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Dispiroketals in Synthesis (Part 19)[1]: Dispiroketals as Enantioselective and Regioselective Protective Agents for Symmetric Cyclic and Acyclic Polyols.

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Abstract: The enantioselective preparation of both enantiomers of a C_2-symmetric diphenyl-bi-dihydropyran **3** and **4** is described. The application of enantiopure bi-dihydropyrans **1** - **4** towards the simultaneous enantioselective differentiation and regioselective protection of a range of cyclic and acyclic symmetrical polyols (**23**, **37**, **43**, **45**, **54**, **61** and **66**) is investigated. Several deprotections utilising trifluoroacetic acid (TFA) and a transketalisation with acidic glycerol are presented.

INTRODUCTION

Acyclic polyols constitute a frequently encountered structural motif within many natural products, forming part of their skeletal framework.[2] The preparation of these units therefore forms an important element in the strategy towards the synthesis of natural products. Cyclic polyols are also found widely in nature and one of the most important examples is *myo*-inositol, which is an important intermediate in the preparation of phosphoinositides and inositol phosphates.[3] The latter are implicated as secondary messengers in intracellular signalling and as membrane protein anchors.[3c,4] As a consequence there is a need for enantiomerically pure inositol derivatives. The preparation of enantiomerically pure materials usually involves optical resolution *via* diastereoisomeric *myo*-inositol derivatives which requires tedious chromatographic separation or recrystallisation procedures, for example *via* camphanic esters,[5] generally with rather low overall efficiency. One approach to the synthesis of enantiopure polyol units, both cyclic and acyclic, is from the desymmetrisation of symmetrical polyols, for which there have been relatively few reports to date.[6] We have reported previously on the desymmetrisation of glycerol using an enantiopure dimethyl-bi-dihydropyran **1**,[7] on the protection of symmetrical 2,5-dibenzoyl-*myo*-inositol,[8] using the enantiopure dienes **1**, **2** and **4**, and on the desymmetrisation of several acyclic *meso*-polyols using the enantiopure diene **1**.[1] Here we wish to present our findings on the extension of this methodology to other symmetrical polyols, both cyclic and acyclic.

RESULTS AND DISCUSSION

The reaction of enantiopure dienes **1**-**4** (Figure 1) with a range of symmetrical cyclic and acyclic polyols under standard spiroketalisation conditions (catalytic camphorsulfonic acid (CSA) in boiling chloroform) affords a number of enantio- and regioselectively differentiated dispoke[7] adducts as single diastereoisomers and this work is detailed below.

Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

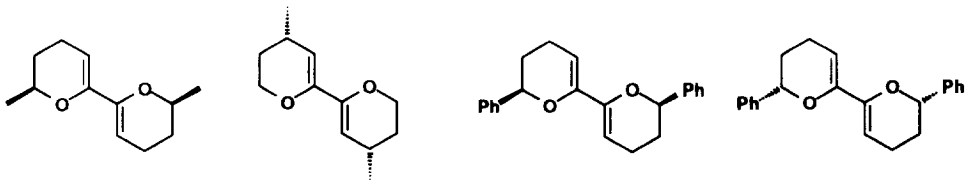
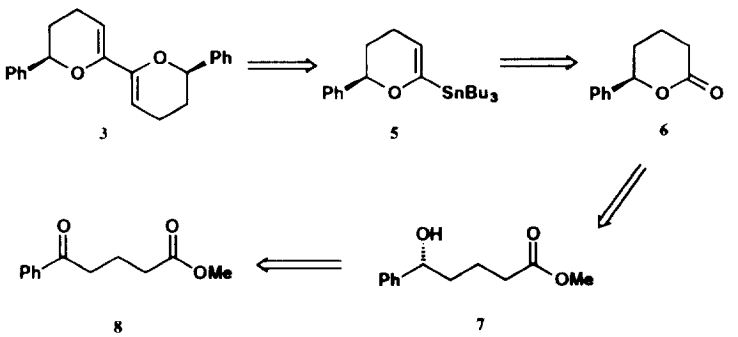


Figure 1

Preparation of (2*R*,2'*R*) and (2*S*,2'*S*)-2,2'-diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran ((2*R*,2'*R*) PDHP 3 and (2*S*,2'*S*) PDHP 4).

The preparation of dienes **3** and **4** in enantiopure form offered an interesting opportunity for *chiral recognition* processes in the coupling of a specific enantiomer of the diene with a particularly configured diol, giving rise to a "matched" dispiroketal adduct with full anomeric stabilisation and all substituents equatorial on both pyran and dioxane rings. The oppositely configured diol would be "mismatched" as it would require either loss of anomeric effects or axially disposed substituents in the dispiroketal so formed. A further reason for the production of substituted dienes was the increased range of milder deprotection conditions which could be envisaged with the appropriate substitution. With these tenets in mind we decided to synthesise both (2*R*,2'*R*) and (2*S*,2'*S*) 2,2'-diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran ((2*R*,2'*R*) PDHP **3** and (2*S*,2'*S*) PDHP **4** respectively).

The phenyl substituent was chosen for its reasonably large steric bulk, its ease of incorporation and for the fact that the diphenyldispiroketals derived form dienes **3** and **4**, having benzylic carbon-oxygen bonds, might be labile towards hydrogenolysis, therefore providing an extremely mild dispoke removal protocol. A retrosynthetic analysis for the formation of diene **3** is given in Scheme 1. This strategy involved the homocoupling of vinylstannane **5** which was disconnected to the key lactone **6**. This lactone, *via* its open chain hydroxyester **7**, can be further disconnected to the corresponding ketoester **8**.

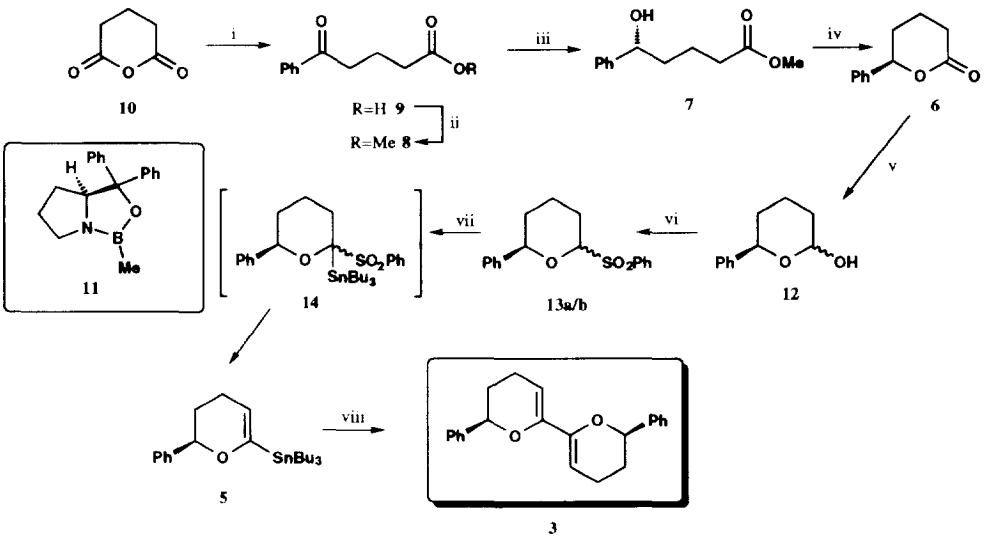


Scheme 1

Synthesis of (2*R*,2'*R*) PDHP 3.

The ketoester **8** was prepared in 97% yield from the known acid **9**[9] (Scheme 2) which was initally prepared by the addition of phenylmagnesium bromide to glutaric anhydride **10** in 66% yield. On a large scale

however, a Friedel-Crafts acylation of benzene with glutaric anhydride **10** and aluminium chloride was found to be superior, giving the acid **9** in 83% yield (Scheme 2).[10]

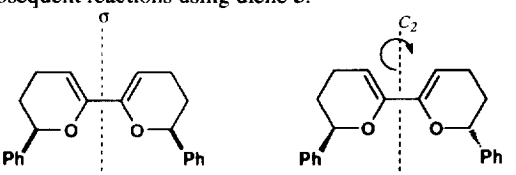


i) $AlCl_3$, benzene, 83%; ii) H_2SO_4, MeOH, 97%; iii) 10 mol% **11**, 0.7eq. BH_3.DMS, THF, -15 °C, iv)10 mol% CSA, DCM, 90% over 2 steps; v) DIBAL-H, PhMe, vi) $PhSO_2H$, $CaCl_2$, DCM, 75-88% over 2 steps; vii) n-BuLi, THF, -78 ° C, Bu_3SnCl, then DIPEA, $CHCl_3$, reflux, 72%; viii) n-BuLi, THF, -78 °C, then $CuCl_2$, $PdCl_2(MeCN)_2$, NH_3/NH_4Cl, 60%

Scheme 2

There are several excellent methods for the asymmetric reduction of prochiral ketones.[11] Initial attempts were made to reduce **8** using BINAL-H,[12] and *via* an enzymatic resolution using porcine pancreatic lipase,[13] however both methods proved unsatisfactory in our case. Attention then turned to the use of the Corey CBS catalyst **11**[14] for the reduction of **8** (Scheme 2). Reduction of **8** using this catalytic system to the hydroxyester **7** was then achieved in 83% e.e. (by analysis of the proton nmr on the derived Mosher ester) on a multigram scale (Scheme 2). Cyclisation to lactone **6** was then accomplished by taking the crude hydroxyester **7** in DCM with catalytic CSA in the presence of 4Å molecular sieves. This gave lactone **6**, which was isolated by crystallisation from ether/petrol, together with unreacted hydroxyester **7**. This could be converted to lactone **6** by taking the now re-enriched hydroxyester and reacidifying. Further lactone was isolated as described and the unreacted hydroxyester reacidified. This process could be repeated four times in total to give the lactone **6** in 90% yield from **8** together with 3% unreacted ketoester and 4% crude hydroxyester. The oxazaborolidine precursor, α,α-diphenylpyrrolidinemethanol, was also recovered from the acidified aqueous phase in 63% yield. The lactone **6** was then reduced to lactol **12** with DIBAL-H and the crude lactol was treated with freshly prepared phenylsulfinic acid in the presence of calcium chloride to give a separable mixture of anomeric sulfone diastereoisomers **13a** and **13b** in 75-88% overall yield from the lactone. Although the sulfones were separable, they could alternatively be used as a mixture of diastereoisomers in the formation of the vinyl stannane **5** by treatment with n-BuLi at -78 °C and quenching of the resultant anion with tributylstannyl chloride, to give the

stannylated sulfone **14** which was not isolated. The sulfone moiety could be eliminated from this compound, *in situ*, by heating it crude in chloroform, under reflux, in the presence of diisopropylethylamine (DIPEA). After work up, the vinyl stannane **5** was obtained in 72% yield. The stannane could then be homocoupled by transmetallation with n-BuLi at -78 °C and adding in one portion a mixture of copper (II) chloride and palladium dichloride (bis-acetonitrile) complex, to give (2*R*,2'*R*) PDHP **3** in 60% yield. The homocoupling enhances the e.e. of the C_2 symmetric PDHP **3** with respect to starting stannane. Statistically, the *R* configured stannane **5** of 83% e.e. should give, assuming equal rates of coupling of *R* to *R*, *S* to *S* and *R* to *S*, the diene **3** in 98% e.e. This optical enhancement has the *quid pro quo* of producing *meso* PDHP **3a** (Figure 2), formed by the coupling of the major *R* configured stannane with the minor enantiomeric *S* configured stannane. Theoretically an 85:15 ratio of C_2 symmetric:*meso* dienes should form during the homocoupling reaction, corresponding to a 70% d.e. On examination of the proton nmr of this diene **3** it could be seen that some *meso* diene **3a** (11%) had indeed been formed during the homocoupling. It did not prove possible to separate this from the major PDHP **3** and so this mixture was used in all subsequent reactions using diene **3**.



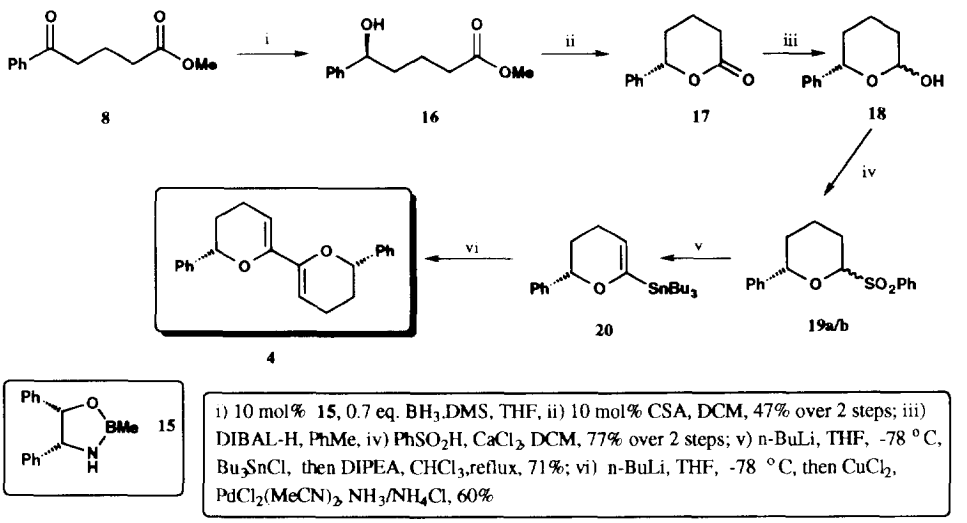
Meso-PDHP **3a** *R,R*-PDHP **3**

Figure 2

Synthesis of (2*S*,2'*S*) PDHP 4.

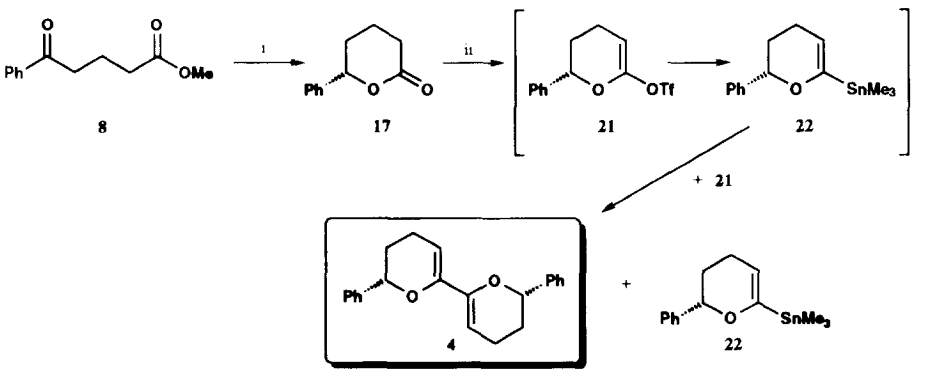
The Corey CBS catalyst offers an efficient system for the introduction of asymmetric centres in prochiral substrates. However, for the synthesis of (2*S*,2'*S*) PDHP **4** we would have required unnatural *R*-proline, the cost of which is prohibitive for a large scale synthesis of the diene **4**. The *B*-methyl diphenyloxazaborolidine[15] **15** offered an interesting cost effective alternative for the synthesis of enantiopure **4** (Scheme 3). Enantioselective reduction of keto-ester **8** using the catalyst **15** afforded the hydroxyester **16** with an enantiomeric excess of greater than 90%, as judged by chiral phase g.c. analysis on the crude material (Scheme 3). Lactonisation using catalytic CSA as described above furnished lactone **17** in 47% yield over the two steps. A result not noted with the *R* configured lactone **6** was that a single crystallisation from ether/petrol afforded the lactone **17** with an e.e. of greater than 99%, as shown by chiral phase g.c. analysis. The enantiopure lactone was then elaborated to the mixture of anomeric sulfones **19a** and **19b**, *via* the lactol **18**, in 77% over the two steps. Preparation of the diene **4**, *via* the stannane **20**, was accomplished as shown in Scheme 3. The proton nmr spectrum of diene **4** showed no trace of *meso* PDHP as observed with the enantiomeric **3**, a reflection of the optical purity of lactone **17** used in its synthesis.

The synthesis of enantiopure diphenyl dienes **3** and **4**, although successful, was lengthy. An improved synthesis was devised in order to make these dienes more synthetically accessible. The use of Brown's chlorodiisopinocamphenylborane (DIP chloride)[16] proved successful for the enantioselective reduction of the ketoester **8** (Scheme 4). This was lactonised, *in situ*, to give the enantio-enriched lactone **17** in 88% yield, with an e.e. of greater than 90%, as determined by optical rotation comparison with an enantiopure sample of lactone **17**. The enantiomeric excess could be improved by a single crystallisation as described above. A second one pot coupling then provided diene **4** in 58% yield, as described below. The lactone **17**



Scheme 3

could be converted to the bi-dihydropyran using an adaptation of the procedure of Kocienski[17] for the preparation of vinyl stannanes. Preparation of the enol triflate (LHMDS; $PhN(OTf_2)$) followed by the addition of lithium chloride, hexamethylditin and palladium tetrakis(triphenylphosphine), is expected to produce vinyl stannane **22**. However, by employing only 0.5 equivalents of hexamethylditin, in principle half of the triflate remains unreacted, which undergoes a Stille coupling[18] with the stannane **22** to give the bi-dihydropyran **4** directly. In practice however, formation of the triflate is not quantitative and so 19% of unconsumed vinyl stannane **22** is also isolated.

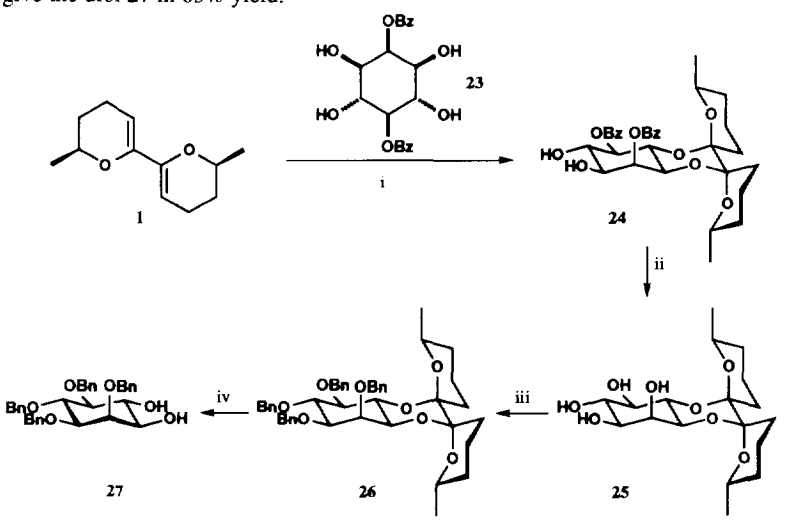


Scheme 4

With gram quantities of enantiopure dienes **1**-**4** in hand, we next turned our attention to the desymmetrisation of symmetrical polyol substrates.

Desymmetrisation of Symmetrical Cyclic Polyols.

