning how molecules nucleate and assemble in the pre-gelation phase and whether the lyotropic structures in the solution resemble those in the gel are the keys required to comprehensively answer questions (1) to (3).

LMOGs self-assemble through highly specific interactions, allowing preferential two-dimensional growth, usually to form fibres, strands, tapes *etc*. These elongated objects join into three dimensional networks that encapsulate the liquid component and inhibit its flow. Many of the solid structures are colloidal in nature and gelation occurs when the individual colloids interact physically while pervading the liquid volume. These elongated objects can immobilise efficiently a large volume of liquid *via* surface tension and associative forces (π-π *etc*) and Van der Waals can be sufficient too.

Classes of Organogelators

It is not yet possible to select a molecule to gel definitively a selected liquid. Discoveries of new gelators or thickeners remain mainly fortuitous and as an aid to developing strategies for the molecular design of new LMOGS, many of the known ones have been grouped separately. However, this grouping is under the subjective influence of the authors of such research.

Well-known organogelators include, for instance, certain cholesterol and anthracene derivatives, fatty acids and derivatives, organometallic complexes, surfactants, porphyrins and phthalocyanines, carbohydrate and peptide derivatives, various ureas, phenylenevinylene derivatives and oligoamides.[90] A common feature of these molecules is that they can self-assemble through highly specific, non-covalent interactions into long fibrous structures, which in turn form an entangled network in the liquid.

As previously noted, the simplest organogelator class was found to be large chain *n*-alkanes, C_nH_{2n+2} where n = 24-36, the gelation ability of which increases with chain length.[89]

Fatty acid derivatives are a well known and studied class of organogelators and for decades their properties have been utilised in the lubrication industry. 12-Hydroxyoctadecanoic acid **108** and its derived salts are known to create hardened materials from organic solvents (Scheme 3.1). The 3-D networks of aggregated fatty acid molecules **108** act as a "sponge", maintaining the oil component in lubricating greases close to the friction regions of metallic surfaces in various mechanical systems.


108
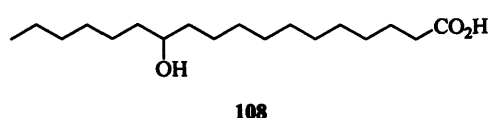
Scheme 3.1

Lecithin **109** is a fatty acid derivative (phosphatidyl choline) that also forms gels, which have been the studied extensively.[91] Organogels from naturally occurring lecithin form after adding trace amounts of water to a non-aqueous lipid solution or after applying an external electric field to an oil/water system. Although they are made up of non-macromolecular constituents, their rheology is similar to that found for entangled polymers in the semi-dilute regime. The rheological properties are caused by the formation of a three-dimensional network from so-called "equilibrium" polymers, consisting of long tubular reverse micellar aggregates. The lecithin organogel is a self-organized supramolecular assembly in which the role of water is crucial to its formation. This points to a strong dependence of properties on the balance of interactions in the polar moiety but the nature of linking of lipid molecules in the tubular aggregates is still unknown.


109
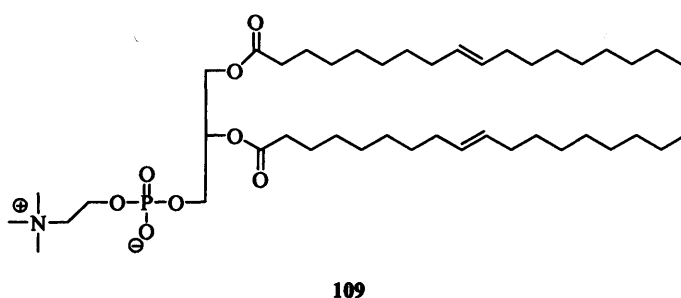
Some steroid derivatives (such as deoxycholic acid **110** and derived salts) thicken aqueous salt solutions and dihydrolanosterol **111** at 1-10 wt% gels various mineral, synthetic and silicone oils.

Some simple esters of cholesterol such as cholesteryl phenylacetate and to a lesser extent cholesteryl laureate and cinnamate also gel some silicone oils (Scheme 3.2). Substitution at the C_3 position by a hydroxyl group markedly increases the efficacy of steroids to mediate gelation.
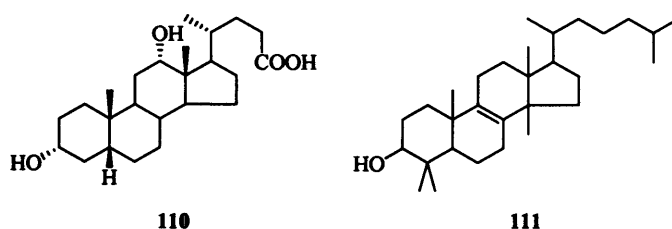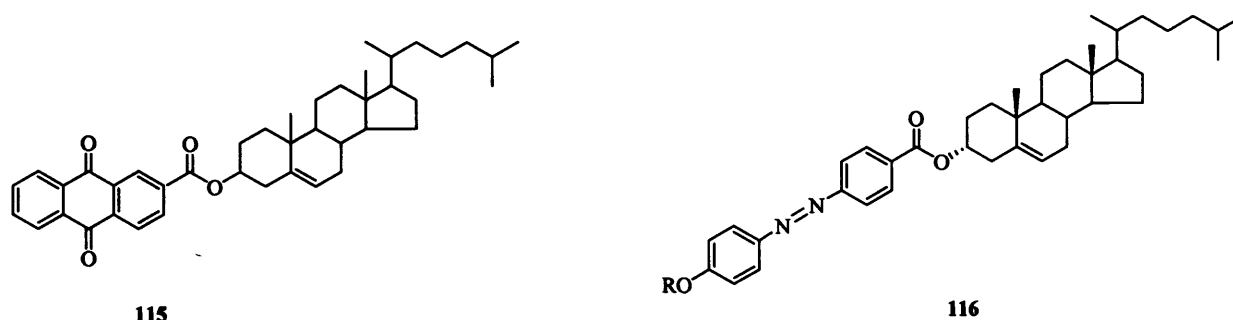

Scheme 3.2

Anthryl derivatives are well known gelators; 2,3-*bis-n*-decyloxyanthracene **112** (DDOA) is able to gel various alkanes, alcohols, aliphatic amines and nitriles. The related anthraquinone **113** is a gelator but the structurally similar 2,3-dialkyloxynaphthalene **114** is not (Scheme 3.3).
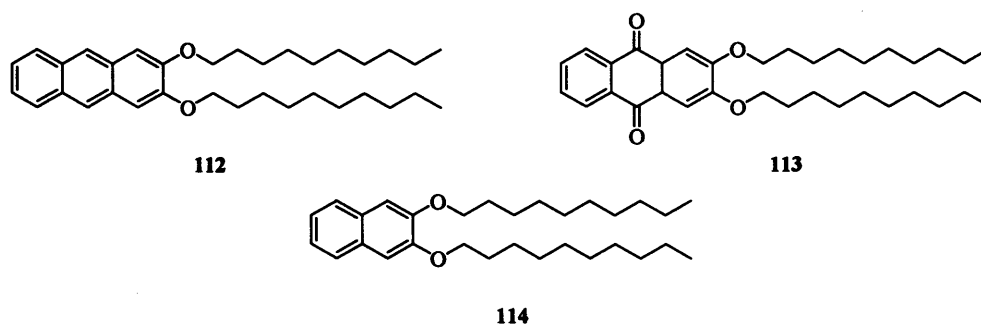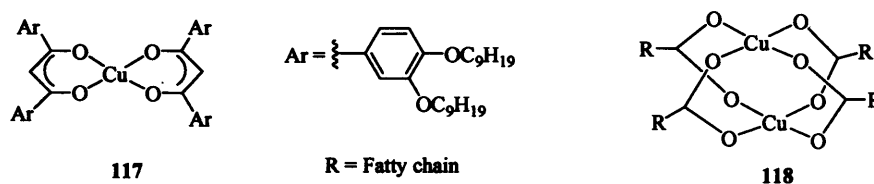

Scheme 3.3

Gelators containing both a steroidal and condensed aromatic ring can be considered as a separate class, rather than making the putative decision to place the molecules in the steroid or condensed aromatic ring class. Anthryl- and anthraquinone-appended steroid-based gelators, in contrast to steroids whose gelation ability relies upon the presence of a hydroxyl group at C_3, are another class of LMOGs, grouped under the acronym "ALS". These are also functionalised at C_3 like the efficient steroid gelators but cannot be H-bond donors but still are efficient gelators of many organic liquids. These gelators consist of an aromatic group A connected to a steroidal moiety S by a linking group L illustrated below by the adeptly named CAQ **115**, cholesterylanthraquinone and an azobenzene derivative **116** (Scheme 3.4)

115

116

Scheme 3.4

Some organométallic compounds have the propensity to gelate solvents. Mononuclear copper β-diketonates **117** are disc-like molecules and are shaped favourably to stack and form rod-like aggregates. Bi-nuclear complexes also form gels, illustrated by the *tetra*-carboxylate **118** (Scheme 3.5). Structural similarities are repeated here in that each complex possesses long chain "fatty" chains.

117

$Ar = $ —OC$_9$H$_{19}$, OC$_9$H$_{19}$

R = Fatty chain

118

Scheme 3.5

Calix[n]arenes (n = 4-8) are macrocyclic gelators when they possess long alkanoyl chains at the *para*-position of the phenolic ring **119**.

119
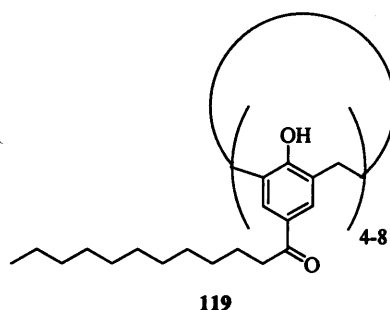
Many poly-ols including sugar derivatives and sorbitol have been found to be organogelators; 1,3:2,4-di-*O*-benzylidene-D-sorbitol (DBS) **120** is a chiral poly-ol that can gel numerous liquids from hexadecane to dimethyl phthalate but significantly racemic DBS does not form gels. An

84

example of a sugar derived gelator **121** is also shown below (Scheme 3.6).[82] Cyclodextrins have also shown gelation ability; β-cyclodextrin is a cyclic heptasaccharide of α-1,4-linked glucosidic units and this moiety adapts a toroidal shape. β-Cyclodextrin will gel chloroform and toluene but only when these solvents have trace amounts of water present, in the similar fashion to the gelation behaviour of lecithin **109** (see above).
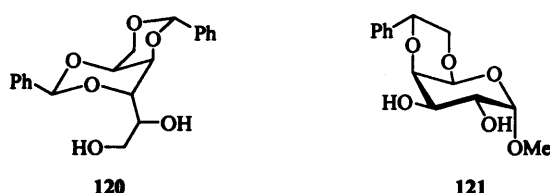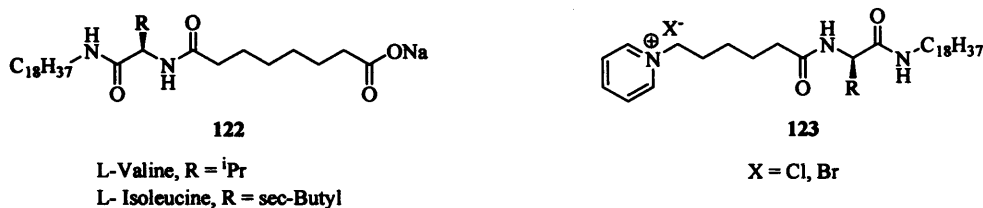
Scheme 3.6

Partially fluorinated *n*-alkanes (*n* = 8 and 12) form bi-refringent gels with *n*-hydrocarbons. Fluorinated solvents are used as replacement media for blood, liquid ventilation and contrast agents for ultrasound imaging,[92] however these solvents need to be formulated with polymers and surfactants in order to introduce the necessary additional physical characteristics. In the case of the partially fluorinated gelators, the incompatibility of the fluorocarbon and hydrocarbon segments drives the aggregation of the molecules into the gel state.

N-Alkyl perfluoroalkanamides, $F(CF_2)_nCON(CH_2)_mH$ form very stable gels with a wide variety of organic liquids, including the first example of the gelation of a *n*-perfluoroalkane and other liquids gelled by few other gelators. The molecular structures of these LMOGs contain "incompatible" segments: a fluorocarbon segment and hydrocarbon residue, the cross sectional areas of which are 28.3Å and 18.5Å respectively, each segment being joined by an amide moiety whose intermolecular H-bonding interactions may enforce additional packing constraints.[93] It is the joining of these two incompatible segments that allows the system to gel fluorinated media. In the "design" of these gelators, it was reasoned that insertion of the amide link between the alkyl and perfluoroalkyl portions of the gelator would increase the strength of intermolecular interactions *via* hydrogen bonding and thereby increasing the gelation ability of this system.

Very recent publications have shown the synthesis of very simple and efficient gelators based on L-valine and L-isoleucine derivatives (Scheme 3.7).[94,95] Typical solvents that were successfully gelled were water, ethanol, methanol, cyclohexane, hexane, hexanone, acetonitrile, carbon tetrachloride, dichloromethane, chloroform and mixtures thereof. The minimum gel concentration for the amino-carboxylates **122** ranged from 3-30 mg/ml and for the amino-pyridinium gelators **123** was in the range 4-25 mg/ml.

122

L-Valine, R = ^{i}Pr
L- Isoleucine, R = sec-Butyl

123

X = Cl, Br

Scheme 3.7

Natural proteins possess mechanisms for the physical association of peptide segments; the two most widespread are β-strand for sheet and fibril assembly and coiling of helicies to form spherical bundles. Both assemblies are capable of linking peptide or protein chains together to form gel networks in aqueous solution, classic examples being the gels formed from gelatin, bile acids and acid denatured insulin.

Two equivalents of 4-(4-alkoxybenzoyloxy)-4-stilbazoles (nSZ) such as **124** and one equivalent of L-tartaric acid **125** can be formulated into a gel system known as a as binary organogel. Formation of intermolecular H-bonds between nSZ and L-tartaric acid in the complexes has been confirmed by FT-IR spectroscopy with the indicative appearance of two broad absorbances at *ca* 2450 cm^{-1} and 1930 cm^{-1} (Scheme 3.8).[96]

124

125
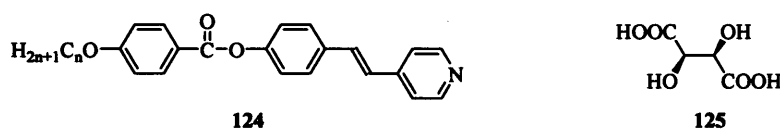
Scheme 3.8

Cholesterol derivatives, *e.g.* **116**, containing an azobenzene chromophore coupled to C3 of the steroidal moiety (Scheme 3.4) exhibit reversible sol-gel phase transitions in certain organic solvents, induced synchronously by light-mediated *cis-trans*-isomerization of the azobenzene moiety. The sol-gel phase transition of these switch-functionalized cholesterols can be detected by circular dichroism.[97] Polymerisable gelators have also been synthesised. One such example is based on (1*R*,2*R*)-*trans*-1,2-*bis*(ureido)cyclohexane **126** resulting in the formation of highly stable organogels.[98] Gels of **126** were prepared in the presence of 5 mol% of the photoinitiator 2,2-dimethoxy 2-phenylacetophenone and the photoinitiation was achieved with a 200 W high pressure Hg lamp. FT-IR of dried gel samples revealed that the characteristic CH vibrations (3120 and 3050 cm^{-1}) of the methacrylate moieties had disappeared and extraction with chloroform did not yield any of the monomer. The polymer matrices showed high stability

towards heating, maintaining their shape at temperatures greater than 100°C above the boiling point of the gelation solvent (butyl acetate).
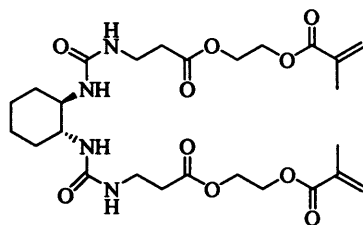
126

Another example of a polymerisable organogel system is shown by diacetylene-cholesterol system linked by two urethane linkages **127**. Upon gelation with an appropriate solvent, photoirradiation resulted in the polymerisation of the diacetylene moiety through a 1,4-addition forming a polydiacetylene, indicated by a colour change in the gel. The colours varied from red, orange, pink, to dark blue and the particular colours were indicative of the extent of delocalisation of the π electrons in the poly(eneyne) backbone, with blue polydiacetylenes having longer effective lengths. Polydiacetylenes/polybisacetylenes are attractive materials because of their potential use as nanowires and in molecular devices and molecular electronic systems as connecting wires.[99]
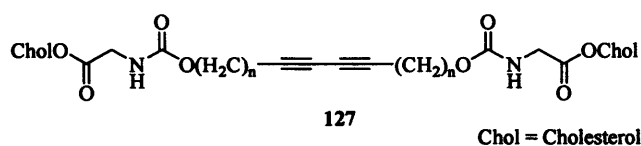

127

Chol = Cholesterol

Structure Elucidation

Although the formation of organogels from small organic molecules is an excellent example of a supramolecular self-assembly process, most organogelators have been found by serendipity rather than by design and many aspects of organogels are still poorly understood. Therefore, the elucidation of the structures of these organogels is a challenge even to the most experienced.

Scanning electron microscopy (SEM) and tunnelling electron microscopy (TEM), small angle neutron scattering (SANS), small angle X-ray scattering (SAXS) and atomic force microscopy (AFM) allow many features of organogels to be deciphered at the 1000-10 nm distance scales (*i.e.* LMOG strand shapes and dimensions). However, they do not provide direct information on the 0.1 nm to 1 nm scale (*i.e.* shape and organisation of individual LMOGs within the strands)

and extrapolation from supramolecular scale to molecular scale using any of these methods is not definitive. Structural information at the molecular level has been derived from conventional techniques such as NMR, FT-IR and semi-empirical calculations or assumptions that the gelator super-structure is the same shape as the gelator's xerogel (solid state) morphology.

A representative NMR study, undertaken by Yoza and co-workers, studied the gelation of 1-*O*-methyl-4,6-*O*-benzylidene derivatives.[100] It was expected that the molecular motion of the gelators would drastically change at the sol-gel phase transition temperature, T_{gel}. This was monitored by line broadening effects in ^1H NMR spectra, specifically by measurement of the half height peak width, $\delta_{1/2}$, of the benzylic methine proton (Scheme 3.9).
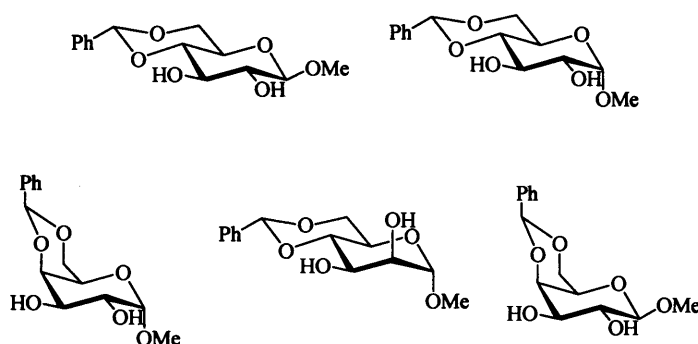
Scheme 3.9: Sugar derivatives studied

The width, $\delta_{1/2}$, of the methine proton in the derivatives shown in Scheme 3.9 were nearly constant above T_{gel}, while these increased with falling temperature below T_{gel}. This implies that the mobility of the gelator molecules is significantly suppressed in the gel phase but comparable to that of a homogenous solution in the solution phase. Plots of $\delta_H OH$ *versus* temperature showed that δ_H has a maximum downfield value at T_{gel}; in general, strong H-bonds with OH groups induces a downfield shift of δ_H. Hence, the H bonds with the OH groups are strengthened with lowering temperature from the sol phase to the T_{gel} region due to intermolecular aggregation near the gel region (intermolecular hydrogen bonds). However, as the temperature is reduced further, the NMR data is indicative of a weakening in the H-bonds. It is presumed that in the T_{gel} region the formation of the "soft gel" is governed by intermolecular H-bonds but at lower temperatures, much lower than T_{gel}, the formation of the pseudo-crystalline "hard gel" is governed not only by H-bond interaction but also by other internal forces such as π-π and London dispersion interactions. In the cases where the latter forces cannot harmonise with the hydrogen bond interaction (*i.e.* steric mismatching), the hydrogen bonds may be weakened.

Therefore, NMR, in this case, showed promise as a potential tool for deciphering the phenomenon that is gelation.

FT-IR has also been utilised in the study of the gelators (Scheme 3.9). The υ_{OH} of free OH groups (*ca* 3600 cm^{-1}) was not observed for solid samples of the benzylidene gelators. This was indicative that all the OH groups formed intermolecular or intramolecular H-bonds. The gels, in contrast, exhibited two absorbances at 3220-3475 cm^{-1} and 3533-3588 cm^{-1} suggestive of a hydrogen bonded OH and a free OH respectively.

The peak intensity ratio of hydrogen bonded OH to free OH abruptly increased at the sol-gel phase transition concentration, supporting the observed NMR data of an increase in H-bonding at gel-sol transition. The foregoing FT-IR information consistently supports the view that gelation in the parent system of the benzylidene gelators is stabilised by hydrogen bonding (intermolecularly).

Raman spectroscopy can also be used to determine organogel structures, however this requires that the system under study is Raman active to deduce any useful information.[101]

ECD (electronic circular dichroism) is a chiroptical technique used to observe the molecular effects accompanying the sol-gel phase transition of chiral gelators. The closely related technique VCD (vibrational circular dichroism) is one of the few techniques that reliably reflects the detailed stereochemical information of chiral small and large molecules and their complexes. Functional groups in the chiral aggregation can be clearly followed and evaluated.[102]

In the cases of analyses by SEM and TEM, quite simply the organogel is freeze-dried, leaving the supramolecular structure intact and this is then prepared for analysis, typically by sputtering the sample with palladium, platinum, osmium or gold. The result (in most cases) is a picture of the supramolecular structure of the gel; in many cases, one can clearly see a fibrous network, the size of which can be determined, thereby revealing details of how the gelator may be self-assembling.

Techniques such as SAXS and SANS are comparable, even though SANS uses neutrons and SAXS uses X-rays. This is because of the wave-particle duality that is associated with neutrons and X-rays, that is, both the X-ray and a neutron can be treated as a particle and a wave. The wavelength of an analytical particle/wave will interact with an object of comparable size and in the cases of SANS and SAXS the wavelength of the particle/wave is in the order of angstroms. Therefore, these techniques will reveal information on the shape and dimension of the supramolecular make-up. These techniques are especially useful for the study of soft matter, providing sizes and shapes of particles in dilute solution; polymers, micelles, colloids, proteins, precipitates and of course gels.

SAXS is an important tool as it can be used to determine absolute quantities such as diameters, lengths or topologies in gels and, because the synchrotron X-rays used are almost 10^6 times stronger than conventional X-rays, has a great advantage for a diluted system such as organogels. With SANS, neutrons interact with atomic nuclei *via* very short range forces (femto-metre) and with unpaired electrons *via* a magnetic dipole interaction.

The data recorded from both SANS and SAXS is manipulated against model systems until a suitable match is found, so these techniques, although powerful in determining supramolecular structure size and shape, require an excellent understanding in the practical and theoretical aspects of the techniques. However, it must be emphasised the data obtained from these techniques are extrapolated to putative models.

Applications

Gels have numerous industrial applications due to the great diversity of the structures that they display on microscopic and mesoscopic scales. Their thermoreversibility, chemical sensitivity and diversity are intrinsic characteristics which make them excellent candidates for future applications.

Gels are important in areas such as hydrometallurgy, cosmetics, food processing and lubrication. Various complex mixtures of surface active components in water and oil are utilised in many ointments and creams. Many aqueous gels are employed for macromolecular separations, protein crystallisation, *etc* and numerous applications take advantage of the associated drag effect, due to the steric and hydrodynamic interactions between permeating macromolecules and the disordered fibrous media.

When the liquid is evaporated from a gel, a meniscus develops and the sample shrinks to give a xerogel. If a supercritical drying process is used at high temperatures and pressures, an extremely porous structure, called an aerogel, can be obtained. The remarkable damping of sound and suppression of heat transport in some aerogels portends insulation and acoustic applications. Presently, only organometallic oxides have been utilised to form these aerogels.

Optical applications of gels have been well studied. For example, dye-doped organogels have been used as a new medium for two photon pumped lasing and other optical applications.[103] The work achieved a stable and efficient two photon lasing from gelatin organogels containing a two photon up-converting dye DAST [4-(dimethyl-amino)-*N*-methylstilbazolium tosylate], used extensively as a second order non-linear material. Since lasing output in glass and polymer bulk samples is limited by dye decomposition and localised heating of the matrix, organogels offer an

advantage due to their thermoreversibility and flexibility leading to a longer optical lifetime and higher damage threshold.

Gelators can be used with additives to create templated materials; membranes with nano-sized pores can be manufactured by gel template-leaching process.[104] This method takes advantage of the unique features of organogelators to reversibly form elongated fibres with well defined dimensions and geometry. A gel-template leaching process is when a gel is prepared in polymerisable solvents (*e.g.* methacrylates, styrene) in the presence of a cross linking agent. Post polymerisation, the gelator is extracted leaving the cross-linked polymer with the fibre network imprinted in the matrix-porous membranes with channels of sub-micrometer and even nanometre dimensions.

The gel-template leaching can also be applied to inorganic materials such as silicas; chiral gelators are used to template silica and post gelation, the gelator is removed by calcination of the sample, leaving helical silica fibres with single screw sense. These silica nano-assemblies could have potential use in catalysis.

A very interesting application of gels was the synthesis of a visible light harvesting organogel composed of a cholesterol perylene derivative **128**.[105] The gel phase is a unique phase, different from either the solid phase or the liquid phase and this unique medium is expected to provide a novel environment to arrange functional molecules indispensable to a natural photosynthetic system. This application and related derivatives could be of significant importance in the near future due to the planet's impending crisis with regard to demand and huge consumption of our energy reserves. The gel system was indeed a suitable system for a light harvesting application and this work demonstrated promise in the area of photonic devices, L.E.Ds, signal amplifiers, etc (Scheme 3.10).
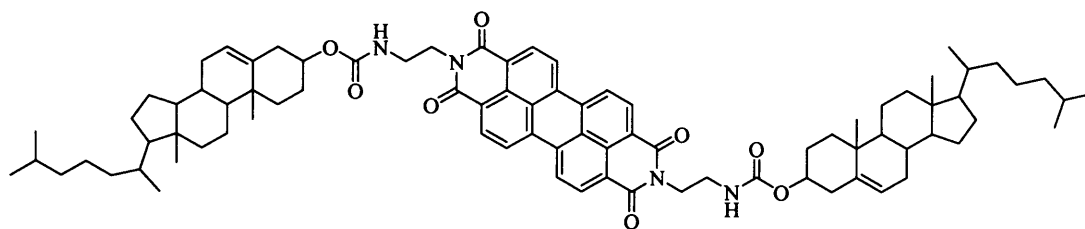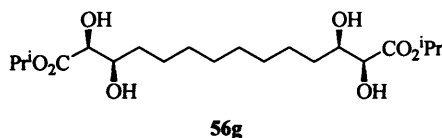
128

Scheme 3.10

The application of organogel systems is vast and the magnitude of their utilisation cannot be done justice in this brief literature review, therefore it must be emphasised that the information reviewed here is not exhaustive. If one wishes to witness the vast plethora of publications then application of simple key words such as gel, organogel and hydrogel in appropriate search engines will provide the relevant and more importantly most up-to-date information.

Chapter 4

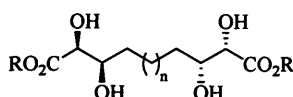# Organogelators:

Results & Discussion.

Results and Discussion

Most discoveries of LMOGs have and continue to be serendipitous and even, initially, looked upon as an undesirable nuisance.

$$\text{Pr}^i\text{O}_2\text{C} \overset{\text{OH}}{\underset{\text{OH}}{\bigwedge}} \diagup\diagup\diagup\diagup \overset{\text{OH}}{\underset{\text{OH}}{\bigwedge}} \text{CO}_2{}^i\text{Pr}$$

56g

During the course of investigations into the novel SAE ligands, the tetra-ol **56g** was synthesised and as noted in Chapter 2 the ligand had an undesirable propensity to gelate practically all solvents used in its (attempted) purification. The purification complication was overcome by adding a hot chloroform solution of the tetra-ol **56g** into a vast excess of hexane in which it is insoluble, this provided a precipitate (gelatinous in character) that could be filtered.

Initially, this phenomenon was considered a mild annoyance and no thought was put into the matter, but a sample of the tetra-ol **56g**, forthwith to be called a gelator, was submitted to the departmental expert (Dr P. C. Griffiths) in soft matter (colloids, surfactants, *etc*) thinking that its gelation properties might be of use. During the studies by Griffiths and co-workers the gelator was found to be of great interest. Therefore, this occurrence required further research to try and discern whether the result was a "one off" only associated with the gelator **56g**.

Two main aspects of the gelator **56g** were to be investigated: the effect of changes to the ester (*i.e.* butyl, isobutyl *etc*) and of varying the alkyl chain length between the two dihydroxy ester termini (Scheme 4.1).

$$\text{RO}_2\text{C} \overset{\text{OH}}{\underset{\text{OH}}{\bigwedge}} \diagup\diagup \overset{}{(\,)_n} \diagup \overset{\text{OH}}{\underset{\text{OH}}{\bigwedge}} \text{CO}_2\text{R}$$

Scheme 4.1: Generic structure

As gelator **56g** was the only isopropyl ester of this molecular type synthesised at the time (*cf.* **56a-f**, Scheme 4.2) it seemed prudent to initially investigate the effect of the alkyl chain length and therefore, the isopropyl ester variants of the series **56a-e** were synthesised.
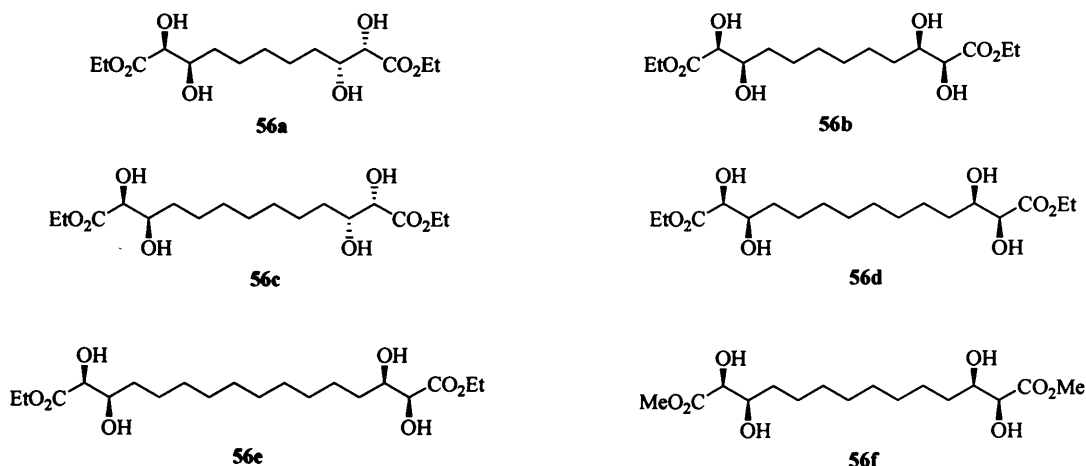
Scheme 4.2: Non-gelating ligands

The *bis*-α,β,unsaturated esters **129a,b,d** were synthesised employing the highly efficient cross metathesis reaction from the corresponding α,ω-diene or cycloalkene. The only exception was diester **129c**, which was synthesised from the *bis*-olefination of 1,9-decanedial **54c** using the MR-HWE method because of the lack of easy access to any suitable alkene (Scheme 4.3).
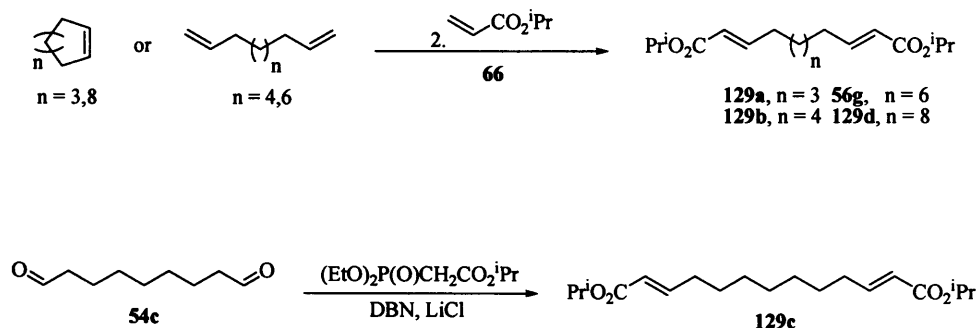
Scheme 4.3

During the course of the *bis*-dihydroxylations, it was clear that the tetra-ol products **130a-d** were possible gelators due to the gelation of the AD mixture to varying extents. Despite this, the gelators **130a-d** were isolated in good yield and purity (Scheme 4.4).