The symmetric 2,5-dibenzoyl-*myo*-inositol **23**, prepared according to known procedures,[19] offered us an appropriate substrate with which to test the chiral recognition properties of enantiopure dienes **1-4**. Reaction of (2*S*,2'*S*) MDHP **1** under standard spiroketalisation conditions with symmetrical *myo*-inositol derivative **23** gave the 1,6-protected dispoke adduct **24** in 70% yield (Scheme 5). This dispoke adduct is fully anomerically stabilised due to the oxygen substituents at the spiro centres adopting axial orientations. Regioselectivity is achieved *via* the use of enantiomerically pure diene **1** which has the ability to selectively protect one pair of enantiomeric vicinal diols in the substrate **23**, to give a "matched" dispoke adduct, with the side chain methyl substituents equatorial. Protection of the enantiotopic vicinal diol pair would lead to a "mismatched" dispoke adduct with axial side chain substituents, and therefore is disfavoured. It is important to note that the dibenzoyl inositol derivative **23** is a *meso* compound and therefore all the starting material is utilised in the step leading to the dissymmetric dispoke adduct **24**. Debenzoylation was achieved using 1% sodium hydroxide in methanol/diethyl ether to give the tetrol **25** in 96% yield. This compound was then benzylated using sodium hydride/benzyl bromide in DMF with catalytic tetra-*n*-butylammonium iodide to give the fully protected dispoke adduct **26** in 74% yield. The diol was subsequently unmasked by treatment of **26** with 95% trifluoroacetic acid (TFA)/water to give the diol **27** in 63% yield.

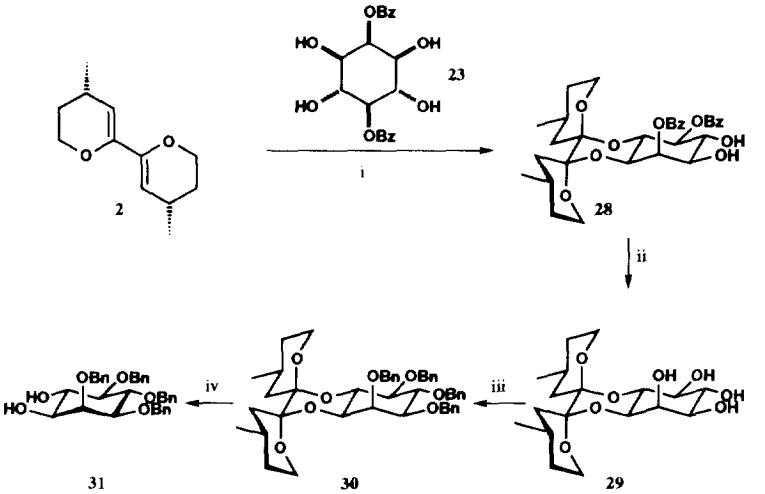


i) $CHCl_3$, CSA, reflux 70%; ii) 1% NaOH, MeOH/Et_2O (9:1) 96%; iii) NaH, BnBr, n-Bu_4NI, DMF 74%; iv) 95% TFA 63%.

Scheme 5

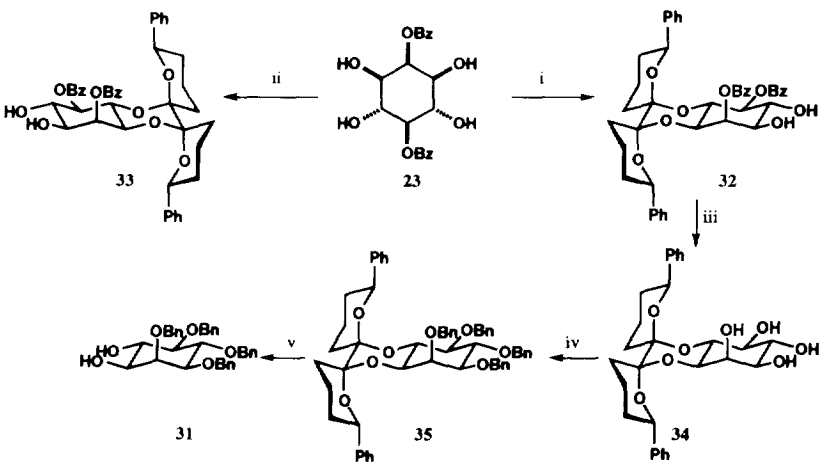
The enantiomer of diol **27**, namely **31**, can been prepared from both ((4*S*,4'*S*) MDHP) **2**, (Scheme 6) and ((2*S*,2'*S*) PDHP) **4** (Scheme 7). Enantioselective reaction of symmetrical 2,5-dibenzoyl-*myo*-inositol **23** using ((4*S*,4'*S*) MDHP) **2**, under standard conditions, gave the dispoke adduct **28** in 63% yield where the 3,4 vicinal diol moiety has been regioselectively protected. Dispoke adduct **28** was isolated as a single isomer, with the two methyl side chain substituents in the stable equatorial positions. The stereochemical outcome can be rationalised again in terms of a "matched"/"mismatched" chiral recognition process occuring during spiroketalisation. The dispoke adduct **28** was then subjected to debenzoylation conditions to give the tetrol **29**

in 91% yield, with the tetrabenzyl derivative **30** being produced in 87% yield from the tetrol **29** using sodium hydride/benzyl bromide and catalytic tetra-*n*-butylammonium iodide. The diol **31** was deprotected using 95% TFA/water in an unoptimised 18% yield. Diol **31** is a suitable intermediate in the synthesis of the glycosylphosphatidylinositol anchor of *Trypanosoma brucei* Varient Surface Glycoprotein.[20]



i) $CHCl_3$, CSA, reflux, 63%; ii) 1% NaOH, MeOH/Et_2O (9:1), 91%; iii) NaH, BnBr, n-Bu_4NI, DMF, 87%; iv) 95% TFA, 18%.

Scheme 6



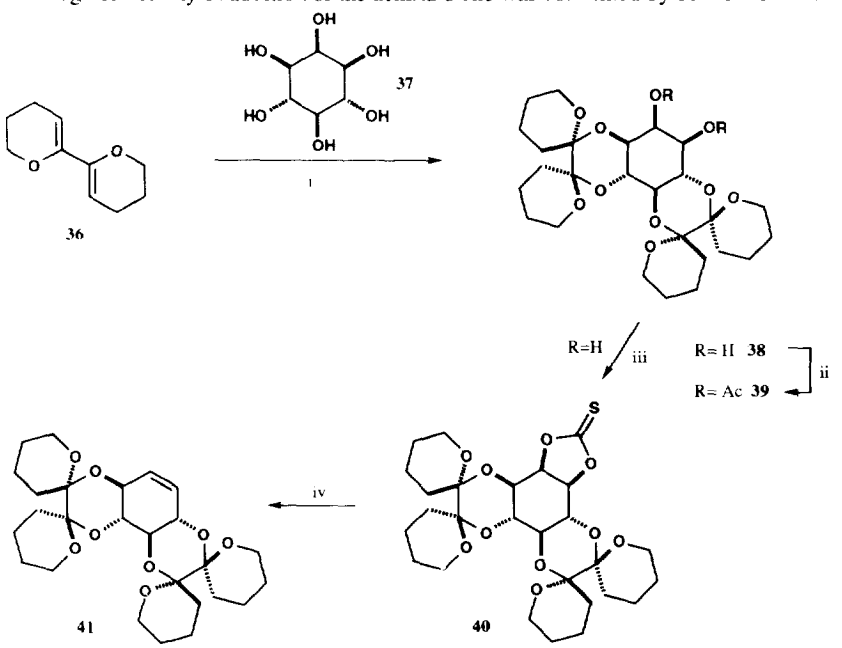
i) **4**, $CHCl_3$, CSA, reflux, 52%; (ii) **3**, $CHCl_3$, CSA, reflux, 33%; iii) 1% NaOH, MeOH/Et_2O (9:1), 98%; iv) NaH, BnBr, n-Bu_4NI, DMF, 99%; v) 95% TFA, 33%.

Scheme 7

The same diol **31** can also be formed from enantioselective reaction of the *myo*-inositol derivative **23** with ((2*S*,2'*S*) PDHP) **4**. Reaction of diene **4** under standard conditions gave the dispoke adduct **32** in 52% yield, isolated as a single isomer (Scheme 7). Here, regioselective 3,4-diol protection has been achieved with the optically pure diene **4**. The enantiocomplementary protection of symmetric tetrol **23** can be achieved using diene **3** which gives exclusive 1,6-protection to give adduct **33** in 33% yield. Dispoke adduct **32** was converted into the tetrabenzyl intermediate **35**, *via* tetrol **34**, under similar conditions to those employed above. Deprotection of the dispiroketal moiety was achieved using 95% TFA/water to give the enantiopure diol **31** in an unoptimised yield of 33%, which was identical to that obtained previously from **2**.

Desymmetrisation of Free *myo*-Inositol: An Approach to Conduritol-B.

Free *myo*-inositol represents another candidate for desymmetrisation using C_2 symmetric dienes. However, in this case the insolubility of *myo*-inositol in the preferred solvents for spiroketalisation, chloroform and toluene, necessitates the use of hot (100 °C) DMF as solvent. Thus reaction of the achiral *bis*-dihydropyran **36** with free *myo*-inositol **37** in hot DMF containing catalytic CSA gave the *bis*-dispoke adduct **38** in 40% yield (Scheme 8). The regioselectivity of addition of the achiral diene was confirmed by conversion of **38** to its



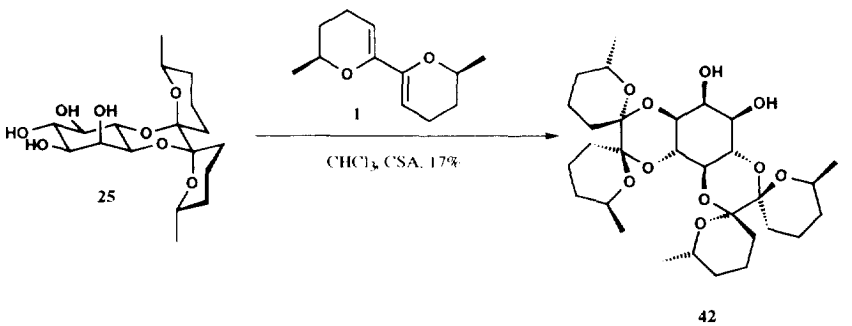
i) DMF, CSA, 100 °C, 40%; ii) Ac_2O, Et_3N, DMAP (Cat.), 95%; iii) Thiocarbonyldiimidazole, DCM, 86%; iv) $P(OMe)_3$, reflux, 61%.

Scheme 8

diacetate **39**. Examination of the proton nmr spectrum of this compound indicated the protection pattern shown. This presented us with the opportunity of forming racemic Conduritol-B, which is a potential glycosidase inhibitor.[21] Thus *bis*-adduct **38** was subjected to the Corey-Winter[22] protocol to install the double bond.

Reaction of adduct **38** with thiocarbonyldiimidazole gave the thionocarbonate **40** in 86% yield. De-oxygenation was accomplished by refluxing in trimethylphosphite to give alkene **41** in 61% yield. Deprotection to racemic Conduritol-B was not attempted as it subsequentially proved impossible to spiroketalise free *myo*-inositol with enantiopure diene **4**. This reaction using enantiopure diene **4** was repeated using differing catalysts, such as triphenylphosphonium hydrobromide,[23] and more polar solvents, DMF and DMSO, but in all cases only decomposition of the diene was observed. Thus, due to the lack of reactivity of enantiopure diene **4** and free *myo*-inositol, this approach to the formation of Conduritol-B was abandoned.

Another approach to the formation of enantiopure Conduritol-B was from the reaction of tetrol **25**, formed from an enantioselective reaction of 2,5-dibenzoyl-*myo*-inositol **23** with diene **1**, *vide supra*, with a further equivalent of diene **1**. Tetrol **25** possesses two *trans* vicinal diol pairs capable of reacting with diene **1**. However, by using the required "matched" diene **1**, reaction of tetrol **23** in boiling chloroform gave the required regioselectively protected *bis*-adduct **42** in 17% yield (Equation 1). However as the yield of adduct was low, presumably due to the poor solubility of tetrol **25** in chloroform, this approach to Conduritol-B was also not explored further.

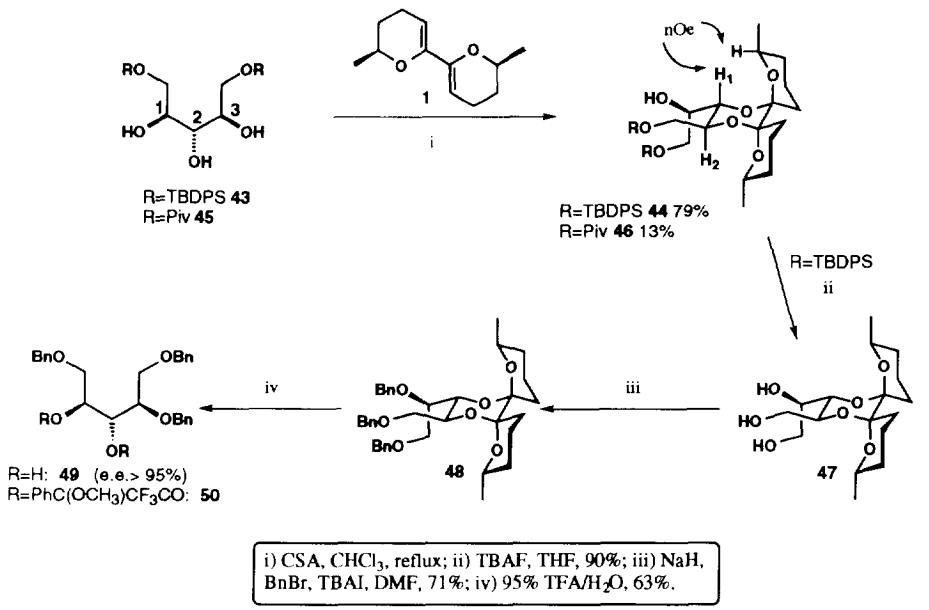


Equation 1

Desymmetrisation of Acyclic Symmetrical Polyols.

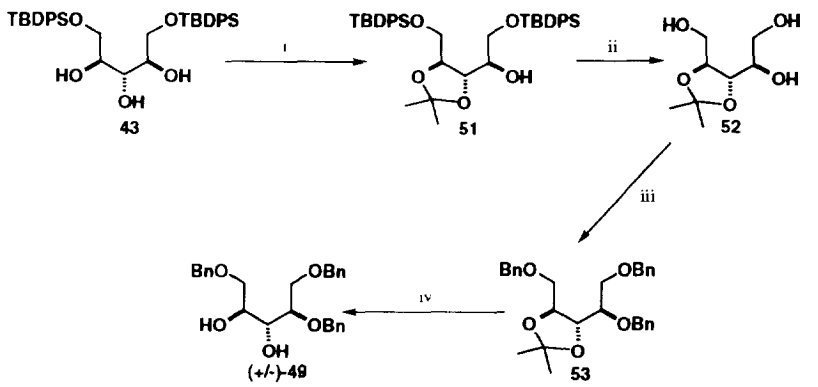
The use of enantiopure dienes to regio- and enantioselectively differentiate symmetrical polyols has also been successfully applied to the desymmetrisation of a number of acyclic, symmetrical polyols. Reaction of enantiopure diene **1** with the symmetrical 1,5-disilylated-xylitol derivative **43** in boiling chloroform containing catalytic CSA gave the enantioselectively protected poylol **44** as the only isolated product in 79% yield (Scheme 9). The dispiroketal is formed from reaction of the enantiopure diene with only one of the enantiotopic diol pairs in the substrate polyol (C_1OH-C_2OH). The reaction is completely diastereoselective arising from a chirality "matched" situation. That is, the product formed is the most thermodynamically stable in which the two side chain methyl groups and the two hydroxylated side chains on the dioxane ring are equatorially orientated, with the spirocentres fully anomerically stabilised. The "mismatched" adduct would result from the side chain substituents on the dioxane ring adopting axial configurations which, due to severe 1,3-diaxial interactions, disfavoures the formation of this isomer. The stereostructure of adduct **44** was proven by a combination of 2D NMR experiments (COSY, NOESY and HMQC) which showed both dioxane substituents to be equatorially disposed, (J (H_1-H_2)= 9.8 Hz).

In a similar fashion, reaction of the *meso*-1,5-dipivaloyl-xylitol derivative **45** with the enantiopure diene **1** gave the dispoke derivative **46** isolated in only 13% yield (Scheme 9). Again reaction of the enantiopure diene **1** with diol pair (C_1OH-C_2OH) had occurred. This low reaction yield may be attributed to the removal/migration of the pivaloyl group under the acidic reaction conditions either from the starting polyol **45**, or from the adduct **46**. Other, inseparable, isomers were isolated, in low yield, from this reaction, but their structure remains undetermined. The stereostructure of adduct **46** was derived again from 2D NMR experiments (COSY, NOESY and HMQC), which showed the di-equatorial substitution pattern on the dioxane ring, (J (H_1-H_2) = 9.0 Hz) and from the observation of a cross peak in the NOESY spectrum between a spiroketal ($CH(CH_3)$) and ($CHCH_2OSi$).



Scheme 9

The dispiroketal **44** was elaborated as follows (see Scheme 9). Removal of the silicon protecting groups with tetra-n-butylammonium fluoride (TBAF) gave the triol **47** in 90% isolated yield. This material was then fully benzylated using sodium hydride, benzyl bromide and catalytic tetra-n-butylammonium iodide (TBAI) to give the dissymmetric dispiroketal **48** in 71% yield. Removal of the dispiroketal moiety was then achieved using 95% TFA/water to give the polyol derivative **49** in 63% isolated yield. A racemic sample of this diol was prepared by reaction of symmetrical disilylated triol **43** with acetone containing catalytic PPTS and anhydrous copper sulfate, giving the acetonide **51** in 90% yield (Sceme 10). Removal of the silicon protecting groups was then achieved in 79% yield using TBAF to give the triol **52**. This material was benzylated using sodium hydride and benzyl bromide in DMF to give the fully protected derivative **53** in 89% yield. Removal of the acetonide was subsequently achieved in 70% yield (based on recovered starting material **53**) using CSA in methanol at 40 °C to afford the racemic diol. Comparison of the bis-Moshers ester of enantioenriched and racemic **49** gave an enantiomeric excess of at least 95%[24] as determined by 500MHz proton and 235 MHz fluorine nmr spectroscopy.

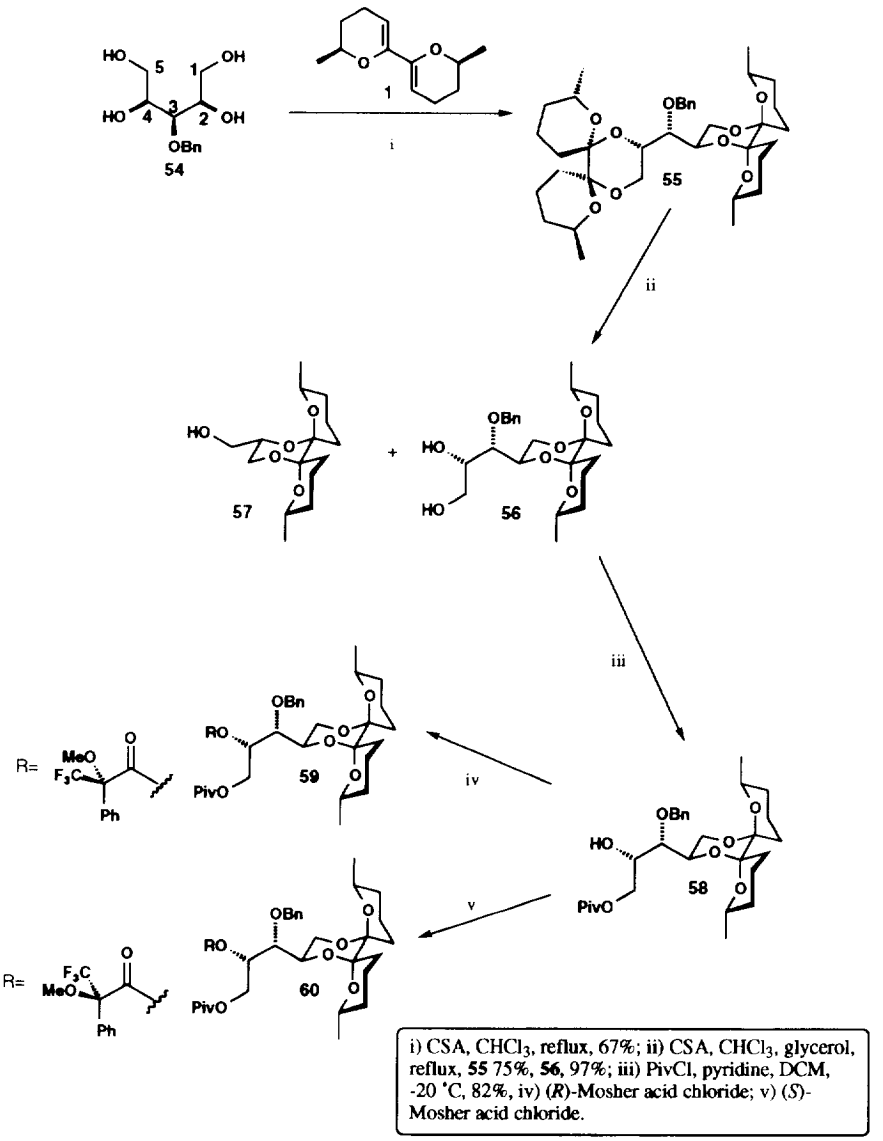


i) $CuSO_4$, PPTS, Acetone, 90%; ii) TBAF, THF, 79%; iii) NaH, BnBr, DMF, 89%; iv) CSA, MeOH, 40 °C, 70%

Scheme 10

Further, the symmetrical mono-protected 3-*O*-benzyl-adonitol derivative **54** reacts with two equivalents of diene **1** to give the bis-dispiroketal **55**, isolated in 67% yield, as shown in Scheme 11. In this reaction, therefore, there has been a good chirality match with one diol pair (corresponding to the (C_1OH-C_2OH) diol pair) and diene **1**, but the other diol pair, which is relatively unhindered, also reacts with diene **1**. In this compound the matched portion has the two methyl groups on the spiroketal equatorially orientated as well as the side chain containing the benzyl group. However, in order to accommodate "mismatched" chirality, one of the tetrahydropyran rings in the second spiroketal adopts a boat conformation to give an equatorial dioxane substituent. This reduces steric interactions, and overrides anomeric stabilisation, which would be present in greater amounts if all three rings were fully anomerically stabilised and the benzyl containing substituent was axially disposed. This is manifest in the carbon NMR spectrum of compound **55**, with different resonances for the two boat acetal signals seen. The least thermodynamically stable spiroketal unit containing the boat conformation can be selectively deprotected by adding glycerol and catalytic CSA in boiling chloroform. This removes the spiroketal unit to give the unsymmetrical diol **56**, isolated in 75% yield, together with the glycerol trapped spiroketal **57**, isolated in 97% yield. This adduct was isolated with the two methyl groups on the spiroketal and the hydroxymethylene in the stable equatorial orientation, thereby providing an extremely efficient re-cycling process since, during the deprotection step, the chiral protecting group is preserved. Furthermore, the cleaved spiroketal also protects, and desymmetrises, a further *meso*-polyol, glycerol.[7] Diol **56** then underwent a selective pivaloylation, at low temperature, to give exclusively the primary protected alcohol **58**, isolated in 82% yield. This therefore provides the required specifically decorated material with which to determine the absolute configuration of the secondary alcohol. This was necessary to determine which diol pair in the starting polyol **54** formed the "matched" dispiroketal, since deprotection of the "mismatched" dispiroketal freed this secondary alcohol. Subsequent formation of both (*R*)-**59** and (*S*)-**60** Mosher ester derivatives led to the assignment of (*S*)- stereochemistry at the alcohol position in compound **58**. This was based on chemical shift differences of neighbouring protons according to the method of Kakisawa *et al*[25] This stereochemistry was subsequently confirmed by an X-ray crystal structure determination of compound

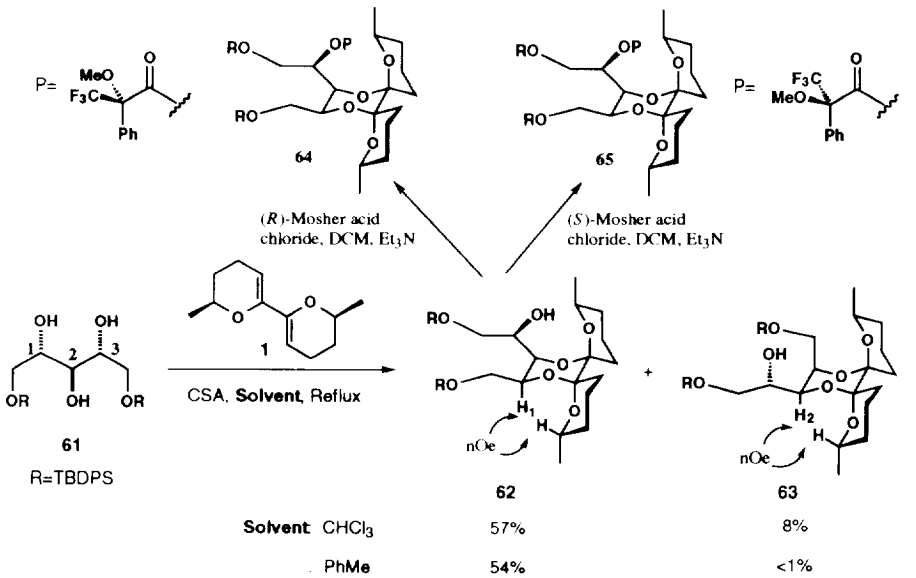
58 which showed that both pyran and dioxane rings were in a chair conformation and confirmed the configuration as shown.



Scheme 11

The symmetrical adonitol derivative **61** can similarly be reacted with diene **1** as shown in Scheme 12. When the reaction is performed in boiling chloroform an 8.2:1 ratio of dispiroketals **62**:**63** was formed in 57% and 8% yields respectively. In this reaction, desymmetrisation of polyol **61** to produce **62** is achieved with the methyl groups on the spiroketal and one of the appended side chains on the dioxane ring equatorially orientated, thus matching of diene **1** with the (C_1OH-C_2OH) diol pair has occurred. However, the remaining side chain containing the free hydroxyl group is axially disposed. Evidence for this structure comes from 2D NMR

experiments (COSY, NOESY and HMQC) and from the preparation of both *R*- and *S*-Mosher ester derivatives **64** and **65** respectively of compound **62**. For adduct **62** there was a cross peak in the NOESY spectrum between a spiroketal (C*H*(CH_3)) and H_1 and for adduct **63** a cross peak between a spiroketal (C*H*(CH_3)) and H_2. The Mosher's ester derivatives led to the (*R*)-stereochemical assignment at the secondary alcohol in **62**. This assignment was also supported by molecular modelling[26] which suggests this structure is the more thermodynamically stable, as compared to **63**, by approximately 10 kJ mol^{-1}. This gives a calculated ratio of approximately 10:1 for **62**:**63** as compared to the experimentally observed value of 8.2:1. The structures of both adducts **62** and **63** represent a compromise between an all chair conformation having an unfavourable 1,3 diaxial interaction between the substituent and a carbon-oxygen bond, and a structure possessing a twist boat conformation for the dioxane ring which relieves this steric interaction at the expense of eclipsing strain and reduced anomeric stabilisation. The minor diastereoisomer **63**, which has the hydroxy containing chain equatorial, is less thermodynamically stable for two reasons. Firstly, the close proximity of the *tert*-butyldimethylsilyloxymethylene group to the pyran ring causes severe steric strain. This is compared to the major isomer **62** where this substituent is now equatorial, and thus further away from the pyran ring. This substituent appears to be one controlling element for enantioselective reaction of diene **1** with polyol **61**.

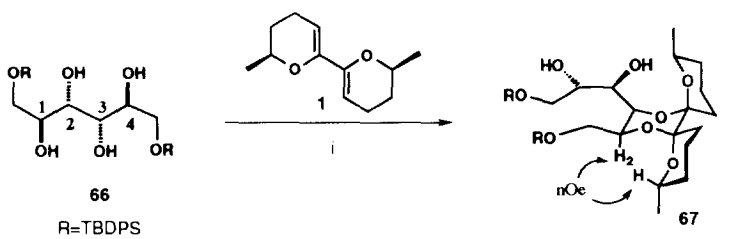


Scheme 12

Additionally, molecular modelling showed that in compound **62** the free hydroxyl group was approximately equidistant between one pyran and one dioxane ring oxygen, and within hydrogen bonding distance. This suggested that the hydrogen bonding interaction also contributes to the stability of this isomer compared to **63**, where no such stabilising hydrogen bonding interaction is present. Proton nmr spectra of the major isomer **62** revealed a significant solvent effect on the chemical shift of one spiroketal (C*H*(CH_3); δ= 3.78-3.75 ($CDCl_3$) compared to 3.98-3.91 (D_6-DMSO)), a corollary of the disruption in the hydrogen bonding network caused by the polar solvent. The formation of isomer **62** as the exclusive product of the reaction of polyol **61** with diene **1**, in toluene, compared to an 8.2:1 ratio of **62**:**63** in chloroform could be interpreted in terms of a slight

disruption of the hydrogen bonding network in the more polar solvent, chloroform, compared to toluene. The disruption of this stabilising influence makes **62** and **63** less different in energy, resulting in the production of a mixture of the two at equilibrium.

Lastly, we have examined the reaction of enantiopure diene **1** with the racemic C_2-symmetric dulcitol derivative **66** by reaction in boiling chloroform containing catalytic CSA. This gave the dissymmetric adduct **67** in 35% yield, as shown in Scheme 13. Again the stereochemistry (both pyran ring methyl groups and one dioxane substituents being equatorial, with the second dioxane substituent containing the free hydroxyls in the axial position), was deduced from 2D NMR experiments (COSY, NOESY and HMQC). A cross peak between a spiroketal ($CH(CH_3)$) and H_2 in the NOESY spectrum being observed showing the stereochemistry given. This "matched" adduct therefore arises from the reaction of the enantiopure diene **1** with the diol pair (C_1OH-C_2OH) in the dulcitol derivative **66**. A trace amount (<4%) of several other, inseparable, unassigned compounds were seen, which could be due to thermodynamically less stable isomers of **67**. Regio and enantioselectivity is achieved *via* a resolution procedure, only one enantiomer of the C_2-symmetric polyol **66** reacting with the enantiopure diene **1** to give the "matched" dispoke adduct **67**.



i) CSA, $CHCl_3$, reflux, 35%.

Scheme 13

SUMMARY AND CONCLUSIONS

In this paper we have demonstrated the formation of two enantiomerically pure dienes **3** and **4**. These dienes, and others (**1**-**2**), have been shown to regioselectively and enantioselectively differentiate a range of cyclic and acyclic symmetric polyols, **23**, **37**, **43**, **45**, **54**, **61** and **66**, to give "matched" dispoke derivatives. Reaction with polyol **54** gives a bis-dispiroketal **55** which undergoes a selective transketalisation to remove only one dispiroketal unit. In one case, **66** regio- and enantioselective desymmetrisation is achieved *via* a resolution procedure to give **67**. In several instances the dispoke adduct has been further manipulated and an enantiopure diol isolated upon treatment of the fully protected adduct with 95% TFA/H_2O. These reactions have amply demonstrated the potential that enantiopure dienes display for enantioselectively and regioselectively differentiating cyclic and acyclic symmetric polyols. This technology should provide opportunities for the preparation of enantiopure compounds from symmetrical polyol substrates, many of which are important intermediates in natural product synthesis.

EXPERIMENTAL SECTION

Proton and carbon NMR spectra were recorded on Bruker AC200, AC250, WM250, AC400 and DRX500 machines. Chemical shifts are quoted in ppm relative to residual protic solvent ($CHCl_3$, δ_H=7.26) or deuteriochloroform ($CDCl_3$, t, δ_C=77.0). Coupling constants are measured in Hertz. ^{13}C NMR assignments were confirmed by DEPT or APT spectra. Infra-red spectra were recorded on a Perkin-Elmer 983G or 1620 FTIR machine, or on a Paragon 1000 FTIR machine. Mass spectra were recorded on VG-7070B, VG 12-253 or VG ZAB-E instruments at the Department of Chemistry, Imperial College, or at the University of Cambridge Chemistry Department using a Kratos MS890MS spectrometer, or by the SERC mass spectrometry service at Swansea. Microanalyses were performed by the University Chemistry Department microanalytical service, Cambridge. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured with an Optical Activity AA-1000 polarimeter. Flash column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh). Solvents and reagents were purified by standard procedures where necessary or used as purchased. Analytical thin layer chromatography was performed using precoated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised by uv light, or acidic ammonium molybdate.

5-Oxo-5-phenylpentanoic acid 9

Method 1. Grignard addition[9]

Phenylmagnesium bromide (1 M solution in ether; 307 mL, 307 mmol) was added dropwise to a stirred solution of glutaric anhydride **10** (70 g, 613 mmol) in THF (700 mL) at 0 °C under argon. The yellow solution was warmed to room temperature and stirred for a further 19 hours. The resultant creamy white emulsion was poured into NH_4Cl (sat. aq. 300 mL) and extracted with ether (3 x 300 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give an orange solid. The crude product was recrystallised from boiling ethyl acetate to furnish the ketoacid **9** (38.95 g, 202.6 mmol, 66%) as an off white solid; m.p. 127-129 °C (EtOAc) (lit.[9] 127 °C (H_2O)); δ_H (270 MHz, $CDCl_3$) 7.97 (2H, d, *J* 7.6, 2x *o*-Ar-*H*), 7.50 (3H, m, 2x *m*- and 1 x *p*-Ar-*H*), 3.09 (2H, t, *J* 7.1, 2x *H*-4), 2.51 (2H, t, *J* 7.1, 2x *H*-2), 2.10 (2H, m, 2x *H*-3); ν_{max} ($CHCl_3$)/cm^{-1} 3056, 2965, 1691, 1673, 1597, 1577, 1448, 1408, 1378, 1290, 1232, 1195, 1073, 938, 914, 771, 736, 691; *m/z* (EI) 192 $(M)^+$, 174 $(M-H_2O)^+$, 146 $(M-CO_2H-H)^+$, 105 $(PhCO)^+$ and 77 $(Ph)^+$; Found: C, 68.90; H, 6.36%. $C_{11}H_{12}O_3$ requires C, 68.74; H, 6.29%.

Method 2. Friedel Crafts acylation[10]

A solution of glutaric anhydride **10** (38.65 g, 339 mmol) in benzene (250 mL) was added to a vigorously stirred suspension of aluminium chloride (99.63 g, 747 mmol) in benzene (100 mL) at 0 °C, at such a rate that the internal temperature did not rise above 20 °C (approximately 20 minutes). The resultant thick dark brown slurry was stirred at room temperature for a further 12 hours. The reaction was quenched at 0 °C by the cautious addition of water (200 mL) followed by H_2SO_4 (conc., 70 mL). The mixture was extracted with chloroform (3 x 500 mL), the organic extracts combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a pale orange solid. The crude acid was recrystallised from boiling ethyl acetate to give **9** as an off white solid (53.89 g, 280.3 mmol, 83%) with physical data consistent with that above.

Methyl 5-oxo-5-phenylpentanoate 8

A solution of ketoacid **9** (27.57 g, 143.3 mmol) in methanol (500 mL) was acidified with H_2SO_4 (conc., 0.5 mL) and stirred for 1 hour. The reaction was poured into water (200 mL) and extracted with DCM (2 x 200 mL). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil which

was purified by Kugelrohr distillation (b.p. 200 °C/15 mmHg) to give the ketoester **8** as a colourless mobile oil (28.67 g, 139.0 mmol, 97%); δ_H (200 MHz , $CDCl_3$) 7.89 (2H, m, 2x *o*-Ar-*H*), 7.51 (3H, m, 2x *m*- and 1 x *p*-Ar-*H*), 3.68 (3H, s, OCH_3), 3.06 (2H, t, *J* 7.1, 2x *H*-4), 2.45 (2H, t, *J* 7.2, 2x *H*-2), 2.08 (2H, m, 2x *H*-3); ν_{max} (film)/cm^{-1} 2951, 1738, 1731, 1688, 1681, 1598, 1580, 1449, 1372, 1214, 1002, 881, 747, 692; *m/z* (EI) 206 $(M)^+$, 175 $(M\text{-}OCH_3)^+$, 147 $(M\text{-}CO_2CH_3)$, 105 $(PhCO)^+$ and 77 $(Ph)^+$; Found: C, 69.91; H, 6.70%. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84%.

2-Methyl-4,4-diphenyl-3-oxa-1-aza-2-borabicyclo[3.3.0]octane 11[14c]

Trimethylboroxine (356 μL, 2.54 mmol) was added to a solution of (2*S*)-α,α-diphenyl pyrrolidinemethanol (966 mg, 3.81 mmol) in toluene (5 mL) under argon and this was then stirred for 50 minutes. The toluene was removed from the thick white suspension by distillation at atmospheric pressure, and the solid was then further azeotroped with toluene (3 x 10 mL) at atmospheric pressure. On the final evaporation the volume was reduced to 6.6 mL giving an approximately 0.58 M solution of oxazaborolidine **11** in toluene, which was stored under argon and used without direct isolation or characterisation. (Note that on prolonged storage, precipitation of the oxazaborolidine from the solution occured but did not diminish the e.e.'s obtained during reduction).

(5*R*) Methyl 5-hydroxy-5-phenylpentanoate 7

A solution of ketoester **8** (5.562 g, 27.0 mmol) in THF (50 mL) was dried over activated 4Å molecular sieves for 3 hours and decanted from them, rinsing with THF (2 x 10 mL) under argon. Oxazaborolidine solution **11** (0.58 M in toluene; 2.3 mL, 1.35 mmol) was added to the ketoester solution which was then cooled to -15 °C and borane dimethylsulfide complex (2M in THF; 9.5 mL, 18.9 mmol) was added slowly so that the internal temperature did not rise above -15 °C (approximately 20 minutes). After 1 hour at that temperature methanol (30 mL) was cautiously added (**Caution**! Exothermic evolution of hydrogen with approximately 2 minute induction period) and the pale yellow solution was allowed to warm to room temperature and stirred for 16 hours. Evaporation of solvents *in vacuo* gave a viscous yellow oil which was dissolved in DCM (100 mL), washed with HCl (aq., 1 M; 100 mL), dried ($MgSO_4$) and the solvents removed *in vacuo* to give crude *hydroxyester* **7**, a small sample of which was purified by column chromatography on silica gel eluting with ether/petrol (7:3) to give **7** as a colourless mobile oil, contaminated with lactone **6** (approximately 5%); δ_H (200 MHz , $CDCl_3$) 7.35 (5H, m, 5x Ar-*H*), 4.67 (1H, m, *H*-5), 3.65 (3H, s, OCH_3), 2.34 (2H, t, *J* 8.0, 2x *H*-2), 1.8 (4H, m, 2x *H*-3, 2x *H*-4); ν_{max} (film)/cm^{-1} 3447, 3062, 3029, 2951, 2874, 1957, 1738, 1603, 1492, 1437, 1241, 1202, 604; *m/z* (EI) 208 $(M)^+$, 191 $(M\text{-}OH)^+$, 176 $(M\text{-}CH_3OH)^+$, 159 $(M\text{-}CH_3OH\text{-}OH)^+$, 107 $(PhCHOH)^+$, 77 $(Ph)^+$; Found $(M)^+$, 208.1105. $C_{12}H_{16}O_3$ requires 208.1099.