AD mix β: K₃Fe(CN)₆, K₂CO₃,
K₂OsO₂(OH)₄, (DHQD)₂PHAL.

130a, n = 3 56g, n = 6
130b, n = 4 130d, n = 8
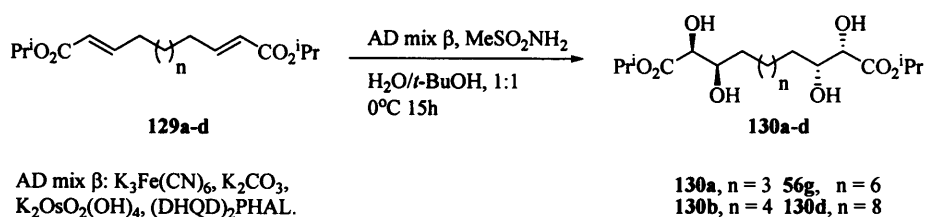
Scheme 4.4

During solvent gelling studies, the compounds **130a-d** and **56g** were found to be gelators. This represented a true gelator system in which the polarity of the gelator could be changed, thereby tuning the physical properties of the gelators. The minimum gel concentrations and gelation media will be discussed in depth later.

As mentioned above, the series of ligands **56a-f** did not show any gelation ability; nonetheless, in the search for other gelators that may have even better characteristics, the investigation was increased to encompass different esters, but keeping the alkyl chain length constant (Scheme 4.4). The chain length chosen was analogous to **130b** because the materials needed were easier and cheaper to gain access to.

a) R = ^{i}Bu,
b) R = ^{t}Bu,
c) R = ^{i}Am,
d) R = Cy,
e) R = 3-pentyl.
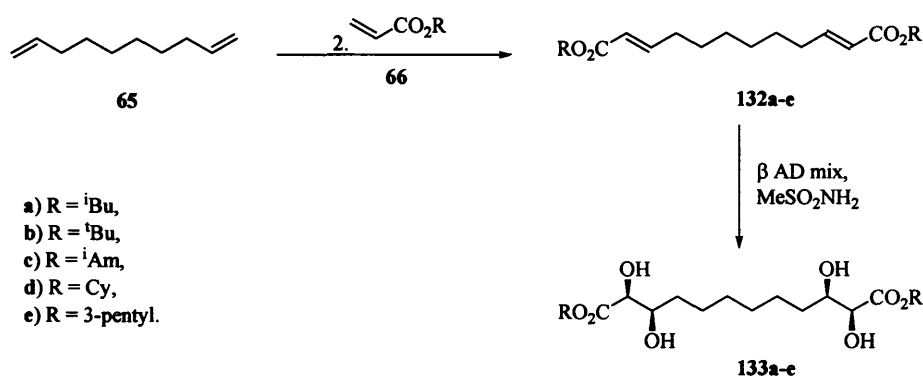
Scheme 4.4

The rationale behind the choices of esters were as follows; the isobutyl ester **133a** is comparable to the isopropyl ester **130b** in the sense that it is a branched ester but with the branch being one carbon removed to the β position and similarly the isoamyl ester **133c** is a γ branched ester. The *t*-butyl ester **133b** was synthesised to investigate whether the gelation phenomenon was as a result of increased steric bulk of the ester (*cf.* ethyl and isopropyl). The cyclohexyl **133d** and 3-pentyl **133e** esters were believed to be more similar to the isopropyl ester in the sense that they are all alpha branched, the only difference being that the 3-pentyl ester is essentially an α,α-diethyl ester (*cf.* α,α-dimethyl of isopropyl) and the cyclohexyl ester is obviously an α,α-ring system.

Surprisingly, none of these systems (Scheme 4.4) mediated gelation of any solvents used, including water, toluene, chloroform/hexane and water/ethanol. This is not a large assay of solvents however the range of solvent polarity (*i.e.* water to toluene) is almost a complete span and therefore, the study was very robust. One can postulate a reason for the gelation behaviour of the isopropyl tetra-ols; the "window" may be a very narrow one in which there is a subtle interplay of sterics and lipophilicity with respect to the esters. The isopropyl ester may be

exerting a high steric influence with the minimum increase in lipophilicity that falls in the "window" of a successful gelator and the other esters synthesised did not have this correct balance of lipophilicity and steric encumberment.

The variance of esters was not exhaustive, the esters chosen were believed to be of sufficient variety for the scope of the studies. It is most probable that there are other ester moieties (hydrocarbon or other) that can mediate gelation of organic solvents and water, however as mentioned in the introduction, one cannot predict whether a compound is a gelator or not and therefore the synthesis of further variants was deemed probably not worthwhile and thus was not pursued.

Samples of the successful gelators based on the isopropyl ester series (**130a-d, 56g**) were tested by Griffiths and co-workers in a study of the gelation of fluorinated solvents.[106] The solvents used were HFB (1H, 1H-heptafluorobutanol) and HPFP (2H, 3H-perfluoropentane). The gelators were insoluble in HPFP but soluble in HFB and this provided the means of synthesising the gels: the gelators were dissolved in HFB, then to this solution HPFP was added. Providing there was a significantly high gelator concentration, the gel would form spontaneously at room temperature.

The simplest and most widely accepted method of determining gelation is the "stable to inversion" test: a suspected gel sample contained in a test tube or sample vial is simply inverted. If no flow or other movement is observed, it is said to be a gel. The macroscopic phase behaviour was found to depend greatly on the solvent ratio, temperature, gelator alkyl chain length and gelator concentration. For example, in a solvent mixture of 10:90 HFB:HPFP: at lower gelator concentrations (< 0.2 wt%) clear liquids were observed with a viscosity directly comparable to that of the pure solvents. With increasing gelator concentration, the samples are heterogeneous with aggregates of transparent gel forming within the fluorosolvent blend. At higher concentration of gelator (*ca.* 0.4 wt%) a transparent macroscopically homogeneous gel formed. Increasing the gelator concentration even further introduced a "haze" to the gel, forming fibrils that may be collected by the removal of the solvent, or simply gelator precipitation. For highly concentrated gelator systems, the gels form instantaneously. At lower concentrations, gel formation appears to pass through a growth stage; clear aggregates of gel co-existing with the remaining solvent appear within a few hours and these then coalesce to form a gel throughout the entire sample over a period of days.

The concentration above which gelation occurs is a decreasing function of increasing chain length *i.e.* less gelator is required to achieve gelation, to such an extent that the gelator **130d** is considered to be a supergelator, forming gels in 10:90 HFB:HPFP at only 0.2 wt % gelator.

The gel-sol transition temperature T_{gel} of the fully gelled samples was measured by immersing the glass vials containing the samples in a temperature controlled water bath. The temperature at

which the sample underwent phase transition was noted. It was found that for a given gelator, T_{gel} increases with increasing gelator concentration and that for samples with the same solvent composition, T_{gel} increases with the chain length.

The morphology of the aggregates formed were quantified by a preliminary SANS carried out on the LOQ instrument at the ISIS facility, Rutherford Appleton Laboratories, Didcot, UK. For a fixed concentration of gelator, the solvent composition had a pronounced effect on the observed scattering, correlating well with the macroscopic phase behaviour observations. Stronger scattering was observed for gelator **130d** at 1 wt % in a 10:90 HFB:HPFP mix than a 20:80 mix, indicating a different packing of the gelator. Guinier analysis showed a characteristic signature of a cylinder geometry in the gelled samples. The radius (R) of the cylinders extracted from the SANS data was found to vary with both gelator concentration and solvent composition. For a given solvent ratio, the radius R increased with gelator concentration. Considering the solvent composition 50:50 with gelator **130d**: At 3.75 wt %, R = 25±1Å, and 5 wt %, R = 32±1Å then at 6.0 wt %, R = 42±1Å.

At constant gelator concentration, R varies according to the ratio of solvents. Increasing the proportions of HPFP in the solvent mix results in an increase of R. In 100:0 HFB:HPFP, R = 22±1Å, in 50:50, R = 30±7Å, in 20:80 HFB:HPFP, R = 38±1Å and finally in 10:90 HFB:HPFP, R = 60±1Å.

Therefore these aggregated structures obtained from these gelling processes appear to be entangled rod-like fibres that are built up through non-covalent interactions such as weak Van der Waals attractions and strong hydrogen bonding. Freeze drying shows a swollen fibrous structure, of a larger volume than is observed when a gel is left to dry in ambient air.

The gelator series **130a-d** and **56g** represents the first non-fluorinated system to gelate fluorous media, as all previous fluoro-gelators contained fluorinated segments. In addition, the simplicity of the synthesis of these gelators is an inherent advantage over the other fluoro-gelators.

Studies additional to those involving fluorogelation involved selecting a range of solvents of varying properties and then determined the minimum concentration of gelator, such that the system being studied passed the "stable to inversion test" (Table 4.1).

Table 4.1: Minimum gel concentration

Gelator	Water	Toluene	DCM	CHCl$_3$/Hexane (1:10)	Ethanol/Water (1:10)
130a	ppt	10.34	ppt	ppt	ppt
130b	12.56	4.87	94.36	3.93	12.42
130c	5.53	3.37	53.25	5.36	5.63
56g	1.70	3.20	33.76	5.27	1.70
130d	ppt	3.84	7.08	4.08	1.81

The figures in the table show the minimum
Gel concentration in mg gelator/ml of solvent.

The data from these studies were extrapolated by calculations to yield the number of molecules gelled per molecule of gelator and Table 4.2 and Graph 4.1 summarise these.

Table 4.2: Number of solvent molecules gelled

Gelator	Water	Toluene	DCM	CHCl$_3$/Hexane (1:10)	Ethanol/Water (1:10)
130a	ppt	331	ppt	ppt	ppt
130b	1674	730	63	783	1575
130c	3943	1095	187	595	3605
56g	13285	1194	188	627	12365
130d	ppt	1064	958	866	12415

Graph 4.1

Graph showing number of solvent molecules gelled per molecule of gelator.
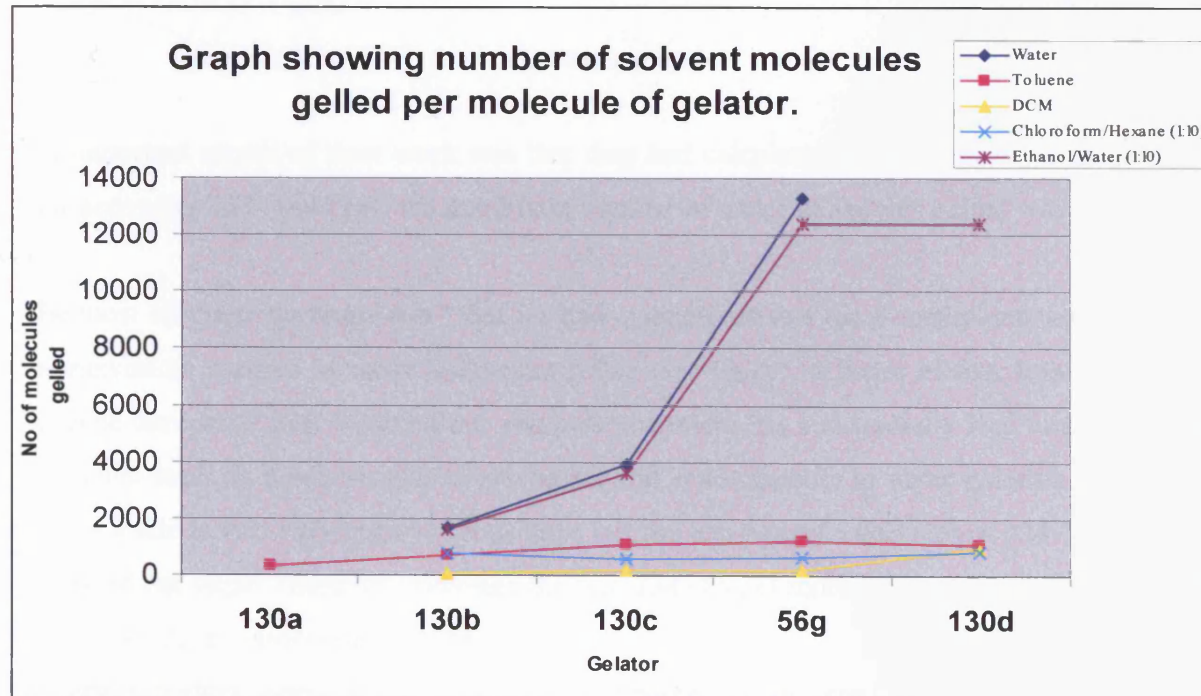
From the results a general trend can be formulated; upon increasing the chain length of the gelator molecules, the propensity to gelate the solvent in question also increases, unless the gelator in question is incapable of gelating the medium. However, for the gelators **56g** and **130d**;

the difference in the number of solvent molecules gelled (in the examples of toluene and water/ethanol) is relatively small and therefore this indicates that the chain spacing of eight and ten methylene units respectively, arguably, represents the optimal chain lengths. Therefore, one can postulate that further increase in chain length may not provide enhanced gelation ability and it may even decrease the efficacy of these larger gelators. Further studies are needed to resolve this issue.

During these later studies, a paper appeared in which Bhattacharya and co-workers repeated the syntheses of sugar derivatives **134-138** based on an azobenzene core (Scheme 4.5). By far the most efficient gelator was the tetracarboxylic acid **134** and their work concentrated on the study of this moiety.


134, X = OH,
135, X = nBuO,
136, X = NHBn,
137, X = NHCH$_2$CO$_2$Et,
138, X = NHCH$_2$CO$_2$H.
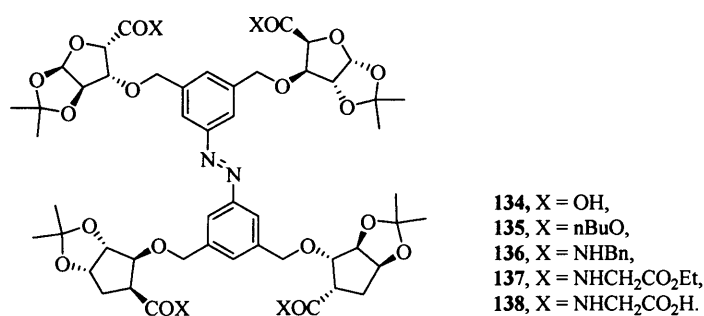
Scheme 4.5

An important aspect of their work was that they had calculated the number of water molecules that derivative **134** could gel: the maximum number of water molecules gelled was 55,000 at pH 4!

The most efficient "hydrogelator" that we had synthesised was the 8-methylene tetra-ol **56g** and the maximum number of water molecules gelled was 13,285, a factor of four less than the azo-benzene derivative **134**. Nonetheless, our gelator system has substantially less functionality and molecular mass, is much simpler to synthesise and is not specific to water gelation. Our gelators can be made in two very high yielding steps but the azo-benzene derivatives **134-138** require in excess of ten steps! Therefore, although the acid **134** can gel more water, our gelators have many more advantages associated with them.[107]

A very important aspect of our gelators still remained unanswered, that of their optical purity. This question was equally important to the asymmetric epoxidation studies. Therefore, in order to determine the optical purity (ee), the racemate of one of the gelators had to be synthesised and the gelator *rac*-**56g** was chosen as it had been extensively used in the SAE studies. The synthesis

was identical to that of **56g** except that the chiral ligand in the AD was replaced with quininclidine (Scheme 4.6).[9]
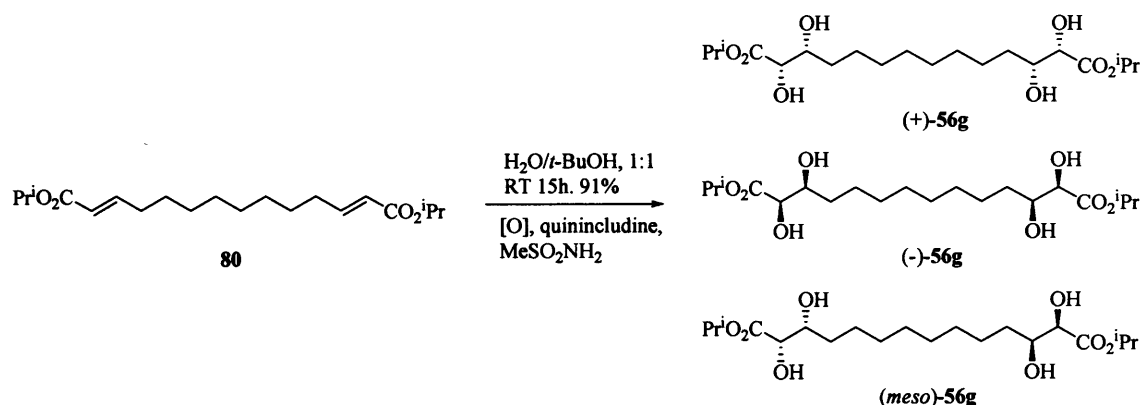
Scheme 4.6

From the non-asymmetric dihydroxylation conditions used, formation of a statistical mixture of (+)-**56g**:(-)-**56g**:(*meso*)-**56g** in a ratio of 1:1:2 was expected. However, initial HPLC studies apparently showed the presence of only two species, albeit without base line separation and therefore, an alternative assay was sought. GC of the TFA derivative of the "racemic" **56g** using the chiraldex GTA column was successful and two peaks were seen in a 1:1 intensity ratio (GC Trace 4.1 and 4.2).

Trace 4.1   **Trace 4.2**
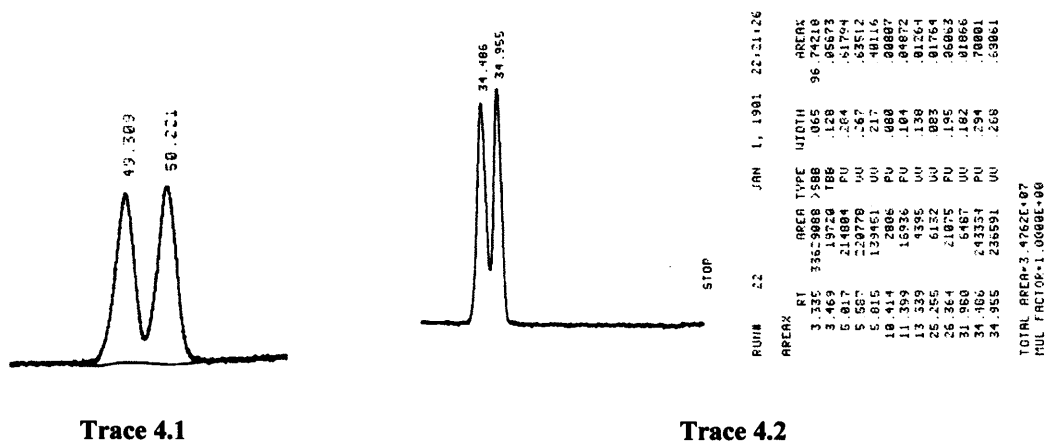
Two explanations seemed likely; either one peak was the *meso* isomer and the other the unseparated *d/l* mixture or the two peaks represented completely separated *d* and *l* forms and no *meso* had been formed. The 1:1 ratio seemed inconsistent or at least unlikely in the case of the first explanation, while formation of no *meso* form seemed very surprising. Of course, a sample of the tetra-ol (+)-**56g** was available (see Chapter 2) and its enantiomer (-)-**56g** was readily prepared using (DHQ)$_2$PHAL. Repeat analyses using these samples (GC traces 4.3, 4.4 and 4.5)

clearly showed that the two peaks were due to these two enantiomers and therefore, no *meso* tetra-ol was made during the non-asymmetric dihydroxylation of **80**, an unprecedented result.
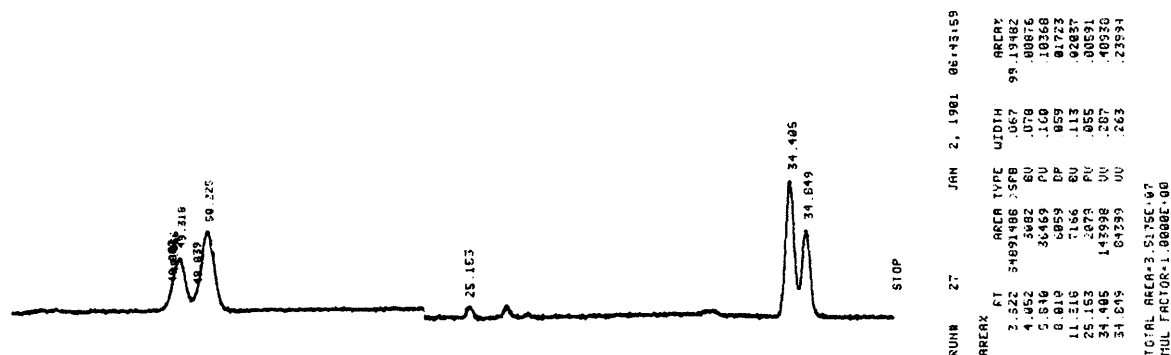
Trace 4.3 (DHQ)₂PHAL Spike   **Trace 4.4 (DHQD)₂PHAL Spike**
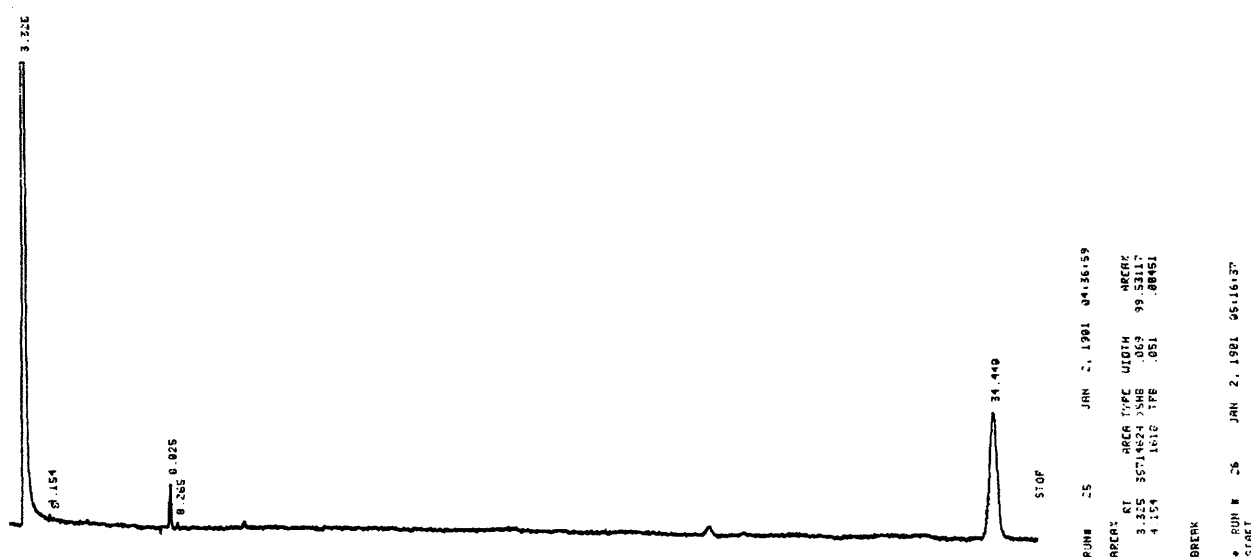
Trace 4.5: (DHQD)₂PHAL (+)-56g

An hypothesis is suggested for this unprecedented result: the occurrence of a secondary catalytic cycle (Scheme 4.7) in the dihydroxylation mechanism is well known and the conditions of the reaction (biphasic) serve to prevent this catalytic pathway that lowers the ee of products in ADs. The existence of this cycle has been confirmed by isolation of the proposed intermediates analogous to **140** (Scheme 4.7).[119] In a dihydroxylation with no chiral ligand, if the *bis*-α-β-unsaturated ester **80** has been mono-dihydroxylated **139**, it would not be unreasonable to suggest that the second dihydroxylation can occur without dissociation of the mono-diol, *i.e.* the

molecule could snap round and thus form a "chelate" **140**. This secondary dihydroxylation has two outcomes:

i) The tetra-ol product is *meso*

ii) The tetra-ol product has the identical absolute configuration inferred into the relative configurations, *i.e.* if the configuration 2*S*, 3*R* is initially formed, the secondary cycle would form providing 12*R*, 13*S* stereochemistry and therefore results in the synthesis of (+)-**56g**. Likewise, the tetra-ol (-)-**56g** would form if the initial configuration was 2*R*, 3*S*. Hence, when using a racemic (achiral) ligand such as quinunclidine, the *dl* pair is obtained and no *meso* isomer is formed, as observed.

Therefore, from the experimental observation that no *meso*-**56g** was produced, one can conclude that the second outcome did occur during the non-asymmetric dihydroxylations. In the AD reactions, this effect would result in no *meso* compounds being formed and the product would be provided in much greater enantiomeric excess.

Returning to the original target of these investigations, that being the enantiomeric excess of the ligand/gelator **56g**. GC of the tetra-ol (+)-**56g** [derived form (DHQD)₂PHAL] showed the presence of only one species (GC trace 4.5) and no (-)-enantiomer of the tetra-ol **56g** was observed (within detection limits of the GC). Therefore, the enantiomeric excess of the gelator/ligand **56g** is >99% ee. This result signifies that when used in epoxidation studies when the ligand **56g** shows inadequacies they are not due to asymmetric epoxidation mediated by a minor enantiomer (or asymmetric amplification epoxidation by a minor species) and the results the studies carried out were robust.

The secondary catalytic cycle hypothesis is illustrated below (Scheme 4.7):
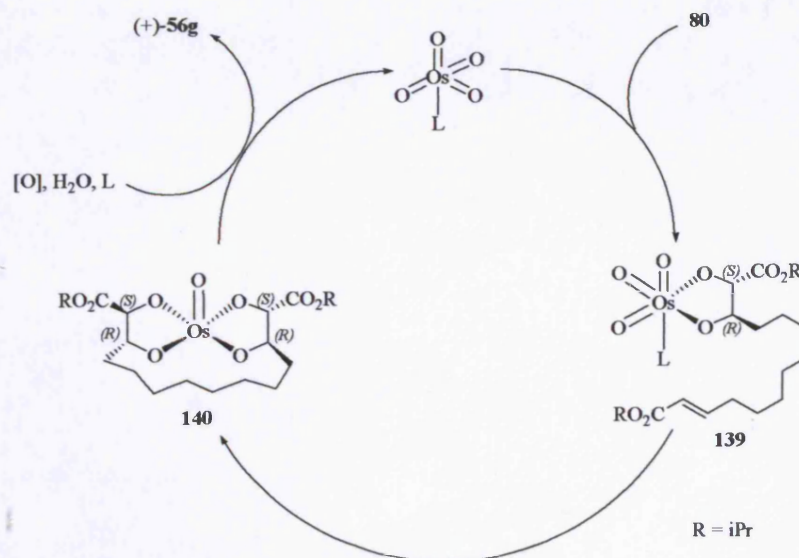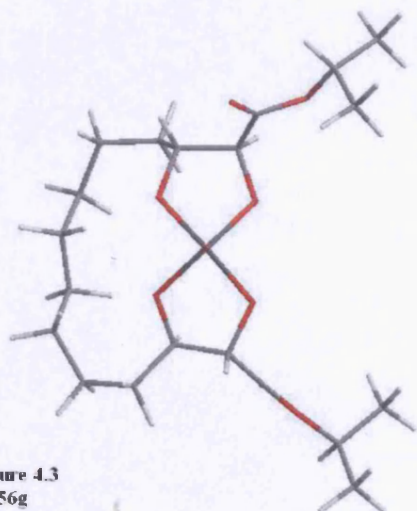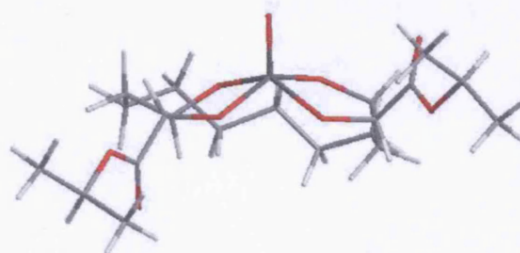
Scheme 4.7

Further evidence was sought and the molecular modelling of the osmate chelate **141** (*meso*) and **140** was undertaken using Gaussian 03, geometry optimisation using the B3LYP/LanL2DZ level of theory. The optimised structures are shown below (Pictures 4.1-4.4)

Picture 4.1
(meso)
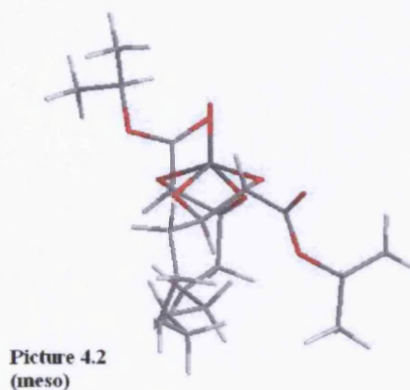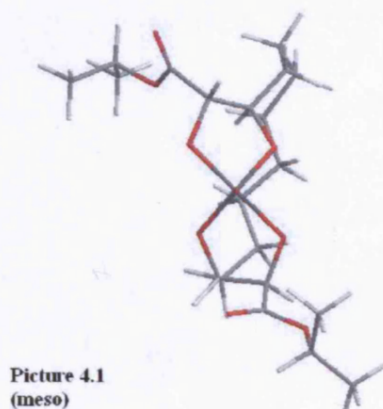
Picture 4.2
(meso)

Chelate 141

Picture 4.3
(+)-56g

Picture 4.4
(+)-56g

Chelate 140

Although no specific energy calculations could be obtained for the foregoing complexes, in my opinion the chelate **140** (single enantiomer) looks more stable and more ordered. The osmium oxygen bonds in the *meso*-chelate **141** are skewed and the alkyl chain is in close proximity to the osmium centre and one of the isopropyl esters, therefore I believe this would be the less favoured geometry.

An experiment was conducted to determine the minimum gel concentration of *rac*-**56g** in toluene and thus investigate the difference in using a non-optically pure, racemic gelator. The minimum gel concentration was 12.31 mg gelator per ml of toluene, a factor of 4 more gelator than was required when (+)-**56g** was used (3.20 mg/ml), clearly this is not an experimental discrepancy. Therefore, the addition of the other enantiomer, (-)-**56g** resulted in the reduction of the ability of the tetra-ol **56g** to gelate toluene, but the mechanism of this effect is unknown.

The microscopic structure (mechanism of bonding) of the gels still remained elusive, therefore efforts were sought to determine this. In the ^{1}H-NMR spectra of all the related tetra-ol ligands/gelators (**56a-g**, **130a-d** and **133a-e**) common, albeit odd, features were found in the coupling constants of the dihydroxy-ester segments. The following snippet of characterisation from ligand **56e** shows this: δ_H 4.08 (2H, dd, J = 5.1 and 2.0, 2-,15-H), 3.88 (2H, dtd, J = *ca* 9, 7 and 2, 3-,14-H), 3.05 (2H, d, J = 5.1, 2-,15-OH), 1.87 (2H, d, J = 9.1, 3-,14-OH).

56e
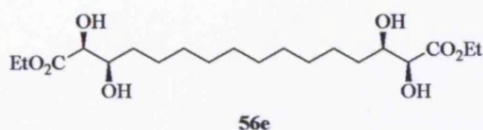
The magnitude of the coupling constants can be explained if one considers the proposed hydrogen bonding between the β-OH and the ester carbonyl, together with an equatorial position for the remainder of the molecule ("R") in a chair like conformation which, due to the stereochemistry, forces the α-OH axial (Scheme 4.8).
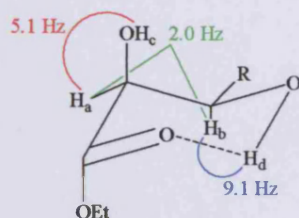
Scheme 4.8

The following spectra show these resonances (Spectra 4.1 and 4.2) and then after a D_2O shake (Spectra 4.3).
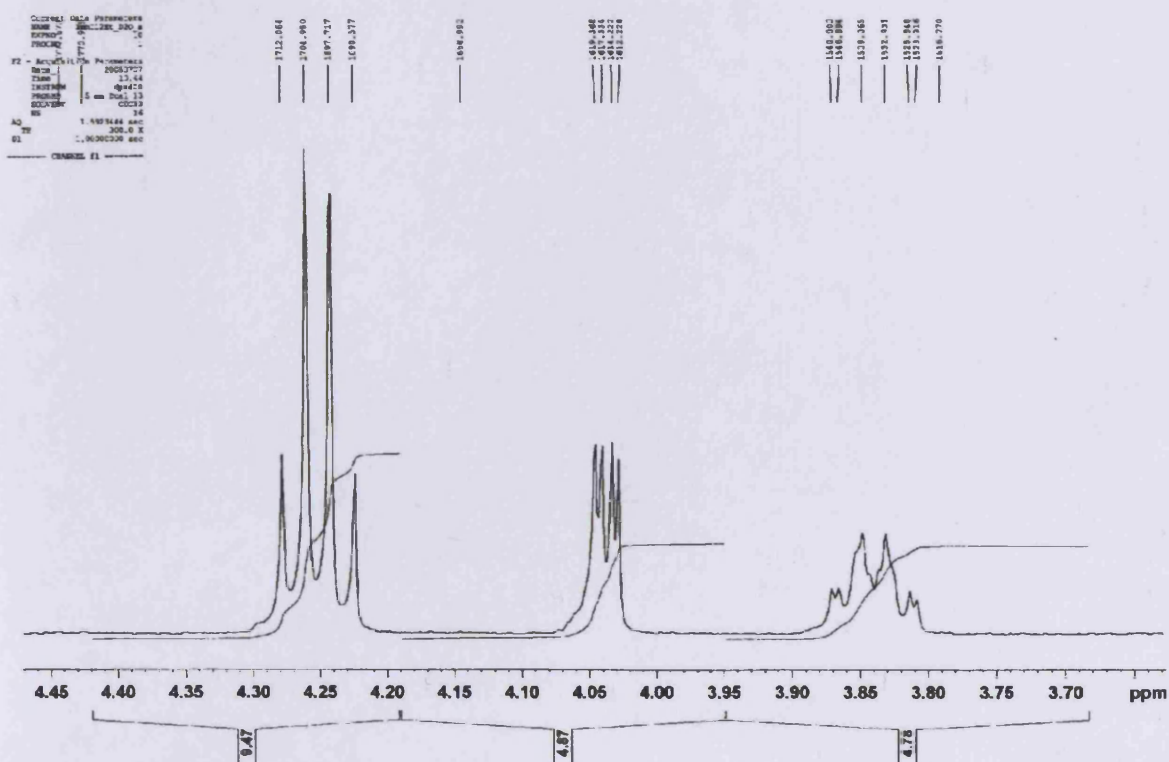
Spectra 4.1

Spectra 4.2

Spectra 4.3

With the structure in solution resolved, it seems fair to argue that a similar structure could exist in the gel phase because this cyclohexane structure has a mechanism by which it could form bonds between other molecules *i.e.* self organi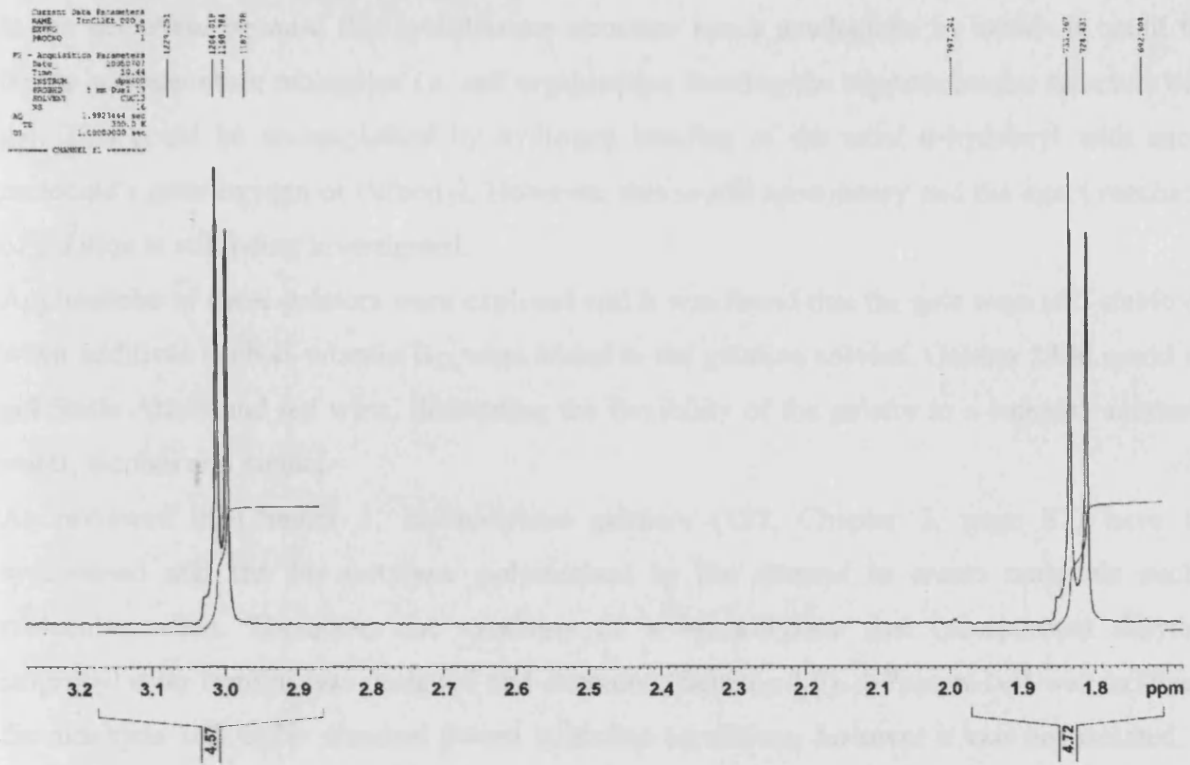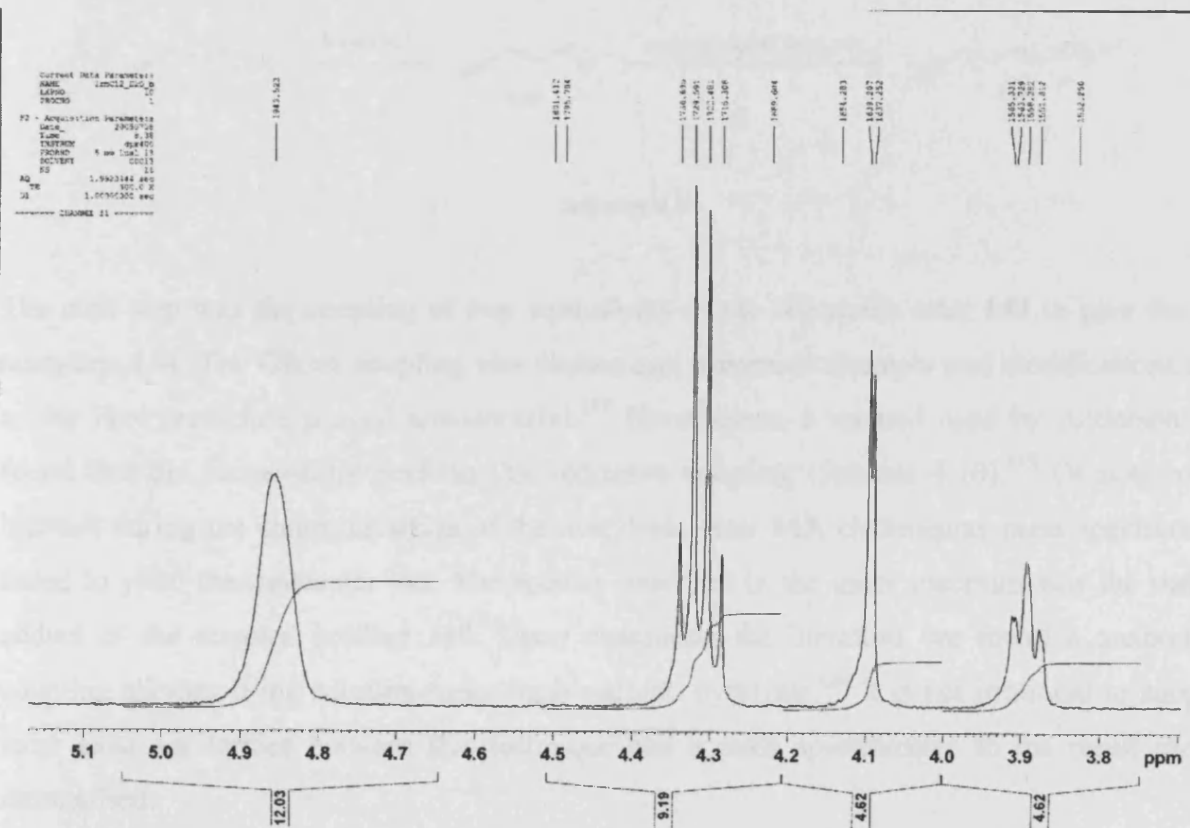sation forming the supramolecular structure of the gel. This could be accomplished by hydrogen bonding of the axial α-hydroxyl with another molecule's ester oxygen or carbonyl. However, this is still speculatory and the exact mechanism of gelation is still being investigated.

Applications of these gelators were explored and it was found that the gels were still stable even when additives such as vitamin B_{12} were added to the gelation solvent. Gelator **130d** could even gel Stella Artois and red wine, illustrating the flexibility of the gelator in a complex mixture of water, alcohol and sugars.

As reviewed in Chapter 3, *bis*-acetylene gelators (**127**, Chapter 3, page 87) have been synthesised and the *bis*-acetylene polymerised in the attempt to create materials such as molecular wires. Therefore, the synthesis of a *bis*-acetylene that incorporated dihydroxy isopropyl ester termini was designed and executed (Scheme 4.9). 4-Pentyn-1-ol was oxidised to the aldehyde **142** under standard Swern oxidation conditions, however it was not isolated. The filtrate was added to the phosphonium sodium salt of isopropyl diethylphosphonoacetate and the acetylenic ester **143** was obtained in an excellent yield of 95%.
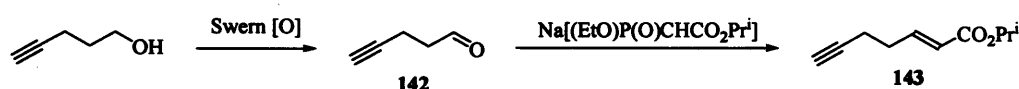
Scheme 4.9

The next step was the coupling of two equivalents of the acetylenic ester **143** to give the *bis*-acetylene **144**. The Glaser coupling was chosen and numerous attempts and modifications such as the Hay procedure proved unsuccessful.[117] Nonetheless, a method used by Anderson was found that did successfully perform this oxidative coupling (Scheme 4.10).[118] Of noteworthy interest, during the characterisation of the acetylenic ester **143**, electrospray mass spectrometry failed to yield the molecular ion. The species observed in the mass spectrum was the sodium adduct of the coupled product **140**. Upon examining the literature, we found a method for coupling alkynes using solution-spray flash vacuum pyrolysis.[120] It is not irrational to suppose there exist similarities between this technique and a mass spectrometer so the result can be rationalised.
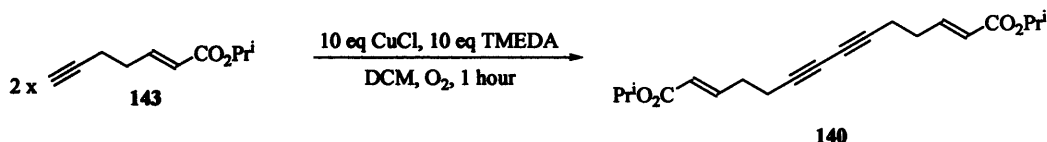
Scheme 4.10

Subsequent *bis*-dihydroxylation of the *bis*-alkyne **140** provided the target molecule **141** in good yield and it was immediately apparent that the *bis*-acetylene **141** was a gelator (Scheme 4.11). Although all efforts were used to prevent exposure of the *bis*-acetylene **141** to daylight, upon examining the compound one could see that the sample was changing to a red colour indicating that the *bis*-acetylene was polymerising. In an attempt to remove the polymer the *bis*-acetylene was dissolved in chloroform and then filtered through a plug of silica. The red tape like polymer was removed and it seemed that the polymerisation of the material was only on the surface of the material.
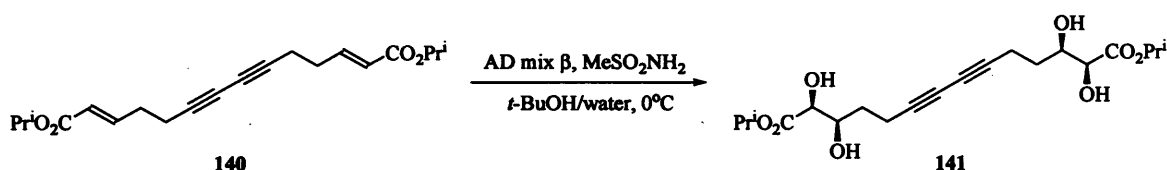
Scheme 4.11

A sample of the *bis*-acetylene **141** was immediately used to form a toluene gel and subsequently treated with UV light. The *bis*-acetylene gel did not polymerise so in an attempt to initiate polymerisation a drop of cumene hydroperoxide was added to the heated toluene solution of the gelator. Over a few days the gel changed to a red colour (Picture 4.5-4.6) but only in half the sample. This was confirmed by heating the sample and only the un-polymerised gelator melted into the solution phase then allowed to re-gel upsidedown (Picture 4.7). A few days later the unpolymerised material had polymerised and formed the red polymer as shown in Picture 4.8, the re-heating of the gel probably re-initiated the radical polymerisation.
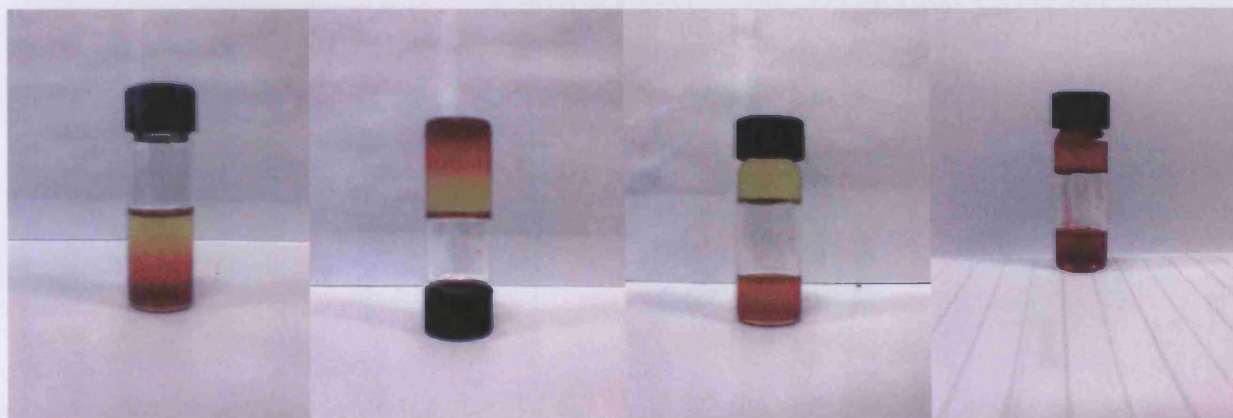
Picture 4.5   **Picture 4.6**   **Picture 4.7**   **Picture 4.8**

The experiment was repeated using dichloromethane/hexane as the gelation medium and CHP was again used as the radical initiator and over the period of a weekend, the *bis*-acetylene **141** polymerised and formed a dark blue/purple polymer.

Disappointingly, the *bis*-acteylene **141** did not gel water (precipitated) however, upon standing over a period of days, a dark blue gelatinous polymer "grew" in the sample vial with a distinct fibrous nature, but how and why this occurs remains a mystery.

As noted previously, the *bis*-acetylene **141** did polymerise in air as indicated by the red colour on the surface of the polymer. In futher investigations a sample of the *bis*-acetylene was dissolved in dichloromethane and chloroform and these solutions of the *bis*-acetylene were allowed to evaporate in the presence of air overnight. Both samples changed to a blue/purple colour overnight, indicating the formation of a polymer (Pictures 4.9 and 4.10).
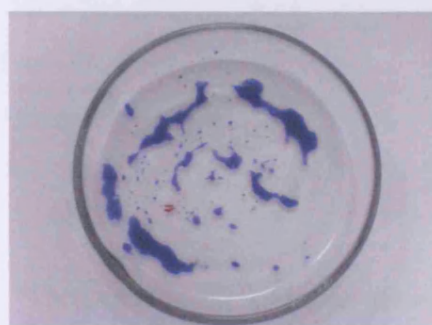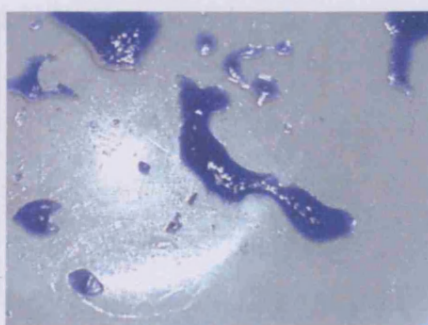
Picture 4.9   **Picture 4.10**

The solid shown was a hard and relatively brittle material and upon adding a sample of it to chloroform the colour changed from purple to red and the volume of the material shrank. A sample of this polymer was analysed by FTIR spectroscopy: the IR spectrum (IR 2) had comparable features to that of the parent material (IR 1) but did also contain additional features.
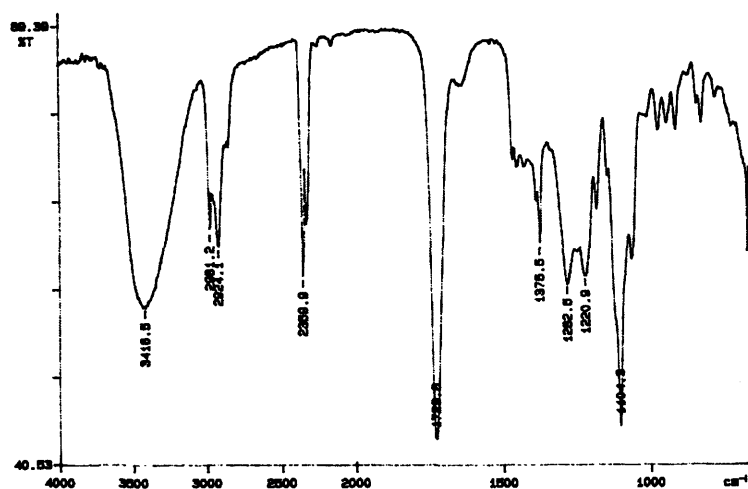
IR 1: **141**
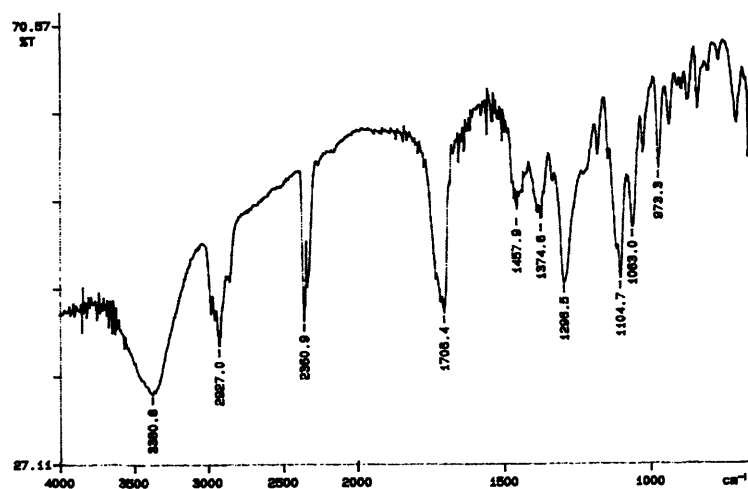
IR 2: **141** polymerised

The peaks in the polymer were less well resolved indicating different envirmonments within the material and the spectra now differed in the region of 1300-1500 cm^{-1}. A new signal at 973 cm^{-1} had also appeared and this was indicative of a *trans*-carbon-carbon double bond therfore, this confirms the polymerisation because it is known that *bis*-acetylenes polymerise forming poly(eneyne)s[99] (Scheme 4.12).
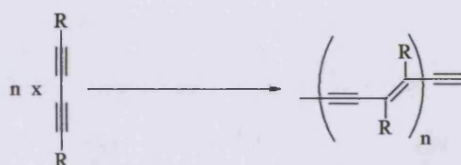
Scheme 4.12

Another oddity in this area came from the filtration of some heavily surface-polymerised *bis*-acetylene; the red polymer was filtered off and the fluted filter-paper was allowed to stand in air overnight (Picture 4.11). The red polymer can clearly been seen and of noteworthy interest is the polymerisation of the material within the paper (purple colour around the edges). The exact scientific contribution of these phenomena are questionable however, the aesthetic value is great.
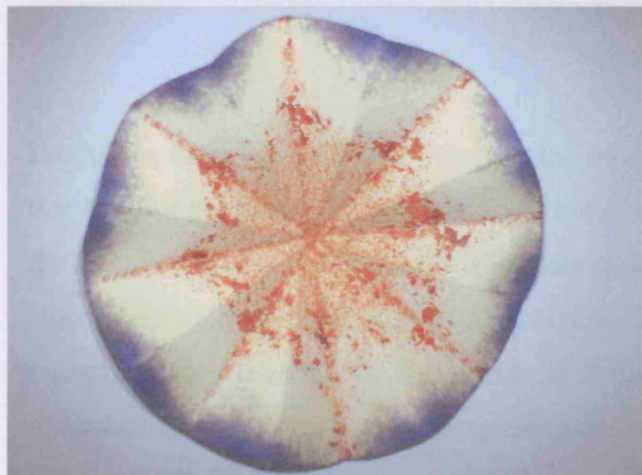
Picture 4.11

So what do the colours mean? Upon polymerisation of *bis*-acetylenes, an extended conjugated polyenyne system is formed and the electronic properties of such polymers are due to this delocalisation.[99] These electrical properties can be modified by doping the material pre-polymerisation, for example, iodine can be added and can result in a polymer that has conductivity characteristics comparable to metals. The colour of *bis*-acetylene polymers is directly related to the extent of delocalisation of the conjugated system. The appearance of the colours implies that poly-*bis*-acetylenes have been produced; the particular colour depends on the effective delocalization length of the π-electrons in the polyenyne backbone, with blue poly-*bis*-acetylenes having longer effective lengths than do red ones.

112

Conclusion
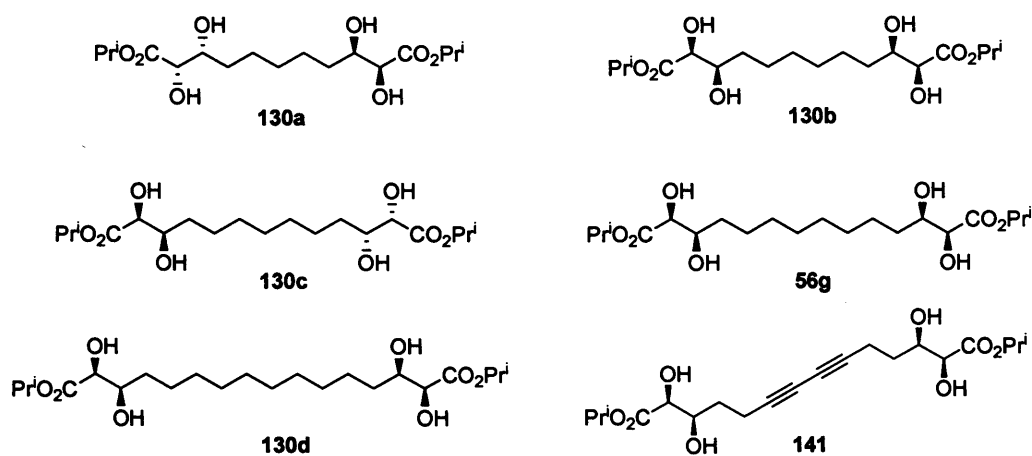
Scheme 4.12

Herein we have reported the discovery and development of a novel gelator series (Scheme 4.12) that has the propensity to gelate a wide range of solvents from toluene to water and represents the first example of a non-fluorous species capable of gelating fluorinated media. Although the macroscopic structure (cylinders) has been deduced by SANS, the exact mechanism of how the molecules spontaneously self-assemble to form the gels remains a mystery. This aspect of the work is to be examined in much greater detail with further research. The applications of the gelators/derivatives such as **141** will also be examined in much greater detail and plans already exist for the synthesis and design of functionalised molecules that contain the "gelating" *bis*-dihydroxy isopropyl ester moieties.

This phenomenon of gelation may provide a different insight into the mechanism of asymmetric epoxidation using the tetra-ol ligands (*e.g.* **56g**). It is likely that the gelator molecules can arrange in a chain like fashion, head-to-tail, creating the rod shapes as observed by SANS. Therefore a similar head-to-tail stacking mechanism could be present in the epoxidation mixture *i.e.* instead of hydrogen bonding the titanium(IV) acts as to effect bonding between the dihydroxy ester "head" of one molecule and to the "tail" of another in a polymer like fashion. This type of complex could still function as an active catalyst, the only difference would be that the hydrocarbon strap would not be part of the complex, it would be acting as a linker. This idea is supported by the Sharpless dimer (**27c**, page 18) in that his system did not efficiently mediate kinetic resolution but the dimer complex was forming in solution (evidence from isopiestic methods, Signer) thereby inferring that the dimer system with a strap in the complex diminishes kinetic resolution. However, as previously discussed (pages 18-19) the alkoxide used in the

Sharpless studies was *tert*-butoxide and further experiments showed that this alkoxide leads to diminished kinetic resolution of secondary allylic alcohols. Therefore, this ligand by-stander effect may be the actual reason why the Sharpless complex did not mediate kinetic resolution and not the effect of the hydrocarbon linker/strap.

Moreover, a significant piece of experimental evidence that would count against this theory is that our novel catalytic system has different recognition characteristics with respect to substrate epoxidation selectivity (2,3,3-trisubstituted allylic alcohols had poorer enantioselectivity, up to 17% ee less). This diminished substrate selectivity cannot be explained if the ligands complex in the "head-to-tail" mode arguably, this type of complex would not suffer from the steric encumberment that would affect the recognition characteristics of the system. Only a *bis*-chelate complex **84** as shown below and on page 62, could alter the recognition characteristics of the SAE system, as explained previously (Chapter 2, page 50).

R = ^{i}Pr   **56g, y = 4**   **84**
X = O^{i}Pr
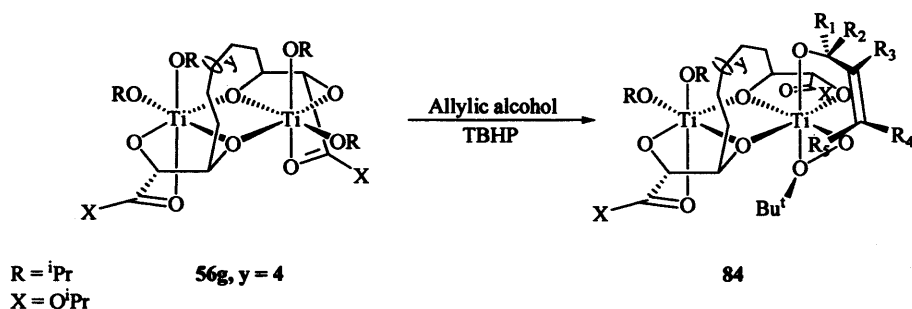
Chapter 5

Experimental.

General Experimental Details.

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR as thin films on sodium chloride plates unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AM 400 (400 MHz, PFT) instrument, with ^{13}C spectra being recorded at 100 MHz, unless otherwise stated. The following abbreviations were used; s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets etc; all coupling constants are measured in hertz (Hz). The abbreviations δ_H and δ_C denote ^{1}H and ^{13}C NMR, respectively taken at 300 K. Chemical shift abbreviations (δ_H and δ_C) are reported in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 (CHCl$_3$) ppm for ^{1}H NMR and 77.30 (CHCl$_3$), centre line for ^{13}C NMR. Unless stated, deuteriochloroform was used as a solvent for all NMR measurements. All reactions using air/moisture sensitive reagents were performed in flame dried apparatus, under an atmosphere of nitrogen. 'Petrol' refers to light petroleum ether, b.p. 40-60°C; ether refers to diethyl ether. Anhydrous tetrahydrofuran was obtained by fresh distillation from sodium wire. Dry dichloromethane was obtained by distillation from calcium hydride. Anhydrous dimethylsulphoxide was obtained from Aldrich 'Sure Seal' packaged bottles. Column chromatography was performed using matrix® (35-70 µm) silica gel and the solvents specified. Powdered 4 Å and 3 Å molecular sieves were pre-activated by flame drying under high vacuum for ten minutes and stored in an electric oven @200°C. "Drying" refers to the organic extracts from aqueous workups being dried by brief exposure to dried magnesium sulphate followed by filtration. Evaporation is the removal of the volatiles in question using a Büchi rotavaporator under reduced pressure (*ca* 12 mmHg) with a water bath at the appropriate temperature for the solvent being removed. New batches of catalysts (*i.e.* repeat syntheses of catalysts) were tested for efficiency before being used in novel investigations.

General Experimental Procedure A: Cross metathesis:

To a stirred solution of an α,ω-alkadiene or a cycloalkene (1.0 eq) and an acrylic ester (2.0 eq) in dry dichloromethane (*ca* 0.5 M solution) was added "Grubbs second generation catalyst" **66** (typically 0.15 - 0.2 mol %) and the resulting solution refluxed overnight under a nitrogen atmosphere. The dichloromethane was evaporated and the residue was eluted through a pad of silica with hexane/diethyl ether (9:1) providing the cross metathesis product(s) as colourless oils in good to excellent yields.

Representative procedure:

(2*E*,10*E*)-Diethyl dodeca-2,10-diendioate 55b
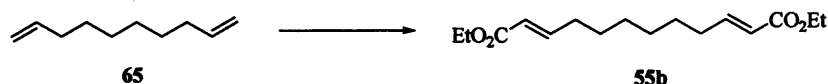
An oven-dried 50 ml round bottomed flask equipped with a reflux condenser was charged with anhydrous dichloromethane (11 ml), 1,9-decadiene **65** (0.50 ml, 2.75 mmol), ethyl acrylate (0.60 ml, 5.50 mmol) and Grubbs second generation catalyst **66** (47 mg, 1 mol%) and the pale red solution was refluxed overnight whereupon ^{1}H NMR indicated reaction completion. The dichloromethane was evaporated and the residue was filtered through a pad of silica (10 cm) with hexane/diethyl ether (9:1) furnishing the *bis-α,β-unsaturated ester* **55b** (0.70 g, 2.48 mmol, 90%) as a colourless oil of sufficient purity. Analytical data is shown later.

General Experimental Procedure B:
Sharpless Asymmetric Dihydroxylation:[9,65]

Potassium ferricyanide (3 eq per olefin), potassium carbonate (3 eq per olefin), methanesulphonamide (1 eq per olefin), potassium osmate (*ca* 0.1 mol %), the chiral ligand [(DHQD)$_2$PHAL or (DHQ)$_2$PHAL (*ca* 0.2 mol %)], were added to water/*t*-butanol (1:1 v/v, *ca* 0.1 M solution wrt olefin) and the vigorously stirred mixture cooled with an ice bath and allowed to equilibrate for ten minutes. To this heterogeneous slurry was added the *bis*-α,β-unsaturated ester and the mixture was allowed to stir overnight at 0°C then quenched by the addition of sodium sulphite (12 eq), diluted with water (1 vol) and extracted with ethyl acetate (3 x 1 vol). The combined organic extracts were washed sequentially with 1M potassium hydroxide (1 vol), saturated ammonium chloride (1 vol), water (1 vol), brine (1 vol), then dried (MgSO$_4$) and

evaporated to leave the tetra-ol ligands as colourless solids of good purity. Where necessary, these could be purified by recrystallisation from $CHCl_3$/hexane or filtration through a small pad of silica eluting with ethyl acetate.