(6*R*) 6-Phenyltetrahydro-2*H*-pyran-2-one 6

CSA (0.10 g, catalytic) was added to a solution of crude hydroxyester **7** (27.0 mmol from previous reaction) in DCM (300 mL) at room temperature under argon. The reaction was stirred for 4 hours after which time no further reaction appeared to take place (as evidenced by tlc). Polyvinylpyridine (0.50 g) was added to the pale yellow solution and stirring continued for 10 minutes, after which time the reaction mixture was filtered and the residue washed with DCM (10 mL). The combined filtrate and washings were evaporated *in vacuo* to give a mobile yellow oil containing a mixture of lactone **6** and uncyclised starting material **7**. The lactone was partially removed from the oil by crystallisation from ether/petrol, and the residual mixture enriched in

hydroxyester was recyclised with CSA as above. This method of cyclisation/ crystallisation/ cyclisation was repeated four times to eventually give recovered hydroxyester **7** (0.21 g, 1.04 mmol, 4%) and ketoester **8** (167 mg, 0.81 mmol, 3%) each as an oil, together with *lactone* **6** as a white crystalline solid (4.272 g, 24.24 mmol, 90%); m.p. 92-96 °C ; $[\alpha]_D^{25}$ = + 38.5 (c = 1.00, $CHCl_3$); δ_H (200 MHz , $CDCl_3$), 7.36 (5H, m, 5x Ar-*H*), 5.36 (1H, dd, *J* 10.0, 3.6, *H*-6), 2.65 (2H, m, 2x *H*-3), 2.18 (1H, m, *H*-5_{ax}), 2.06-1.60 (3H, m, 2x *H*-4, *H*-5_{eq}); ν_{max} ($CHCl_3$)/cm^{-1} 3040, 2970, 1731, 1458, 1433, 1376, 1342, 1309, 1287, 1246, 1164, 1038, 1000, 969, 934, 901, 858, 765, 707; *m/z* (EI) 176 $(M)^+$, 159 $(M\text{-}OH)^+$, 132 $(M\text{-}CO_2)^+$, 104 $(PhCHCH_2)^+$, 77 $(Ph)^+$; Found $(M)^+$ 176.0831. $C_{11}H_{12}O_2$ requires 176.0837; Found: C, 74.89; H, 6.85%. $C_{11}H_{12}O_2$ requires C, 74.98; H 6.86%.

(2*RS*, 6*R*) 2-Hydroxy-6-phenyltetrahydropyran 12

DIBAL-H (1.5 M in toluene; 11.1 mL, 16.6 mmol) was added dropwise to a cooled (-78 °C) solution of lactone **6** (2.345 g, 13.31 mmol) in toluene (160 mL) under argon. The solution was stirred at -78 °C for 2 hours, water (8 mL) and ethyl acetate (70 mL) were then added and the mixture was then allowed to warm to room temperature. Na_2SO_4 and $NaHCO_3$ were then added. The gel obtained was vigorously stirred for 1 hour and the granular solids obtained were filtered and washed with ethyl acetate. The combined filtrate and washings were evaporated *in vacuo* to give *lactol* **12** (2.427 g, assumed quantitative) as a colourless viscous oil which was used without purification in the next reaction. A small sample was purified by column chromatography on silica gel eluting with ethyl acetate/petrol (3:7) to give *lactol* **12** as a 1:1 mixture of diastereoisomers as a waxy white solid m.p. 66-89 °C, $[\alpha]_D^{25}$ = + 24.9 (c = 1.00, $CHCl_3$); δ_H (200 MHz , $CDCl_3$) 7.37 (10H, m, 10 x Ar-*H*), 5.47 (1H, br.d, *J* 2.2, *H*-2_{trans}), 5.02 (1H, dd, *J* 11.1, 2.5, *H*-6_{trans}), 4.86 (1H, ddd, *J* 9.2, 5.7, 1.9, *H*-2_{cis}), 4.48 (1H, dd, *J* 10.8, 2.1, *H*-6_{cis}), 3.31 (1H, d, *J* 5.8, O*H*$_{trans}$), 2.78 (1H, br.s, O*H*$_{cis}$), 2.10-1.40 (12H, m, 4x *H*-3, 4x *H*-4, 4x *H*-5); ν_{max} ($CHCl_3$)/cm^{-1} 3391, 2940, 1357, 1068, 1031, 973, 697; *m/z* (EI) 178 $(M)^+$, 177 $(M\text{-}H)^+$, 161 $(M\text{-}OH)^+$, 160 $(M\text{-}H_2O)^+$, 105 $(PhCO)^+$ and 77 $(Ph)^+$; Found $(M)^+$ 178.0987. $C_{11}H_{14}O_2$ requires 178.0994.

(2*R*,6*R*) and (2*S*,6*R*) 2-Benzenesulfonyl-6-phenyltetrahydropyran 13a and 13b

Freshly prepared benzenesulfinic acid (3.80 g, 26.6 mmol) was added in one portion to a slurry of $CaCl_2$ (4.40 g, 39.9 mmol) and crude lactol **12** (2.427 g, 13.31 mmol) in DCM (50 mL) and stirred under argon at room temperature for 16 hours. The reaction mixture was poured into a mixture of $NaHCO_3$ (25 mL; sat. aq.) and H_2O (50 mL) and extracted with DCM (3 x 70 mL). The combined organic extracts were then washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. The crude products were chromatographed on silica gel eluting with DCM/ether/petrol (1:2:7) to give a 1:1 mixiture of *cis* and *trans sulfones* **13a** and **13b** (2.991 g, 9.89 mmol, 75% from lactone **6**) as a white solid; δ_H (200 MHz , $CDCl_3$) 7.90 (2H, d, *J* 7.3, 2x *o*-SO_2Ar-*H*), 7.51 (3H, m, 2x *m*- and 1 x *p*-SO_2Ar-*H*), 7.27 (5H, m, 5x Ar-*H*), 5.50 (1H, dd, *J* 10.2, 2.9, *H*-6_{trans}), 4.79 (1H, dd, *J* 6.1, 2.4, *H*-2_{trans}), 4.59 (1H, dd, *J* 10.9, 2.2, *H*-2_{cis}), 4.40 (1H, dd, *J* . 11.1, 1.8, *H*-6_{cis}), 2.70-1.70 (12H, m, 4x *H*-3, 4x *H*-4, 4x *H*-5); ν_{max} ($CHCl_3$)/cm^{-1} 2923, 2854, 1460, 1377, 1312, 1150, 1084, 1028; *m/z* (EI) 302 $(M)^+$, 285 $(M\text{-}OH)^+$, 161 $(M\text{-}SO_2Ph)^+$, 142 $(HSO_2Ph)^+$, 104 $(PhCHCH_2)^+$ and 77 $(Ph)^+$; Found $(M)^+$ 302.0977. $C_{17}H_{18}O_3S$ requires 302.0977. Found: C, 67.46; H, 5.92%. $C_{17}H_{18}O_3S$ requires C, 67.52; H, 6.06%.

(2*R*) 2-Phenyl-6-(tributylstannyl)-3,4-dihydro-2*H*-pyran 5

A solution of sulfones **13a** and **13b** (22.55 g, 74.58 mmol) in THF (100 mL) were dried over activated 4Å molecular sieves for 1 hour. The supernatant liquid was decanted under argon from the sieves which were rinsed with THF (2 x 25 mL). The resultant sulfone solution was cooled to -78 °C and n-BuLi (2.5 M in hexanes; 34.0 mL, 85.0 mmol) was added dropwise. The dark orange solution was then stirred at -78 °C for 40 minutes. Tributyltin chloride (25.4 mL, 93.1 mmol) was added and the resultant pale yellow solution was allowed to warm to room temperature over a period of 15 minutes. The solution was then evaporated *in vacuo* to give a yellow oil which was passed through a short Florisil® pad eluting with $CHCl_3$ (600 mL). DIPEA (40 mL, 231 mmol) was added to the filtrate and the yellow solution was heated under reflux for 1.5 hour, cooled to room temperature and evaporated *in vacuo* to give the crude stannane as a yellow oil. The crude product was then purified by column chromatography on Florisil® eluting with ether/petrol (5:95) to give *stannane* **5** as a colourless mobile oil (24.12 g, 53.70 mmol, 72%); $[\alpha]_D^{25}$ = + 26.6 (c = 1.00 in $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.30 (5H, m, 5x Ar-*H*), 4.30 (2H, m, *H*-2, *H*-5), 2.40-1.70 (4H, m, 2x *H*-3, 2x *H*-4), 1.60-1.20 (12H, m, $(CH_3CH_2CH_2CH_2)_3Sn$), 0.90 (15H, m, $(CH_3CH_2CH_2CH_2)_3Sn$); ν_{max} (film)/cm^{-1} 2954, 2923, 1606, 1454, 1376, 1329, 1269, 1221, 1054, 954, 863, 753, 697; *m/z* (EI) 391 $(M\text{-}Bu)^+$, 337, 317, 291, 259, 235, 177, 120, 104 $(PhCHCH_2)^+$ and 77 $(Ph)^+$; Found 1233 $(M\text{-}Bu)^+$ 393.1233; $C_{19}H_{29}OSn$ requires $(M\text{-}Bu)^+$; 393.1240.

(2*R*,2'*R*) 2,2'-Diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran 3

n-BuLi (2.5 M in hexane; 19.1 mL, 48.1 mmol) was added dropwise to a solution of stannane **5** (20.55 g, 45.74 mmol) in THF (380 mL) at -78 °C. The yellow solution was stirred under argon for 30 minutes after which time a mixture of anhydrous copper (II) chloride (6.46 g, 48.1 mmol) and palladium (II) chloride (bis-acetonitrile) complex (0.24 g, 0.92 mmol) was added in one portion. The resultant brown slurry was stirred vigorously at -78 °C. After 3.25 hours, ammonia (20% 0.88 solution in sat. aq., NH_4Cl; 500 mL) was added and the mixture warmed to room temperature. The layers were separated, the aqueous phase extracted with ether (3 x 200 mL) and the combined organic extracts were then washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The residue was chromatographed on silica gel eluting with DCM/petrol (15-40% gradient elution) to give *C_2 symmetric (2R,2'R) PDHP* **3** (contaminated with approximately 11% *meso PDHP* **3a** as shown in the proton nmr) as a white crystalline solid (4.369 g, 13.72 mmol, 60%); m.p. 118-130 °C; $[\alpha]_D^{25}$ = + 104.5 (c = 1.00, $CHCl_3$); δ_H (200 MHz , $CDCl_3$) 7.40 (10H, m, 10 x Ar-*H*), 5.40 (2H, br.t, *J* 3.8, *H*-5, *H*-5'), 4.94 (11% minor *meso* isomer, dd, *J* 10.0, 2.4, *H*-2, *H*-2') 4.90 (2H, dd, *J* 10.0, 2.4, *H*-2, *H*-2'), 2.40-1.80 (8H, m, 2x *H*-3, 2x *H*-3', 2x *H*-4, 2x *H*-4'); ν_{max} ($CHCl_3$ solution)/cm^{-1} 2922, 2853, 1628, 1494, 1456, 1376, 1333, 1283, 1226, 1065, 1042, 959, 910, 868, 773, 759, 700; *m/z* (EI) 318 $(M)^+$, 214 $(M\text{-}PhCHCH_2)^+$, 201, 131, 104 $(PhCHCH_2)^+$, 77 $(Ph)^+$; Found $(M)^+$ 318.1615. $C_{22}H_{22}O_2$ requires 318.1620; Found: C, 83.09; H, 6.97%. $C_{22}H_{22}O_2$ requires C, 82.99; H 6.96%.

(4*S*,5*R*) 4,5-Diphenyl-2-methyl-3-oxa-1-aza-2-borolidene 15[15]

A suspension of (1*S*, 2*R*) 2-amino-1,2-diphenylethanol (5.0 g, 23.44 mmol) in toluene (150 mL) was heated at approximately 60 °C under argon until all solids had dissolved, upon which trimethylboroxine (2.2 mL, 15.7 mmol) was added at 60 °C. The solution was then stirred for 16 hours at room temperature and then

concentrated to a volume of 50 mL by distillation at atmospheric pressure. The solution was then further azeotroped with toluene (3 x 50 mL) at atmospheric pressure and on the final evaporation the volume was reduced to 50 mL, giving an approximately 0.48 M yellow solution of oxazaborolidine **15** in toluene which was stored under argon and used without direct isolation or characterisation. (Note that, as with oxazaborolidine **11**, on prolonged storage precipitation of the oxazaborolidene **15** from the solution occured but did not diminish the e.e.'s obtained during reduction).

(6*S*) 6-Phenyltetrahydro-2*H*-pyran-2-one 17

A solution of ketoester **8** (28.47 g, 138.0 mmol) in THF (500 mL) was dried over activated 4Å molecular sieves for 3 hours and decanted from the molecular sieves, rinsing with THF (2 x 20 mL) under argon. Oxazaborolidene solution (**15**, 0.58 M in toluene; 28 mL, 13.5 mmol) was added to the ketoester solution which was then cooled to -15 °C. Borane dimethyl sulfide complex (9.2 mL, 96.63 mmol) in THF (38 mL) was added slowly so that the internal temperature did not rise above 20 °C (approximately 1 hour). After an additional 1 hour stirring at room temperature, methanol (190 mL) was cautiously added. (**Caution!** Exothermic evolution of hydrogen with approximately 2 minute induction period). The pale yellow solution was allowed to warm to room temperature and was stirred for 16 hours. Evaporation of solvents *in vacuo* gave a viscous yellow oil which was chromatographed on silica gel eluting with ether/petrol (7:3) to give, in order of elution unreacted ketoester **8** (3.42 g, 16.56 mmol, 12%), and *hydroxyester* **16** as a colourless mobile oil (contaminated with lactone **17**).

CSA (100 mg, catalytic) was added to the solution of crude hydroxyester **16** in DCM (300 mL) at room temperature under argon. The reaction was stirred for 1 hour after which time no further reaction appeared to take place (as evidenced by tlc). Polyvinylpyridine (0.5 g) was added to the pale yellow solution and stirring continued for 10 minutes, after which time the reaction mixture was filtered, the residue washed with DCM (10 mL) and the combined filtrate and washings evaporated *in vacuo* to give a mobile yellow oil containing a mixture of lactone **17** and uncyclised starting material **16**. The lactone was partially removed from the oil by crystallisation from ether/petrol, and the residual crude hydroxyester was recyclised as above. This method of cyclisation/ crystallisation/ cyclisation was repeated four times to eventually give *lactone* **17** as a white crystalline solid (11.36 g, 64.5 mmol, 47%), $[\alpha]_D^{25}$ = -35.9 (c = 1.00, $CHCl_3$). The lactone was enantiomerically enriched by recrystallisation from ether/petrol giving **17** (9.009 g, 51.1 mmol, 37%), $[\alpha]_D^{25}$ = - 41.2 (c = 1.00, $CHCl_3$), with spectral data identical to enantiomeric **6** above. The e.e. of the recrystallised lactone **17** was determined to be >99% by chiral phase g.c. analysis.

(2*RS*,6*S*) 2-Hydroxy-6-phenyltetrahydropyran 18

DIBAL-H (1.5M in toluene; 27.5 mL, 41.19 mmol) was added dropwise to a cooled (-78 °C) solution of lactone **17** (5.807 g, 32.95 mmol) in toluene (400 mL) under argon. The solution was stirred at -78 °C for 2 hours, water (20 mL) and ethyl acetate (250 mL) were then added and the mixture allowed to warm to room temperature upon which time Na_2SO_4 and $NaHCO_3$ were added. The gel obtained was vigorously stirred for 1 hour and the granular solid obtained was filtered and washed with ethyl acetate (3 x 40 mL). The combined filtrate and washings were evaporated *in vacuo* to give *lactol* **18** (5.978 g, assumed quantitative) as a colourless viscous oil which was used without purification in the next reaction. A small sample was purified by column

chromatography on silica gel eluting with ethyl acetate/petrol (3:7) to give *lactol* **18** as a waxy white solid m.p. 62-65 °C; with spectral data identical to enantiomeric **12** above.

(2*S*,6*S*) and (2*R*,6*S*) 2-Benzenesulfonyl-6-phenyl-tetrahydro-2*H*-pyran 19a and 19b

Freshly prepared benzenesulfinic acid (9.37 g, 65.9 mmol) was added in one portion to a slurry of $CaCl_2$ (10.9 g, 98.85 mmol) and crude lactol **18** (2.427 g, 13.31 mmol) in DCM (150 mL) which was then stirred under argon at room temperature for 16 hours. The reaction mixture was poured into $NaHCO_3$ (sat. aq., 200 mL) and extracted with DCM (3 x 150 mL). The combined organic extracts were then washed sequentially with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. The crude products were chromatographed on silica gel eluting with DCM/ether/petrol (2:3:5) to give a 1:1 mixture of *cis* and *trans sulfones* **19a** and **19b** (7.665 g, 25.35 mmol, 77% from lactone) as a white solid, with identical spectral data to that of the mixture of **13a** and **13b** above.

(2*S*) 2-Phenyl-6-(tributylstannyl)-3,4-dihydro-2*H*-pyran 20

A pre-dried solution (over activated 4Å molecular sieves for 1 hour) of sulfones **19a** and **19b** (31.48 g, 104 mmol) in THF (200 mL) was cooled to -78 °C and n-BuLi (1.6 M in hexanes; 71.6 mL, 114.50 mmol) was added dropwise. The dark orange solution was then stirred at -78 °C for 45 minutes. Tributyltin chloride (33.9 mL, 125.00 mmol) was added and the resultant pale yellow solution was allowed to warm to room temperature over a period of 15 minutes. The solution was evaporated *in vacuo* to give a yellow oil which was passed through short Florisil® pad eluting with $CHCl_3$ (100 mL). DIPEA (22 mL, 127 mmol) was added to the filtrate and the yellow solution was heated under reflux for 2 hours, cooled to room temperature and evaporated *in vacuo* to give the crude stannane as a yellow oil. The crude product was then purified by column chromatography on Florisil® eluting with ether/petrol (5:95) to give *stannane* **20** (33.13 g, 73.75 mmol, 71%) as a colourless mobile oil $[\alpha]_D^{25}$ = - 29.1 (c = 1.00, in $CHCl_3$), with identical spectral data to enantiomeric **5** above.