Representative procedure:

(2*S*,3*R*,10*R*,11*S*)-Diethyl 2,3,10,11-tetrahydroxydodecane-1,12-dioate 56b
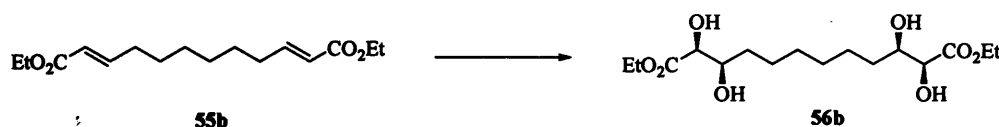
To a 100 ml round-bottomed flask equipped with an efficient stir bar was sequentially added potassium ferricyanide (8.01 g, 24.32 mmol), potassium carbonate (3.36 g, 24.32 mmol), methanesulphonamide (0.77 g, 8.11 mmol), (DHQD)₂PHAL (0.063 g, 0.08 mmol), potassium osmate (0.03 g, 0.08 mmol), *t*-butanol (20 ml) and water (20 ml). The mixture was cooled to 0°C and stirred vigorously for ten minutes to allow the heterogeneous system to equilibrate. To the resulting bright orange suspension was added the *bis*-α,β-unsaturated ester 55b (1.14 g, 4.05 mmol) and the heterogeneous slurry was stirred at 0°C overnight. Whilst still at 0°C the reaction was quenched by the addition of sodium sulphite (6.08 g, 48 mmol) and the resulting mixture stirred at room temperature for 0.5 h, then diluted with water (80 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with 1M potassium hydroxide (100 ml), water (100 ml), brine (100 ml) then dried and evaporated. The residue was dried under high vacuum to give the crude ligand as an off-white solid. Recrystallisation from chloroform/petroleum ether yielded the pure *ligand* 56b (1.11 g, 3.17 mmol, 78%) as colourless powder showing; m.p 102-103°C; $[\alpha]_D^{25}$ +34.7 (c 0.0044, MeOH); [Found: C, 54.85; H, 8.45. $C_{16}H_{30}O_8$ requires C, 54.84; H, 8.63 %]; v_{max}/cm⁻¹ (KBr) 3382, 2937, 2850, 1715, 1461, 1385, 1290, 1103, 1069 and 1040; δ_H 4.32 (4H, q, J = 7.3, 2 x CH₂O), 4.10 (2H, app br s, 2-, 11-H), 3.84-3.91 (2H, m, 3-, 10-H), 3.08 (2H, app s, 2-, 11-OH), 1.92 (2H, d, J = 10.9, 3-, 10-OH), 1.70-1.56 (4H, m, 4-, 9-CH₂), 1.57-1.37 (8H, m, 4 x CH₂) and 1.34 (6H, t, J = 7.3, 2 x Me); δ_C 173.7 (2 x C=O), 73.1 (2-, 11-CH), 72.5 (3-, 10-CH), 62.2 (2 x CH₂O), 33.7 (4-, 9-CH₂), 29.3 (2 x CH₂), 25.6 (2 x CH₂) and 14.2 (2 x Me); m/z (APCI) 351 (M+1)⁺ 100 %; HRMS (ES⁺): calcd. for $C_{16}H_{31}O_8$, (M + H)⁺: 351.2013, found: 351.2014.

General Experimental Procedure C:
Masamune Roush modification of the Horner-Wadsworth-Emmons reaction:[64]

To a dry flask was added lithium chloride (2.0 eq), anhydrous acetonitrile (1 vol), triethyl phosphonoacetate (2.1 eq) and DBN (2.1 eq) and the resulting mixture stirred and cooled to 0°C (Scheme 2.3). A dialdehyde 54a-e (1 eq) was slowly added at 0°C and then the reaction was allowed to stir at ambient temperature overnight. The reaction was next diluted with water (1/2 vol), extracted with ether/hexane (1:99, 4 x 1 vol). This solvent system results in a triphasic extraction, aqueous, acetonitrile, then the hexane/ether layer and the advantage of this system is that the products are of sufficient purity for the subsequent step. The combined hexane/ether solutions were washed sequentially with saturated aqueous ammonium chloride (1 vol), water (1 vol), saturated aqueous potassium carbonate (1 vol), water (1 vol) and brine (1 vol), then dried (MgSO$_4$) and evaoporated yielding the *bis-α,β-unsaturated esters* 55a-e as colourless oils. Representative preparation:

(2E,9E)-Diethyl undeca-2,9-dienedioate 55a
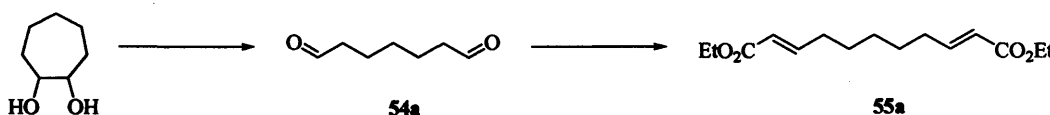
To a 250 ml round bottom flask was added LiCl (1.02 g, 24.12 mmol), anhydrous acetonitrile (100 ml), triethyl phosphonoacetate (5.90 g, 26.53 mmol) and DBN (3.16 ml, 26.53 mmol). The mixture was cooled with an ice bath and 1,7-hepatnedial[108] 54a (1.55 g, 12.06 mmol) was slowly added and the resulting mixture was stirred at room temperature overnight, then quenched with water (100 ml) and extracted with hexane-ether (99:1, 3 x 100 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride (100 ml), saturated aqueous potassium carbonate (100 ml), water (100 ml) and brine (100 ml) then dried and evaporated yielding the *bis-α,β-unsaturated ester* 55a (2.90 g, 10.81 mmol, 89%) as a pale yellow oil of sufficient purity; analytical data is shown later.

General Experimental Procedure D:
Swern Oxidation:[59]

To a flame dried 250 ml round-bottomed flask equipped with a stir bar was added dry dichloromethane (2.0 ml/mmol diol) and the liquid cooled to $-78°C$. Oxalyl chloride (4.4 eq) was added and to the resulting solution was slowly added dimethyl sulphoxide (9.6 eq). After two minutes of stirring, an α,ω-diol 52c-e (1 eq) was added and the reaction was stirred at $-78°C$ for 1h. After a further hour at $-25°C$, triethylamine (10 eq) was slowly added and the mixture was allowed to stir at ambient temperature for four hours, then quenched with water (2 vol) and extracted with ether (3 x 1 vol). The combined organic extracts were washed with saturated aqueous ammonium chloride (2 x 1 vol), water (1 vol) and brine (1 vol), then dried and evaporated to give the crude α,ω-dialdehydes 52c-e, purified by column chromatography.

(2E,9E)-Diethyl undeca-2,9-dienedioate 55a
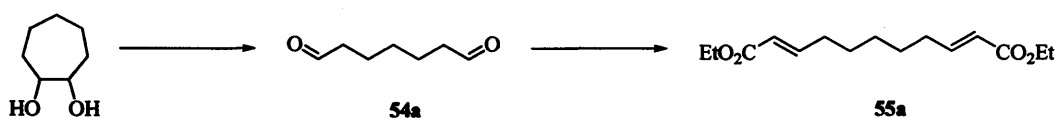
To a 250 ml round-bottomed flask equipped with an efficient magnetic stir bar was added ether (175 ml) and Matrex® silica (65 g). With vigorous stirring, a warm solution of sodium metaperiodate (6.25 g, 29.25 mmol) in water (65 ml) was slowly added to the suspension. 1,2-Cycloheptanediol (2.90 g, 22.28 mmol) was then added and the reaction progress was monitored by tlc. After one hour, the silica was removed by filtration and the organics were evaporated yielding *1,7-heptanedial* 54a as a colourless oil, (2.56 g, 19.92 mmol, 89 %) showing; v_{max}/cm^{-1} δ_H 9.78 (2H, t, J = 1.5, CHO), 2.47 (4H, td, J = 7.0 and 1.5, 2- and 6-CH$_2$), 1.62-1.71 (4H, m, 3- and 5-CH$_2$) and 1.33-1.44 (2H, m, 4-CH$_2$), which was used immediately without further purification:

The title compound 55a was prepared by general procedure C from 1,7-hepatnedial 54a (1.55 g, 12.06 mmol), yielding the *bis-α,β-unsaturated ester* 55a (2.90 g, 10.81 mmol, 89%) as a pale yellow oil showing; v_{max}/cm^{-1} 2981, 2932, 2858, 1719, 1464, 1368, 1309, 1268, 1044 and 981; δ_H 6.88 (2H, dt, J = 15.6 and 7.0, 3-, 9-H), 5.75 (2H, dt, J = 15.6 and 1.5, 2-, 10-H), 4.12 (4H, q, J = 7.0, 2 x CH$_2$O), 2.13 (4H, app q, J = 7.0, 4-, 8-CH$_2$), 1.46-1.24 (6H, m, 5-, 6-, 7-CH$_2$), 1.22 (6H, t, J = 7.0, 2 x Me); δ_C 166.7 (2 x C=O), 149.1 (3-, 9-CH), 121.4 (2-, 10-CH), 60.2 (2 x

CH_2O), 32.0 (4-, 8-CH_2), 28.8 (6-CH_2), 27.8 (5-, 7-CH_2) and 22.1 (2 x Me); m/z (APCI) 269 $(M+1)^+$ 100 % [HRMS (ES^+): calcd. for $C_{15}H_{25}O_4$, $(M + H)^+$: 269.1747, found: 269.1750].

(2S,3R,9R,10S)-Diethyl 2,3,9,10-tetrahydroxyundecanedioate 56a
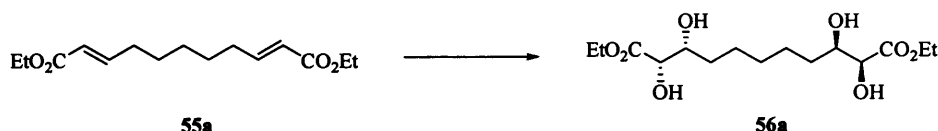
Prepared using general procedure **B** and *bis*-α,β-unsaturated ester **55a** (2.15 g, 8.00 mmol). Recrystallisation of the crude product from chloroform/petroleum ether yielded the pure *ligand* **56a** (2.00 g, 5.95 mmol, 74 %) as a colourless powder showing; m.p 73-74°C; [Found: C, 53.27; H, 8.39. $C_{15}H_{38}O_8$ requires C, 53.57; H, 8.39 %]; v_{max}/cm^{-1} (KBr) 3413, 2933, 2850, 1735, 1464, 1291, 1206, 1100 and 1069; δ_H 4.23 (4H, q, J = 7.1, 2 x CH_2O), 4.01 (2H, app d, J = 2.5, 2-, 10-H), 3.82 (2H, app td, J = 6.8 and 2.5, 3-, 9-H), 2.20-2.00 (4H, br res, 4 x OH), 1.60-1.30 (10H, 5 x CH_2) and 1.26 (6H, t, J = 7.1, 2 x Me); δ_C 174.0 (2 x C=O), 73.1 (2-, 10-CH), 72.5 (3-, 9-CH), 62.1 (2 x CH_2O), 33.6 (4-, 8-CH_2), 29.3 (CH_2), 25.6 (2 x CH_2) and 14.2 (2 x Me); m/z (APCI) 337 $(M+1)^+$ 100 %.

(2E,10E)-Diethyl dodeca-2,10-dienoate 55b
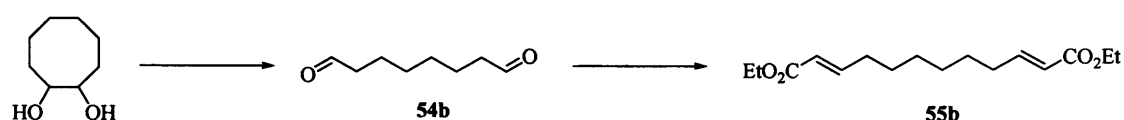
To a 250 ml round-bottomed flask equipped with an efficient magnetic stir bar was added ether (200 ml) and Matrex® silica (40.0 g). With vigorous stirring, a warm solution of sodium metaperiodate (3.90 g, 18.20 mmol) in water (34 ml) was slowly added to the suspension of silica. 1,2-Cyclooctanediol (2.00 g, 13.86 mmol) was added and the reaction was monitored by tlc. After one hour the silica was removed by filtration, then the solution was dried and evaporated yielding *1,8-octanedial* **54b** (1.87 g, 13.12 mmol, 95%) as a colourless oil showing; v_{max}/cm^{-1} 2932, 2856, 2720, 1719, 1462, 1410, 1391, 1116, 1025; δ_H 9.78 (2H, t, J = 1.4, 2 x CHO), 2.45 (4H, dt, J = 7.5 and 1.4, 2- and 7-CH_2), 1.60-1.65 (4H, m, 2 x CH_2), 1.32-1.37 (4H, m, 2 x CH_2); δ_C 204.0 (2 x C=O), 44.0 (2- and 7-CH_2), 29.1 (2 x CH_2), 22.2 (2 x CH_2), which was used immediately without further purification.

The title compound **55b** was prepared by general procedure **C** using 1,8-octanedial **54b** (1.64 g, 11.66 mmol) and yielded the *bis-α,β-unsaturated ester* **55b** (1.33 g, 4.72 mmol, 41 %) as a light tan oil showing; v_{max}/cm^{-1} 2981, 2935, 2859, 1712, 1653, 1464, 1391, 1367, 1226, 1181, 1044 and 980; δ_H 6.97 (2H, dt, J = 15.6 and 7.0, 3- and 10-H), 5.82 (2H, dt, J = 15.6 and 1.3, 2- and 11-H), 4.20 (4H, q, J = 7.1, 2 x CH$_2$O), 2.20 (4H, app qd, J = 7.2 and 1.3, 4- and 9-CH$_2$), 1.30-1.50 (8H, m, 4 x CH$_2$) and 1.30 (6H, t, J = 7.1, 2 x Me); δ_C 166.4 (2 x C=O), 149.0 (3-, 10-CH), 121.2 (2-, 11-CH), 59.9 (2 x CH$_2$O), 31.9 (4-, 9-CH$_2$), 28.7 (2 x CH$_2$), 27.7 (2 x CH$_2$) and 14.1 (2 x Me); m/z (APCI) 283 (M+1)$^+$ 100 % [HRMS (ES$^+$): calcd. for C$_{16}$H$_{27}$O$_4$, (M + H)$^+$: 283.1904, found: 283.1902].

(2*E*,12*E*)-Diethyl trideca-2,11-dienoate 55c
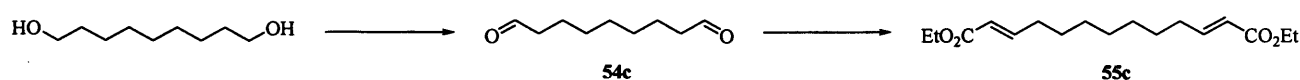
The dialdehyde **54c** was prepared from general procedure **D**, using 1,9-nonanediol **52c** (2.40 g, 15 mmol). Column chromatography (50% ether/petrol, R_f = 0.21) of the crude reaction product yielded *1,9-nonanedial* **54c** (1.22 g, 7.82 mmol, 52%), as a colourless oil showing; v_{max}/cm^{-1} 2930, 2856, 1725, 1463, 1420, 191, 1104 and 1026; δ_H 9.79 (2H, t, J = 1.8, 1-, 9-H), 2.42 (4H, qd, J = 7.2 and 1.8, 2-, 8-CH$_2$), 1.57-1.64 (4H, m, 2 x CH$_2$) and 1.29-1.35 (6H, m, 3 x CH$_2$); δ_C 202.9 (2 x C=O), 43.8 (2-, 8-CH$_2$), 29.0 (5-CH$_2$), 28.8 (2 x CH$_2$) and 21.9 (2 x CH$_2$); m/z (APCI) 157 (M + 1)$^+$; used immediately due to its assumed instability:

The *bis*-α,β-unsaturated ester **55c** was prepared by using general procedure **C** and 1,9-nonanedial **54c** (1.15 g, 7.40 mmol) and yielded the *bis-α,β-unsaturated ester* **55c** (1.25 g, 4.22 mmol, 57 %) as a light tan oil showing; v_{max}/cm^{-1} 2982, 2930, 2856, 1712, 1654, 1464, 1367, 1307, 1266, 1178, 1044 and 981; δ_H 6.88 (2H, dt, J = 15.6 and 7.0, 3-, 11-H), 5.75 (2H, br res d, J = 15.6, 2-, 12-H), 4.15 (4H, q, J = 7.1, 2 x CH$_2$O), 2.20 (4H, app q, J = 7.1, 4-, 10-CH$_2$), 1.40-1.45 (4H, m, 2 x CH$_2$), 1.27-1.32 (6H, m, 3 x CH$_2$) and 1.26 (6H, t, J = 7.1, 2 x Me); δ_C 166.7 (2 x C=O), 149.3 (3-, 11-CH), 121.2 (2-, 12-CH), 60.0 (2 x CH$_2$O), 32.1 (4-, 10-CH$_2$), 29.1 (CH$_2$), 28.9 (2 x CH$_2$), 27.9 (2 x CH$_2$) and 14.2 (2 x Me); m/z (APCI) 297 (M + 1)$^+$ 100 % [HRMS (ES$^+$): calcd. for C$_{17}$H$_{32}$NO$_4$, (M + NH$_4$)$^+$, 314.2326, found: 314.2328].

(2*S*,3*R*,11*R*,12*S*)-Diethyl 2,3,11,12-tetrahydroxy-trideca-1,13-dioate 56c

55c → **56c**
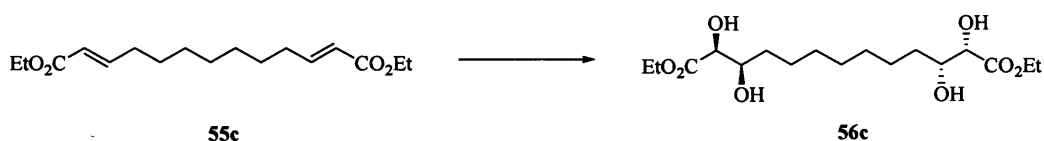
Prepared by general procedure **B**, using the *bis*-α,β-unsaturated ester **55c** (1.20 g, 4.05 mmol). Recrystallisation of the crude product from chloroform/petroleum ether yielded the pure *ligand* **56c** (0.836 g, 2.29 mmol, 57 %) as colourless powder showing: m.p 94-95°C; $[\alpha]_D^{25}$ +22.4 (c 0.0055, MeOH) [Found: C, 55.82; H, 8.75. $C_{17}H_{32}O_8$ requires C, 56.03; H, 8.85 %]; v_{max}/cm^{-1} (KBr) 3380, 2912, 2844, 1715, 1284, 1079 and 1045; δ_H 4.29 (4H, q, J = 7.2, 2 x CH₂O), 4.07 (2H, br d, J = 2.4, 2-, 12-H), 3.81 (2H, dtd, J = ca 9, 7 and 2, 3-, 11-H), 3.06 (2H, d, J = 4.9, 2-, 12-OH), 1.89 (2H, d, J = 9.2, 3-, 11-OH), and 1.56-1.64 (8H, m, 2 x CH₂) 1.33-1.51 (6H, m, 3 x CH₂) and 1.32 (6H, t, J = 7.2, 2 x CH₃); δ_C 173.7 (2 x C=O), 73.0 (2-, 12-CH), 72.5 (3-, 11-CH), 62.2 (2 x CH₂O), 33.8 (4-, 10-CH₂), 29.4 (2 x CH₂), 29.3 (CH₂), 25.7 (2 x CH₂) and 14.2 (2 x CH₃); m/z (APCI) 365 (M+1)⁺ 100 %.

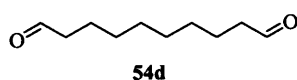## 1,10-Decanedial 54d[109]

54d

Method i)[59] The dialdehyde **54d** was prepared by general procedure **D** using 1,10-decanediol **52d** (2.61 g, 15 mmol). Column chromatography (50% ether/petrol, R_f = 0.25) of the crude product yielded *1,10-decanedial* **54d** (1.80 g, 10.56 mmol, 70 %), as a colourless oil, which showed spectroscopic and analytical data identical to those given below.

Method ii)[60] To a flame dried 250 ml round bottomed flask was added dry dichloromethane (100 ml), 1,10-decanediol (5.00 g, 28.29 mmol), celite® (20 g) and the stirred reaction mixture cooled with an ice bath. Pyridinium chlorochromate (14.84 g, 68.85 mmol) was slowly added and the resulting slurry was allowed to stir at room temperature overnight. The reaction was diluted with hexane (150 ml) and the slurry filtered through a plug (10 cm) of silica. The plug of silica was washed with ether (200 ml) and evaporation of the volatiles yielded *1,10-decanedial* **54d** (3.80 g, 22.32 mmol, 78%) as a colourless oil showing; δ_H 9.70 (2H, t, J = 1.7, 1-, 10-H), 2.32 (4H, td, J = 7.4 and 1.7, 2-, 9-CH₂), 1.52-1.58 (4H, m, 2 x CH₂) and 1.20-1.26 (8H, m, 4 x CH₂); δ_H 202.1

(2 x C=O), 44.2 (2-, 9-CH$_2$), 29.5 (2 x CH$_2$), 29.4 (2 x CH$_2$) and 22.4 (2 x CH$_2$). Both samples were pure enough for use in the subsequent step, which was carried out without delay.

(2*E*,12*E*)-Diethyl tetradeca-2,12-dienoate 55d
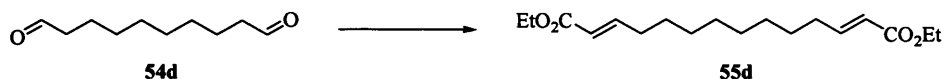
The title compound was prepared by general procedure C using 1,10-decanedial **54d** (1.80 g, 10.56 mmol) furnishing the *bis-α,β-unsaturated ester* **55d** (2.62 g, 8.45 mmol, 80 %) as a light tan oil showing; v_{max}/cm^{-1} 2980, 2930, 2855, 1722, 1653, 1579, 1531, 1464, 1367, 1266, 1178, 1097, 1043, 980 and 918; δ_H 6.96 (2H, dt, *J* = 15.6 and 7.0, 3-, 12-H), 5.80 (2H, dt, *J* = 15.6 and 1.4, 2-, 13-H), 4.18 (4H, q, *J* = 7.1, 2 x CH$_2$O), 2.12 (4H, qd, *J* = 7.0 and 1.4, 4-, 11-CH$_2$), 1.40-1.47 (4H, m, 2 x CH$_2$), 1.27-1.32 (8H, m, 4 x CH$_2$) and 1.28 (6H, t, *J* = 7.1, 2 x Me); δ_C 167.1 (2 x C=O), 149.8 (3-, 12-CH), 121.6 (2-, 13-CH), 60.5 (2 x CH$_2$O), 32.5 (4-, 11-CH$_2$) 29.6 (2 x CH$_2$), 29.5 (2 x CH$_2$), 28.4 (2 x CH$_2$) and 14.7 (2 x Me); m/z (APCI) 311 (M+1)$^+$ 100 % [HRMS (ES$^+$): calcd. for C$_{18}$H$_{31}$O$_4$, (M + H)$^+$: 311.2217, found: 311.2212].

(2*S*,3*R*,12*R*,13*S*)-Diethyl 2,3,12,13-tetrahydroxytetradeca-1,14-dioate 56d
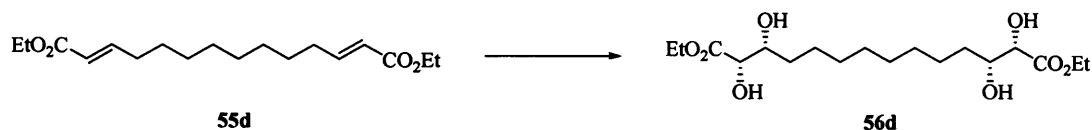
Prepared by means of general procedure **B**, from (1.00 g, 3.23 mmol) of the *bis*-α,β- unsaturated ester **55d**. Recrystallisation of the crude product from chloroform/petroleum ether yielded the pure *ligand* **56d** (0.77 g, 2.03 mmol, 63 %) as colourless powder showing; m.p 106°C; $[\alpha]_D^{25}$ +29.1 (c 0.0056, MeOH) [Found: C, 57.00; H, 8.97. C$_{18}$H$_{34}$O$_8$ requires C, 57.12; H, 9.06 %]; v_{max}/cm^{-1} (KBr) 3574, 2930, 2857 and 1731; δ_H 4.30 (4H, q, *J* = 7.1, 2 x CH$_2$O), 4.08 (2H, dd, *J* = 5.1 and 2.0, 2-, 13-H), 3.88 (2H, dtd, *J ca* 9, 7 and 2, 3-, 12-CH), 3.03 (2H, d, *J* = 5.1, 2-, 13-OH), 1.85 (2H, d, *J* = 9.2, 3-, 12-OH), 1.70-1.20 (16H, m, 8 x CH$_2$) and 1.22 (6H, t, *J* = 7.1, 2 x Me); δ_C 174.0 (2 x C=O), 73.5 (2-, 13-CH), 72.9 (3-, 12-CH), 62.5 (2 x CH$_2$O), 34.2 (4-, 11-CH$_2$), 29.8 (2 x CH$_2$), 29.7 (2 x CH$_2$), 26.1 (2 x CH$_2$), and 14.6 (2 x CH$_3$); m/z (APCI) 379 (M+1)$^+$ 100 %.

(2*E*,14*E*)-Diethyl hexadeca-2,14-dienedioate 55e
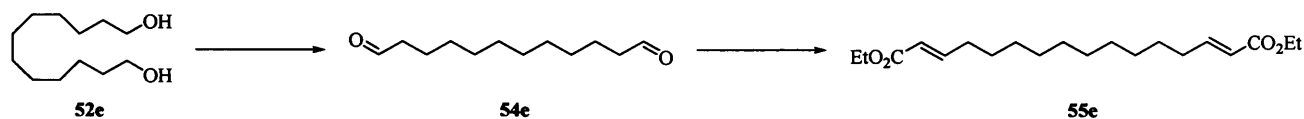
The dialdehyde **54e** was prepared as exemplified in general experimental **D** using 1,12-dodecanediol **52e** (3.04 g, 15 mmol) yielding the crude dialdehyde, **54e**, as a yellow oil. Column chromatography (40% ether/petrol, R_f = 0.66) yielded *1,12-dodecanedial* **54e** (1.00 g, 5.00 mmol, 34 %), as a colourless oil showing; v_{max}/cm^{-1} 2929, 2855, 2716, 1724, 1464, 1409, 1390 and 1074; δ_H 9.76 (2H, t, *J* = 1.7, 1-, 12-H), 2.42 (4H, td, *J* = 7.4 and 1.7, 2-, 11-CH$_2$), 1.57-1.67 (4H, m, 2 x CH$_2$) and 1.25-1.35 (12H, m, 6 x CH$_2$); δ_C 202.9 (2 x C=O), 43.8 (2- and 11-CH$_2$), 29.2 (4 x CH$_2$), 29.0 (2 x CH$_2$) and 21.9 (2 x CH$_2$); m/z (APCI) 199 (M+1)$^+$ 100 %; used immediately:

The title compound was prepared by general procedure **C** from 1,12-dodecanedial **54e** (0.95 g, 4.80 mmol) and provided the *bis-α,β-unsaturated ester* **55e** (1.24 g, 3.67 mmol, 76 %) as a light tan oil showing; v_{max}/cm^{-1} 2980, 2925, 2854, 1721, 1654, 1465, 1367, 1309, 1265, 1181, 1132, 1096, 1044 and 980; δ_H 6.95 (2H, dt, *J* = 15.6 and 6.9, 3-, 14-H), 5.80 (2H, dt, *J* = 15.6 and 1.4, 2-, 15-H), 4.18 (4H, q, *J* = 7.1, 2 x CH$_2$O), 2.19 (4H, qd, *J* = 7.1 and 1.4, 4-, 13-CH$_2$), 1.40-1.5 (4H, m, 2 x CH$_2$) 1.24-1.30 (12H, m, 6 x CH$_2$) and 1.18 (6H, t, *J* = 7.1, 2 x Me); δ_C 166.8 (2 x C=O), 149.5 (3-, 14-CH), 121.2 (2-, 15-CH), 60.1 (2 x CH$_2$O), 32.2 (4-, 13-CH$_2$), 29.5 (2 x CH$_2$), 29.4 (2 x CH$_2$), 29.1 (2 x CH$_2$), 28.0 (2 x CH$_2$) and 14.28 (2 x Me); m/z (APCI) 339 (M+1)$^+$ 100 % [HRMS (ES$^+$): calcd. for C$_{20}$H$_{35}$O$_4$, (M + H)$^+$: 339.2530, found: 339.2531].

(2*S*,3*R*,14*R*,15*S*)-Diethyl 2,3,14,15-tetrahydroxyhexadeca-1,16-dioate 56e
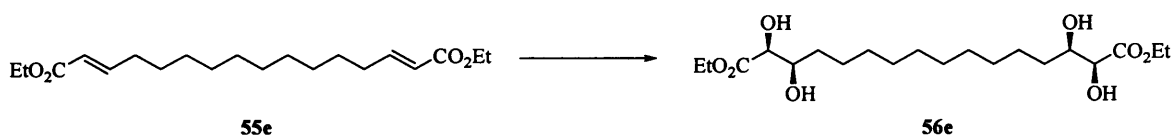
Synthesised using general procedure **B** from the *bis*-α,β-unsaturated ester **55e** (1.19 g, 3.53 mmol). Recrystallisation of the crude product from chloroform/hexane yielded the pure *ligand* **56e** (0.634 g, 1.56 mmol, 44 %) as colourless powder showing: m.p 100-101°C; $[\alpha]_D^{25}$ +25.4 (c

0.0057, MeOH) [Found: C, 58.66; H, 9.30 %. $C_{20}H_{38}O_8$ requires C, 59.09; H, 9.42 %]; v_{max}/cm^{-1}

(KBr) 3345, 2914, 2846, 1719, 1462, 1369, 1280, 1209, 1126 and 1087; δ_H (500 MHz, CD_2Cl_2)

4.30 (4H, q, $J = 7.1$, 2 x CH_2O), 4.08 (2H, dd, $J = 5.1$ and 2.0, 2-, 15-H), 3.88 (2H, dtd, $J = ca$ 9,

7 and 2, 3-, 14-H), 3.05 (2H, d, $J = 5.1$, 2-, 15-OH), 1.87 (2H, d, $J = 9.1$, 3-, 14-OH), 1.57-1.65

(4H, m, 4-, 13-CH_2), 1.24-1.50 (16H, m, 8 x CH_2) and 1.32 (6H, t, $J = 7.1$, 2 x Me); δ_C 174.0 (2

x C=O), 73.4 (2-, 15-CH), 72.9 (3-, 14-CH), 62.6 (2 x CH_2O), 34.4 (4-, 13-CH_2), 29.9 (6 x CH_2),

26.1 (2 x CH_2) and 14.7 (2 x Me); m/z (APCI) 407 $(M+1)^+$ 100 % [HRMS (ES^+): calcd. for

$C_{20}H_{39}O_8$, $(M + H)^+$: 407.2639, found: 407.2640].

Methyl 3-(4-benzyloxyphenyl)propanoate 59[121]

59
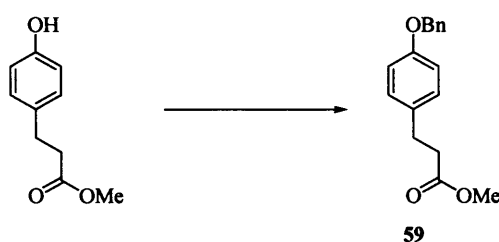
A 250 ml round bottom flask was charged with anhydrous tetrahydrofuran (150 ml) and sodium hydride dispersion (3.37 g, 84.36 mmol, 60 % in mineral oil) and the suspension cooled with an ice bath. Methyl 3-(4-hydroxyphenyl)propionate (15.2 g, 84.36 mmol) was slowly added to the cooled suspension allowing only gentle effervescence and, after a hour of stirring at room temperature, benzyl bromide (10.1 ml, 84.36 mmol) was added and the reaction was allowed to stir at ambient temperature overnight. The tetrahydrofuran was evaporated and the residue was taken up in ether (200 ml) and washed sequentially with saturated aqueous potassium carbonate (150 ml), water (2 x 150 ml) and brine (150 ml) then dried and evaporated to give the crude product **59** as a viscous tan oil. Subsequent crystallisation from chloroform/hexane furnished the *title compound* **59** (13.60 g, 50.31 mmol, 60%) as a pale yellow powder showing: m.p 65-66°C; [Found: C, 75.33; H, 6.69 %. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71 %]; v_{max}/cm^{-1} δ_H 7.30-7.45 (5H, m, 5xArH), 7.11 (2H, app d, $J = 8.5$, 2-, 6-ArH), 6.90 (2H, app d, $J = 8.5$, 3-, 5-ArH), 5.03 (2H, s, OCH_2Ph), 3.67 (3H, s, OMe), 2.89 (2H, t, $J = 7.8$, 3-CH_2) and 2.60 (2H, t, $J = 7.8$, 2-CH_2); δ_C (125MHz) 173.4 (C=O), 157.3 (4-ArC), 137.0 (ArC), 132.0 (ArC), 129.2 (2 x ArCH), 128.5 (2 x ArCH), 127.9 (ArCH) 127.4 (2 x ArCH), 70.4 (OCH_2Ph), 51.6 (OMe), 36.0 (3'-CH_2) and 30.1 (2'-CH_2); m/z (APCI) 271 $(M+1)^+$ 100 %.