(2*S*,2'*S*) 2,2'-Diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran 4

n-BuLi (2.5 M in hexane; 5.0 mL, 12.59 mmol) was added dropwise to a solution of stannane **20** (5.385 g, 11.9 mmol) in THF (100 mL) at -78 °C and stirred under argon for 30 minutes. A mixture of anhydrous copper (II) chloride (1.693 g, 12.59 mmol) and palladium (II) chloride (bis-acetontrile) complex (0.06 g, 0.24 mmol) was added in one portion and the resultant brown slurry was stirred vigorously at -78 °C. After 3.25 hours, ammonia (20% 0.88 solution in sat. aq. NH_4Cl; 250 mL) was added and the mixture warmed to room temperature. The aqueous phase was extracted with ether (3 x 200 mL) and the combined organic extracts were then washed sequentially with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The oil was chromatographed on silica gel doped with triethylamine, eluting with DCM/petrol (15-40% gradient elution) to give *diene* **4**, with no *meso* diene visible by proton nmr, as a white crystalline solid (1.358 g, 3.589 mmol, 60%) m.p. 116-124 °C, $[\alpha]_D^{25}$ = -119.9 (c = 1.00, $CHCl_3$); δ_H (200 MHz, $CDCl_3$), 7.40 (10H, m, 10 x Ph-*H*), 5.40 (2H, br.t, *J* 3.8, *H*-5, *H*-5'), 4.90 (2H, dd, *J* 10.0, 2.4, *H*-2, *H*-2'), 2.40-1.80 (8H, m, 2 x *H*-3, 2 x *H*-3', 2 x *H*-4, 2 x *H*-4'). Diene **4** diplayed indentical I.R. and mass spectral characteristics to that of enantiomeric **3**.

Alternative Preparation of (6*S*) 6-Phenyltetrahydro-2*H*-pyran-2-one 17

A solution of (-)-DIP-Cl (24.77 g, 77 mmol) in THF (50 mL) was cooled to -25 °C, causing some precipitation. The ketoester (dried over activated molecular sieves, 13.61 g, 66 mmol) was added neat *via* a cannula, the flask being rinsed with THF (3 x 10 mL). The now yellow solution was stirred for 24 hours, until tlc showed no starting material to be present. The reaction was quenched by the cautious addition of 10% NaOH solution (20 mL), warmed to ambient temperature and a further portion of NaOH solution added (40 mL) followed by water (10 mL). The mixture was stirred overnight, then diluted with ether (100 mL) and petrol (50 mL) and extracted with sodium bicarbonate solution (2 x 100 mL). The combined aqueous phases were acidified with conc. HCl (to pH 1) and extracted with chloroform (3 x 150 mL). The organic extracts were dried ($MgSO_4$) and evaporated. The residue was taken up in toluene (150 mL), CSA added (0.08 g) and 30 mL of toluene distilled off to drive lactonisation to completion. The cooled solution was washed with sodium bicarbonate solution (100 mL) and brine (100 mL), then dried ($MgSO_4$) and evaporated. The combined aqueous washings were further extracted with ethyl acetate (50 mL), the extract dried ($MgSO_4$), combined with the first portion and evaporated. The crude product was purified by flash column chromatography using ether:petrol (2:1) to afford the lactone (10.19 g, 88%) with an enantiomeric excess estimated as >90% by its optical rotation comparison with an authentic enantiopure sample of **17**. The enantiomeric excess could be improved by recrystallisation as before. Lactone **17** then displayed identical physical properties to that isolated previously.

Alternative Preparation of (2*S*,2'*S*) 2,2'-Diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran 4

To a cold (-78 °C) solution of LHMDS (1M in THF, 15.6 mL, 15.6 mmol, 1.4 eq.) was added DMPU (2.0 mL, 16.5 mmol, 1.5 eq.) and THF (10 mL). The lactone **17** (1.97 g, 11.2 mmol) was added as a solution in THF (15 mL) *via* cannula, the flask being rinsed with THF (2 x 5 mL). After 2 hours, *N*-phenyltrifluoromethanesulfonimide (4.79 g, 13.4 mmol, 1.2 eq.) was added as a solution in THF (25 mL). The solution was warmed to 0 °C over 2 hours, then kept at this temperature for a further 2 hours. Lithium chloride (2.84 g, 67.0 mmol, 6 eq.), hexamethylditin (1.16 mL, 5.6 mmol, 0.5 eq.) and palladium tetrakis(triphenylphosphine) (0.388 g, 0.34 mmol, 3 mol%) were placed in a flask equipped with a reflux condenser and placed under argon. To this flask was added *via* a cannula the crude enol triflate solution prepared above. The flask was rinsed with THF (2 x 10 mL) and the mixture heated to reflux for 27 hours. The reaction was worked-up by the addition of conc. NH_3 (50 mL), water (100 mL) and ether (150 mL). The ether layer was separated, washed with brine (100 mL), dried ($MgSO_4$) and evaporated. The combined aqueous phases were further extracted with ether (2 x 100 mL), the organic extracts were then dried ($MgSO_4$), evaporated under reduced pressure and combined with the first extract. Purification by flash column chromatography (2% triethylamine/petrol to 5% DCM/2% triethylamine/petrol) on silica doped with triethylamine afforded the vinyl stannane **22** (0.693 g, 19%) and the desired diene **4** (1.035 g, 58%) which had identical physical properties to that isolated previously.

(2'*S*,2''*S*,6'*S*,6''*S*) 2-*O*,5-*O*-Dibenzoyl-1-*O*,6-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-L-*myo*-inositol 24

A solution of 2-*O*,5-*O*-dibenzoyl-*myo*-inositol **23** (0.20 g, 0.515 mmol), (2*S*,2'*S*) 2,2'-dimethyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran **1** (0.130 g, 0.67 mmol) and CSA (0.013 g, 0.05 mmol) in $CHCl_3$ (20 mL) was heated under reflux for 16 hours. The solution was cooled to room temperature, diluted with DCM

(10 mL) and sodium bicarbonate (10 mL; sat. aq.) added. The layers were separated and the organic phase washed with brine (10 mL) and dried ($MgSO_4$). The organic fraction was then evaporated *in vacuo* and subjected to flash column chromatography on silica gel eluting with ethyl acetate/petrol (4:6) to give, in order of elution, *diol* **24** as an amorphous white solid (0.19 g, 0.331 mmol, 70% based on recovered **23**); m.p. 115-117 °C; $[\alpha]_D^{27}$ = -71.1 (c = 0.41, $CHCl_3$); δ_H (400 MHz , $CDCl_3$) 8.30 (4H, d, *J* 7.5, 4 x *o*-Ar-*H*), 7.59 (2H, t, *J* 7.4, 2 x Ar-*H*), 7.48-7.44 (4H, m, 4 x Ar-*H*), 5.72 (1H, apparent t, *J* 2.7, *H*-5), 5.29 (1H, apparent t, *J* 9.6, *H*-2), 4.42 (1H, apparent t, *J* 10.2, *H*-3 (or *H*-1)), 4.06 (1H, apparent t, *J* 9.5, *H*-1 (or *H*-3)), 3.96-3.90 (2H, m, 1 x *H*-4, 1 x *H*-6), 3.84-3.80 (1H, m, 1 x dispoke C*H*(CH_3)), 3.78-3.72 (1H, m, 1 x dispoke C*H*(CH_3)), 3.01 (2H, br.s, 2 x O*H*) 1.77-1.67 (4H, m, 2 x dispoke CH_2), 1.54-1.28 (8H, m, 4 x dispoke CH_2), 1.14 (3H, d, *J* 6.2, 1 x dispoke CH(CH_3)), 1.13 (3H, d, *J* 6.2, 1 x dispoke CH(CH_3)); δ_C (100 MHz, $CDCl_3$) 167.09, 166.95 (2 x *C*=O), 133.30, 133.15 (2 x Ar(*C*H)), 130.31 (Ar(*C*)), 129.98, 129.82, 128.40 (3 x Ar(*C*H)), 97.69, 97.36 (2 x acetal(*C*)), 74.53, 73.43, 72.18, 72.11, 66.28, 66.08, 65.80 (7 x *C*HO), 32.46, 32.34, 27.66, 27.60 (4 x dispoke *C*H_2), 21.87, 21.80 (2 x dispoke CH(*C*H_3)), 18.33, 18.20 (2 x dispoke *C*H_2); ν_{max} ($CHCl_3$)/cm^{-1} 3438, 2923, 2854, 1728, 1457, 1376, 1271, 1214, 1195, 1175, 1152, 1112, 1050, 1027, 988, 952, 711; *m/z* (+FAB) 605 $(MNa)^+$, 582 $(M)^+$, 530, 496, 441, 371, 281, 221, 195; Found $(MNa)^+$ 605.2305. $C_{32}H_{38}NaO_{10}$ requires $(MNa)^+$ 605.2362. Together with starting tetrol **23** (0.016 g, 0.04 mmol, 8% recovery), identical in all respects to that isolated previously.

(2'*R*,2''*R*,6'*S*,6''*S*) 1-*O*,6-*O*-(6,6'-Dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-L-*myo*-inositol 25

NaOH solution (1% aq., 4 mL) was added to a suspension of diol **24** (0.162 g, 0.278 mmol) in MeOH/Ether (9:1; 5 mL) and stirred vigorously for 16 hours. The reaction mixture was then diluted with H_2O (10 mL), extracted with $CHCl_3$ (3 x 20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give *tetrol* **25** as an amorphous white solid (0.10 g, 0.27 mmol, 96%); m.p. >325 °C; $[\alpha]_D^{25}$ = - 19.1 (c = 0.37 in MeOH); δ_H (400 MHz , CD_3OD) 3.96-3.89 (3H, m, 3 x C*H*O), 3.74 (1H, m, 1 x dispoke C*H*(CH_3)), 3.65 (1H, t, *J* 9.4, 1 x C*H*O), 3.51 (1H, dd, *J* 10.2, 2.1, 1 x C*H*O), 3.41-3.31 (2H, m, 2 x C*H*O), 2.02-1.55 (4H, m, 2 x dispoke CH_2), 1.50-1.41 (8H, m, 4 x dispoke CH_2), 1.11 (6H, d, *J* 6.2, 2 x dispoke CH(CH_3)); δ_C (100 MHz, CD_3OD) 98.99, 98.44 (2 x acetal(*C*)), 75.24, 74.27, 73.85, 72.14, 69.28, 69.21, 67.26, 66.98 (8 x *C*HO), 33.77, 33.73, 29.17, 28.94 (4 x dispoke *C*H_2), 22.17, 22.12 (2 x dispoke CH(*C*H_3)), 19.58, 19.51 (2 x dispoke *C*H_2); ν_{max} (nujol)/cm^{-1} 3422, 2923, 2854, 1461, 1376, 1152, 1030, 722; *m/z* (EI) 374 $(M)^+$, 302, 261, 244, 217, 195, 168, 115, 97, 86, 69, 55; Found $(M)^+$ 374.1965. $C_{18}H_{30}O_8$ requires $(M)^+$ 374.1941.

(2'*R*,2''*R*,6'*S*,6''*S*) 1-*O*,6-*O*-(6,6'-Dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)2-*O*,3-*O*,4-*O*,5-*O*-tetrabenzyl-L-*myo*-inositol 26

A solution of tetrol **25** (0.45 g, 1.20 mmol), benzyl bromide (1.03 g, 6.01 mmol) and one crystal of TBAI in dry DMF (12 mL) was cannulated into a stirred suspension NaH (0.17 g, 7.22 mmol) in dry DMF (12 mL) at 0 °C under argon. The mixture was then warmed slowly to room temperature and stirred for a further 3 hours at this temperature. After this time, the mixture was heated at 50 °C for 2 hours before being cooled to room temperature. Water (30 mL) was added together with ether (10 mL). The layers were separated and the aqueous re-extracted with ether (3 x 20 mL). The organic extracts were combined, washed with water (50 mL) and dried ($MgSO_4$) and evaporated *in vacuo*. The crude oil was subjected to flash column chromatography on

silica gel eluting with ether/petrol (1:9) to give *tetrabenzylether* **26** as a colourless foam (0.561 g, 0.89 mmol, 74%); $[\alpha]_D^{25}$ = - 55.1 (c = 0.36 in CH_3OH); δ_H (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* 6.8, 2 x *o*-Ar-*H*), 7.41-7.04 (18H, m, 18 x Ar-*H*), 5.04 (1H, d, *J* 10.8, 1 x C*H*O), 4.94-4.77 (5H, m, 5 x C*H*O), 4.66 (2H, s, CH_2Ar), 4.36 (1H, apparent t, *J* 9.9, 1 x C*H*O), 4.03-3.92 (3H, m, 2 x C*H*O, 1 x dispoke C*H*(CH_3)), 3.74-3.69 (1H, m, 1 x dispoke C*H*(CH_3)), 3.60-3.45 (3H, m, 3 x C*H*O), 1.96-1.76 (4H, m, 2 x dispoke CH_2), 1.66-1.41 (6H, m, 3 x dispoke CH_2), 1.23-1.19 (2H, m, 1 x dispoke CH_2), 1.17-1.14 (6H, m, 2 x dispoke CH(CH_3)); δ_C (100 MHz, $CDCl_3$) 139.20, 139.16, 138.67 (3 x Ar(*C*)), 128.49, 128.34, 128.29, 128.26, 128.03, 127.95, 127.52, 127.49, 127.45, 127.40, 127.26 (11 x Ar(*C*H)), 97.27, 96.99 (2 x acetal(*C*)), 82.19, 81.73, 80.80 (3 x *C*HO), 76.09, 75.57 (2 x *C*H_2Ar), 74.71 (1 x *C*HO), 74.00, 72.32 (2 x *C*H_2Ar), 69.17, 68.71, 65.99, 65.56 (4 x *C*HO), 32.65, 32.60, 28.19, 27.99 (4 x dispoke *C*H_2), 22.12, 22.04 (2 x dispoke CH(*C*H_3)), 18.91, 18.63 (2 x dispoke *C*H_2); ν_{max} (film)/cm^{-1} 3029, 2926, 1496, 1453, 1358, 1273, 1195, 1150, 1092, 1056, 1026, 990, 952, 905, 852, 734, 696; *m/z* (+FAB) 734 $(M)^+$, 733 $(M-H)^+$, 643 $(M-Bn)^+$, 553, 429, 398, 361, 339, 307, 292, 279, 250, 228, 211, 195, 181, 154, 136; Found $(M-H)^+$ 733.3738. $C_{46}H_{53}O_8$ requires $(M-H)^+$ 733.3740; Found $(M-Bn)^+$ 643.3248. $C_{39}H_{47}O_8$ requires $(M-Bn)^+$ 643.3271.

2-*O*,3-*O*,4-*O*,5-*O*-Tetrabenzyl-L-*myo*-inositol 27

The benzylated adduct **26** (0.091 g, 0.12 mmol) was stirred under argon in 95% TFA/water (1 mL) for 75 minutes. After this time, the mixture was loaded directly onto a silica column and eluted with ether/petrol (2:1) to give diol **27** in 63% yield; $[\alpha]_D^{25}$ = - 15.8 (c = 0.13 in $CHCl_3$) (Lit.[5] $[\alpha]_D^{25}$ = -15.5); δ_H (400 MHz, $CDCl_3$) 7.34-7.25 (20H, m, 20 x Ar-*H*), 5.04-4.69 (8H, m, 4 x CH_2Ar), 4.02 (2H, apparent t, *J* 9.2, *H*-3 and *H*-4), 3.83 (1H, apparent t, *J* 9.4, *H*-6), 3.48 (1H, dd, *J* 9.8, 2.0, *H*-1), 3.38 (1H, dd, *J* 9.6, 2.0, *H*-2), 3.32 (1H, apparent t, *J* 9.2, *H*-5), 2.50 (2H, br.s, 2 x O*H*); δ_C (100 MHz, $CDCl_3$) 138.63, 138.57, 138.14 (3 x Ar(*C*)), 128.50, 128.45, 128.40, 128.34, 128.03, 127.89, 127.75, 127.69, 127.65, 127.59 (10 x Ar(CH)), 82.98, 81.46, 81.32, 77.32 (4 x *C*H), 75.75, 75.37, 74.85 (3 x *C*H_2), 73.88 (1 x *C*H), 73.15 (1 x *C*H_2), 72.13 (1 x *C*H); ν_{max} ($CHCl_3$ solution)/cm^{-1} 3564, 2926, 1361, 1051, 987; *m/z* (+FAB) 541 $(MH)^+$, 539 $(M-H)^+$, 449, 407, 389, 359, 307, 181, 165, 154; Found $(MH)^+$ 541.2546. $C_{34}H_{37}O_6$ requires $(MH)^+$ 541.2590; Found $(M-H)^+$ 539.2459. $C_{34}H_{35}O_6$ requires $(M-H)^+$ 539.2434.

(2'*S*,2''*S*,4'*S*,4''*S*) 2-*O*,5-*O*-Dibenzoyl-1-*O*,6-*O*-(4,4'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-D-*myo*-inositol 28

A solution of 2-*O*,5-*O*-dibenzoyl-*myo*-inositol **23** (0.27 g, 0.70 mmol), (4*S*,4'*S*) 4,4'-dimethyl-3,3'-dihydro-6,6'-bi-2*H*-pyran **2** (0.22 g, 1.1 mmol) and CSA (0.017 g, 0.07 mmol) in $CHCl_3$ (6 mL) was heated under reflux for 28 hours. The solution was cooled to room temperature, and evaporated *in vacuo*. The residue was subjected to flash column chromatography on silica gel eluting with ether/petrol (1:4) to give *diol* **28** as an amorphous white solid (0.26 g, 0.44 mmol, 63%); m.p. 126-128 °C; $[\alpha]_D^{27}$ = + 41.7 (c = 1.46, $CHCl_3$); δ_H (400 MHz , $CDCl_3$) 8.10-7.99 (4H, m, 4 x *o*-Ar-*H*), 7.59-7.55 (2H, m, 2 x p-Ar-*H*), 7.53-7.35 (4H, m, 4 x *m*-Ar-*H*), 5.73 (1H, apparent t, *J* 2.8, 1 x C*H*O), 5.30 (1H, aparent t, *J* 9.8, 1 x C*H*O), 4.35 (1H, apparent t, *J* 10.2, 1 x C*H*O), 4.05 (1H, apparent t, *J* 9.6, 1 x C*H*O), 3.94 (1H, dd, *J* 10.2, 2.8, 1 x C*H*O), 3.87 (1H, dd, *J* 9.7, 2.7, 1 x C*H*O), 3.73-3.62 (4H, m, 4 x C*H*O), 3.21 (2H, br.s, 2 x O*H*), 1.85-1.73 (1H, m, 1 x dispoke C*H*), 1.72-1.63 (3H, m, 3 x dispoke C*H*), 1.48-1.45 (1H, m, 1 x dispoke C*H*), 1.28-1.24 (2H, m, 2 x dispoke C*H*), 1.14-0.84 (3H, m, 3 x dispoke C*H*), 0.78 (3H, d, *J* 6.5, 1 x dispoke CH(CH_3)), 0.73 (3H, d,

J 6.5, 1 x dispoke CH(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$) 166.92, 166.73 (2 x *C*=O), 133.26, 133.12 (2 x Ar(*C*H)), 130.24 (Ar(*C*)), 129.98, 129.83, 128.42, 128.41 (4 x Ar(*C*H)), 97.56, 97.09 (2 x acetal(*C*)), 74.25, 73.25, 71.96, 71.74, 66.43, 66.14 (6 x *C*HO), 60.89, 60.56 (2 x dispoke *C*H$_2$O), 36.85, 36.68, 33.38 (3 x dispoke *C*H$_2$), 24.34, 24.12 (2 x dispoke *C*H(CH$_3$)), 15.26 (2 x dispoke CH(*C*H$_3$)); ν_{max} ($CHCl_3$ solution)/cm^{-1} 3583, 2932, 1726, 1452, 1315, 1272, 1188, 1095, 1070, 1026, 995, 909, 866, 712, 651; *m/z* (+FAB) 583 (MH)$^+$, 582 (M)$^+$, 565, 537, 469, 439, 391, 371, 354, 289, 249, 233, 219, 196 (**2**)$^+$, 195 (**2**-H)$^+$, 167, 154; Found (MH)$^+$ 583.2539. $C_{32}H_{39}O_{10}$ requires (MH)$^+$ 583.2543.