7-[2'-(4-Benzyloxyphenyl)-ethyl]-trideca-1,12-dien-7-ol 60
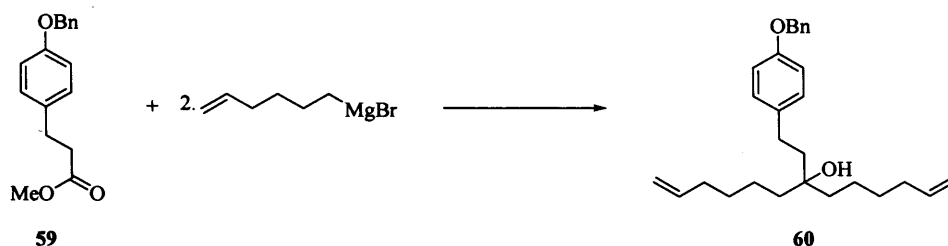
To a flame dried three-necked 250 ml round bottom flask equipped with an efficient stir bar and fitted with a reflux condenser and pressure equalising dropping funnel (50 ml) was added magnesium turnings (0.88 g, 36.23 mmol). The flask was put under high vacuum and the magnesium turnings were simultaneously stirred and flame dried. The turnings were further stirred at room temperature for one hour under high vacuum. The vacuum was replaced with a nitrogen atmosphere and sufficient anhydrous tetrahydrofuran was added to cover the magnesium and then one small crystal of iodine was added. A solution of 6-bromo-1-hexene (4.05 ml, 30.19 mmol) in anhydrous tetrahydrofuran (40 ml) was slowly added *via* the funnel so as to prevent reflux. The funnel was washed out with anhydrous tetrahydrofuran (10 ml) and the reaction mixture was stirred at 30°C for 30 minutes. A solution of methyl 3-(4-benzyloxy-phenyl)-propionoate 59 (3.89 g, 14.38 mmol) in anhydrous tetrahydrofuran (50 ml) was added to the Griginard reagent over a period of 30 minutes and then the reaction was stirred at ambient temperature for 24 hours, quenched with water (100 ml) and extracted with ether (3 x 100 ml). The combined organic extracts were washed with brine (100 ml), then dried and evaporated. Column chromatography of the residue (20-40 % ether/petrol) yielded the title *bis-α,ω-olefin* 60 (4.40 g, 12.59 mmol, 88%, R_f = 0.30, 40% ether/petrol) as a colourless oil showing: v_{max}/cm^{-1} 3549, 3073, 3031, 2939, 2861, 1639, 1611, 1510, 1454, 1380, 1297, 1240, 1175, 1025, 993 and 910; δ_H 7.30-7.45 (5H, m, 5xArH), 7.11 (2H, app d, J = 8.5, 2- and 6-ArH), 6.91 (2H, app d, J = 8.5, 3- and 5-ArH), 5.82 (2H, ddt, J = 17.0, 10.2 and 6.7, 2- and 12-H), 5.05 (2H, s, OCH₂Ph), 5.01 (2H, dd, J = 17.0 and 1.4, 1- and 13-H-*trans*), 4.98 (2H, dt, J = 10.2 and 0.8, 1- and 13-H-*cis*), 2.46-2.54 (2H, m, 2'-CH₂), 2.08 (4H, app q, J ca 7, 3- and 11-CH₂), 1.75-1.80 (2H, m, 1'CH₂) and 1.21-1.51 (12H, m, 6 x CH₂); δ_C 157.0 (ArC), 138.9 (2- and 12-CH), 137.2 (ArC), 135.0 (ArC), 129.3 (2 x ArCH), 128.6 (2 x ArCH), 128.0 (ArCH), 127.5 (2 x ArCH), 114.8 (2 x ArCH), 114.6 (1- and 13-CH₂) 74.9 (7-C), 70.1 (benzyl CH₂), 41.6 (1'-linker CH₂), 39.0 (6- and 8-CH₂), 33.8 (3- and 11-CH₂), 29.5 (2 x CH₂), 29.1 (2'-linker CH₂) and 23.0 (2 x CH₂); m/z

(APCI) 429 (M+23)⁺, 100% [HRMS (ES⁺): calcd. for $C_{28}H_{42}NO_2$, (M+NH₄)⁺ 424.3210, found: 424.3213].

7-[2'-(4-Benzyloxyphenyl)-ethyl]-7-methoxy-trideca-1,12-diene 67
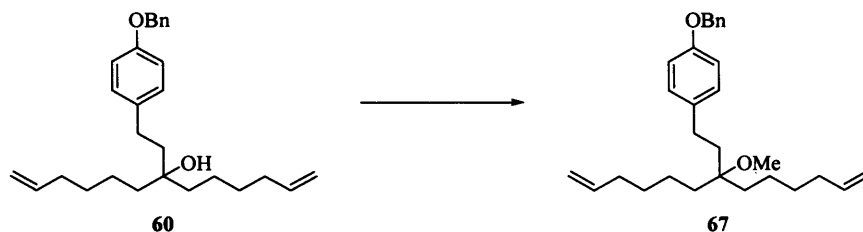
To a flame dried 250 ml round bottom flask, equipped with a stir-bar and under an atmosphere of nitrogen were added the *bis*-α,ω-olefin **60** (5.55 g, 13.65 mmol) and anhydrous tetrahydrofuran (150 ml). Upon cooling the solution with an ice bath, butyl lithium (5.46 ml of a 2.5M solution in hexanes, 13.65 mmol) was slowly added over five minutes and the reaction was stirred without further cooling for one hour. The reaction was re-cooled to 0°C and iodomethane (1.79 ml, 28.76 mmol) was added and the stirring continued at ambient temperature for a further 72 hours, then the reaction was quenched with water (150 ml) and extracted with ether (3 x 100 ml). The combined organic extracts were washed with water (2 x 100 ml) and brine (150 ml) then dried and evaporated. Column chromatography of the residues (30 % ether/petrol) yielded the title *methyl ether* **67** (4.42 g, 10.51 mmol, 77 %, R_f = 0.59) as a colourless oil showing: v_{max}/cm⁻¹ 3028, 2938, 2860, 1639, 1611, 1583, 1510, 1454, 1379, 1240, 1175, 1002, 1025, 993 and 909; δ_H 7.30-7.45 (5H, m, 5 x Ar'H), 7.10 (2H, d, J = 8.5, 2-, 6-ArH), 6.90 (2H, d, J = 8.5, 3-, 5-ArH), 5.82 (2H, ddt, J = 17.0, 10.0 and 7.1, 2-, 12-H), 5.04 (2H, s, CH₂O), 5.03 (2H, br d, J = 17.0, 1-, 13-H-*trans*), 4.94 (4H, br d, J = 10.0, 1-, 13-H-*cis*), 3.15 (3H, s, OMe), 2.49 (2H, m, 2'-CH₂), 2.06 (4H, q, J = 7.1, 3-, 11-CH₂), 1.67 (2H, m, 1'-CH₂) and 1.51-1.15 (12H, m, 6 x CH₂); δ_C 157.0 (4-ArC), 139.0 (2-, 12-CH), 137.2 (Ar'C), 135.2 (1-ArC), 129.2 (2-, 6-ArCH), 128.6 (3'-, 5'-ArCH), 127.9 (4'-ArCH), 127.5 (2'-, 6'-ArCH), 114.8 (3-, 5-ArCH), 114.5 (1-, 13-CH₂), 78.3 (7-C), 70.1 (benzyl CH₂), 48.4 (OMe), 36.7 (1'-linker CH₂), 34.2 (6-, 8-CH₂), 33.8 (3-, 11-CH₂), 29.5 (4-, 10-CH₂), 28.7 (2'-linker CH₂) and 22.7 (5-, 9-CH₂); m/z (APCI) 389 (M⁺-31) 100% [HRMS (ES⁺): calcd. for $C_{29}H_{44}NO_2$, (M+NH₄)⁺ 438.3367, found: 438.3361].

Diethyl (2*E*,13*E*)-8-[2'-(4-benzyloxyphenyl)-ethyl]-
8-methoxy-pentadeca-2,13-dieneoate 68
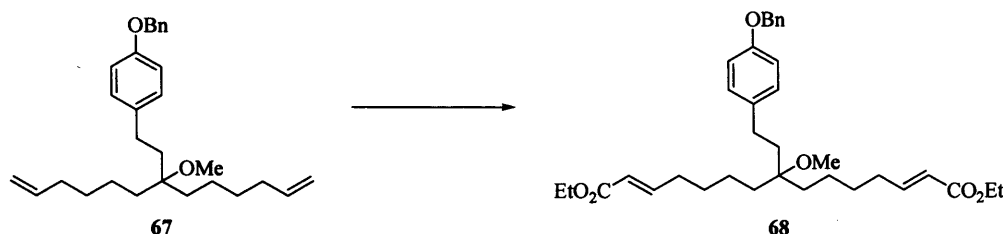
By general procedure **A**, the reaction between the methyl ether **67** (2.5 g, 5.94 mmol), ethyl acrylate (1.29 ml, 11.89 mmol) and Grubbs second generation catalyst (75 mg, 0.75 mol %) followed by chromatography (40% ether/petrol) gave the title compound **68** (2.88 g, 5.10 mmol, 86 %, R_f = 0.23) as a colourless oil showing: v_{max}/cm^{-1} 2981, 2940, 2863, 1715, 1653, 1510, 1464, 1368, 1310, 1268, 1240, 1178, 1081 and 981; δ_H 7.30-7.48 (5H, m, 5 x ArH), 7.09 (2H, app d, *J* = 8.5, 2-, 6-ArH), 6.96 (2H, dt, *J* = 15.6 and 6.9, 3-, 13-H), 6.90 (2H, app d, *J* = 8.5, 3-, 5-ArH), 5.82 (2H, d, *J* = 15.6, 2-, 14-H), 5.04 (3H, s, OCH₂Ph), 4.17 (4H, q, *J* = 7.1, 2 x OCH₂), 3.15 (3H, s, OMe), 2.40-2.49 (2H, m, 2'-CH₂), 2.20 (4H, app q, *J* = 6.9, 4-, 12-CH₂), 1.60-1.70 (2H, m, CH₂), 1.42-1.50 (10H, m, 5 x CH₂) and 1.28 (6H, t, *J* = 7.1, 2 x Me); δ_C 166.7 (2 x C=O), 156.8 (ArCO), 148.8 (3-, 13-CH), 137.0 (Ar'C), 134.7 (ArC), 128.9 (2 x ArCH), 128.3 (2 x ArCH), 127.7 (ArCH), 127.2 (2 x ArCH), 121.3 (2-, 14-CH), 114.6 (2 x ArCH), 77.8 (COMe), 69.8 (PhCH₂O), 59.9 (2 x CH₂O), 48.2 (OMe), 36.4 (2'CH₂), 33.9 (4-, 12-CH₂), 31.9 (2 x CH₂), 28.5 (1'-CH₂), 28.3 (2 x CH₂), 22.6 (2 x CH₂) and 14.1 (2 x Me); m/z (APCI) 533 (M⁺-31) 100% [HRMS (ES⁺): calcd. for C₃₅H₅₂NO₆ (M+NH₄)⁺ 582.3789, found: 582.3787].

Diethyl (2*S*,3*R*,13*R*,14*S*)-8-[2'-(4-benzyloxyphenyl)-ethyl]
-2,3,13,14-tetrahydroxy-8-methoxypentadecadioate 69
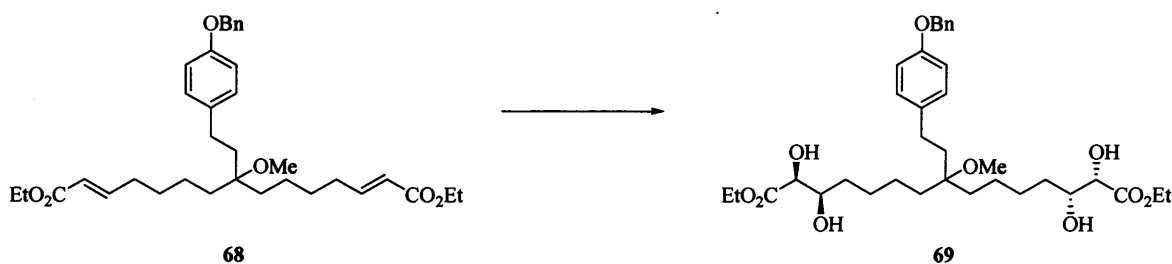
Prepared by general procedure **B** from the *bis*-α,β-unsaturated ester **68** (2.74 g, 4.85 mmol) and the title compound **69** (2.95 g, 4.66 mmol) was obtained as a viscous light tan oil showing:

v_{max}/cm^{-1} 3474, 3032, 2939, 2886, 1736, 1611, 1583, 1510, 1454, 1369, 1238, 1082, 1025, 912, 862 and 821; δ_H 7.28-7.42 (5H, m, 5 x ArH), 7.09 (2H, app d, J = 8.4, 2-, 6-ArH), 6.89 (2H, app d, J = 8.4, 3-, 5-ArH), 5.01 (2H, s, PhCH$_2$O), 4.24 (4H, q, J = 7.1, 2 x CH$_2$O), 4.08 (2H, br res, 2-, 14-H), 3.86-3.92 (2H, m, 3-, 13-H), 3.83 (2H, br s, 2 x OH), 3.14 (3H, s, OMe), 3.08 (2H, br res, 2 x OH), 2.45-2.50 (2H, m, 2'-CH$_2$), 1.54-1.76 (6H, m, 3 x CH$_2$), 1.28-1.54 (12H, m, 6 x CH$_2$) and 1.28 (6H, t, J = 7.1, 2 x Me); δ_C 173.5 (2 x C=O), 156.6 (ArCO), 136.9 (ArCH), 134.7 (ArC), 128.9 (2 x ArH), 128.3 (2 x ArCH), 127.6 (1 x ArCH), 127.2 (2 x ArCH), 114.5 (2 x ArCH), 78.1 (8-C), 73.2 (2-, 14-H), 72.3 (3-, 13-CH), 69.7 (PhCH$_2$O), 61.6 (2 x CH$_2$O), 48.1 (OMe), 36.3 (2'-CH$_2$), 33.9 (2 x CH$_2$), 33.2 (2 x CH$_2$), 28.3 (1 x CH$_2$), 26.0 (2 x CH$_2$), 22.8 (1 x CH$_2$), 22.7 (1 x CH$_2$) and 13.9 (2 x Me).

Diethyl (2*S*,3*R*,13*R*,14*S*)-8-[2'-(4-hydroxyphenyl)-ethyl] -2,3,13,14-tetrahydroxy-8-methoxypentadecadioate 70
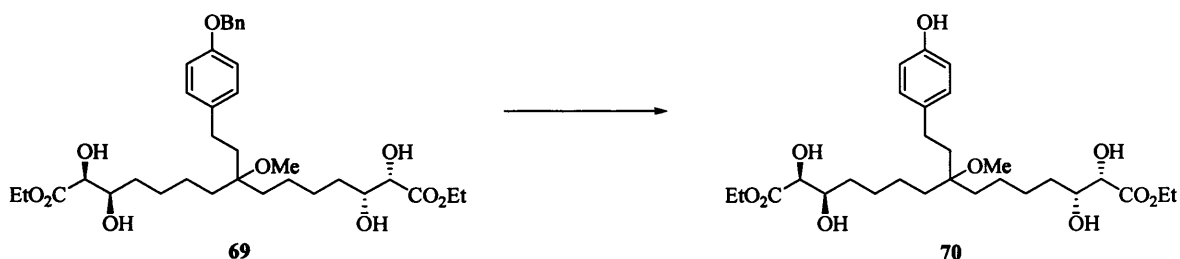
A solution of the benzyl ether **69** (1.00g, 1.58 mmol) in methanol (20 ml) was added to a suspension of 20 wt% palladium-carbon catalyst (0.50 g, 30 mol%) in methanol (10 ml) and the mixture was stirred vigorously overnight under 1 atmosphere of hydrogen; at this stage, no further hydrogen uptake was observed. The reaction mixture was filtered through a pad of celite®, the solid washed with methanol (50 ml) and the combined filtrates and washings were evaporated yielding the crude deprotected product **70** (0.82 g, 1.51 mmol, 96 %) as a sticky oil of sufficient purity, showing: v_{max}/cm^{-1} 3412, 2941, 2863, 1732, 1515, 1464, 1370, 1263, 1221, 1122, 1081 and 1027; δ_H 7.02 (2H, app d, J = 8.3, 2-, 6-ArH), 6.74 (2H, app d, J = 8.3, 3-, 5-ArH), 4.28 (4H, q, J = 7.0, 2 x CH$_2$O), 4.07-4.09 (2H, br res, 2-, 14-H), 3.89 (2H, app t, J = 6.0, 3-, 13-H), 3.14 (3H, s, OMe), 2.43-2.49 (2H, m, 2'-CH$_2$), 1.58-1.70 (6H, m, 3xCH$_2$), 1.40-1.50 (6H, m, 3xCH$_2$), 1.20-1.40 (6H, m, 3 x CH$_2$) and 1.30 (6H, t, J = 7.0, 2 x Me); δ_C 174.7 (2 x C=O), 156.4 (ArCOH), 134.7 (ArC), 130.2 (2-, 6-ArCH), 116.3 (3-, 5-ArCH), 79.9 (COMe), 74.8 (2-, 14-CH), 73.6 (3-, 13-CH), 62.2 (2 x CH$_2$O), 48.7 (OMe), 38.0 (2'-CH$_2$), 35.1 (2 x CH$_2$), 34.1 (2 x CH$_2$), 29.8 (1 x CH$_2$), 27.3 (2 x CH$_2$), 24.1 (2 x CH$_2$) and 14.6 (2 x Me); m/z (CI) 560

(M$^+$ + H, 52%), 528 (M$^+$ - 14, 100%). [HRMS (ES): calcd. for C$_{28}$H$_{50}$NO$_{10}$ (M+NH$_4$)$^+$ 560.3429, found: 560.3422].
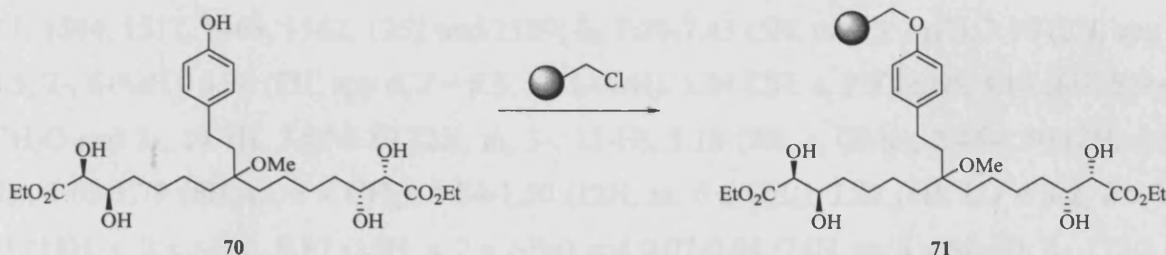
Immobilised diethyl (2*S*,3*R*,13*R*,14*S*)-8-[2'-(4-hydroxyphenyl)-ethyl]-2,3,13,14-tetrahydroxy-8-methoxypentadecadioate 71

Into a dry 100 ml round bottomed flask equipped with a 5 mm teflon stir bar were added Merrrifield benzyl chloride resin (0.97 g, 1.07 mmol, 1.1 mmol of Cl per gram), a solution of penta-ol **70** (0.87 g, 1.60 mmol) in anhydrous dimethylformamide (50 ml), caesium carbonate (1.04 g, 3.194 mmol) and tetrabutyl ammonium iodide (0.10 g, 0.27 mmol) and the reaction was maintained at 80°C with gentle stirring for 24 h. Upon cooling, the resin was filtered and washed with water (100 ml), dimethylformamide (100 ml), acetone (100 ml), dichloromethane (100 ml) and finally diethyl ether (100 ml). Subsequent subjection to high vacuum yielded a *resin* (0.96 g, 1.07 mmol). The lack of increase in mass and absence of carbonyl resonance in an infrared spectrum led to the conclusion that the reaction was unsuccessful.

Diethyl (2*S*,3*R*,13*R*,14*S*) 8-[2'-(4-hydroxyphenyl)-ethyl]-2,3,13,14-tetra-(*t*-butyldimethylsilyloxy)-8-methoxypentadecadioate 72

To dry 150 ml round bottomed flask was added a solution of the tetra-ol **69** (2.00 g, 3.16 mmol) in anhydrous dimethylformamide (85 ml) followed by *t*-butyldimethylsilyl chloride (2.38 g, 15.81 mmol) and imidazole (2.15 g, 31.63 mmol) and the resulting solution stirred at 35°C for 14

h under a nitrogen atmosphere. The mixture was diluted with ether (250 ml) and washed with water until there was no further change in volume of the organic layer. The organic layer was further washed with saturated aqueous ammonium chloride (100 ml), saturated aqueous potassium carbonate (50 ml) and brine (100 ml), then dried and evaporated. Column chromatography (20% ether/petrol) of the reaction residue yielded the *tetra-TBDMS ligand* **72** (2.46 g, 2.26 mmol, 71 %, R_f = 0.43) as a colourless oil showing: v_{max}/cm^{-1} 2952, 2857, 1753, 1611, 1584, 1511, 1463, 1362, 1252 and 1109; δ_H 7.30-7.43 (5H, m, 5 x ArH), 7.10 (2H, app d, J = 8.5, 2-, 6-ArH), 6.90 (2H, app d, J = 8.5, 3-, 5-ArH), 5.04 (2H, s, PhCH$_2$O), 4.15 (6H, br res, 2 x CH$_2$O and 2-, 14-H), 3.80-3.87 (2H, m, 3-, 13-H), 3.14 (3H, s, OMe), 2.45-2.50 (2H, m, 2'-CH$_2$), 1.63-1.79 (6H, m, 3 x CH$_2$), 1.24-1.50 (12H, m, 6 x CH$_2$), 1.27 (6H, t, J = 7.2, 2 x Me), 0.91 (18H, s, 2 x *t*-Bu), 0.87 (18H, s, 2 x *t*-Bu) and 0.07-0.04 (24H, m, 4 x MeSi); δ_C 172.2 (2 x C=O), 156.9 (ArCO), 137.1 (ArC), 135.1 (ArC), 129.1 (2 x ArCH), 128.5 (2 x ArCH), 127.8 (1 x ArCH), 127.4 (2 x ArCH), 114.7 (2 x ArCH), 78.0 (8-C), 74.8 (2-, 14-H), 74.5 (3-, 13-CH), 70.0 (PhCH$_2$O), 60.5 (2 x CH$_2$O), 48.3 (OMe), 36.7 (2'-CH$_2$), 34.3, 32.6, 29.0, 28.6, 26.4, 23.4 (9 x CH$_2$), 25.6 and 25.7 (2 + 2 CMe$_3$), 18.3 and 18.3 (4 x CMe$_3$), 14.2 (2 x Me), -4.3, -4.4, -4.8 and -5.1 (8 x MeSi); m/z (ES) 1111.8 (M+Na)$^+$ 50% and 1106 (M-18)$^+$ 100%.

### Diethyl (2*S*,3*R*,13*R*,14*S*) 8-[2'-(4-hydroxyphenyl)-ethyl] -2,3,13,14- tetra-(*t*-butyldimethylsilyloxy)-8-methoxypentadecadioate 73

A solution of the protected ligand **72** (2.45 g, 2.25 mmol) in ethanol (50 ml) was added to a suspension of 20 wt% palladium-carbon (Pd-C) catalyst (0.71 g, 30 mol%) in ethanol (10 ml) and the resulting mixture was stirred vigorously overnight under 1 atmosphere of hydrogen; at this stage no further hydrogen uptake was observed. The reaction mixture was filtered through a pad of celite®, the solid washed with ethanol (50 ml) and ethyl acetate (50 ml) and then the combined filtrates and washings evaporated yielding the crude de-protected product **73** (2.24 g, 2.24 mmol, 99 %) of good purity, showing: $[\alpha]_D$ +2.35 (c = 0.01, CHCl$_3$); v_{max}/cm^{-1} 3424, 2931, 2857, 1753, 1731, 1614, 1515, 1472, 1361, 1254, 1110, 1031, 911 and 837; δ_H 7.04 (2H, app d, J

= 8.4, 2-, 6-ArH), 6.75 (2H, app d, J = 8.4, 3-, 5-ArH), 4.10-4.20 (6H, m, 2 x CH$_2$O and 2-, 14-H), 3.80-3.85 (2H, m, 3-, 13-H), 3.14 (3H, OMe), 2.46 (2H, m, 2'-CH$_2$), 1.64-1.78 (4H, m, 2 x CH$_2$), 1.33-1.48 (4H, m, 2 x CH$_2$), 1.24-1.33 (10H, m, 5 x CH$_2$), 1.27 (3H, t, J = 7.1, Me), 1.24 (3H, t, J = 7.1, Me), 0.90 (18H, s, 2 x *t*-Bu), 0.87(18H, s, 2 x *t*-Bu) and 0.03-0.07 (24H, 8 x MeSi); δ_C 172.5 (2 x C=O), 154.4 (ArCO), 133.7 (1-ArC), 129.0 (2-, 6-ArCH), 115.2 (3-, 5-ArCH), 78.5 (COMe), 74.7 (2-, 14-CH), 74.4 (3-, 13-CH), 60.6 (2 x CH$_2$O), 48.1 (OMe), 36.5 (2'-CH$_2$), 34.2, 32.5, 28.5, 26.3 and 23.2 (9 x CH$_2$), 25.7 (6 x Me), 25.6 (6 x Me), 18.2 (2 x CMe$_3$), 17.9 (2 x CMe$_3$) 14.0 (2 x Me), -4.4, -4.5, -4.9 and -5.2 (8 x MeSi); m/z (ES) 1116 (M+NH$_4$)$^+$ 78% and 1021 (M+23)$^+$ 100%. [HRMS (ES$^+$): calcd. for C$_{52}$H$_{106}$NO$_{10}$Si$_4$ (M+NH$_4$)$^+$ 1016.6888, found: 1016.6894].

Immobilised diethyl (2*S*,3*R*,13*R*,14*S*)-8-[2'-(4-hydroxyphenyl)-ethyl]-2,3,13,14-tetra-(*t*-butyldimethylsilyloxy)-8-methoxypentadecadioate 75
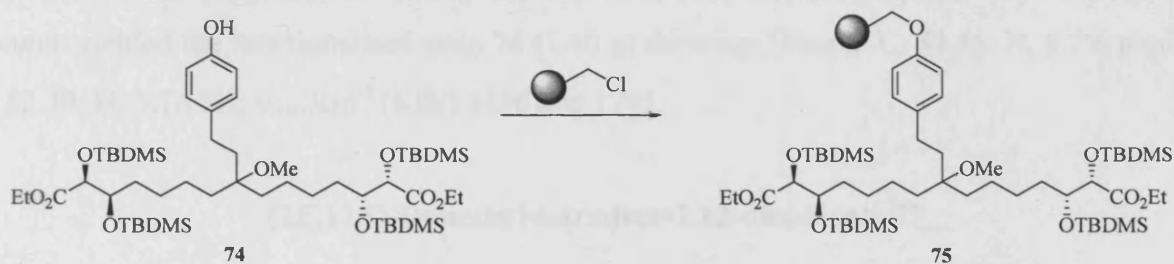
To a dry 100 ml round bottomed flask was added: Merrrifield benzyl chloride resin (0.91 g, 1.00 mmol, 1.1 mmol of Cl per gram), a solution of **73** (1.00 g, 1.00 mmol) in anhydrous tetrahydrofuran (50 ml), caesium carbonate (1.30 g, 4.00 mmol), tetrabutyl ammonium iodide (0.37 g, 1.00 mmol) and the reaction was refluxed for 24 h. Upon cooling the resin was filtered and washed with water (100 ml), dimethylformamide (100 ml), tetrahydrofuran (100 ml), acetone (100 ml), dichloromethane (100 ml) and finally diethyl ether (100 ml). Subsequent subjection to high vacuum yielded the functionalised resin **75** (1.74 g) showing: [Found: C, 77.9; H, 8.74. requires C, 76.29; H, 9.13 %]; ν_{max}/cm^{-1} (KBr) 1719-1754.

133

Immobilised diethyl (2*S*,3*R*,13*R*,14*S*)-8-[2'-(4-hydroxyphenyl)-ethyl]- -2,3,13,14-tetrahydroxy-8-methoxypentadecanedioate 76
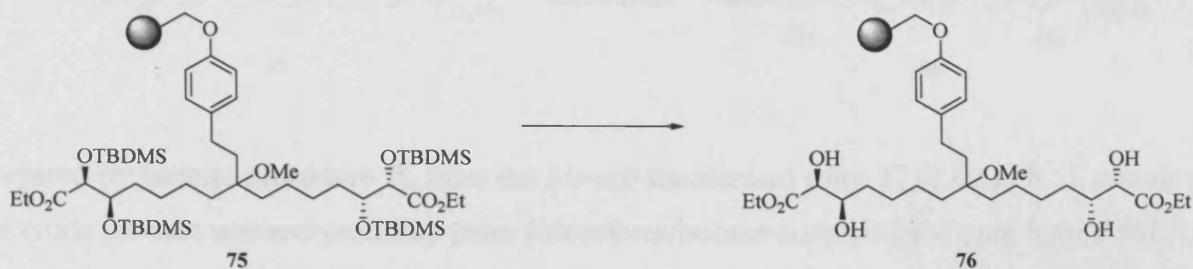
Into a 100 ml round bottomed flask equipped with a minature teflon stirrer was added the resin **75** 1.73 g), tetrahydrofuran (40 ml) and tetrabutylammonium fluoride solution (6 ml, 6.00 mmol, 1.0 M in tetrahydrofuran) and was stirred gently for 10 hours. The resin was filtered and washed with water (100 ml), dimethylformamide (100 ml), tetrahydrofuran (100 ml), acetone (100 ml), dichloromethane (100 ml) and finally diethyl ether (100 ml). Subsequent subjection to high vacuum yielded the functionalised resin **76** (1.40 g) showing: [Found: C, 80.45; H, 8.79. requires C, 82.39; H, 5.76 %]; ν_{max}/cm^{-1} (KBr) 3450 and 1745.

(2*E*,12*E*)-Dimethyl-tetradeca-2,12-diendioate 77

The *bis*-α,β-unsaturated ester **77** was prepared as illustrated in general procedure **C** from 1,10-deacanedial **54d** (3.23 g, 18.98 mmol) and yielded the *bis-α,β-unsaturated ester* **77** (2.51 g, 8.90 mmol, 47 %) as a light tan oil showing; ν_{max}/cm^{-1} 2928, 2855, 1721, 1657, 1436, 1313, 1272, 1197, 1175, 1041 and 980; δ_H 6.90 (2H, dt, J = 15.6 and 7.0, 3- and 12-H), 5.75 (2H, dt, J = 15.6 and 1.5 2- and 13-H), 3.66 (6H, s, MeO), 2.13 (4H, qd, J = 7.0 and 1.5, 4- and 11-CH$_2$) and 1.44-1.13 (12H, m, 6 x CH$_2$); δ_C 167.0 (2 x C=O), 149.5 (3-, 12-CH), 120.7 (2-, 13-CH), 50.8 (2 x MeO), 32.1 (4-, 11-CH$_2$), 29.0 (2 x CH$_2$), 28.9 (2 x CH$_2$) and 27.9 (2 x CH$_2$); m/z (APCI) 283 (M+1)$^+$ 100 % [HRMS (ES$^+$): calcd. for C$_{16}$H$_{27}$O$_4$ (M + H)$^+$: 283.1904, found: 283.1907].