(2'*S*,2''*S*,4'*S*,4''*S*) 1-*O*,6-*O*-(4,4'-Dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-D-*myo*-inositol 29

NaOH solution (1% aq., 10 mL) was added at 0 °C to a suspension of diol **28** (0.095 g, 0.16 mmol) in MeOH/Ether (9:1; 7 mL) and stirred vigorously for 14 hours. The reaction mixture was then diluted with H_2O (10 mL), extracted with $CHCl_3$ (3 x 40 mL), the aqueous was re-extracted with ethyl acetate (3 x 40 mL) and the organic fractions combined. The organic fraction was dried ($MgSO_4$) and evaporated *in vacuo* to give *tetrol* **29** as an amorphous white solid (0.151 g, 0.26 mmol, 91%); m.p. 154-7 °C; $[\alpha]_D^{25}$ = + 62.0 (c = 0.24, $CHCl_3$); δ_H (200 MHz , CD_3OD) 4.01-3.94 (2H, m, 2 x C*H*O), 3.90-3.84 (1H, dt, *J* 12.6, 1.6, 1 x C*H*O), 3.74-3.66 (4H, m, 4 x C*H*O), 3.58-3.55 (1H, dd, *J* 10.3, 2.2, 1 x C*H*O), 3.45-3.35 (2H, m, 2 x C*H*O), 1.99-1.78 (3H, m, 3 x dispoke C*H*), 1.57 (2H, m, 2 x dispoke C*H*), 1.26-1.10 (5H, m, 5 x dispoke C*H*), 0.94 (6H, d, *J* 6.5, 2 x dispoke CH(C*H*$_3$)); δ_C (100 MHz, CD_3OD) 98.79, 98.23 (2 x acetal(*C*)), 75.29, 74.20, 73.86, 72.08, 69.36 (5 x *C*HO), 61.80, 61.68 (2 x dispoke *C*H$_2$O), 38.46, 38.22, 34.89, 34.81 (4 x dispoke *C*H$_2$), 25.88, 25.66 (2 x dispoke *C*H(CH$_3$)), 22.85, 22.79 (2 x dispoke CH(*C*H$_3$)); ν_{max} ($CHCl_3$ solution)/cm^{-1} 3416, 2952, 2931, 2873, 1456, 1380, 1298, 1204, 1156, 1113, 1010, 996, 964, 892, 865, 604; *m/z* (+FAB) 375 (MH)$^+$, 374 (M)$^+$, 329, 307, 289, 273, 195, 176, 154, 136; Found (MH)$^+$ 375.2002. $C_{18}H_{31}O_8$ requires (MH)$^+$ 375.2019.

(2'*S*,2''*S*,4'*S*,4''*S*) 1-*O*,6-*O*-(4,4'-Dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-2-*O*,3-*O*,4-*O*,5-*O*-tetrabenzyl-D-*myo*-inositol 30

A solution of tetrol **23** (0.15 g, 0.40 mmol), benzyl bromide (0.34 g, 2.0 mmol) and one crystal of TBAI in dry DMF (2 mL) was cannulated into a stirred suspension NaH (0.052 g, 2.2 mmol) in dry DMF (1 mL) at 0 °C under argon. The mixture was then warmed slowly to room temperature and stirred for 22 hours at room temperature. After this time water (10 mL) was added together with ether (10 mL). The layers were separated and the aqueous phase re-extracted with ether (3 x 20 mL). The organic extracts were combined, washed with water (30 mL) and dried ($MgSO_4$) and evaporated *in vacuo*. The crude oil was subjected to flash column chromatography on silica gel eluting with ether/petrol (1:9) to give *tetrabenzyl ether* **30** as a colourless solid (0.257 g, 0.35 mmol, 87%); m.p. 127-128 °C; $[\alpha]_D^{25}$ = + 53.0 (c = 1.03 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.48 (2H, dd, *J* 6.7, 1.2, 2 x *o*-Ar-*H*), 7.38-7.21 (18H, m, 18 x Ar-*H*), 5.01-4.74 (6H, m, 6 x C*H*O), 4.62 (2H, s, 1 x C*H*$_2$Ar), 4.37 (1H, apparent t, *J* 10.0, 1 x C*H*O), 4.04-3.96 (2H, m, 2 x C*H*O), 3.86 (1H, dt , *J* 13.0, 2.0, 1 x C*H*O), 3.72 (2H,dd, *J* 11.2, 4.6, 2 x C*H*O), 3.66-3.54 (3H, m, 3 x C*H*O), 3.43 (1H, dd, *J* 9.8, 2.5, 1 x C*H*O), 2.03-1.79 (4H, m, 4 x dispoke C*H*), 1.54-1.51 (1H, m, 1 x dispoke C*H*), 1.26-1.10 (5H, m, 5 x dispoke C*H*), 0.93 (6H, d, *J* 6.4, 2 x dispoke CH(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$) 139.09, 138.48 (2 x Ar(*C*)), 128.30, 128.25, 128.16, 128.06, 128.00, 127.91, 127.56, 127.50, 127.44, 127.22 (10 x

Ar(*C*H)), 97.07, 96.87 (2 x acetal(*C*)), 82.02, 81.56, 80.81 (3 x *C*HO), 76.09, 75.58 (2 x *C*H_2O), 74.36 (1 x *C*HO), 73.75, 72.51 (2 x *C*H_2O), 69.28, 68.72 (2 x *C*HO), 60.78, 60.61 (2 x dispoke *C*H_2O), 37.20, 33.57 (2 x dispoke *C*H_2), 24.99, 24.60 (2 x dispoke *C*H(CH_3)), 22.44, 22.36 (2 x dispoke CH(*C*H_3)); ν_{max} ($CHCl_3$ solution)/cm^{-1} 3066, 3007, 2931, 2873, 1496, 1454, 1359, 1264, 1188, 1142, 1071, 1050, 1028, 994, 915, 865, 698, 613; *m/z* (+FAB) 734 $(M)^+$, 733 $(M-H)^+$, 643, 613, 596, 551, 529, 460, 443, 349, 307, 289, 195, 181, 154; Found $(M-H)^+$ 733.3747. $C_{46}H_{53}O_8$ requires 733.3740.

2-*O*,3-*O*,4-*O*,5-*O*-Tetrabenzyl-D-*myo*-inositol 31

The benzylated adduct **30** (0.025 g, 0.03 mmol) was stirred under argon in 95% TFA/water (1 mL) for 195 minutes. After this time, the mixture was loaded directly onto a silica column and eluted with ether/petrol (2:1) to give diol **31** in (0.025 g, 0.005 mmol, 18%); $[\alpha]_D^{25}$ = + 14.3 (c = 0.04 in $CHCl_3$); and identical in all other respects to that isolated previously.

(2'*R*,2''*R*,6'*R*,6''*R*) 2-*O*,5-*O*-Dibenzoyl-1-*O*,6-*O*-(6,6'-diphenyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-L-*myo*-inositol 33

A solution of 2-*O*,5-*O*-dibenzoyl-*myo*-inositol **23** (0.14 g, 0.40 mmol), (2*R*,2'*R*) 2,2'-diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran **3** (0.17 g, 0.524 mmol) and CSA (0.02 g, catalytic) in $CHCl_3$ (3 mL) was heated under reflux for 16 hours. The solution was cooled to room temperature, evaporated *in vacuo* and subjected to flash column chromatography on silica gel eluting with ether/petrol (8:2) to give *diol* **33** as an amorphous white solid (0.09 g, 0.134 mmol, 33%); m.p. 195-207 °C; $[\alpha]_D^{27}$ = + 46.5 (c = 1.00, $CHCl_3$); δ_H (200 MHz , $CDCl_3$) 8.20 (2H, m, 2 x *o*-OCOAr-*H*), 7.80 (2H, m, 2 x *o*-OCOAr-*H*), 7.60-7.05 (16H, m, 4 x *m*- and 2 x *p*-OCOAr-*H*, 10 x Ar-*H*), 5.75 (1H, br.t, *J* 2.5, *H*-2), 5.26 (1H, t, *J* 9.9, *H*-5), 4.73 (2H, br.d, *J* 11.4, *H*-6', *H*-6''), 4.43 (1H, t, *J* 9.9, *H*-4), 3.96 (2H, m, *H*-6, *H*-3), 3.80 (1H, br.dd, *J* 10.0, 2.5, *H*-1), 3.10 (2H, br.s, 2 x O*H*), 2.05-1.30 (12H, 6 x dispoke CH_2); δ_C (50.3 MHz, $CDCl_3$) 166.9, 166.6, 143.2, 142.9, 133.3, 132.8, 129.82, 129.77, 128.4, 128.3, 127.2, 127.0, 125.7, 125.5, 98.1, 97.8, 73.9, 73.0, 72.1, 71.8, 71.5, 66.5, 66.1, 33.6, 33.2, 28.0, 27.8, 18.8, 18.6; ν_{max} ($CHCl_3$ solution)/cm^{-1} 3422, 2944, 1729, 1602, 1450, 1270, 1177, 1096, 1049, 1027, 968, 698; *m/z* (+FAB) 729 $(MNa)^+$, 707 $(MH)^+$, 689 $(M-OH)^+$, 585, 530, 391, 371, 319 $(3H)^+$; Found $(MH)^+$ 707.2807. $C_{42}H_{43}O_{10}$ requires 707.2855.

(2'*S*,2''*S*,6'*S*,6''*S*) 2-*O*,5-*O*-Dibenzoyl-1-*O*,6-*O*-(6,6'-diphenyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-D-*myo*-inositol 32

A solution of 2-*O*,5-*O*-dibenzoyl-*myo*-inositol **23** (0.20 g, 0.525 mmol), (2*S*,2'*S*) 2,2'-diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran **4** (0.17 g, 0.540 mmol) and CSA (0.03 g, catalytic) in $CHCl_3$ (5 mL) was heated under reflux for 16 hours. The solution was cooled to room temperature, evaporated *in vacuo* and subjected to flash column chromatography on silica gel eluting with ether/petrol (4:1) to give *diol* **32** as an amorphous white solid (0.17 g, 0.239 mmol, 46%); m.p. 198-202 °C; $[\alpha]_D^{25}$ = - 51.6 (c = 1.00, $CHCl_3$); with identical spectral data to enantiomeric **33** as described above.

(2'*S*,2''*S*,6'*S*,6''*S*) 1-*O*,6-*O*-(6,6'-Diphenyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-D-*myo*-inositol 34

NaOH solution (1% aq., 2 mL) was added to a suspension of diol **32** (0.05 g, 0.0716 mmol) in MeOH/Ether (9:1; 5 mL) and stirred vigorously for 40 minutes. The reaction mixture was then diluted with H_2O (10 mL), extracted with $CHCl_3$ (3 x 20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give *tetrol* **34** as an amorphous white solid (0.035 g, 0.0702 mmol, 98%); m.p. >230 °C; $[\alpha]_D^{25}$ = - 16.4 (c = 0.25 in EtOH); δ_H (200 MHz , CD_3OD) 7.40-7.10 (10H, m, 10 x Ar-*H*), 4.83 (1H, partially obscured by CD_3O*H*, *H*-6' (or *H*-6")), 4.65 (1H, dd, *J* 11.7, 2.3, *H*-6" (or *H*-6'), 3.92 (1H, t, *J* 2.8, *H*-2), 3.90 (1H, t, *J* 9.9, *H*-5), 3.60-3.45 (4H, m, *H*-1, *H*-3, *H*-4, *H*-6), 2.20-1.30 (12H, m, 6 x dispoke CH_2); δ_C (100 MHz, $CDCl_3$) 142.91 (Ar(*C*)), 128.28, 128.24, 127.38, 127.32, 126.20, 125.70 (6 x Ar(*C*H)), 98.21, 97.66 (2 x acetal(*C*)), 73.69, 72.14, 72.07, 70.16, 67.72, 67.64 (6 x *C*HO), 49.88, 49.67, 49.46, 49.24, 49.03 (5 x CH_2O), 33.55, 33.39, 28.29, 28.02, 18.73, 18.68, (6 x dispoke CH_2); ν_{max} (nujol)/cm^{-1} 3415, 2938, 1454, 1201, 1169, 1043, 980, 754, 698; *m/z* (EI) 499 $(MH)^+$, 498 $(M)^+$, 480 $(M-H_2O)^+$, 319 $(4H)^+$; Found $(MH)^+$ 499.2295. $C_{28}H_{35}O_8$ requires $(MH)^+$ 499.2332 ; Found (M^+) 498.2256. $C_{28}H_{34}O_8$ requires (M^+) 498.2253.

(2'*S*,2''*S*,6'*S*,6''*S*) 1-*O*,6-*O*-(6,6'-Diphenyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)2-*O*,3-*O*,4-*O*,5-*O*-tetrabenzyl-D-*myo*-inositol 35

Tetrol **34** (0.03 g, 0.060 mmol) was added to a stirred suspension NaH (0.012 g, 0.301 mmol) in dry DMF (0.5 mL) and stirred for 30 minutes. Benzyl bromide (38 µL, 0.301 mmol) was added and the reaction was further stirred for 16 hours. The reaction was quenched by addition of H_2O (10 mL), extracted with ether (3 x 15 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude oil was subjected to flash column chromatography on silica gel eluting with ether/petrol (1:9) to give *tetrabenzyl ether* **35** as a colourless mobile oil (0.052 g, 0.06 mmol, 99%); $[\alpha]_D^{25}$ = - 29.5 (c = 1.00 in $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.32-7.01 (30H, m, 30 x Ar-*H*), 5.09-4.57 (10H, m, 1 x *H*-6', 1 x *H*-6", 4 x ArCH_2O), 4.42 (1H, t, *J* 9.7, *H*-4), 3.98 (1H, t, *J* 2.4, *H*-2), 3.95 (1H, t, *J* 9.5, *H*-5), 3.61 (1H, dd, *J* 10.3, 2.0, *H*-1 (or *H*-3)), 3.53 (1H, t, *J* 9.2, *H*-6), 3.42 (1H, dd, *J* 9.7, 2.5, *H*-3 (or *H*-1)), 2.20-1.30 (12H, m, 6 x dispoke CH_2); δ_C (100 MHz, $CDCl_3$) 143.50, 143.23, 139.38, 139.24, 138.95, 138.62 (6 x Ar(*C*)), 128.34, 128.29, 128.21, 128.11, 128.02, 127.93, 127.70, 127.60, 127.51, 127.38, 127.32, 127.29, 127.13, 126.94, 125.86 (15 x Ar(*C*H)), 97.75, 97.45 (2 x acetal(*C*)), 82.03, 81.57, 80.63 (3 x *C*H), 75.93, 75.26 (2 x CH_2), 74.92 (*C*H), 74.07, 72.45 (2 x CH_2), 71.79, 71.33, 69.45, 68.88 (4 x *C*H), 33.43, 33.32, 28.55, 28.33, 19.23, 19.01 (6 x dispoke CH_2); ν_{max} (film)/cm^{-1} 3026, 2933, 1605, 1492, 1451, 1359, 1205, 1164, 1062, 969, 728, 697; *m/z* (CI) 858 $(M)^+$, 765, 643, 319 $(4H)^+$, 241, 117, 91 $(C_7H_7)^+$; Found $(M)^+$ 858.4086. $C_{56}H_{58}O_8$ requires 858.4131.

2-*O*,3-*O*,4-*O*,5-*O*-Tetrabenzyl-D-*myo*-inositol 31

The benzylated adduct **35** (0.022g, 0.026 mmol) was stirred under argon in 95% TFA/water (1 mL) for 75 minutes. After this time, the mixture was loaded directly onto a silica column and eluted with ether/petrol (2:1) to give diol **31** in (0.004 g, 0.0071 mmol, 33%), which was spectroscopically identical to that isolated previously.

(2*R,2'*R**,2''*R**,2'''*R**)-3-*O*,4-*O*:5-*O*,6-*O*-Di-(3,3',4,4',5,5',6,6'-octahydro-6,6'-bi-2*H*-pyran-2,2'-diyl)-DL-*myo*-inositol 38**

A solution of *myo*-inositol **37** (0.212 g, 1.17 mmol) and CSA (0.05 g, 0.22 mmol) in dry DMF (10 mL) under argon was heated to 100 °C and treated with the *bis*-DHP **36** (0.57 g, 3.43 mmol). The mixture was heated at this temperature for 24 hours and then allowed to cool to room temperature. Solid $NaHCO_3$ (~2 g, ~ 23.8 mmol) was added and the resulting mixture extracted with ethyl acetate (3 x 20 mL). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil. This was subjected to flash column chromatography on silica gel, eluting with ether/petrol (1:1), to give the *bis*-adduct **38** as a colourless solid (0.21 g, 0.47 mmol, 40%); m.p 228-229 °C (DCM/petrol); δ_H (200 MHz , $CDCl_3$) 4.15-3.95 (4H, m, 4 x C*H*O), 3.90-3.50 (10H, m, 2 x C*H*O, 4 x dispoke CH_2O), 2.60 (2H, br.s, 2 x O*H*), 1.90-1.30 (24H, m, 12 x dispoke CH_2); δ_C (50 MHz , $CDCl_3$) 97.41, 96.86, 96.31, 96.16 (4 x acetal(*C*)), 70.51, 70.12, 69.30, 68.32, 67.17, 64.96, 60.86, 60.72, 60.62, 28.75, 28.70, 28.48, 28.27, 25.04, 24.82, 18.33, 18.05, 17.91, 14.05; ν_{max} (nujol)/cm^{-1} ; 3486, 3415, 1463, 1377, 1191, 1080, 1030, 950; *m/z* (EI) 512 $(M)^+$, 413, 383, 365, 312, 293, 254, 235, 201, 167, 112, 101, 94, 83, 66, 55; Found $(M)^+$ 512.2622. $C_{26}H_{40}O_{10}$ requires $(M)^+$ 512.2621.