(2*S*,3*R*,12*R*,13*S*)-Dimethyl-2,3,12,13-tetrahydroxytetradecadioate 56f

Prepared by general procedure **B**, from the *bis*-α,β-unsaturated ester **77** (2.40 g, 8.51 mmol) and the crude product was recrystallised from chloroform/hexane supplying the pure *ligand* **56f** (1.94 g, 5.53 mmol, 65 %) as colourless powder showing; m.p 108-109°C; $[\alpha]_D^{25}$ +44.3 (c 0.0051, MeOH); [Found: C, 54.80; H, 8.57. $C_{16}H_{30}O_8$ requires C, 54.84; H, 8.63 %]; v_{max}/cm^{-1} (KBr) 3373, 2915, 2845, 1733, 1463, 1437, 1277, 1069 and 1012; δ_H (CD$_3$OD, 500MHz) 4.10 (2H, d, *J* = 2.8, 2-, 13-H), 3.85 (2H, qd, *J* = 6.7 and 2.8, 3-, 12-H), 3.78 (6H, s, MeO), 1.62-1.55 (4H, m, 4-, 11-CH$_2$), 1.53-1.43 (4H, br res, 4 x OH) and 1.41-1.33 (12H, m, 6 x CH$_2$); δ_C 177.7 (2 x C=O), 77.4 (2-, 13-CH), 76.2 (3-, 12-CH), 55.0 (2 x OMe), 36.6 (4-, 11-CH$_2$), 33.1 (2 x CH$_2$), 33.1 (2 x CH$_2$) and 29.5 (2 x CH$_2$); m/z (APCI) 351 (M+1)$^+$ 100 %. [HRMS (ES$^+$): calcd. for $C_{16}H_{31}O_8$ (M + H)$^+$: 351.2013, found: 351.2015].

(2*E*,12*E*)-Diisopropyl tetradeca-2,12-dienedioate 80
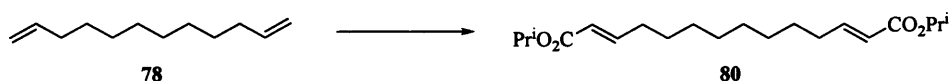
The *bis*-ester **80** was prepared according to general procedure **A** using 1,11-dodecadiene **78** (2.5 g, 15.03 mmol), isopropyl acrylate (3.84 ml, 30.06 mmol) and Grubbs second generation catalyst **66** (35 mg, 0.04 mmol, 0.13 mol%) and furnished the *bis-ester* **80** (4.27 g, 12.62 mmol, 84%) as a colurless oil showing; v_{max}/cm^{-1} 2980, 2930, 2856, 1716, 1654, 1467, 1270, 1182, 1111, 1027 and 981; δ_H 6.94 (2H, dt, *J* = 15.6 and 7.1, 3-, 12-H), 5.79 (2H, dt, *J* = 15.6 and 1.5, 2-, 13-H), 5.06 (2H, app hept, *J* = 6.3, 2 x CHMe$_2$), 2.18 (4H, qd, *J* = 7.1 and 1.5, 4-, 11-CH$_2$), 1.50-1.25 (12H, m, 6 x CH$_2$), 1.26 (12H, d, *J* = 6.3, 4 x Me); δ_C 165.4 (2 x C=O), 149.3 (3-, 12-CH), 121.2 (2-, 13-CH), 66.7 (2 x Me$_2$CHO), 31.8 (4-, 11-CH$_2$), 28.9 (2 x CH$_2$), 28.7 (2 x CH$_2$), 27.7 (2 x CH$_2$) and 21.5 (2 x Me); m/z (APCI) 339 (M + 1)$^+$ 100 % [HRMS (ES$^+$): calcd. for (M + H)$^+$: 339.2530, found: 339.2530].

(2*S*,3*R*,12*R*,13*S*)-Diisopropyl 2,3,12,13-tetrahydroxytetradecadioate 56g
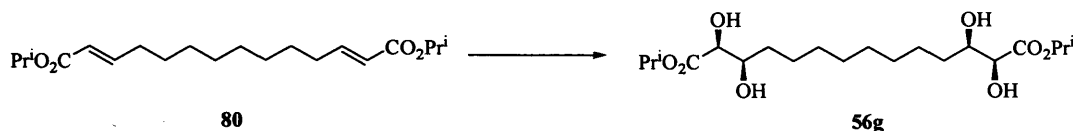

Prepared by general procedure **B**, from the *bis*-α,β-unsaturated ester **80** (3.00 g, 8.88 mmol). Extensive washing procedures during the reaction work up are necessary [1M NaOH (2 x 1 vol), sat. NH₄Cl (2 x 1 vol) and H₂O (2 x 1 vol)] to obtain analytically pure product because, the ligand **56g** formed gels during recrystallisation attempts. Trituration with ether/petrol (1:1) can also be used to purify insufficiently pure compound and the final alternative is to dissolve the ligand in the minimum amount of hot chloroform then pour this solution into a 15 fold excess of vigorously stirred hexane; the precipitated gel-like material can then be filtered and collected. The *ligand* **56g** was obtained (40-90% yield) as a colourless glassy solid showing; m.p 110-111°C; $[\alpha]_D^{25}$ +22.5 (c 0.0087, MeOH); [Found: C, 59.63; H, 9.61. $C_{20}H_{38}O_8$ requires C, 59.09; H, 9.42 %]; v_{max}/cm^{-1} (KBr) 3373, 2919, 2847, 1708, 1460, 1372, 1291, 1105 and 1067; δ_H 5.15 (2H, hept, *J* = 6.2, 2 x OCHMe₂), 4.03 (2H, dd, *J* = 5.1 and 2.1, 2-, 13-H), 3.84 (2H, br res 3-, 12-H), 3.10 (2H, d, *J* = 5.1, 2-, 13-OH), 1.93 (2H, d, *J* = 9.1, 3-, 12-OH), 1.56-1.62 (4H, m, 2 x CH₂) 1.28-1.34 (12H, m, 6 x CH₂) and 1.30 (12H, d, *J* = 6.2, 4 x Me); δ_C 173.6 (2 x C=O), 73.5 (2-, 13-CH), 73.0 (3-, 12-CH), 70.5 (2 x Me₂CHO), 34.2 (4-, 11-CH₂), 29.9 (2 x CH₂), 29.8 (2 x CH₂), 26.1 (2 x CH₂) and 22.1 (4 x Me); m/z (APCI) 407 (M+1)⁺ 100 % [HRMS (ES): calcd. for (M + H)⁺: 407.2639, found: 407.2635].

Epoxidations:

## Representative Procedures for the Sharpless Asymmetric Epoxidations:

Acid sensitive substrate E:

(2*R*,3*R*)-Epoxy-cinnamyl alcohol 58:
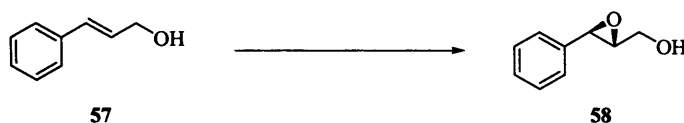
To a 100ml Schlenk tube, equipped with a magnetic stirring bar, was added, dry dichloromethane (15 ml), the ligand **56d** (0.200 g, 0.345 mmol active catalyst), activated powdered 4Å molecular sieves (0.25 g) and titanium tetraisopropoxide (0.167 ml, 0.574mmol) and the resulting mixture stirred for 20 minutes at room temperature. Upon cooling to -20°C, 5.5M *t*-butyl hydroperoxide solution in decane (0.50 ml) was added and the mixture was stirred –20°C for one hour to allow the active catalytic complex to equilibrate. A solution of cinnamyl alcohol (0.185 g, 1.38 mmol) in dry dichloromethane (10 ml) was added to the reaction mixture over a period of one hour, which was then stirred for a further 15 hours at –20°C. The reaction was quenched by the addition of 1 ml of a 10% solution of sodium hydroxide saturated with sodium chloride. Ether (20 ml) was added and the reaction was allowed to warm to 10°C; stirring was maintained at 10°C whilst magnesium sulphate (1 g) and celite® (1 g) were added. After a final 15 minutes of stirring the reaction mixture was filtered through a pad of celite® and the solid residue washed with ether (50 ml). Evaporation of the filtrate yielded the crude epoxy alcohol. Chromatography using 1:1 ether/petrol as the elutent, yielded colourless crystals, *(2R,3R)-(+)-epoxy-cinnamyl alcohol*, **58**, (0.134 g, 0.89 mmol, 65%); m.p 50-52°C (lit. m.p. 51.5 – 53.0°C)[41]; GC (cyclodextrin α) 96% ee; υ_{max}/cm^{-1} (CHCl$_3$) 3580, 3450, 2980, 2920, 2870, 1600, 1450, 1380, 1100, 1070, 1020, 880, 860 and 845; δ_H 7.27-7.40 (5H, m, 5 x ArH), 4.06 (1H, ddd, J = 12.7, 5.5 and 1.8, OCH*H*), 3.94 (1H, d, J = 2.0, 3-H), 3.81 (1H, ddd, J = 12.7, 6.2 and 3.6, OC*H*H), 3.22-3.25 (1H, m, 2-H) and 1.83 (1H, dd, J = 6.2 and 5.5, OH) which was in full accordance with authentic material and literature data.[41]

Non-Acid sensitive, F:

(2*R*,3*R*)-Propyloxirane methanol 81
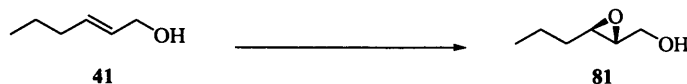
To a 100ml Schlenk tube equipped with a magnetic stirring bar, was added dry dichloromethane (15 ml), ligand **56g** (0.150 g, 0.369 mmol) activated powdered 4Å molecular sieves (0.5 g) and titanium tetraisopropoxide (0.183 ml, 0.616 mmol) and the resulting mixture stirred for 20 minutes at room temperature. Upon cooling to -20°C, a 5.5 M solution of *t*-butyl hydroperoxide in decane (0.54 ml, 2.96 mmol) was added and the mixture stirred at –20°C for one hour. (*E*)-2-Hexene-1-ol **41** (174 µL, 1.48 mmol) was added in four equal portions over a period of one hour and the reaction was allowed to stir for a further 15 hours at –20°C. The reaction was then quenched by the addition of a saturated aqueous citric acid (20 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with saturated aqueous potassium carbonate (50 ml), water (100 ml), brine (50 ml), then dried and evaporated to leave a mixture of the crude product, excess hydroperoxide, *t*-butyl alcohol, isopropanol and ligand **56g**. Flash chromatography using 1:1 ether/petrol as the elutent, yielded, (2*R*,3*R*)-(+)-propyloxiranemethanol, **81**, (0.070 g, 0.602 mmol, 41%); GC (Astec GTA) 88% ee; δ_H 3.91 (1H, dd, *J* = 12.6 and 2.0, OCH*H*), 3.61 (1H, dd, *J* = 12.6 and 4.2, OC*H*H), 2.95 (1H, ddd, *J ca* 2, 4 and 2, 2-H), 2.92 (1H, app dt, *J ca* 2 and 7, 3-H), 1.40-1.60 (4H, m, 2xCH$_2$) and 0.95 (3H, t, *J* = 7.2) which was in full accordance with authentic material and literature data.[41]

(2*R*,3*R*)-Epoxy-geraniol 82a
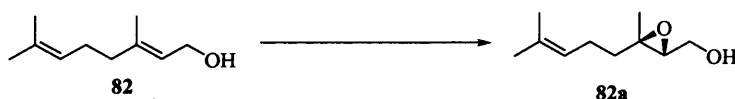
2*R*,3*R*-Epoxy-geraniol **82a** was synthesised by general procedure F using geraniol **82** (250 µL, 1.44 mmol) and ligand **56g** (0.150 g, 0.369 mmol) or D-DIPT (157 µL, 0.739 mmol) furnishing (2*R*,3*R*)-epoxy geraniol **82a** in 52% yield, 72% ee and 51% yield and 84% ee respectively showing: δ_H 5.07 (1H, br res t, *J* = 7.1, 6-H), 3.82 (1H, dd, *J* = 12.1 and 4.0, OCH*H*), 3.66 (1H, dd, *J* = 12.1 and 6.8, OC*H*H), 2.97 (1H, dd, *J* = 6.8 and 4.0, 2-H), 2.13 (1H, br res, OH), 2.06 (2H, app q, *J* = 7.1, 5-CH$_2$), 1.67 (3H, s, Me), 1.62-1.70 (1H, m, 4-CH*H*), 1.59 (3H, s, Me),

1.40-1.50 (1H, m, 4-C*H*H) and 1.29 (3H, s, Me) which was in full accordance with authentic material and literature data.[41]

## (2*R*,3)-Epoxy-3-methylbutan-1-ol 83a
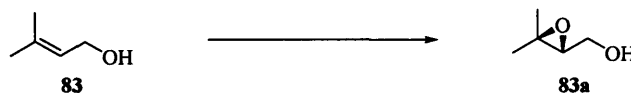
2*R*-Epoxy-3-methylbutan-1-ol **83a** was synthesised by general procedure **F** using; 3-methylbut-2-en-1-ol **83** (150 μL, 1.478 mmol) and ligand **56g** (0.150 g, 0.369 mmol) or D-DIPT (157 μL, 0.739 mmol) furnishing *2R,3R-Epoxy-3-methylbutan-1-ol* **83a** in 34% yield, 70% ee and 38% yield, 87% ee respectively showing: δ_H 3.84 (1H, dd, J = 12.0 and 4.3, OCH*H*), 3.68 (1H, dd, J = 12.0 and 6.8, OC*H*H), 2.98 (1H, dd, J = 6.8 and 4.3, 2-H), 1.35 (3H, s, Me) and 1.31 (3H, s, Me).[115]

(2*R*,3*S*)-Epoxy-hexen-1-ol 86

(2*R*,3*S*)-Epoxy-hexen-1-ol **86** was synthesised according to general procedure **F** using; (*Z*)-2-hexen-1-ol (241 μL, 2.05 mmol) and ligand **56g** (0.200 g, 0.492 mmol) the only difference was that the a different hydroperoxide was used, 88% cumene hydroperoxide in cumene (683 μL, 4.10 mmol). The reaction residue was purified by flash chromatography yielding *(2R,3S)-Epoxy-hexen-1-ol* **86** (0.150 g, 1.29 mmol, 63%), 67% ee showing; δ_H 3.78 (1H, dd, J = 4.0 and 12.2, OCH*H*), 3.60 (1H, dd, J = 12.2 and 7.0, OC*H*H), 3.10 (1H, app dt, J = 7.0 and 4.0, 2-H), 2.98 (1H, br res 3-H), 1.36-1.50 (4H, m, 4-, 5-CH₂) and 0.92 (3H, t, J = 7.2, Me) in full accordance with the literature data.[56]

Recycle Runs (Table 2.8):

### Recycle Run 0: (2*R*,3*R*)-Propyloxirane methanol 81
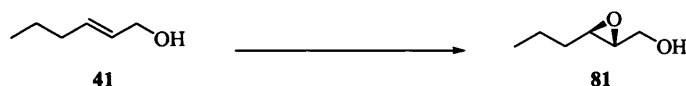
Performed according to general procedure **F** using: ligand **56g** (1.58 g, 3.88 mmol), Ti(O^{i}Pr)$_4$ (1.84 ml, 6.47 mmol), *t*-BuOOH (5.48 ml of a 5.5M solution in decane, 30.15 mmol) and (*E*)-hexen-1-ol (1.78 ml, 15.08 mmol). The reaction was quenched by the addition of a saturated solution of citric acid (1/2 vol) at -20°C and allowed stir at ambient temperature for ten minutes or until all titanium residues were homogeneous. The mixture was then extracted with ethyl acetate (2 x 1 vol) and the combined organics were washed with saturated aqueous potassium carbonate (2 x 1 vol) and water (2 x 1 vol), then dried and the volatiles evaporated. The residues were dissolved in the minimum amount of hot chloroform and slowly added to vigorously stirred pentane (12 vol of CHCl$_3$), then filtered to yield the ligand **56g** as a solid and the volatiles were evaporated. The residues were purified by flash chromatography using 1:1 ether/petrol as the elutent, yielded the *epoxy alcohol* **81** (1.10 g, 9.47 mmol, 63%) as a colourless oil in 86% ee. The ligand was purified by dissolution into ethyl acetate (250 ml) and sequential washing with 2M sodium hydroxide (2 x 100 ml), 2M hydrochloric acid (2 x 100 ml), saturated aqueous potassium carbonate (100 ml), water (150 ml), brine (100 ml), then dried and evaporated. Treatment of the residue to high vacuum yielded the *ligand* **56g** (1.29 g, 82%) as a colourless glassy solid showing data in accordance with authentic material; m.p 100-102°C.

Recycle Run 1: (2*R*,3*R*)-Propyloxirane methanol 81
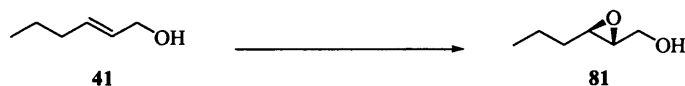
Performed according to general procedure **F** using: ligand **56g** (1.00 g, 2.46 mmol), Ti(O^{i}Pr)$_4$ (1.17 ml, 4.10 mmol), *t*-BuOOH (3.73 ml of a 5.5M solution in decane, 20.50 mmol) and (*E*)-hexen-1-ol (1.21 ml, 10.25 mmol). The reaction was quenched by the addition of a saturated solution of citric acid (1/2 vol) at -20°C and allowed stir at ambient temperature for ten minutes or until all titanium residues are homogeneous. The mixture was then extracted with ethyl

acetate (2 x 1 vol) and the combined organics were washed with saturated aqueous potassium carbonate (2 x 1 vol) and water (2 x 1 vol), then dried and the volatiles evaporated. The residues were dissolved in the minimum amount of hot chloroform and slowly added to vigorously stirred pentane (12 vol of $CHCl_3$), then filtered to yield the ligand **56g** as a solid and the volatiles were evaporated. The residues were purified by flash chromatography using 1:1 ether/petrol as the elutent, yielded the *epoxy alcohol* **81** (0.56 g, 4.82 mmol, 47%) as a colourless oil in 84% ee. The ligand was purified by dissolution into ethyl acetate (250 ml) and sequential washing with 2M sodium hydroxide (2 x 100 ml), 2M hydrochloric acid (2 x 100 ml), saturated aqueous potassium carbonate (100 ml), water (150 ml), brine (100 ml), then dried and evaporated. Treatment of the residue to high vacuum yielded the *ligand* **56g** (0.77 g, 77%) as a colourless glassy solid and with spectroscopic data in accordance with authentic material; m.p 100-101°C.

Recycle Run 2: (2*R*,3*R*)-Propyloxirane methanol 81

41   **81**
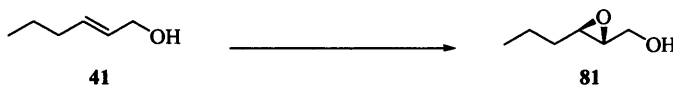
Performed according to general procedure **F** using: ligand **56g** (0.74 g, 1.82 mmol), $Ti(O^iPr)_4$ (0.90 ml, 3.03 mmol), *t*-BuOOH (2.76 ml of a 5.5M solution in decane, 15.17 mmol) and (*E*)-hexen-1-ol **41** (0.90 ml, 7.59 mmol). The reaction was quenched by the addition of a saturated solution of citric acid (1/2 vol) at -20°C and allowed stir at ambient temperature for ten minutes or until all titanium residues are homogeneous. The mixture was then extracted with ethyl acetate (2 x 1 vol) and the combined organics were washed with saturated aqueous potassium carbonate (2 x 1 vol) and water (2 x 1 vol), then dried and the volatiles evaporated. The residues were purified by flash chromatography using 1:1 ether/petrol as the elutent, yielding the *epoxy alcohol* **81** (0.45 g, 3.83 mmol, 50%) as a colourless oil in 82% ee and the *ligand* **56g** (0.39 g, 52%) as a colourless glassy solid with spectroscopic data in accordance with authentic material; m.p 99-101°C.

Recycle Run 3: (2*R*,3*R*)-Epoxy cinnamyl alcohol 58
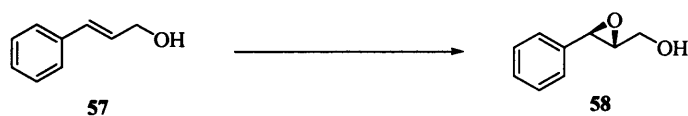
Performed according to general procedure **E** using: ligand **56g** (0.42 g, 1.02 mmol), Ti(O^{i}Pr)$_4$ (0.51 ml, 1.70 mmol), *t*-BuOOH (1.55 ml of a 5.5M solution in decane, 4.25 mmol) and (*E*)-cinnamyl alcohol (0.57 ml, 4.25 mmol). The reaction was quenched by the addition of water (4.25 ml) at -20°C and allowed stir at ambient temperature for ten minutes, then dried and filtered through a pad of celite®. The filtrate was evaporated and purified by column chromatography using 1:1 ether/petrol as the elutent, yielding the *epoxy alcohol* **58** (0.17 g, 1.10 mmol, 26%) as a colourless oil in 97% ee and the *ligand* **56g** (0.34 g, 81%) as a colourless glassy solid with spectroscopic data in accordance with authentic material; m.p 98-100°C.

General Procedure G:
Synthesis of racemic secondary allylic alcohols

Into a dry round-bottom flask was added anhydrous tetrahydrofuran (1.5 ml per mmol), the α,β-unsaturated aldehyde (1 eq) and then the mixture was cooled with an ice bath. The BuLi or alkyl magnesium halide (1.3 eq) was slowly added and the reaction stirred overnight with no further cooling. The reaction was quenched by the addition of saturated aqueous ammonium chloride (100 ml) and then extracted with diethyl ether (2 x 1 vol). The combined organics were washed with water (2 x 1vol), brine (1vol), then dried and evaporated yielding the *secondary allylic alcohols* as sweet smelling free flowing colourless oils of sufficient purity for the kinetic resolution studies.

Rac-(E)-oct-2-en-4-ol 93
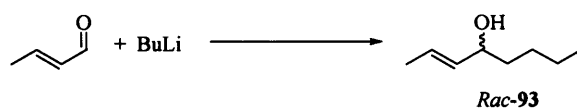
Prepared using general procedure **G** and crotonaldehyde (7.00 ml, 84.49 mmol), BuLi (44 ml of a 2.5 M solution in hexane, 109.84 mmol) and yielded the *title compound* (10.04 g, 93 %) as a light tan free flowing liquid with the odour of bracken, showing; δ$_H$ 5.65 (1H, dq, *J* = 15.4 and

6.7, 2-H), 5.48 (1H, ddd, J = 15.4, 7.2 and 1.2, 3-H), 3.99-4.06 (1H, m, 4-H), 1.70 (1H, app d, J = 6.7, 1-Me), 1.28-1.60 (6H, m, 3 x CH_2) and 0.90 (3H, t, J = 6.7, Me) which was in full agreement with the literature data.[110]
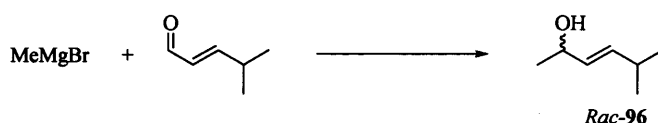
Rac-(E)-hept-3-en-2-ol 94

rac-94
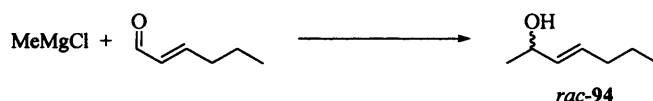
Prepared using general procedure **G** and *trans*-2-hexen-1-ol (8.79 ml, 75.76 mmol), MeMgBr (30.3 ml of a 3 M solution in ether, 90.91 mmol) and yielded the *title compound* (8.12 g, 71.13 mmol, 94 %) as a colourless free flowing liquid with the odour of apples, showing; δ_H 5.63 (1H, dt, J = 15.1 and 6.8, 4-H), 5.51 (1H, ddt, J = 15.1, 6.5 and 1.1, 3-H), 4.26 (1H, app pent, J = 6.5, 2-H), 1.99 (2H, app q, J = 6.8, 5-CH_2), 1.35-1.45 (2H, 6-CH_2), 1.26 (3H, d, J = 6.5, 1-Me) and 0.90 (3H, t, J = 7.3, 7-Me) which was in full agreement with the literature data.[111]

Rac-(E)-2-methylhex-4-en-3-ol 95

Rac-95
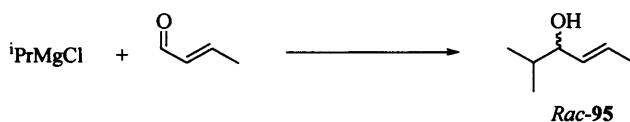
Prepared using general procedure **G** and crotonaldehyde (6.00 ml, 72.42 mmol), isopropylmagnesium chloride (43.5 ml of a 2.0 M solution in tetrahydrofuran, 86.9 mmol) and yielded the *title compound* (7.11 g, 62.31 mmol, 86 %) as a colourless free flowing liquid of a sweet odour, showing; δ_H 5.48 (1H, ddq, J = 15.3, 7.4 and 1.5, 4-H), 5.65 (1H, app dqd, J = 15.3, 0.8 and 6.5, 5-H), 3.72–3.80 (1H, m, 3-H), 1.83-1.87 (1H, m, 2-H), 1.71 (3H, dd, J = 6.5 and 1.5, 6-Me), 0.92 (3H, d, J = 6.8, 1 x Me) and 0.87 (3H, d, J = 6.8, 1 x Me), which was in full agreement with the literature data.[112]

Rac-(*E*)-5-methylhex-3-en-2-ol 96

Prepared using general procedure **G** and (*E*)-4-methylpent-2-enal (8.14 ml, 70.00 mmol), MeMgBr (30.3 ml of a 3 M solution in ether, 90.91 mmol) and yielded the *title compound* (6.63 g, 58.1 mmol, 83 %) as a colourless free flowing liquid with a sweet odour, showing; δ_H 5.61 (1H, ddd, J = 15.5, 6.5 and 0.7, 3-H), 5.45 (1H, ddd, J = 15.5, 6.8 and 1.0, 4-H), 4.26 (1H, app pent, J = 6.3, 2-H), 2.27 (1H, app octet, J = 6.8, 5-H), 1.25 (3H, d, J = 6.3, 1-Me) and 0.98 (6H, dd, J = 6.8 and 0.7, 2 x Me) which was in full agreement with the literature data.[113]

General Procedure H:
Sharpless Kinetic Resolution

Representative example

(1*S*,*E*)-1-cyclohexylbut-2-en-1-ol 89
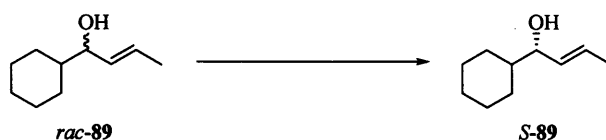
To a 100 ml Schlenk tube, equipped with a magnetic stirring bar, was added dry dichloromethane (20 ml), ligand **56g** (0.200 g, 0.492 mmol), activated powdered 3Å molecular sieves (0.5 g) and titanium tetraisopropoxide (0.244 ml, 0.820 mmol) and stirred for 20 minutes at room temperature. Upon cooling to -20°C, an 88 % solution of cumene hydroperoxide in cumene (0.205 ml, 1.23 mmol, 0.6eq) was added and the mixture stirred –20°C for one hour. (±)-(*E*)-1-Cyclohexylbut-2-en-1-ol (0.316, 2.05 mmol) was then added and the reaction was allowed to stir for a further 20 hours at –20°C then the reaction was quenched using saturated aqueous citric acid (20 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with saturated aqueous potassium carbonate (50 ml), water (100 ml), brine (50 ml), then dried and evaporated to leave the crude product, cumene, cumyl alcohol and ligand. Chromatography of residues using 1:4 ether/petrol as the elutent yielded *(1S)-(E)-1-cyclohexylbut-2-en-1-ol* **89** (0.086 g, 0.558 mmol, 68 %); GC 72% ee; v_{max}/cm^{-1} (neat); δ_H 5.62

(1H, dq, J = 15.4 and 6.4, 3-H), 5.48 (1H, ddq, J = 15.4, 7.5 and 1.3, 2-H), 3.75 (1H, app t, J = 7.5, 1-H), 1.85 (1H, br res, CH), 1.70 (3H, dd, J = 6.4 and 1.3, Me), 1.40 (1H, br res, OH), 1.60-1.80 (2H, m, 2 x CHH), 1.30-1.80 (1H, m, CHH), 1.10-1.30 (4H, m, 4 x CHH) and 0.88-1.20 (3H, m, 3 x CHH).

Kinetic Resolutions:

(2*S,E*)-pent-3-en-2-ol 91

rac-91   *S*-91
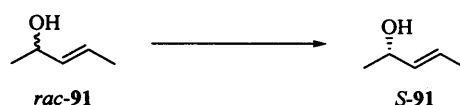
Undertaken as given in general procedure **H** using: ligand **56g** (0.200 g, 0.492 mmol), Ti(O^{i}Pr)$_4$ (244 µL, 0.818 mmol), CHP (205 µL of a 88% solution in cumene, 1.23 mmol) and (2*S,E*)-pent-3-en-2-ol **91** (210 µL, 2.05 mmol). Due to the volatile nature of the allylic alcohol **91** the residues were directly analysed by GC and provided good data for the enantiomeric excess of the resolved allylic alcohol. Thus, the *S*-**91** was provided with >99% ee.

(4*S,E*)-oct-2-en-4-ol 93
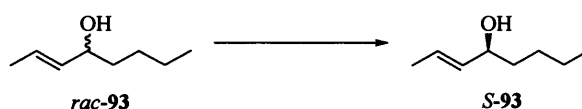
rac-93   *S*-93

Resolved as outlined in general procedure **H** using: ligand **56g** (0.200 g, 0.492 mmol), Ti(O^{i}Pr)$_4$ (244 µL, 0.818 mmol), CHP (205 µL of a 88% solution in cumene, 1.23 mmol) and (*E*)-oct-2-en-4-ol **93** (262 mg, 2.05 mmol). The residues were directly analysed by GC and provided good data for the enantiomeric excess of the resolved allylic alcohol. Thus, the (*S*)-**93** was provided with 90% ee.
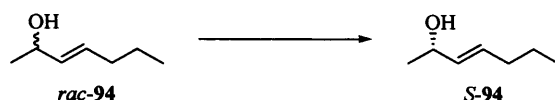
145

(2*S*,*E*)-hept-3-en-2-ol 94

OH
rac-94

OH
S-94

Resolved as outlined in general procedure **H** using: ligand **56g** (0.200 g, 0.492 mmol), Ti(O^{i}Pr)$_4$ (244 μL, 0.818 mmol), CHP (205 μL of a 88% solution in cumene, 1.23 mmol) and (*E*)-hept-3-en-2-ol **94** (234 mg, 2.05 mmol). The residues were directly analysed by GC and provided good data for the enantiomeric excess of the resolved allylic alcohol. Thus, the (*S*)-**94** was provided with >99% ee.

(3*S*,*E*)-2-methylhex-4-en-3-ol 95
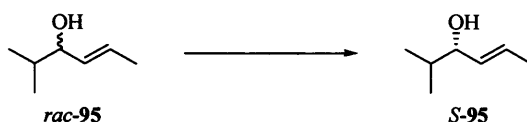
OH
rac-95

OH
S-95

Resolved as outlined in general procedure **H** using: ligand **56g** (0.200 g, 0.492 mmol), Ti(O^{i}Pr)$_4$ (244 μL, 0.818 mmol), CHP (205 μL of a 88% solution in cumene, 1.23 mmol) and (3S,*E*)-2-methylhex-4-en-3-ol **95** (234 mg, 2.05 mmol). Due to the volatile nature of the allylic alcohol **95** the residues were directly analysed by GC and provided good data for the enantiomeric excess of the resolved allylic alcohol. Thus, the (*S*)-**95** was provided with 95±3% ee.

(2*S*,*E*)-5-methylhex-3-en-2-ol 96

OH
rac-96

OH
S-96

Resolved as outlined in general procedure **H** using: ligand **56g** (0.200 g, 0.492 mmol), Ti(O^{i}Pr)$_4$ (244 μL, 0.818 mmol), CHP (205 μL of a 88% solution in cumene, 1.23 mmol) and (*E*)-5-methylhex-3-en-2-ol **96** (234 mg, 2.05 mmol). Due to the volatile nature of the allylic alcohol **96** the residues were directly analysed by GC and provided good data for the enantiomeric excess of the resolved allylic alcohol. Thus, the (*S*)-**96** was provided with >99% ee.
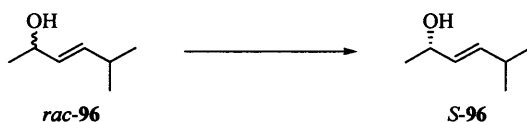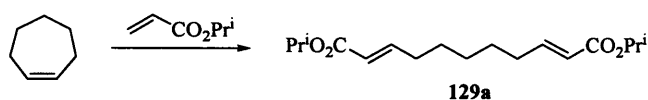
Gelator Studies:

(2*E*,9*E*)-Diisopropyl undeca-2,9-dienedioate 129a

Synthesised by general procedure **A** from; cycloheptene (1.40 ml, 11.96 mmol), isopropylacrylate (3.05 ml, 23.93 mmol), Grubbs second generation catalyst (38 mg, 0.18 mol %) and yielded the *bis-α,β-unsaturated ester* **129a** (2.95 g, 9.95 mmol, 83 %) as a colourless oil showing; v_{max}/cm^{-1} 2979, 2934, 2858, 1718, 1654, 1467, 1373, 1272, 1181, 1109 and 982; δ_H 6.92 (2H, dt, J = 15.6 and 7.0, 3-, 9-H), 5.78 (2H, dt, J = 15.6 and 1.5, 2-, 10-H), 5.04 (2H, hept, J = 6.4, 2 x CHMe$_2$), 2.18 (4H, qd, J = 7.0 and 1.5, 4-, 8-CH$_2$), 1.40-1.50 (4H, m, 2 x CH$_2$), 1.30-1.40 (2H, m, 1 x CH$_2$) and 1.26 (12H, d, J = 6.4, 4 x Me); δ_C 166.1 (2 x C=O), 148.6 (3-, 9-CH), 121.8 (2-, 10-CH), 67.3 (2 x OCH), 31.9 (4-, 8-CH$_2$), 27.7 (5-, 7-CH$_2$), 28.6 (6-CH$_2$) and 21.8 (4 x Me); m/z (APCI) 297 (M+1)$^+$ 100 % [HRMS (ES$^+$): calcd. for C$_{17}$H$_{29}$O$_4$, (M + H)$^+$: 297.2060, found: 297.2057.

(2*S*,3*R*,9*R*,10*S*)-Diisopropyl 2,3,9,10-tetrahydroxyundecadioate 130a

Synthesised by general procedure **B** from; the *bis-α,β-unsaturated ester* **129a** (2.50g, 8.43 mmol) and yielded the *gelator* **130a** (2.70 g, 7.41 mmol, 88%) as a colourless powder showing; m.p 118-119°C; $[\alpha]_D^{25}$ +24.4 (c 0.0054, MeOH); v_{max}/cm^{-1} (KBr) 3371, 2980, 2934, 2848, 1708, 1460, 1373, 1289, 1104, 1069, 992 and 961; δ_H 5.14 (2H, hept, J = 6.2, 2 x CHMe$_2$), 4.03 (2H, dd, J = 5.0 and 1.8, 2-, 10-H), 3.85 (2H, ddt, J ca 9, 2 and 7, 3-, 9-H), 3.12 (2H, d, J = 5.0, 2-, 10-OH), 1.95 (2H, d, J = 9.2, 3-, 9-OH), 1.55-1.68 (4H, m, 2 x CH$_2$), 1.46-1.54 (2H, m, 1 x CH$_2$), 1.34-1.44 (4H, m, 2 x CH$_2$) and 1.30 (12H, d, J = 6.2, 4 x Me); δ_C 174.3 (2 x C=O), 75.0 (2-, 10-CH), 73.7 (3-, 9-CH), 70.1 (2 x CHMe$_2$), 34.3 (4-, 8-CH$_2$), 30.7 (6-CH$_2$), 26.9 (5-, 7-CH$_2$), 22.1 and 22.0 (4 x Me); m/z (CI NH$_3$) 382 (M+NH$_4$)$^+$ 100 % [HRMS (CI NH$_3$): calcd. for C$_{17}$H$_{36}$NO$_8$, (M + NH$_4$)$^+$: 382.2429, found: 382.2429].

(2*E*,10*E*)-Diisopropyl dodeca-2,10-dienedioate 129b
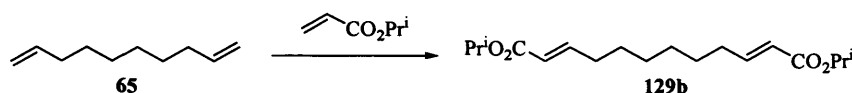
Synthesised by general procedure **A** from; 1,9-decadiene **65** (1.65 g, 11.93 mmol), isopropyl acrylate (3.05 ml, 23.86 mmol) and Grubbs second generation catalyst **66** (32 mg, 0.16 mol %), yielding the *bis-α,β-unsaturated ester* **129b** (3.36 g, 9.92 mmol, 83 %) as a colourless oil showing; v_{max}/cm^{-1} 2980, 2931, 2857, 1717, 1655, 1467, 1373, 1271, 1181, 1111 and 983; δ_H 6.93 (2H, dt, *J* = 15.6 and 7.1, 3-, 10-H), 5.78 (2H, dt, *J* = 15.6 and 1.5, 2-, 11-H), 5.05 (2H, hept, *J* = 6.2, 2xCHMe₂), 2.19 (4H, qd, *J* = 7.1 and 1.5, 4-, 9-CH₂), 1.40-1.50 (4H, m, 2 x CH₂), 1.30-1.35 (4H, m, 2 x CH₂) and 1.26 (12H, d, *J* = 6.2, 4 x Me); δ_C 166.2 (2 x C=O), 148.9 (3-, 10-CH), 121.8 (2-, 11-CH), 67.3 (2 x OCH), 32.1 (4-, 9-CH₂), 28.9 (2 x CH₂), 27.9 (2 x CH₂) and 21.9 (4 x Me); m/z (APCI) 311 (M + H)⁺ 100 % [HRMS (ES⁺): calcd. for $C_{18}H_{31}O_4$ (M + H)⁺ 311.2217, found: 311.2219].

(2*S*,3*R*,10*R*,11*S*)-Diisopropyl 2,3,10,11-tetrahydroxydodecadioate 130b
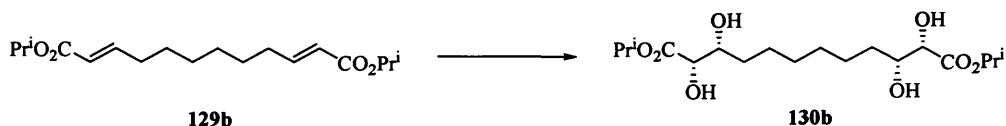
The synthesis was undertaken as shown in general procedure **B** from the *bis*-α,β-unsaturated ester **129b** (3.13 g, 9.24 mmol) and yielded the *gelator* **130b** (3.16 g, 8.33 mmol, 90%) as a colourless powder showing; m.p 101-103°C; $[\alpha]_D^{25}$ +20.5 (c 0.0056, MeOH); v_{max}/cm^{-1} (KBr) 3371, 2980, 2935, 2849, 1709, 1460, 1373, 1286, 1111, 1072 and 1012; δ_H 5.15 (2H, hept, *J* = 6.2, 2 x CHMe₂), 4.03 (2H, br res, 2-, 11-H), 3.85 (2H, ddt, *J ca* 7, 2 and 9, 3-, 10-H), 3.10 (2H, d, *J* = 4.2, 2-, 11-OH), 1.92 (2H, d, *J* = 9.2, 3-, 10-OH), 1.55-1.63 (4H, m, 4-, 9-CH₂), 1.30-1.55 (8H, m, 4 x CH₂) and 1.30 (12H, d, *J* = 6.2, 4 x Me); δ_C 174.3 (2 x C=O), 75.0 (2-, 11-CH), 73.8 (3-, 10-CH), 70.1 (2 x CHMe₂), 34.3 (4-, 9-CH₂), 30.7 (2 x CH₂), 26.9 (2 x CH₂), 22.1 and 22.0 (4 x Me); m/z (APCI) 379 (M + H)⁺ 100 % [HRMS (ES⁺): calcd. for $C_{18}H_{35}O_8$ (M + H)⁺ 379.2326, found: 379.2328].

(2*E*,11*E*)-Diisopropyl trideca-2,11-dienedioate 129c
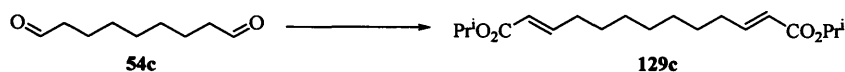
Synthesised by general procedure **C** from; 1,9-nonanedial **54c** (2.90 g, 18.55 mmol), isopropyl(diethylphosphonoacetate) (8.84 g, 37.11 mmol) and yielded the *bis*-α-β-unsaturated ester **129c** (2.89 g, 8.90 mmol, 48%) as a colourless oil showing; v_{max} 2979, 2928, 2856, 1709, 1654, 1467, 1373, 1271, 1178, 1112 and 984; δ_H 6.94 (2H, dt, *J* = 15.6 and 7.0, 3-, 11-H), 5.79 (2H, dt, *J* = 15.6 and 1.5, 2-, 12-H), 5.06 (2H, hept, *J* = 6.5, 2 x CHMe₂), 2.19 (4H, qd, *J* = 7.0 and 1.5, 4-, 10-CH₂), 1.40-1.50 (4H, m, 2 x CH₂), 1.29-1.35 (6H, m, 3 x CH₂) and 1.26 (12H, d, *J* = 6.5, 2 x Me₂); δ_C 166.1 (2 x C=O), 148.8 (3-, 11-CH), 121.6 (2-, 12-CH), 67.1 (2 x OCHMe₂), 32.0 (4-, 10-CH₂), 29.0 (1 x CH₂), 28.8 (2 x CH₂), 27.8 (2 x CH₂) and 21.7 (4 x Me); m/z (APCI) 325 (M + H)⁺ 100 % [HRMS (ES⁺): calcd. for C₁₉H₃₃O₄ (M + H)⁺ 325.2373, found: 325.2375].

(2*S*,3*R*,11*R*,12*S*)-Diisopropyl 2,3,11,12-tetrahydroxytridecadioate 130c
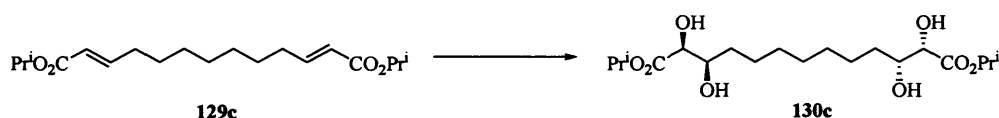
The synthesis was undertaken as shown in general procedure **B** from the *bis*-α,β-unsaturated ester **129c** (2.26 g, 6.41 mmol) and yielded the *gelator* **130c** (2.40 g, 6.11 mmol, 95%) as a colourless powder showing; m.p 102-103°C; $[\alpha]_D^{25}$ +9.7 (c 0.0076, MeOH); v_{max}/cm⁻¹ (KBr) 3372, 2980, 2935, 2848, 1708, 1460, 1373, 1289, 1105, 1078 and 963; δ_H 5.14 (2H, hept, *J* = 6.3, 2 x CHMe₂), 4.04 (2H, br res, 2-, 12-H), 3.81-3.89 (2H, m, 3-, 11-H), 3.06 (2H, d, 2-, 12-OH), 1.86 (2H, d, 3-, 11-OH), 1.56-1.62 (8H, m, 4 x CH₂), 1.30-1.36 (6H, m, 3 x CH₂) and 1.31 (12H, d, *J* = 6.3, 2 x Me₂); δ_C 174.3 (2 x C=O), 75.0 (2-, 12-CH), 73.8 (3-, 11-CH), 70.1 (2 x OCHMe₂), 34.3 (4-, 10-CH₂), 30.7 (3 x CH₂), 27.0 (2 x CH₂), 22.1 and 22.0 (4 x Me); m/z (APCI) 245 (M⁺ - 147) 100 % and 393 (M + H)⁺ 75% [HRMS (ES⁺): calcd. for C₁₉H₃₇O₈ (M + H)⁺ 393.2483, found: 393.2487].

149

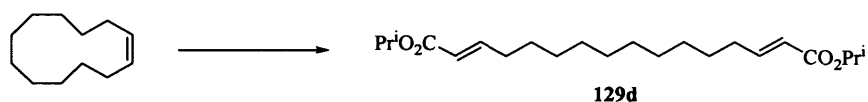## (2*E*,14*E*)-Diisopropyl hexadeca-2,14-diendioate 129d

Synthesised by general procedure **A** from; cyclododecene (3.70 ml, 18.04 mmol), isopropyl acrylate (4.61 ml, 36.08 mmol) and Grubbs second generation catalyst **66** (43 mg, 0.14 mol %), yielding the *bis-α,β-unsaturated ester* **129d** (5.82 g, 15.87 mmol, 88 %) as a colourless oil showing; v_{max}/cm^{-1} 2979, 2927, 2855, 1720, 1654, 1467, 1372, 1271, 1180, 1111 and 982; δ_H 6.94 (2H, dt, *J* = 15.5 and 6.9, 3-, 14-H), 5.88 (2H, dt, *J* = 15.5 and 1.4, 2-, 15-H), 5.05 (2H, app hept, *J* = 6.3, 2 x CHMe$_2$), 2.18 (4H, app qd, *J* = 6.9 and 1.4, 4-, 13-CH$_2$), 1.40-1.50 (4H, m, 2 x CH$_2$), 1.24-1.30 (12H, m, 6 x CH$_2$) and 1.26 (12H, d, *J* = 6.3, 2 x Me$_2$); δ_C 166.1 (2 x C=O), 148.9 (3-, 14-CH), 121.5 (2-, 15-CH), 67.1 (2 x OCH), 32.0 (4-, 13-CH$_2$), 29.3 (2 x CH$_2$), 29.2 (2 x CH$_2$), 29.0 (2 x CH$_2$), 27.9 (2 x CH$_2$) and 21.7 (4 x Me); m/z (APCI) 367 (M + H)$^+$ 100 % [HRMS (ES$^+$): calcd. for C$_{22}$H$_{39}$O$_4$ (M + H)$^+$ 367.2843, found: 367.2839].

## (2*S*,3*R*,14*R*,15*S*)-diisopropyl 2,3,14,15-tetrahydroxyhexadecadioate 130d

The synthesis was undertaken as shown in general procedure **B** from the *bis-α,β-unsaturated ester* **129c** (2.26 g, 6.41 mmol) and yielded the *gelator* **130d** (2.40 g, 6.11 mmol, 95%) as a colourless powder showing; m.p 90-91°C; $[\alpha]_D^{25}$ +22.9 (c 0.0077, MeOH); v_{max}/cm^{-1} (KBr) 3376, 2979, 2918, 2847, 1708, 1460, 1373, 1289, 1106 and 1068; δ_H 5.14 (2H, hept, *J* = 6.3, 2 x CHMe$_2$), 4.04 (2H, br res, 2-, 15-H), 3.82-3.88 (2H, m, 3-, 14-H), 3.10 (2H, br res, 2-, 15-OH), 1.90 (2H, br res, 3-, 14-OH), 1.56-1.63 (4H, m, 4-, 13-CH$_2$), 1.42-1.52 (4H, m, 2 x CH$_2$), 1.22-1.42 (16H, m, 8 x CH$_2$) and 1.29 (12H, d, *J* = 6.3, 2 x Me$_2$); δ_C 174.3 (2 x C=O), 75.0 (2-, 15-CH), 73.8 (3-, 14-CH), 70.1 (2 x OCHMe$_2$), 34.4 (4-, 10-CH$_2$), 30.8 (6 x CH$_2$), 26.9 (2 x CH$_2$), 22.0 and 22.1 (4 x Me); m/z (APCI) 435 (M + H)$^+$ 100% [HRMS (ES$^+$): calcd. for C$_{22}$H$_{42}$O$_8$ (M + H)$^+$ 435.2952, found: 435.2952].

(2*E*,10*E*)-Disoamyl dodeca-2,10-dienedioate 132c
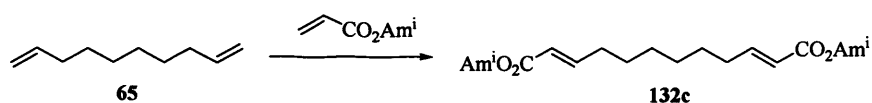
Synthesised by general procedure **A** from; 1,9-decadiene **65** (2.00 ml, 10.85 mmol), isoamyl acrylate (4.42 ml, 21.70 mmol), Grubbs second generation catalyst (32 mg, 0.16 mol%) and yielded the *bis-α,β-unsaturated ester* **132c** (3.73 g, 10.18 mmol, 94 %) as a colourless oil showing; v_{max}/cm^{-1} 2958, 2869, 1720, 1655, 1465, 1386, 1387, 1265, 1181, 1057 and 982; δ_H 6.94 (2H, dt, *J* = 15.6 and 6.9, 3-, 10-H), 5.80 (2H, dt, *J* = 15.6 and 1.4, 2-, 11-H), 4.15 (4H, t, *J* = 6.9, 2 x OCH$_2$), 2.18 (4H, qd, *J* = 6.9 and 1.4, 4-, 9-CH$_2$), 1.70 (2H, app nonet, *J* = 6.9, 2 x CHMe$_2$), 1.54 (4H, app q, *J* = 6.9, 2 x OCH$_2$C*H*$_2$), 1.40-1.50 (4H, m, 2 x CH$_2$), 1.27-1.35 (4H, m, 2 x CH$_2$) and 0.92 (12H, d, *J* = 6.9, 4 x Me); δ_C 166.8 (2 x C=O), 149.1 (3-, 10-CH), 121.3 (2-, 11-CH), 62.8 (2 x CH$_2$O), 37.4 (4-, 9-CH$_2$), 32.1 (2 x CH$_2$), 28.9 (2 x CH$_2$), 27.9 (2 x CH$_2$), 25.1 (2 x CHMe) and 22.5 (4 x Me); m/z (APCI) 367 (M+1)$^+$ 100 % [HRMS (ES$^+$): calcd. for C$_{22}$H$_{39}$O$_4$ (M + H)$^+$: 367.2843, found: 367.2841].

(2*S*,3*R*,10*R*,11*S*)-Diisoamyl 2,3,10,11-tetrahydroxydodecadioate 133c


The synthesis was undertaken as shown in general procedure **B**, from the *bis*-α,β-unsaturated ester **132c** (3.46 g, 8.76 mmol) and recrystallisation from chloroform/hexane yielded the *tetra-ol* **133c** (2.89 g, 6.65 mmol, 76%) as a colourless powder showing; m.p 69-70°C; $[\alpha]_D^{25}$ +14.8 (c 0.01, MeOH); v_{max}/cm^{-1} (KBr) 3405, 2935, 2848, 1714, 1463, 1386, 1282, 1199, 1069, 989 and 870; δ_H 4.26 (4H, t, *J* = 6.9, 2 x OCH$_2$), 4.07 (2H, br res, 2-, 11-H), 3.86 (2H, ddt, *J ca* 7, 2 and 9, 3-, 10-H), 3.06 (2H, d, *J* = 4.8, 2-, 11-OH), 1.90 (2H, d, *J* = 9.1, 3-, 10-OH), 1.70 (2H, app nonet, 2 x CHMe$_2$), 1.57 (4H, app q, *J* = 6.9, 2 x OCH$_2$C*H*$_2$), 1.57-1.65 (4H, m, 2 x CH$_2$), 1.33-1.42 (8H, m, 4 x CH$_2$) and 0.93 (12H, d, *J* = 6.9, 4 x Me); δ_C 174.8 (2 x C=O), 74.9 (2-, 11-CH), 73.8 (3-, 10-CH), 64.7 (2 x CH$_2$O), 38.5 (2 x CH$_2$), 34.3 (4-, 9-CH$_2$), 30.7 (2 x CH$_2$), 26.9 (2 x CH$_2$), 26.2 (2 x CHMe$_2$) and 22.9 (4 x Me); m/z (CI NH$_3$) 452 (M + NH$_4$)$^+$ 100 % [HRMS (ES$^+$): calcd. for (M + H)$^+$, 452.3218 found: 452.3215].

## (2*E*,10*E*)-Dicyclohexyl dodeca-2,10-diendioate 132d
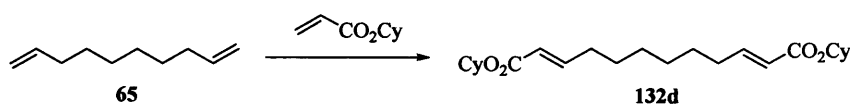
Synthesised by general procedure **A**, from 1,9-decadiene **65** (2.00 ml, 10.85 mmol), cyclohexyl acrylate (3.41 ml, 21.70 mmol), Grubbs second generation catalyst (50 mg, 0.27 mol%) which yielded the *bis-α,β-unsaturated ester* **132d** (3.97 g, 10.18 mmol, 94 %) as a colourless oil showing; v_{max}/cm^{-1} 2969, 2933, 2879, 1717, 1654, 1462, 1268, 1183, 1106 and 982; δ_H 6.93 (2H, dt, *J* = 15.6 and 6.9, 3-, 10-H), 5.79 (2H, dt, *J* = 15.6 and 1.4, 2-, 11-H), 4.80 (2H, tt, *J* = 8.9 and 3.9, 2 x OCH), 2.18 (4H, qd, *J* = 6.9 and 1.4, 4-, 9-CH₂), 1.83-1.92 (4H, m, 2 x CH₂), 1.68-1.77 (4H, m, 2 x CH₂), 1.50-1.60 (2H, m, 2 x CH*H*) and 1.20-1.50 (18H, m, 9 x CH₂); δ_C 166.1 (2 x C=O), 148.8 (3-, 10-CH), 121.8 (2-, 11-CH), 72.31 (2 x OCH), 32.1 (4-, 9-CH₂), 31.7 (4 x CH₂), 28.9 (2 x CH₂), 27.9 (2 x CH₂), 25.4 (2 x CH₂) and 23.8 (4 x CH₂); m/z (CI NH₃) 391 (M + 1)⁺ 100 % [HRMS (ES⁺): calcd. For $C_{24}H_{39}O_4$ (M + H)⁺, 391.2843, found: 391.2845].

(2*S*,3*R*,10*R*,11*S*)-Dicyclohexyl 2,3,10,11-tetrahydroxydodecadioate 133d
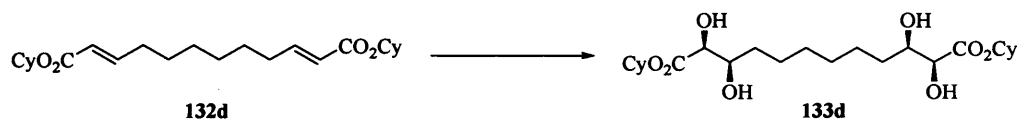
Synthesised by general procedure **B** from the *bis-α,β-unsaturated ester* **132d** (3.20 g, 8.12 mmol) and recrystallisation of the crude product from chloroform/hexane yielded the *tetra-ol* **133d** (3.06 g, 6.67 mmol, 82%) as a colourless, slate-like solid showing; m.p 96-97°C; $[\alpha]_D^{25}$ +7.7 (c 0.0059, MeOH); v_{max}/cm^{-1} (KBr) 3468, 3354, 2932, 2854, 1736, 1730, 1452, 1281, 1130, 1082 and 1014; δ_H (500 MHz) 4.91 (2H, tt, *J* = 9.0, and 3.9, 2 x OCH), 4.05 (2H, dd, *J* = 4.9 and 2.2, 2-, 11-H), 3.85 (2H, ddt, *J ca* 9, 7 and 2, 3-, 10-H), 3.05 (2H, d, *J* = 4.9, 2-, 11-OH), 1.87 (2H, d, *J* = 9.2, 3-, 10-OH), 1.83-2.03 (4H, m, 2 x CH₂), 1.67-1.79 (4H, m, 2 x CH₂), 1.21-1.65 (24H, m, 12 x CH₂); δ_C 174.2 (2 x C=O), 75.0 (2-, 11-CH), 74.8 (2 x OCH), 73.8 (3-, 10-CH), 33.8, 31.5, 31.4, 29.4, 25.7, 25.3, 23.6 and 23.5 (all CH₂); m/z (APCI) 459 (M+1)⁺ 100 % [HRMS (ES⁻): calcd. for (M - H)⁻, 457.2801, found: 457.2779].

3-Pentyl acrylate

To a flame dried 250 ml two necked round bottom flask under an atmosphere of nitrogen were added anhydrous dichloromethane (125 ml), 3-pentanol (12.2 ml, 113.44 mmol) and triethylamine (18.79 ml, 136.13 mmol). This mixture was cooled with an ice bath and then acryloyl chloride (10.14 ml, 124.78 mmol) was slowly added over ten minutes and the resulting pale yellow mixture was allowed to stir at ambient temperature for two hours. The reaction was quenched with water (100 ml) and the organics were washed sequentially with saturated ammonium chloride solution (100 ml), 1M HCl (100 ml), saturated aqueous potassium carbonate (100 ml), water (100 ml), brine (100 ml), then dried and evaporated. The crude tan residue was distilled (b.p 46°C at 15 mmHg) and yielded *3-pentyl acrylate* (12.10 g, 85.08 mmol, 75%) as a free-flowing colourless liquid showing; v_{max}/cm^{-1} 2970, 2940, 2881, 1727, 1638, 1619, 1462, 1406, 1296, 1272, 1198 and 1050; δ_H 6.38 (1H, dd, J = 17.3 and 1.6, 3'-H-*trans*), 6.05 (1H, dd, J = 17.3 and 10.3, 2'-H), 5.74 (1H, dd, J = 10.3 and 1.6, 3'-H-*cis*), 4.77 (2H, tt, J = 6.6 and 5.8, OCH), 1.56-1.66 (4H, m, 2 x CH$_2$) and 0.83 (6H, t, J = 7.5, 2 x Me); δ_C 165.8 (C=O), 129.8 (3'-CH$_2$), 128.8 (2'-CH), 76.5 (OCH), 26.2 (2 x CH$_2$) and 9.3 (2 x Me).

(2*E*,10*E*)-3'-Dipentyl dodeca-2,10-diendioate 132e
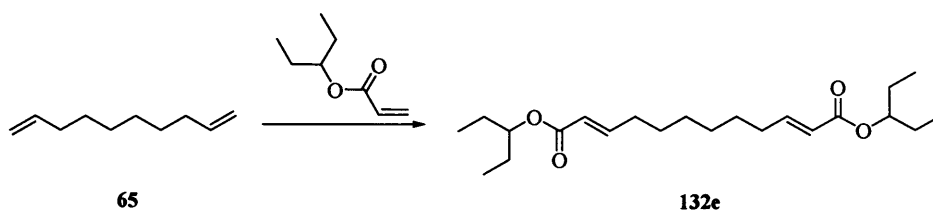
Synthesised by general procedure **A** from; 1,9-decadiene **65** (1.50 ml, 8.14 mmol), 3-pentyl acrylate (2.31 g, 16.27 mmol), Grubbs second generation catalyst (40 mg, 0.29 mol%) which yielded the *bis-α,β-unsaturated ester* **132e** (3.97 g, 10.18 mmol, 94 %) as a colourless oil showing; v_{max}/cm^{-1} 2967, 2929, 2879, 1721, 1654, 1461, 1268, 1182, 1106, 1035 and 982; δ_H 6.93 (2H, dt, J = 15.6 and 6.9, 3-, 11-H), 5.80 (2H, dt, J = 15.6 and 1.4, 2-, 12-H), 4.80 (2H, tt, J = 6.8 and 5.6, 2 x OCH), 2.20 (4H, qd, J = 6.9 and 1.4, 4-, 9-CH$_2$), 1.53-1.63 (8H, m, 4 x CH$_2$), 1.26-1.50 (8H, m, 4 x CH$_2$) and 0.87 (12H, t, J = 7.3, 4 x CH$_3$); δ_C 166.6 (2 x C=O), 148.8 (3-,

10-CH), 121.5 (2-, 11-CH), 76.2 (2 x OCH), 32.0 (4-, 9-CH₂), 28.8 (2 x CH₂), 27.8 (2 x CH₂), 26.4 (4 x CH₂) and 9.5 (4 x Me); m/z (CI NH₃) 367 (M +1)⁺ 100% [HRMS (ES⁺): calcd. for C₂₂H₃₉O₄ (M + H)⁺ 367.2843, found: 367.2844].

(2*S*,3*R*,10*R*,11*S*)-3'-Dipentyl 2,3,10,11-tetrahydroxydodecadioate 133e

132e   133e

Prepared by general procedure **B** from the *bis*-α,β-unsaturated ester **132e** (2.90 g, 7.35 mmol) and recrystallisation of the crude product from chloroform/hexane yielded the *tetra-ol* **133e** (2.33 g, 5.36 mmol, 73%) as a colourless powder showing; m.p 94-95°C; $[\alpha]_D^{25}$ +8.6 (c 0.0079, MeOH); ν_{max}/cm⁻¹ (KBr) 3488, 3337, 2925, 2845, 1740, 1720, 1458, 1348, 1268, 1137 and 1077; δ_H 4.90 (2H, tt, *J* = 6.9 and 5.5, 2 x OCH), 4.07 (2H, br res, 2-, 11-H), 3.87 (2H, br res, 3-, 10-H), 3.12 (2H, d, *J* = 4.6, 2-, 11-OH), 1.89 (2H, d, *J* = 6.2, 3-, 10-OH), 1.55-1.72 (12H, m, 6 x CH₂), 1.30-1.55 (8H, m, 4 x CH₂) and 0.90 (12H, dd, *J* = 7.4 and 13.6, 4 x CH₃); δ_C 174.7 (2 x C=O), 79.2 (2 x OCH), 74.9 (2-, 11-CH), 73.8 (3-, 10-CH), 34.5 (2 x CH₂), 30.7 (2 x CH₂), 27.6 (2 x CH₂), 27.5 (2 x CH₂) 26.9 (2 x CH₂) and 10.1 (4 x Me); m/z (APCI) 435 (M+H)⁺ 100 % [HRMS (ES⁺): calcd. for C₂₂H₄₃O₈ (M + H)⁺ 435.2952, found: 435.2954].

(2*E*,10*E*)-Di-*t*-butyl dodeca-2,10-diendioate 132b

65   BuᵗO₂C   132b   CO₂ᵗBu
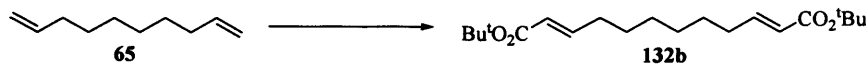
Synthesised by general procedure **A** from 1,9-decadiene (2.00 ml, 10.85 mmol), *t*-butyl acrylate (3.19 ml, 21.7 mmol), Grubbs second generation catalyst (32 mg, 0.17 mol%) which furnished the *bis*-α,β-*unsaturated ester* **132b** (3.46 g, 10.22 mmol, 94 %) as a colourless oil showing: ν_{max}/cm⁻¹ (KBr) 2978, 2928, 2855, 1714, 1460, 1367, 1258, 1158 and 981; δ_H 6.84 (2H, dt, *J* = 15.6 and 7.0, 3-, 10-H), 5.72 (2H, dt, *J* = 15.6 and 1.5, 2-, 11-H), 2.15 (4H, qd, *J* = 7.0 and 1.5, 4-, 9-CH₂), 1.27-1.47 (8H, m, 4 x CH₂) and 1.47 (18H, s, 2 x ᵗBu); δ_C 166.0 (2 x C=O), 147.9 (3- , 10-CH), 122.9 (2-, 11-CH), 79.8 (2 x OCH), 31.9 (4-, 9-CH₂), 28.9 (2 x CH₂), 28.0 (6 x Me)

and 27.9 (2 x CH_2); m/z (CI NH_3) 339 $(M + 1)^+$ (85%) and 244 $(M - 94)^+$ (100%) [HRMS (ES): calcd. for $C_{20}H_{35}O_4$ $(M + H)^+$ 339.2530, found: 339.2531].

(2*S*,3*R*,10*R*,11*S*)-Di-*t*-butyl 2,3,10,11-tetrahydroxydodecadioate

132b → **133b**
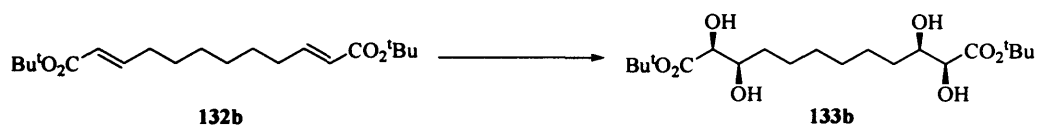
The synthesis was undertaken as iterated in general procedure **B** from the *bis*-α,β-unsaturated ester **132b** (3.00 g, 8.18 mmol) and subsequent recrystallisation from chloroform/hexane yielded the *tetra-ol* **133b** (2.54 g, 6.25 mmol, 76%) as a colourless powder showing; m.p 73-74°C ; $[\alpha]_D^{25}$ +30.9 (c 0.0058, MeOH); v_{max}/cm^{-1} (KBr) 3446, 2933, 1731, 1369, 1256 and 1160; δ_H 3.96 (2H, dd, *J* = 4.8 and 2.2, 2-, 11-H), 3.83 (2H, dtd, *J* = 9.5, 6.9 and 2.2, 3-, 10-H), 3.07 (2H, d, *J* = 4.8, 2-, 11-OH), 1.84 (2H, d, *J* = 9.5, 3-, 10-OH), 1.56-1.64 (4H, m, 2 x CH_2), 1.52 (18H, s, 2 x ^tBu) and 1.34-1.42 (8H, m, 4 x CH_2); δ_C 172.9 (2 x C=O), 83.2 (2 x CMe_3), 73.1 (2-, 11-CH), 72.6 (3-, 10-CH), 33.9 (4-, 9-CH_2), 29.4 (2 x CH_2), 28.0 (6 x Me) and 25.6 (2 x CH_2); m/z (APCI) 407.0 $(M+H)^+$ 100 %. [HRMS (ES): calcd. for $C_{20}H_{39}O_8$ $(M + H)^+$ 407.2639, found: 407.2640].