(2*R,2'*R**,2''*R**,2'''*R**)-1-*O*,2-*O*-Diacetyl-3-*O*,4-*O*:5-*O*,6-*O*-di-(3,3',4,4',5,5',6,6'-octahydro-6,6'-bi-2*H*-pyran-2,2'-diyl)-DL-*myo*-inositol 39**

Diol **38** (0.16 g, 0.3 mmol) was dissolved in a solution of triethylamine (0.14 g, 1.43 mmol) and acetic anhydride (0.22 g, 2.12 mmol) containing DMAP (0.005g, catalytic) and the solution stirred overnight under argon. The reaction was quenched by the addition of $NaHCO_3$ (10 mL; sat. aq.) and stirring continued for 10 minutes. The mixture was then extracted with DCM (3 x 20 mL) and the combined extracts dried ($MgSO_4$) and evaporated *in vacuo*. The residue was then subjected to flash column chromatography, eluting with ether/petrol (2:3) to give the *diacetate* **39** as a colourless oil (0.17 g, 0.29 mmol, 95%); δ_H (200 MHz , $CDCl_3$) 5.60 (1H, apparent t, *J* 7.0, C*H*OAc), 4.95 (1H, dd, *J* 7.0, 2.0, C*H*OAc), 3.90-3.50 (12H, m, *H*-3, *H*-4, *H*-5, *H*-6, 4 x dispoke CH_2), 1.90-1.35 (24H, m, 12 x dispoke CH_2); δ_C (50 MHz , $CDCl_3$) 170.21, 169.88 (2 x *C*=O), 97.25, 96.94, 96.49, 96.19 (4 x acetal(*C*)), 69.54, 69.30, 67.45, 66.93, 66.14, 65.05 (6 x *C*HO), 60.90, 60.83, 60.72 (3 x *C*H$_2$O), 29.30, 28.71, 28.40, 28.30, 25.08, 24.94, 24.78, 20.94 (1 x *C*H$_3$CO), 20.60 (1 x *C*H$_3$CO), 17.80; ν_{max} (film)/cm^{-1} ; 2950, 2875, 1750, 1430, 1370, 1350, 1290, 1140, 1050, 1030, 990, 800, 650; *m/z* (+FAB) 597 $(MH)^+$, 565, 513, 495, 413, 396, 289, 267, 236, 229, 196, 183, 167, 136; Found $(MH)^+$ 597.2868. $C_{30}H_{45}O_{12}$ requires $(MH)^+$ 597.2910.

(2*R,2'*R**,2''*R**,2'''*R**)-1-*O*,2-*O*-Thionocarbonate-3-O,4-O:5-O,6-O-di-(3,3',4,4',5,5',6,6'-octahydro-6,6'-bi-2*H*-pyran-2,2'-diyl)-DL-*myo*-inositol 40**

A solution of diol **38** (0.15 g, 0.29 mmol) in dry DCM (5 mL) was treated with thiocarbonyldiimidazole (0.07 g, 0.39 mmol) and the resulting mixture was stirred for 16 hours. The solution was evaporated *in vacuo* to approximately one quarter of its original volume and the residue subjected to flash column chromatography, eluting with ether/petrol (2:3) to give the *thionocarbonate* **40** as a colourless foam; δ_H (250 MHz , $CDCl_3$) 4.96-4.81 (2H, m, 2 x C*H*OC=S), 4.10-3.88 (3H, m, 3 x *H* of inositol), 3.82-3.53 (9H, m, 1 x *H* of inositol, 4 x dispoke CH_2), 1.91-1.28 (22H, m, 11 x dispoke CH_2), 1.19-1.10 (1H, m, 1 x dispoke C*H*H), 0.90-0.50 (1*H*, m, 1 x dispoke CH*H*); δ_C (50 MHz , $CDCl_3$) 190.80 (*C*=S), 97.80, 97.28, 96.30, 96.26 (4 x acetal(*C*)), 80.64, 70.34, 65.35, 65.18, 64.08, 61.05, 60.96, 60.87, 60.57, 28.54, 28.46, 28.16, 27.97,

24.83, 24.66, 24.51, 18.24, 18.08, 17.72, 17.63; ν_{max} (nujol)/cm^{-1}; 3052, 2983, 2950, 1263; *m/z* (+FAB) 555 (MH)$^+$, 539, 460; Found (MH)$^+$ 555.2297. $C_{27}H_{39}SO_{10}$ requires (MH)$^+$ 555.2297. Found C: 58.46; H: 7.00%. $C_{27}H_{38}SO_{10}$ requires C: 58.47; H: 6.91%.

(2*R,2'*R**,2''*R**,2'''*R**)-3-*O*,4-*O*:5-*O*,6-*O*-di-(3,3',4,4',5,5',6,6'-octahydro-6,6'-bi-2*H*-pyran-2,2'-diyl)-conduritol B 41**

Thionocarbonate **40** (0.06 g, 0.11 mmol) in trimethylphosphite (10 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature and evaporated to dryness. The residue was azeotroped with toluene (3 x 10 mL) to give a colourless oil. This was subjected to flash column chromatography on silica gel, using ether/petrol (3:2) as eluent to give *alkene* **41** as a colourless foam (0.032 g, 0.067 mmol, 61%); δ_H (250 MHz , $CDCl_3$) 5.62 (2H, s, 2 x C*H*=C), 4.54-4.47 (2H, m, 2 x C=CC*H*O), 4.07-4.00 (2H, m, 2 x C*H*O), 3.88-3.58 (8H, 4 x dispoke CH_2), 1.91-1.49 (24H, m, 12 x dispoke CH_2); δ_C (50 MHz , $CDCl_3$) 127.40 (1 x *C*=C), 97.80, 96.92 (2 x acetal(*C*)), 69.42, 67.73, (2 x *C*HO), 60.84, 60.51 (2 x *C*H_2O), 28.85, 28.67, 25.00, 24.86, 18.28, 17.94 (6 x dispoke *C*H_2); ν_{max} (CH_2Cl_2 solution)/cm^{-1}; 3044, 2948, 2877, 1466, 1452, 1440, 1384, 1354, 1287, 1209, 1192, 1174, 1161, 1144, 1090, 1058, 963, 934, 918, 896, 878, 854, 820, 652, 623; *m/z* (+FAB) 479 (MH)$^+$, 295, 277, 260, 236, 213, 183, 167, 154, 136; Found (MH)$^+$ 479.2607. $C_{26}H_{39}O_8$ requires (MH)$^+$ 497.2607.

(2'*R*,2''*R*,2'''*R*,2''''*R*,6'*S*,6''*S*,6'''*S*,6''''*S*)-1-*O*,6-*O*:3-*O*,4-*O*-Di-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-L-*myo*-inositol 42

To a solution of tetrol **25** (0.07 g, 0.19 mmol) and diene **1** (0.045 g, 0.23 mmol) in dry $CHCl_3$ (6 mL; passed through a plug of alumina) was added CSA (0.01 g, 0.04 mmol). The solution was refluxed, under argon, for 24 hours and then cooled to room temperature. After evaporation of the solution, *in vacuo*, the residue was subjected to flash column chromatography, using ether/petrol (1:1) as eluent to give diol **42** (0.018 g, 0.03 mmol, 17%) as a colourless oil; $[\alpha]_D^{25}$ = - 68.5 (c = 0.26 in $CHCl_3$); δ_H (500 MHz , $CDCl_3$) 4.12 (1H, apparent t, *J* 2.7, *H*-2), 4.06 (1H, apparent t, *J* 9.9, *H*-6), 3.98 (1H, apparent t, *J* 9.9, *H*-4), 3.94-3.86 (2H, m, 2 x dispoke C*H*O), 3.83-3.80 (1H, m, 1 x dispoke C*H*O), 3.79-3.67 (2H, dd, *J* 9.4, 2.5, 1 x dispoke C*H*O, *H*-3), 3.63 (1H, apparent t, *J* 9.9, *H*-5), 3.56-3.54 (1H, dd, *J* 9.9, 2.7, *H*-1), 2.10 (1H, br.s, O*H*), 1.88-1.74 (8H, m, 4 x dispoke CH_2), 1.59-1.52 (8H, m, 4 x dispoke CH_2), 1.48-1.25 (8H, m, 4 x dispoke CH_2), 1.16-1.11 (12H, m, 4 x overlapping dispoke CH(CH_3)); δ_C (100 MHz , $CDCl_3$) 98.20, 97.68, 97.01, 96.71 (4 x acetal(*C*)), 72.15, 70.60, 70.16, 69.35, 68.25, 67.61, 67.49, 65.76, 65.71, 65.00 (10 x *C*HO), 38.75, 37.19, 32.85, 32.54, 32.49, 28.28, 28.22, 27.85, (8 x dispoke *C*H_2), 23.41, 22.27, 22.07, 21.97 (4 x *C*H(CH_3)), 19.83, 18.61, 18.52, 18.39 (4 x dispoke *C*H_2); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3588, 3019, 2934, 1516, 1444, 1382, 1213, 1090, 1047, 987, 940, 748; *m/z* (EI) 591 (MNa)$^+$, 568 (M)$^+$, 567 (M-H)$^+$, 250; Found (MNa)$^+$ 591.3105. $C_{30}H_{48}NaO_{10}$ requires (MNa)$^+$ 591.3145.

(2*S*,2'*R*,2''*R*,3*S*,4*S*,6'*S*,6''*S*)-1-*O*,5-*O*-Di-(*tert*-butyldiphenylsilyl)-2-*O*,3-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-xylitol 43

For the preparation of compound **43**, see reference 1.

(2*S*,2'*R*,2''*R*,3*S*,4*S*,6'*S*,6''*S*)-1-*O*,5-*O*-Di-(pivaloyl)-2-*O*,3-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-xylitol 45

To a solution of triol **45**[27] (0.149 g, 0.46 mmol) and diene **1** (0.109 g, 0.56 mmol) in dry $CHCl_3$ (5 mL; passed through a plug of alumina) was added CSA (0.023 g, 0.10 mmol). The solution was refluxed, under argon, for 25 hours and then cooled to room temperature. After evaporation of the solvent, *in vacuo*, the residue was subjected to flash column chromatography on silica gel, using ether/petrol (3:7) as eluent to give alcohol **46** (0.032 g, 0.056 mmol, 13%) as a colourless oil; $[\alpha]_D^{25}$ = - 25.1 (c = 1.07 in $CHCl_3$); δ_H (400 MHz , $CDCl_3$) 5.25-5.23 (1H, ddd, *J* 9.0, 4.8, 2.3, C*H*HCH$_2$OCO(C(CH$_3$)$_3$)), 4.61-4.58 (1H, dd, *J* 12.2, 5.2, C*H*HOCOC(CH$_3$)$_3$), 4.21-4.17 (1H, dd, *J* 12.2, 2.2, CH*H*OCO(CH$_3$)$_3$), 4.06-4.01 (1H, apparent t, *J* 11.0, C*H*HCH(OH), 3.94-3.91 (1H, dt, *J* 11.2, 3.0, C*H*(OH)), 3.78-3.74 (1H, m, 1 x dispoke C*H*(CH$_3$)), 3.64 (1H, d, *J* 9.0, C*H*CH(OH)), 3.63 (1H, m, 1 x dispoke C*H*(CH$_3$)), 3.42-3.39, (1H, dd, *J* 11.0, 3.0, CH*H*CH(OH)), 1.86-1.68 (4H, m, 2 x dispoke C*H*$_2$), 1.58-1.54 (4H, m, 2 x dispoke C*H*$_2$), 1.48-1.33 (2H, m, 1 x dispoke C*H*$_2$), 1.32-1.23 (2H, m, 1 x dispoke C*H*$_2$), 1.22-1.07 (24H, m, 2 x C(C*H*$_3$)$_3$, 2 x dispoke CH(C*H*$_3$)); δ_C (100 MHz , $CDCl_3$) 178.22, 177.16 (2 x *C*OC(CH$_3$)$_3$), 97.10, 95.91 (2 x acetal(*C*)), 69.80, 68.38, 66.14, 66.07, 65.17 (5 x *C*HO), 62.75, 59.16 (2 x *C*H$_2$OCO(CH$_3$)$_3$), 32.50, 32.39, 27.21, 27.13 (4 x dispoke *C*H$_2$), 22.13, 21.73 (2 x C(*C*H$_3$)$_3$), 18.48, 18.27 (2 x dispoke *C*H$_2$); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3540, 2974, 2936, 2873, 1723, 1480, 1458, 1382, 1281, 1148, 1028, 989, 962, 904; *m/z* (+FAB) 514 $(M)^+$, 513 $(M-H)^+$, 497 $(M-OH)^+$, 441, 400, 357, 303, 269, 229, 195; Found $(M)^+$ 514.3159. $C_{27}H_{46}O_9$ requires $(M)^+$ 514.3142.

(2*S*,2'*R*,2''*R*,3*S*,4*S*,6'*S*,6''*S*)-2-*O*,3-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-xylitol 47

To a solution of alcohol **44** (0.246 g, 0.3 mmol) in dry THF (3 mL) was added a solution of TBAF (1.1 M, 0.6 mL, 0.66 mmol, 2.2 eq.). The solution was stirred, under argon, for 40 hours before being evaporated *in vacuo* . The residue was subjected to flash column chromatography on silica gel, using DCM/MeOH (10:1) as eluent, to give *triol* **47** (0.094 g, 0.27 mmol, 90%); m.p. 215-216°C (MeOH); $[\alpha]_D^{25}$ = + 18.2 (c = 0.2 in CH_3OH); δ_H (400 MHz, CD_3OD) 3.24-3.20 (1H, ddd, *J* 9.6, 4.8, 3.4, C*H*O), 3.11-3.08 (1H, dd, *J* 9.8, 1.7, C*H*O), 3.02-2.84 (7H, m, 7 x C*H*O), 1.09-0.86 (5H, m, 2 x dispoke C*H*$_2$, 1 x dispoke C*H*H), 0.79-0.76 (3H, 1 x dispoke C*H*$_2$, 1 x dispoke CH*H*), 0.68-0.49 (4H, 2 x dispoke C*H*$_2$), 0.35-0.30 (6H, m, 2 x CH(C*H*$_3$)); δ_C (100 MHz, CD_3OD) 98.14, 98.06 (2 x acetal(*C*)), 72.13, 69.76, 69.02, 64.34, 67.17 (5 x *C*HO), 64.09, 62.64 (2 x *C*H$_2$O), 33.72, 28.95, 28.90 (3 x dispoke *C*H$_2$), 27.07, 22.04 (2 x *C*H$_3$), 20.94, 19.80, 19.50 (3 x dispoke *C*H$_2$); *m/z* (EI) 369 $(MNa)^+$, 346 $(M)^+$, 345 $(M-H)^+$, 307 $(M-CH_2OH)^+$, 289 $(M-CH_2OH-H_2O)^+$, 195, 186; Found $(MNa)^+$ 369.1880. $C_{17}H_{30}NaO_7$ requires $(MNa)^+$ 369.1889.

(2*S*,2'*R*,2''*R*,3*S*,4*S*,6'*S*,6''*S*)-1-*O*,4-*O*,5-*O*-Tribenzyl-2-*O*,3-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-xylitol 48

To a solution of triol **47** (0.084 g, 0.24 mmol), benzyl bromide (0.128 g, 0.75 mmol) and one crystal of TBAI in dry DMF (5 mL) was added NaH (0.074 g, 3.1 mmol). The solution was stirred for 24 hours before the addition of water (10 mL) and ether (10 mL). The layers were separated and the aqueous re-extracted with ether (3 x 20 mL). The combined organic fractions were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was then subjected to flash column chromatography on silica gel, eluting with ether/petrol (1:4) to give the *benzyl*

ether **48** as a colourless oil (0.105 g, 0.17 mmol, 71%); $[\alpha]_D^{23}$ - 32.6 (c = 1.75 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.48-7.09 (15H, m, 15 x Ar-*H*), 4.76 (1H, d, *J* 12.1, C*H*O), 4.58-4.38 (5H, m, 5 x C*H*O), 4.20-4.15 (1H, m, 1 x C*H*O), 4.03-4.01 (1H, d, *J* 9.8, 1 x C*H*O), 3.89-3.86 (1H, m, 1 x C*H*O), 3.81-3.67 (4H, m, 4 x C*H*O), 3.45-3.41 (1H, dd, *J* 11.0, 3.0, 1 x C*H*O), 3.32-3.28 (1H, dd, *J* 11.0, 4.8, 1 x C*H*O), 1.91-1.74 (4H, 2 x dispoke CH_2), 1.56-1.36 (6H, 3 x dispoke CH_2); δ_C (100 MHz, $CDCl_3$) 138.80, 138.65, 138.49, (3 x Ar(*C*)), 130.56, 129.67, 129.45, 128.44, 128.36, 128.25, 128.21, 128.12, 127.98, 127.78, 127.69, 127.56, 127.52, 127.43 (14 x Ar(*C*H)), 96.78, 96.08 (2 x acetal(*C*)), 73.37 (*C*HO), 72.33, 70.04, 69.45, 68.85 (4 x CH_2O), 67.62, 67.12, 65.90, 65.81 (4 x *C*HO), 32.76, 32.71, 27.87, 27.84 (4 x dispoke CH_2), 21.93 (2 x dispoke $CH(CH_3)$), 18.66, 18.85 (2 x dispoke CH_2); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3003, 2971, 2933, 2869, 1496, 1454, 1217, 1194, 1175, 1152, 1139, 1093, 1068, 1047, 764, 760, 748, 699; *m/z* (+FAB) 639 $(MNa)^+$, 617 $(MH)^+$, 616 $(M)^+$, 499, 313, 280, 267, 195; Found $(MH)^+$ 617.3522. $C_{38}H_{49}O_7$ requires $(MH)^+$ 617.3478.

(2*S*,3*R*,4*R*)-1-*O*,4-*O*,5-*O*-Tribenzyl-L-xylitol 49 and (2*S*,3*S*,4*R*)-1-*O*,4-*O*,5-*O*-Tribenzyl-2-*O*,3-*O*-di-((*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl-xylitol 50

The benzyl adduct **48** (0.022 g, 0.036 mmol) was dissolved in 95%TFA/water (1 mL) and the solution stirred for 26 hours. After this time, the solution was loaded directly onto a silica column and eluted with ether/petrol (2:8) to give, in order of elution, recovered **48** (0.005 g, 0.008 mmol, 24%) with spectroscopic properties identical to that isolated previously, and diol **49** as a colourless oil (0.0073 g, 0.017 mmol, 63% based upon recovered **48**); $[\alpha]_D^{23}$ - 5.1 (c = 0.39 in $CHCl_3$); δ_H (400 MHz , $CDCl_3$) 7.36-7.25 (15H, m, 15 x Ar-*H*), 4.75 (1H, d, *J* 4.2, C*H*HAr), 4.62-4.49 (5H, m, 2 x CH_2Ar, 1 x C*H*HAr), 3.91 (1H, m, C*H*O), 3.81 (1H, m, C*H*O), 3.76-3.73 (3H, apparent s, 3 x C*H*O), 3.59-3.47 (2H, m, 2 x C*H*O), 3.08 (1H, br.s, O*H*), 2.85 (1H, br.s, O*H*); δ_C (100 MHz , $CDCl_3$) 138.04, 137.99, 137.93 (3 x Ar(*C*)), 128.56, 128.54, 128.49, 128.16, 128.00, 127.84, 127.79 (7 x Ar(*C*H)), 79.07 (*C*HO*C*H$_2$Ar), 73.64, 73.54, 72.70, 71.74 (4 x *C*H$_2$), 71.21, 70.44 (2 x*C*HO), 69.76(*C*H$_2$); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3440, 3062, 3029, 2864, 1496, 1453, 1364, 1208, 1101, 1028, 910, 736, 697; *m/z* (+FAB) 423 $(MH)^+$, 307, 197, 181; Found $(MH)^+$ 423.2202. $C_{26}H_{31}O_5$ requires $(MH)^+$ 423.2171.