(2*E*,10*E*)-Diisobutyl dodeca-2,10-diendioate 132a

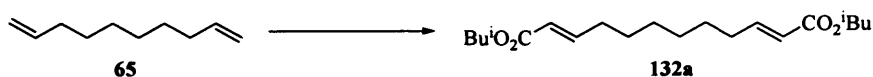**65** → **132a**

Synthesised as iterated by general procedure **A**, from 1,9-decadiene **65** (2.00 ml, 10.85 mmol), *iso*-butyl acrylate (3.15 ml, 21.7 mmol) and Grubbs second generation catalyst (32 mg, 0.17 mol%), yielding the *bis*-α,β-unsaturated ester **132a** (3.72 g, 10.11 mmol, 93 %) as a colourless oil showing; v_{max}/cm^{-1} 2932, 2865, 1720, 1654, 1470, 1377, 1267, 1178 and 1026; δ_H 6.95 (2H, dt, *J* = 15.6 and 7.0, 3-, 10-H), 5.82 (2H, dt, *J* = 15.6 and 1.5, 2-, 11-H), 3.90 (4H, d, *J* = 6.8, 2 x OCH_2), 2.18 (4H, qd, *J* = 7.0 and 1.5, 4-, 9-CH_2), 1.95 (2H, app nonet, *J* = 6.8, 2 x $CHMe_2$), 1.40-1.50 (4H, m, 2 x CH_2), 1.28-1.36 (4H, m, 2 x CH_2) and 0.94 (12H, d, *J* = 6.8, 4 x Me); δ_C 166.5 (2 x C=O), 148.9 (3-, 10-CH), 121.1 (2-, 11-CH), 70.1 (2 x CH_2O), 31.9 (4-, 9-CH_2), 28.7 (2 x CH_2), 27.7 (2 x $CHMe_2$), 27.6 (2 x CH_2) and 18.9 (4 x Me); m/z (APCI) 339 $(M + 1)^+$ 100 % [HRMS (ES^+): calcd. for $C_{20}H_{35}O_4$ $(M + H)^+$ 339.2530, found: 339.2528].

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(2*S*,3*R*,10*R*,11*S*)-Diisobutyl 2,3,10,11-tetrahydroxydodecadioate 133a

Synthesised by general procedure **B** from the *bis*-α,β-unsaturated ester **132a** (3.02 g, 8.20 mmol) and recrystallisation from chloroform/hexane yielded the *tetra-ol* **133a** (2.94 g, 7.23 mmol, 88%) as a colourless powder showing; m.p 99-101 °C; $[\alpha]_D^{25}$ +16.9 (c 0.0062, MeOH); v_{max}/cm^{-1} (KBr) 3406, 2934, 2847, 1728, 1463, 1380, 1285, 1200, 1069 and 1017; δ_H 4.09 (2H, dd, J = 5.0 and 1.8, 2-, 11-H), 4.05 (2H, dd, J = 6.7 and 10.5, 2 x OC*H*H), 3.99 (2H, dd, J = 6.7 and 10.5, 2 x OCH*H*), 3.87 (2H, dtd, J *ca* 7, 2 and 9, 3-, 10-H), 3.08 (2H, d, J = 5.0, 2-, 11-OH), 1.99 (2H, app nonet, J = 6.7, 2 x CHMe₂), 1.92 (2H, d, J = 9.2, 3-, 10-OH) 1.59-1.70 (4H, m, 4-, 9-CH₂), 1.45-1.57 (4H, m, 2 x CH₂), 1.33-1.45 (4H, m, 2 x CH₂) and 0.95 (12H, d, J = 6.7, 4 x Me); δ_C 174.8 (2 x C=O), 74.9 (2-, 11-CH), 73.8 (3-, 10-CH), 72.2 (2 x OCH₂), 34.3 (2 x CH₂), 30.7 (2 x CH₂), 26.9 (2 x CH₂), 29.0 (2 x CHMe₂) and 19.4 (4 x Me); m/z (APCI) 407 (M + 1)⁺ 100 % [HRMS (ES⁺): calcd. for $C_{20}H_{39}O_8$ (M + H)⁺ 407.2639, found: 407.2638].

(*E*)-Isopropyl hept-2-en-6-ynoate 139[116]
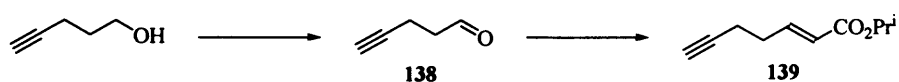
To a tetrahydrofuran (250 ml) solution of oxalyl chloride (13.3 g, 104.78 mmol) was added dropwise dimethyl sulphoxide (7.45 ml, 104.95 mmol) at -78 °C and the mixtures were stirred at -78 °C for 20 min. To this resulting white suspension was added 4-pentyl-1-ol (4.0 g, 47.55 mmol), and the mixtures were stirred at -78 °C for 1 h before treatment with triethylamine (36.00 ml, 258.3 mmol). The reaction was stirred at -60 °C for 45 min, warmed to room temperature and then stirred for an additional 1 h. The mixtures were filtered, the filtercake was washed with THF, and the filtrate was stored under nitrogen at ice bath temperature.

In a separate flask: A suspension of sodium hydride (hexane-prewashed, 71.33 mmol) in tetrahydrofuran (70 ml) was cooled with an ice bath and neat Isopropyl diethyl phosphonoacetate (17.00 g, 71.33 mmol) was added dropwise over 5 min. The solution was stirred at 0 °C for 45 min and then added to the filtrate described above and the solution stirred at 0 °C for 1 h and then

at room temperature for 25 minutes. The reaction was diluted with ether (200 ml), washed with saturated aqueous ammonium chloride (100 ml), 1 M HCl (100 ml), saturated aqueous sodium bicarbonate (200 ml), brine (100 ml), then dried and evaporated furnishing the α,β-unsaturated ester **139** as a yellow oil and was subsequently purified by eluting through a short plug of silica with 10% ether/hexane providing the α,β-unsaturated ester **139** as a slightly yellow oil (7.51 g, 45.19 mmol, 95%) showing; v_{max}/cm^{-1} 3301, 2980, 2934, 2150, 1720, 1656, 1468, 1434, 1274, 1207, 1160, 1110 and 981; δ_H 6.95 (1H, dt, J = 15.7 and 6.6, 3-H), 5.86 (1H, dt, J = 15.7 and 1.5, 2-H), 5.06 (1H, hept, J = 6.2, CHMe₂), 2.40-2.46 (2H, m, 4-CH₂), 2.33-2.38 (2H, m, 5-CH₂), 2.00 (1H, t, J = 2.5, 7-H) and 1.26 (6H, d, J = 6.2, Me₂); δ_C 165.9 (C=O), 146.0 (3-CH), 123.0 (2-CH), 82.8 (6-C), 69.4 (7-CH), 67.6 (OCHMe₂), 31.0 (4-CH₂), 21.9 (2 x Me) and 17.4 (5-CH₂) [HRMS (ES⁻): calcd. for $C_{10}H_{14}O_2$ (M - H)⁻ 165.0921, found: 353.1804, coupled acetylene sodium adduct].

(2*E*,12*E*)-Diisopropyl tetradeca-2,12-dien-6,8-diynedioate 140[118]
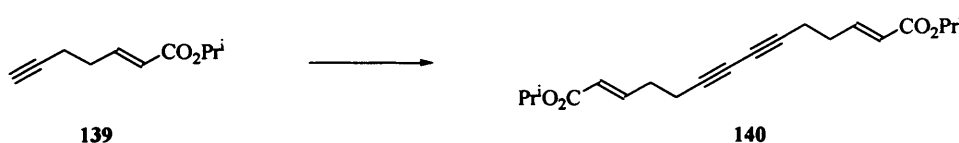
Into 150 ml three necked flask was added dichloromethane (75 ml), cuprous chloride (5.96 g, 6.02 mmol), TMEDA (8.18 ml, 54.18 mmol) then this mixture was stirred gently and finally a stream of oxygen was bubbled through, low rate (*ca* 0.5 ml/s). The α,β-unsaturated ester **139** (1.00 g, 6.02 mmol) was slowly added to the deep blue solution and stirred for 1 hour and during this time the volume of the reaction was maintained by periodical additions of dichloromethane. The oxygen inlet was removed and the reaction was diluted by the addition of ether (200 ml) and washed with water (2 x 100 ml), saturated aqueous ammonium chloride (2 x 100 ml), water (1 x 100 ml), 2M HCl (1 x 100 ml), saturated sodium hydrogen carbonate (1 x 100 ml), brine (1 x 100 ml), then dried and evaporated to yield the *title compound* **140** (0.99 g, 3.00 mmol, 99%) as a colourless solid showing; m.p 64-66°C; v_{max}/cm^{-1} (KBr) 2980, 2930, 2360, 2358, 1713, 1654, 1316, 1297, 1156, 1107 and 982; δ_H 6.88-6.96 (2H, m, 3-, 12-H), 5.85 (2H, d, J = 15.6, 2-, 13-H), 5.06 (2H, app hept, J = 6.2, 2 x CHMe₂), 2.04-2.46 (8H, m, all CH₂) and 1.26 (12H, d, J = 6.2, 2 x Me₂); δ_C 165.8 (2 x C=O), 145.6 (3-, 12-CH), 123.1 (2-, 13-CH), 76.1 (6-, 9-C), 67.6 (2 x CHMe₂), 66.0 (7-, 8-C), 30.9 (4-, 11-CH₂), 21.9 (2 x Me₂) and 18.2 (5-, 10-CH₂) [HRMS (ES⁻): calcd. for $C_{20}H_{26}O_4Na$ (M + Na)⁻ 353.1716, found: 353.1729].

(2*S*,3*R*,12*R*,13*S*)-Diisopropyl 2,3,12,13-tetrahydroxytetradeca-6,8-diynedioate 141
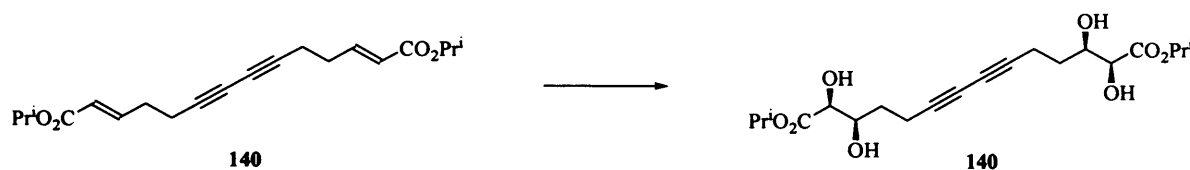
Synthesised by general procedure **B** from the *bis*-acetylene **140** (0.90 g, 2.73 mmol) and then the crude product was filtered through a plug of silica with ethyl acetate as the elutent yielding the *title compound* **140** (1.03 g, 2.60 mmol, 95%) as a colourless solid showing: m.p, polymerised; ν_{max}/cm^{-1} (film) 3149, 2981, 2924, 2360, 2341, 1730, 1376, 1283, 1221 and 1104; δ_H (500 MHz, CD_2Cl_2) 4.98 (2H, pent, J = 6.2, 2 x OCHMe$_2$), 3.89-3.92 (2H, m, 2-, 13-H), 3.97-3.84 (2H, m, 3-, 12-H), 3.55 (2H, d, J = 5.8, 2-, 13-OH), 2.79 (2H, d, J = 7.4, 3-, 12-OH), 2.23-2.37 (2H, m, 5-, 10-CH$_2$), 1.60-1.74 (4H, m, 4-, 11-CH$_2$) and 1.16 (12H, app dd, J = 6.2 and 0.9, 2 x CHMe$_2$); δ_C (125MHz, CD_2Cl_2) 173.3 (2 x C=O), 77.3 (6-, 9-C), 73.9 (2-, 13-CH), 71.8 (3-, 12-CH), 70.5 (2 x OCHMe$_2$), 66.0 (7-, 8-C), 32.8 (4-, 11-CH$_2$), 22.0 (2 x CHMe$_2$) and 16.1 (5-, 10-CH$_2$) [HRMS (ES): calcd. for $C_{20}H_{30}O_8K$ (M + K)$^+$ 437.1578, found: 437.1559].

Upon standing in air the surface of the solid developed a red colour indicating polymerisation of the material. This could not be prevented, even by keeping the material under nitrogen in the dark. Prior to any reaction of the material, the surface polymer was removed by filtration through a plug of silica using ethyl acetate as the elutent.

Gas Chromatography Conditions:

The enantiomeric excess of all epoxy alcohols and chiral secondary allylic alcohols was determined using a Hewlett Packard 5890 Series II Gas Chromatograph (flame ionisation detector, FID) and equipped with a 6890 series integrator. All samples were subjected to split injection under a column head pressure of 50kPa (helium) with a helium flow rate through the column of 1 ml/minute.

Epoxy-cinnamyl alcohol **58**: Ee was determined on a Suppelco α-DEX 120 column[73] [non-bonded; 20% permethylated α-cyclodextrin in SPB-35 poly (35% diphenyl / 65% dimethylsiloxane)] with the oven temperature at 150°C, injection port at 250°C and detector at 250°C.

The aliphatic epoxy-alcohols **81, 82a, 83a**[115] and **86**: Ees were determined using the Astec[73] Chiraldex GTA column (bonded; 2,6-di-*O*-pentyl-3-trifluoroacetyl-γ-cyclodextrin, 30m, 0.25mm internal diameter) with the injection port at 200°C and the detector at 250°C. The oven temperatures are shown below (Table 5.1). In order to achieve the high selectivity (lower oven temperature) the samples were derivatised to the trifluoroacetyl esters by the following preparation:

To a 5 ml screw top vial (rubber septa) was added approximately one drop of the pure epoxy alcohol, anhydrous dichloromethane (2 ml) and TFAA (0.2 ml), then sealed and placed into an oil bath at 60°C for 25 minutes and upon cooling the excess TFAA and dichloromethane were removed under a stream of nitrogen. The residue can then be diluted with an anhydrous solvent of choice, typically dichloromethane, (*ca* 2 ml) and analysed, typical injection volumes in the range 0.1μL to 1.0μL. Exclusion of water is necessary to maintain the integrity of the trifluoroacetylated column intact, therefore the injection sample can be pre-treated with anhydrous sodium sulphate if there are any doubts in the anhydrous nature of the sample.

Table 5.1: Oven temperatures

Epoxy-alcohol	Oven temp/°C
81	75
82a	95
83a	75
86	65

The ee of the resolved secondary allylic alcohols were also determined on the Chiraldex GTA column, but the samples were injected underivatised and the following table shows the oven temperatures used (Table 5.2).

Table 5.2: Oven temperatures

Allylic alcohol	Oven temp/°C
89	110
91	30
93	70
94	60
95	35
96	45

The TFA derivatised ligand/gelator **56g** was prepared as above but during the sample(s) preparation the vials were heated at 100°C for 35 minutes to ensure complete trifluoroacetylisation. The GC oven parameters were: 100°C for 12 minutes, then heat at 15°C/min to reach a maximum temperature of 110°C and held at this temperature for 15 minutes and then finally allowed to cool down to 100°C.

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Appendix

Gelation of fluorinated liquids by non-fluorinated low-molecular-mass molecules†

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A family of tetrahydroxy diesters has been synthesised and observed to gel a range of fluorinated solvents and their mixtures; the phase behaviour and gel microstructure are reported for a homologous family of these diesters in blends of $1H,1H$-heptafluorobutanol (HFB) and $2H,3H$-perfluoropentane (HPFP).

Low-molecular-mass organogelators are small molecules that spontaneously self-assemble to create a three-dimensional network capable of entrapping the solvent and creating gels.[1-4] Such systems exhibit great potential for use in the fields of food science, cosmetics and drug delivery.[5-8] Our interest focuses on gels where the entangled phase is a fluorinated solvent. Such solvents are already used as replacement media for blood, liquid ventilation and as contrast agents for ultrasound imaging.[9] However, they need to be formulated with polymers and surfactants in order to introduce the necessary additional physical characteristics. Gelation of fluorinated media has already been reported,[10] using partially fluorinated n-alkanes as the gelling agents. The incompatibility of the fluorocarbon and hydrocarbon segments drives the aggregation of the molecules. However, in this communication we report what we believe to be the first ever gelation of fluorinated solvents by non-fluorinated molecules.

A family of tetrahydroxy diesters was observed to form gels in mixtures of $1H,1H$ heptafluorobutanol (HFB) and $2H,3H$-perfluoropentane (HPFP). Fig. 1 presents the structure of both the gelators and fluorinated solvents used in this work. These novel gelators are referred to as G_n, with $n = 3, 4, 5$ or 8 according to their backbone length.

The synthesis of the gelator involves first a cross metathesis with isopropyl acrylate and the corresponding bis-alkene, using Grubb's second generation catalyst.[12,13] Then, these bis-α,β-unsaturated esters undergo asymmetric dihydroxylation affording the tetra-hydroxy gelators in excellent yield and purity.[14] Enantiomeric purity (determined by gas chromatography on a Chiraldex GTA column) and yield obtained were respectively > 99% and > 90% (see ESI, Scheme 1† for details of the synthesis).

The tetrahydroxy diesters are soluble in HFB but not in HPFP. Gelation occurs either by first dissolving the gelator in HFB and subsequently adding HPFP, or by the addition of gelator directly
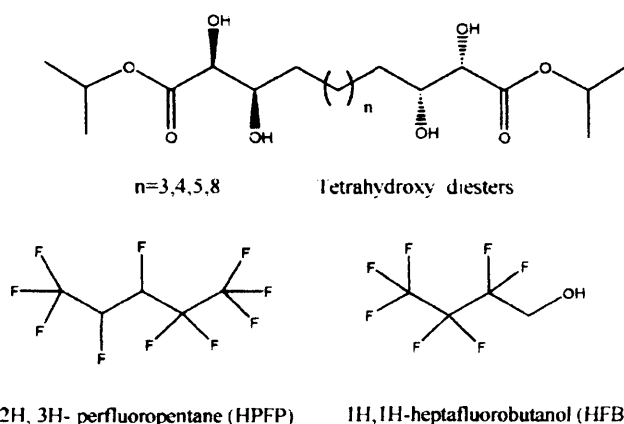
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† Electronic supplementary information (ESI) available: synthesis of the gelators. See http://dx.doi.org/10.1039/b505938k

Fig. 1 Structure of the tetrahydroxy diester gelators[11] and fluorinated solvents used in the gelling systems.

to the solvent blend, in a known and controlled solvents ratio. However, gels prepared by adding the gelator directly to the solvent blend were found to be less reproducible. In this work, all gels were obtained by first dissolving the gelator in HFB then subsequently adding HPFP. Provided there is a significantly high gelator concentration, gelation of pure HFB can also be achieved, while this is not the case for pure HPFP. Often gelation requires a heating-cooling cycle,[15] but these present fluorinated gels form spontaneously at room temperature.

A simple measure of gelation has been used to quantify their phase behaviour. The sample must be stable to tube inversion: a gel shows no flow. The macroscopic phase behaviour was found to depend greatly on the solvent ratio, temperature, gelator alkyl chain length (n) and gelator concentration. The phase behaviour of the gelators in two solvent mixtures is presented in Fig. 2. All compositions are expressed as wt%.

Four different macroscopic states are observed which are indicated as Φ_x, Φ_β, Φ_χ and Φ_δ in Figs. 2(a) and 2(b). At the lower concentration of gelator, a clear liquid is observed with a viscosity comparable to that of the pure solvents (Φ_α). With increasing gelator concentration, the sample becomes heterogeneous with aggregates of transparent gel forming within the fluorosolvent blend (Φ_β). At higher concentration of gelator, a transparent macroscopically homogeneous gel forms (Φ_χ). Increasing the gelator concentration further introduces a "haze" to the gel, forming fibrils that may be collected by removal of the solvent, or simply gelator precipitation (Φ_δ). The kinetics of gel formation also correlates with the appearance of the gels. For highly concentrated gelator systems, the gels form instantaneously. At lower concentrations, gel formation appears to pass through a

(a) 10:90 HFB:HPFP

Φα : liquid, 1 phase

Φβ : aggregates of clear gel in liquid, 2 phases

Φχ : clear gel, 1 phase

Φδ : heterogeneous gel or gelator precipitated, 2 phases

Gelator concentration (wt%)

(b) 20:80 HFB:HPFP

Φα : liquid, 1 phase

Φβ : aggregates of clear gel in liquid 2 phases

Φχ : clear gel, 1 phase

Φδ : heterogeneous gel or gelator precipitated 2 phases

Gelator G₃ precipitates from solution

Gelator concentration (wt%)

(a)

G3
G4
G5
G8

Gelator concentration (wt %)

(b)

20:80 HFB:HPFP
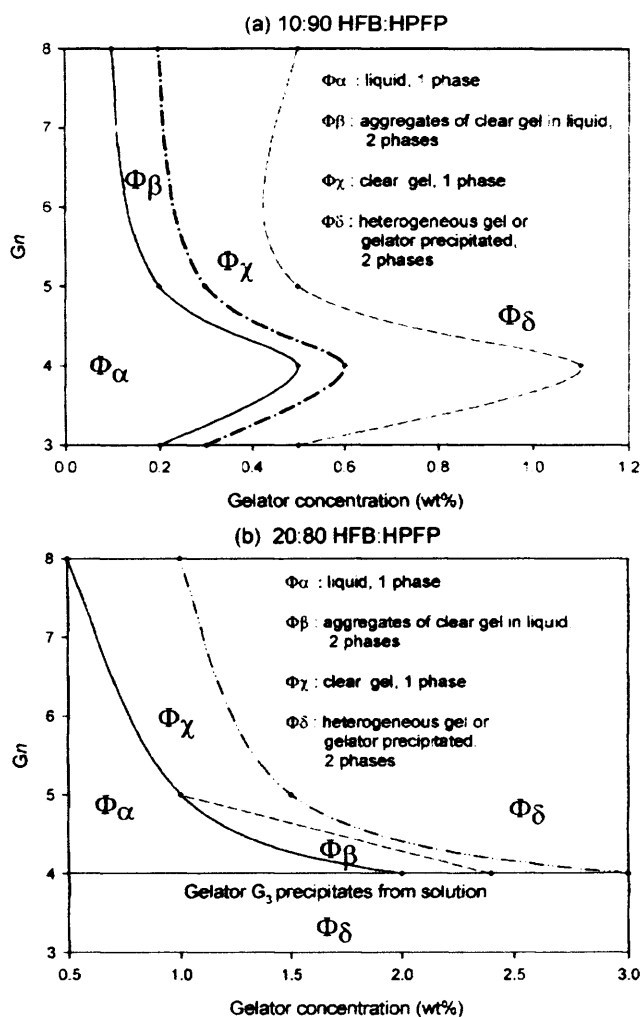10:90 HFB:HPFP

Gelator G8 concentration (wt%)

Fig. 2 Macroscopic phase behaviour of G_n for $n = 3, 4, 5, 8$ in (a) 10 : 90 HFB : HPFP and (b) 20 : 80 HFB : HPFP. All gels were made by first dissolving the gelator in HFB then subsequently adding HPFP.

Fig. 3 $T_{gel-sol}$ for (a) G_3, G_4, G_5, G_8 as a function of G_n concentration in 10 : 90 HFB : HPFP and for (b) G_8 in the two different solvents ratios 10 : 90 and 20 : 80 HFB : HPFP.

growth stage – clear aggregates of gel coexisting with the remaining solvent appear within a few hours, and these coalesce to form a gel throughout the entire sample over a period of days.

For the solvents ratio 10 : 90 HFB : HPFP, from $G_{n \geqslant 4}$, the concentration above which gelation occurs is a decreasing function of increasing n: less gelator is required to achieve gelation. For a 10 : 90 HFB : HPFP ratio, transparent fluorinated gels are obtained with the G_8 gelator at a concentration as low as 0.2 wt%, thus G_8 may be considered a supergelator.[16] A deviation is observed for G_3, which requires less gelator than G_4 to obtain an apparently identical gelling behaviour. However, samples made with G_3 were not stable over 3 weeks: the gelator slowly precipitates within the gel.

In the solvent blend 20 : 80 HFB : HPFP, the same general trend is observed, but in this case no gels were formed with gelator G_3. This shows that there is a delicate balance as far as the chain length (n) is concerned: decreasing n renders this family of gelators less susceptible to self-assembly. Moreover, in the 20 : 80 HFB : HPFP system, a higher concentration of gelator is required to achieve gelation (i.e. the phase behaviour is shifted to the right).
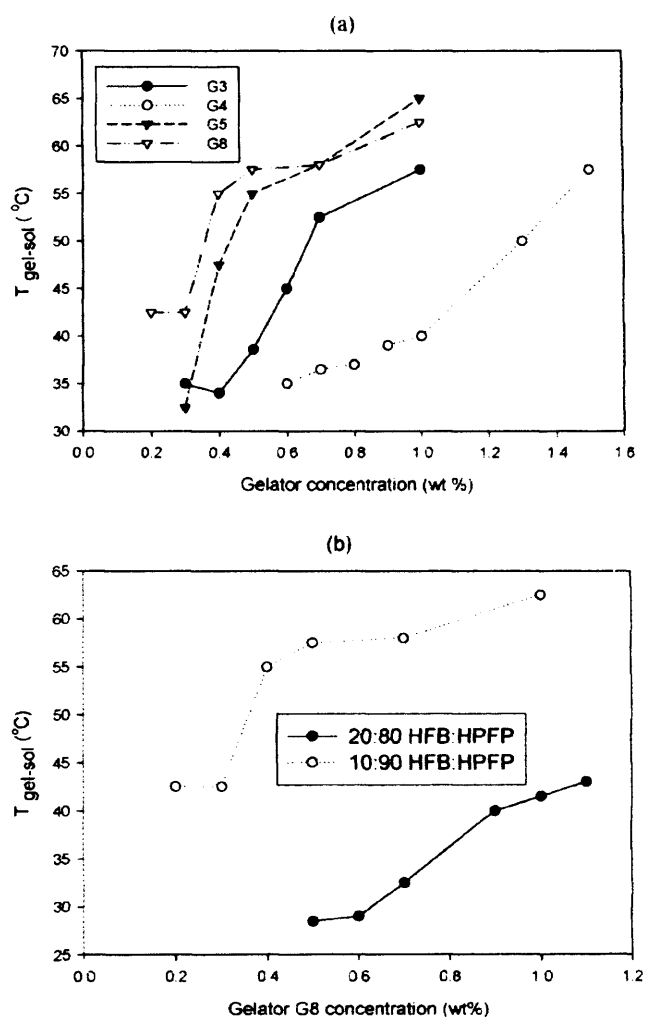
The same trend is observed for both 30 : 70 and 50 : 50 HFB : HPFP as well as pure HFB. Indeed, HFB acts as the solubilising medium, whereas HPFP, unable to dissolve the gelator, destabilises the initially stable sol.

The gel-to-sol transition temperature ($T_{gel-sol}$) of the fully gelled samples was measured by immersing the glass vials containing the samples in a temperature controlled waterbath. The temperature at which a sample undergoes a gel to liquid phase transition was noted. $T_{gel-sol}$ for gelled samples in 10 : 90 HFB : HPFP is presented in Fig. 3(a). A comparison of $T_{gel-sol}$ obtained for gelator G_8 in 10 : 90 HFB : HPFP and 20 : 80 HFB : HPFP is presented in Fig. 3(b).

It is immediately apparent that, for a given gelator, $T_{gel-sol}$ increases with increasing gelator concentration and that for samples with the same solvent composition, $T_{gel-sol}$ increases with the chain length n, with the exception of G_3. Then, the same trend is observed in the 20 : 80 HFB : HPFP solvents ratio environment. However, as seen in Fig. 3(b), the $T_{gel-sol}$ measured are lower than in the 10 : 90 HFB : HPFP ratio, the gelled network requires more gelator to be formed and less energy to be disrupted.
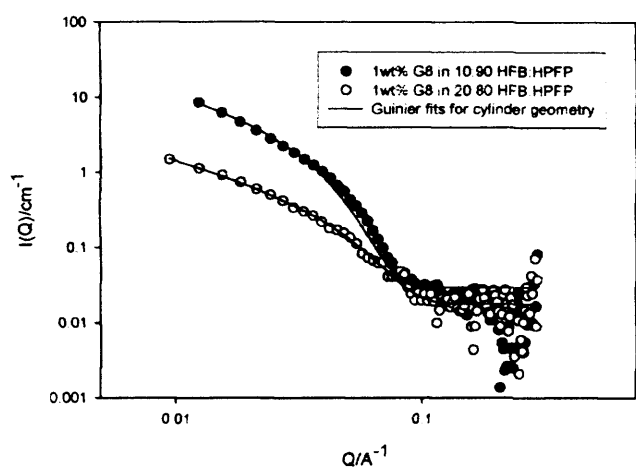
Fig. 4 SANS data obtained for a constant concentration of G_8 in two different HFB : HPFP ratios, along with the Guinier analysis over the low Q region for a cylinder geometry (data representative of all the gelled samples investigated with SANS).

To quantify the morphology of the aggregates formed, a preliminary small-angle neutron scattering (SANS) study has been carried out on the LOQ instrument at the ISIS facility, Rutherford Appleton Laboratories, Didcot, UK. Representative data are displayed in Fig. 4.

First, for a given solvent composition, the scattered intensity increases with concentration. For a fixed concentration of gelator, the solvent composition has a pronounced effect on the observed scattering, correlating well with the macroscopic phase behaviour observations. Stronger scattering is observed for gelator G_8 at 1 wt% in a 10 : 90 HFB : HPFP mix than in a 20 : 80 HFB : HPFP, indicating a different packing of the gelator. A Guinier analysis over the low Q region of the data – $I(Q)$ ~ $Q^{-1}\exp(-Q^2R^2/4)$ – clearly shows the characteristic signature of a cylinder geometry in the gelled samples, as presented in Fig. 4. The radius (R) of the cylinder extracted from the SANS analysis is found to vary both with gelator concentration and solvents ratio. First, for a given solvents ratio, the radius R increases with gelator concentration. Let us consider the 50 : 50 HFB : HPFP ratio with gelator G_8. For G_8 = 3.75 wt%, R = 25 ($\pm$1) Å, for G_8 = 5.0 wt%, R = 32 ($\pm$1) Å and for G_8 = 6.0 wt%, R = 42 ($\pm$1) Å. Then, R varies according to the solvents ratio. Increasing the proportions of HPFP in the solvents mix results in an increase of R. In 100 : 0 HFB : HPFP (i.e. pure HFB), R = 22 ($\pm$1) Å, in 50 : 50 HFB : HPFP R = 30 ($\pm$7) Å, in 20 : 80 HFB : HPFP R = 38 ($\pm$1) Å, and finally in 10 : 90 HFB : HPFP R = 60 ($\pm$1) Å, although this behaviour is clearly modulated by the gelator concentration.

Thus the aggregated structures obtained in this gelling process appear to be entangled rod-like fibers that are built up through non-covalent interactions such as weak van der Waals attractions and strong hydrogen-bonding. Freeze-drying one gelled sample clearly shows a swollen structure. The volume of the freeze-dried sample, then constituted only by the entangled fibers of gelators arranged as they were in the original gelled system, is significantly larger than the volume obtained when the gel is left to dry in ambient air. In this last case, as the solvents evaporate, the gelator network collapses. It is not yet absolutely established what forces drive the gelation. These are however likely to be associated with hydrogen bonding in origin since (i) addition of small amounts of water disrupts the gelation[17] and (ii) there is a clear signature in the IR spectra for the presence of hydrogen bonding. This IR signal correlates well with the onset of gelation but not with the sol–gel transition. The band appears when sufficient gelator is present to achieve gelation but does not disappear as a heated gel passes through the gel to sol phase transition. Further work is concentrating on this issue.

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