(*R*)-(-)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.017 g, 0.07 mmol) was added dropwise to a solution of diol **49** in dry toluene (0.5 mL) containing triethylamine (0.007 g, 0.07 mmol) and one crystal of DMAP. The solution was refluxed for 90 minutes and cooled to room temperature. Ether was added (10 mL) followed by $NaHCO_3$ (10 mL; sat. aq.) and the resulting mixture stirred for 10 minutes. The layers were separated and the aqueous re-extracted with ether (2 x 10 mL). The combined organic fractions were washed sequentially with $NaHCO_3$ (5 mL), NH_4Cl (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Dry DCM (10 mL) was added and the solution filtered through a plug of Florisil®, eluting with dry DCM (5 mL). The solution was then evaporated *in vacuo* to give the *di-Mosher ester derivative* **50**; δ_H (500 MHz, $CDCl_3$) 7.40-7.05 (25H, m, 25 x Ar-*H*), 5.75-5.70 (1H, m, 1 x C*H*OCO), 5.63 (1H, m, 1 x C*H*OCO), 4.45-4.38 (3H, m, 3 x C*H*O), 4.35-4.25 (2H, m, 2 x C*H*O), 3.65-3.60 (1H, m, 1 x C*H*O), 3.55-3.50 (2H, m, 2 x C*H*O), 3.48-3.42 (3H, m, 3 x C*H*O), 3.38 (6H, s, 2 x O*CH*$_3$); δ_F (235 MHz , $CDCl_3$) -72.08 (3F, s, CF_3), -72.18 (3F, s, CF_3).

(2*S,3*S**,4*R**)-1-*O*,5-*O*-Di-(*tert*-butyldiphenylsilyl)-2-*O*,3-*O*-(isopropylidene)-xylitol 51**

To a mixture of anhydrous copper sulfate (0.49 g, 3.1 mmol) and PPTS (0.097 g, 0.38 mmol) in H.P.L.C. grade acetone (11 mL) was added triol **43**[27] (1.76 g, 2.8 mmol). The mixture was stirred, under argon, for 19 hours and then filtered. The solution was evaporated, *in vacuo*, and the residue subjected to flash column chromatography using ether/petrol as eluent (1:5) to give acetonide **51** as a colourless oil (1.69 g, 2.5 mmol, 90%). δ_H (400 MHz, $CDCl_3$) 7.69-7.66 (8H, m, 8 x *o*-Ar-*H*), 7.44-7.36 (12H, m, 8 x *m*-Ar-*H*, 4 x *p*-Ar-*H*), 4.19 (2H, s, 2 x C*H*O), 3.81-3.66 (5H, m, 5 x C*H*O), 2.37 (1H, d, *J* 7.5, O*H*), 1.42 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.06 (9H, s, C(CH_3)$_3$), 1.05 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$); 135.66, 135.62 (2 x Ar(*C*H)), 133.30, 133.15 (2 x Ar(*C*)), 129.76, 127.76 (2 x Ar(*C*H)), 109.29 (acetal(*C*)), 78.02, 77.05, 70.25 (3 x *C*HO), 65.62, 64.12 (2 x *C*H_2O), 27.18, 27.07 (2 x *C*H_3), 26.86 (2 x overlapping C(*C*H_3)$_3$), 19.24 (2 x overlapping *C*(CH$_3$)$_3$); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3256, 2932, 2858, 1462, 1113, 998, 976, 897; *m/z* (+FAB) 669 (MH)$^+$, 653, 611, 535, 515, 475, 453, 397, 337, 269, 241, 221, 197, 183, 135; Found (MH)$^+$ 669.3461. $C_{40}H_{53}O_5Si_2$ requires (MH)$^+$ 669.3431.

(2*S,3*S**,4*R**)-2-*O*,3-*O*-(isopropylidine)-xylitol 52**

To acetonide **51** (1.65 g, 2.6 mmol) in dry THF (10 mL) was added, under argon, TBAF (1.1 M in THF, 4.74 g, 5.2 mL, 2.2 eq.). The resulting solution was stirred for 27 hours before being evaporated *in vacuo*. The residue was loaded directly onto a silica column, eluting with 1% MeOH in ethyl acetate, to give triol **52** (0.398 g, 2.1 mmol, 79%) as a colourless oil; δ_H (400 MHz , CD_3OD) 4.11-4.08 (1H, m, 1 x C*H*O), 3.91-3.89 (1H, d, *J* 8.3, 1 x C*H*O), 3.71-3.56 (5H, m, 5 x C*H*O), 1.39 (3H, s, CH_3), 1.37 (3H, CH_3); δ_C (100 MHz , CD_3OD); 110.28 (acetal(*C*)), 79.43, 78.85, 71.99 (3 x *C*HO), 64.71, 63.39 (2 x *C*H_2O), 27.45, 27.20 (2 x *C*H_3); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3442, 3114, 3107, 3098, 3088, 3056, 3046, 3032, 3014, 3008, 1538, 1466, 1262, 948, 712, 673; *m/z* (EI) 177 (M-CH_3)$^+$ 161, 131, 103, 85, 73, 69, 59, 49, 45; Found (M-CH_3)$^+$ 177.0760. $C_7H_{13}O_5$ requires (M-CH_3)$^+$ 177.0763.

(2*S,3*S**,4*R**)-1-*O*,4-*O*,5-*O*-Tribenzyl-2-*O*,3-*O*-(isopropylidine)-xylitol 53**

A solution of triol **52** (0.36 g, 1.8 mmol), benzyl bromide (0.99 g, 6 mmol) in dry DMF (5 mL) was cannulated into a mixture of NaH (0.28 g, 11.6 mmol) in dry DMF (3 mL) under argon at 0 °C. After warming slowly to room temperature, the mixture was stirred for 17 hours. After this time water (10 mL) and ether (20 mL) were added and the layers separated. The aqueous phase was re-extracted with ether (3 x 20 mL) and the combined organic fractions washed with water (30 mL). The organic fraction was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was then subjected to flash column chromatography, eluting with ether/petrol (1:4) to give the *benzyl ether* **53** as a colourless oil (0.76 g, 1.66 mmol, 89%); δ_H (400 MHz , $CDCl_3$) 7.42-7.33 (15H, m, 15 x Ar-*H*), 4.85 (1H, d, *J* 11.9, C*H*HAr), 4.70 (1H, d, *J* 11.9, CH*H*Ar), 4.59 (2H, s, CH_2Ar), 4.55 (2H, s, CH_2Ar), 4.33-4.29 (1H, m, C*H*O), 4.08 (1H, d, *J* 8.1, C*H*O), 3.76 (3H, s, 3 x C*H*O), 3.62-3.55 (2H, m, 2 x C*H*O), 1.50 (6H, s, 2 x CH_3); δ_C (100 MHz , $CDCl_3$); 138.53, 138.27, 138.21 (3 x Ar(*C*)), 128.83, 128.48, 128.40, 128.27, 128.06, 127.78, 127.72, 127.40 (8 x Ar(*C*H)), 109.42 (acetal(*C*)), 78.52, 76.68, 76.08 (3 x *C*H), 73.54, 73.49, 73.18, 70.81, 70.74 (5 x *C*H_2), 27.29, 27.02 (2 x *C*H_3); ν_{max} ($CHCl_3$ solution)/cm^{-1} 3063, 3030, 2985, 2863, 1496, 1454, 1368, 1250, 1213, 1090, 1028, 909, 858, 736, 697; *m/z* (CI) 480 (MNH_4)$^+$ 463 (MH)$^+$, 447, 405, 354, 341, 313, 295, 225, 205, 198, 181, 157, 108, 91; Found (MH)$^+$ 463.2487. $C_{29}H_{35}O_5$ requires (MH)$^+$ 463.2484.

(2*S,3*R**,4*R**)-1-*O*,2-*O*,5-*O*-Tribenzyl-xylitol 49 and (2*S**,3*S**,4*R**)-1-*O*,2-*O*,5-*O*-Tribenzyl-2-O,3-O-di-((*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl)-xylitol 50**

To the benzyl ether **53** (0.38 g, 0.84 mmol) in dry MeOH (5 mL) was added CSA (0.35 g, 1.50 mmol) and the solution stirred under argon for 36 hours. After this time the mixture was heated at 40 °C for 15 hours and then cooled to room temperature. After evaporation, *in vacuo*, the residue was subjected to flash column chromatography on silica gel, using ether/petrol (2:1) as eluent to give, in order of elution, recovered starting material **53** (0.038 g, 0.08 mmol, 10%), identical in all respects to that isolated previously, and racemic *diol* **49** (0.222g, 0.53 mmol, 70% (based on recovered **53**)) as a colourless oil identical in all respects to that isolated previously.

To this material **(+/-)-49** (0.019 g, 0.046 mmol) in dry toluene (0.5 mL), containing triethylamine (0.01 g, 0.096 mmol) and one crystal of DMAP, was added (*R*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.067 g, 0.29 mmol). The solution was refluxed for 6 hours and cooled to room temperature. Ether (10 mL) and $NaHCO_3$ (10mL; sat. aq.) were added and the layers were separated. The aqueous layer was re-extracted with ether (2 x 10 mL). The combined organic fractions were washed sequentially with $NaHCO_3$ (5 mL), NH_4Cl (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Dry DCM (10 mL) was added and the solution filtered through a plug of Florisil®, eluting with dry DCM (5 mL). The solution was then evaporated *in vacuo* to give the *di-Mosher ester derivative*; **50**; δ_H (500 MHz , $CDCl_3$) 7.54-7.51 (8H, m, 8 x Ar-*H*), 7.40-7.05 (42H, m, 42 x Ar-*H*), 5.75-5.70 (2H, m, 2 x C*H*OCO), 5.66-5.64 (1H, m, 1 x C*H*OCO), 5.61-5.58 (1H, m, 1 x C*H*OCO), 4.76-4.74 (1H, d, *J* 11.3, 1 x C*H*O), 4.69-4.28 (11H, m, 11 x C*H*O), 3.70-3.59 (2H, m, 2 x C*H*O), 3.52-3.50 (4H, m, 4 x C*H*O), 3.46-3.44 (4H, m, 4 x C*H*O), 3.37 (12H, s, 4 x OCH_3); δ_F (235 MHz , $CDCl_3$) -71.86 (3F, s, CF_3) -72.08 (3F, s, CF_3), -72.18 (3F, s, CF_3), -72.21 (3F, s, CF_3).

(2*R*,2'*S*,2''*R*,2'''*R*,2''''*S*,3*S*,4*S*,6'*S*,6''*S*,6'''*S*,6''''*S*)-3-*O*-Benzyl-1-*O*,2-*O*:4-*O*,5-*O*-di-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-adonitol 55

To a solution of diene **1** (0.110 g, 0.56 mmol), benzyl ether **54**[28] (0.116 g, 0.48 mmol) in dry $CHCl_3$ (5 mL; passed through a plug of alumina) was added CSA (0.016 g, 0.069 mmol). The solution was refluxed, under argon, for 25 hours and cooled to room temperature. After evaporation of the solvent, *in vacuo*, the residue was subjected to flash column chromatography on silica gel, using ether/petrol (5:95to 10:90) as eluent, to give *bis*-adduct **55** (0.101 g, 0.16 mmol, 67%) as a colourless oil; $[\alpha]_D^{23}$ - 56.5 (c = 0.65 in $CHCl_3$); δ_H (400 MHz , $CDCl_3$) 7.71-7.24 (5H, m, 5 x Ar-*H*), 4.89 (1H, d, *J* 11.1, C*H*HAr), 4.70 (1H, d, *J* 11.1, CH*H*Ar), 4.32-4.28 (1H, m, C*H*O), 4.14-3.73 (9H, m, 9 x C*H*O), 3.64-3.56 (1H, dd, *J* 11.0, 2.9, 1 x C*H*O), 1.86-1.73 (10H, 5 x dispoke CH_2), 1.55-1.44 (12H, 6 x dispoke CH_2) 1.41-1.20 (2H, m, 1 x dispoke CH_2), 1.13, 1.12, 1.09, 1.06 (12H, 4 x d, *J* 6.2, 4 x CH_3); δ_C (100 MHz , $CDCl_3$) 138.61 (Ar(*C*)), 128.45, 128.26, 127.62 (3 x Ar(*C*H)), 97.95, 97.51, 97.15, 95.92 (4 x acetal(*C*)), 79.50 (*C*HOCH$_2$Ar), 74.58 (*C*H$_2$Ar), 68.53, 67.46, 66.59, 66.40, 65.99, 65.77 (6 x *C*H), 60.53, 58.39 (2 x *C*H$_2$), 32.79, 32.70, 32.62, 28.22, 27.89, 27.74, 27.42 (7 x dispoke *C*H$_2$), 22.04, 21.89, 21.87, 21.74 (4 x *C*H$_3$), 18.63, 18.52 (2 x dispoke *C*H$_2$); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 2937, 1444, 1382, 1093, 1028, 990, 951; *m/z* (+FAB) 630 (M)$^+$, 613, 516, 417, 402, 347, 311, 288, 271, 255, 211, 195, 167, 141; Found (M)$^+$ 630.3825. $C_{36}H_{54}O_9$ requires (M)$^+$ 630.3768.

(2*R*,2'*S*,2''*R*,3*S*,4*S*,6'*S*,6''*S*)-3-*O*-Benzyl-1-*O*,2-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-adonitol 56 and (2*S*,2'*S*,2''*R*,6'*S*,6''*S*)-1-*O*,2-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-glycerol 57

To the *bis*-adduct **55** (0.05 g, 0.079 mmol) and glycerol (0.14 g, 1.6 mmol) in dry $CHCl_3$ (1.5 mL; passed through a plug of alumina) was added CSA (0.005 g, 0.02 mmol) and the mixture refluxed, under argon, for 42 hours. After cooling to room temperature, the solution was evaporated and the residue subjected to flash column chromatography, using ether/petrol (2:3 to 3:2) to give, in order of elution, glycerol adduct **57** (0.022 g, 0.08 mmol, 97%) as a colourless solid; δ_H (500 MHz , $CDCl_3$) 4.06-4.00 (1H, m, C*H*), 3.80-3.71 (3H, m, 2 x dispoke CH(C*H*$_3$), C*H*HO), 3.69-3.54 (2H, m, 1 x C*H*$_2$O), 3.47-3.40 (1H, dd, *J* 11.1, 3.0, CH*H*O), 2.11 (1H, br.s, O*H*), 1.85-1.70 (4H, m, 2 x dispoke C*H*$_2$), 1.56-1.53 (4H, 2 x dispoke C*H*$_2$) 1.48-1.39 (2H, m, 1 x dispoke C*H*$_2$), 1.16-1.14 (8H, m, 1 x dispoke C*H*$_2$, 2 x dispoke CH(C*H*$_3$)); δ_C (100 MHz , $CDCl_3$), 97.03, 96.03 (2 x acetal(*C*)), 67.03, 66.06 (2 x *C*H), 62.48, 59.37 (2 x *C*H$_2$), 32.53, 27.90, 27.85 (3 x dispoke *C*H$_2$), 21.88, 21.81 (2 x dispoke *C*H$_3$), 18.52, 18.44 (2 x dispoke *C*H$_2$); *m/z* (EI) 286 $(M)^+$, 273, 255, 242, 229, 214, 196, 185, 172, 156, 143, 129, 115, 97, 85, 73, 69, 55, 45; Found $(M)^+$ 286.1761. $C_{15}H_{26}O_5$ requires $(M)^+$ 286.1780. Followed by *diol* **56** (0.026 g, 0.06 mmol, 75%) as a colourless oil; $[\alpha]_D^{23}$ - 71.4 (c = 0.79 in $CHCl_3$); δ_H (500 MHz , $CDCl_3$) 7.37-7.28 (5H, m, 5 x Ar-*H*), 4.65 (2H, dd, *J* 11.2, 3.8, 1 x C*H*$_2$Ar), 4.23 (1H, ddd, *J* 11.2, 5.3, 3.4, CH$_2$C*H*CHOCH$_2$Ar), 3.91(1H, m, C*H*(OH)CHOCH$_2$), 3.84-3.69 (5H, m, 2 x dispoke C*H*(CH$_3$), 1 x C*H*$_2$OH, 1 x C*H*HO), 3.58 (1H, dd, *J* 11.2, 3.3, CH*H*O), 3.47 (2H, m, C*H*O(CH$_2$Ar), 1 x CH*H*O), 2.29 (1 x O*H*), 1.81-1.68 (6H, m, 3 x dispoke C*H*$_2$), 1.61-1.55 (4H, m, 2 x dispoke C*H*$_2$), 1.48-1.40 (2H, m, 1 x dispoke C*H*$_2$), 1.16 (3H, d, *J* 6.2, 1 x dispoke CH(C*H*$_3$)), 1 13 (3H, d, *J* 6.2, 1 x dispoke CH(C*H*$_3$)), ; δ_C (100 MHz , $CDCl_3$) 137.62 (Ar(*C*)), 128.56, 128.22, 128.08 (3 x Ar(*C*H)), 97.24, 96.05 (2 x acetal(*C*)), 78.18 (*C*H), 73.80 (*C*H$_2$Ar), 72.58, 68.40, 66.48, 66.16 (4 x *C*H), 63.34, 60.18 (2 x C*H*$_2$), 32.45, 32.36, 27.81, 27.73, (4 x dispoke C*H*$_2$), 21.86, 21.79 (2 x dispoke CH(*C*H$_3$)), 18.53, 18.44 (2 x dispoke C*H*$_2$); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3525, 3345, 1100, 988, 962; *m/z* (+FAB) 437 $(MH)^+$, 436 $(M)^+$, 435 $(M\text{-}H)^+$, 417, 391, 339, 323, 289, 255, 241, 229, 154; Found $(MH)^+$ 437.2569. $C_{24}H_{37}O_7$ requires $(MH)^+$ 437.2539.

(2*R*,2'*S*,2''*R*,3*S*,4*S*,6'*S*,6''*S*)-3-*O*-Benzyl-1-*O*,2-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-5-*O*-pivaloyl-adonitol 58, (2*R*,2'*S*,2''*R*,3*R*,4*S*,6'*S*,6''*S*)-3-*O*-Benzyl-1-*O*,2-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-4-*O*-(*R*)-(α-methoxy-α-(trifluoromethyl) phenylacetyl)-5-*O*-pivaloyl-adonitol 59 and (2*R*,2'*S*,2''*R*,3*R*,4*S*,6'*S*,6''*S*)-3-*O*-Benzyl 1-*O*,2-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-4-*O*-((*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl)-5-*O*-pivaloyl-adonitol 60

To a cold (-30 °C) solution of diol **56** in dry DCM (0.25 mL) containing pyridine (0.038 g, 0.5 mmol), under argon, was added, dropwise, a solution of pivaloyl chloride (0.0047 g, 0.038 mmol) in dry DCM (0.3 mL). The solution was stirred at this temperature for 7 hours before being warmed slowly to room temperature. The solution was evaporated *in vacuo* and the residue loaded directly onto a silica column, eluting with ether/petrol (3:7) to give *ester* **58** (0.017 g, 0.03 mmol, 82 %) as a colourless oil; $[\alpha]_D^{23}$ - 72.4 (c = 0.14 in $CHCl_3$); δ_H (500 MHz , $CDCl_3$) 7.35-7.26 (5H, m, 5 x Ar-*H*), 4.62 (2H, 2 x d, *J* 11.1, C*H*$_2$Ar), 4.37 (1H, dd, *J* 11.8,

2.5, C*H*HOCO), 4.27-4.20 (2H, m, CH*H*OCO, C*H*CHOCH$_2$Ar), 4.05 (1H, m, C*H*(OH)), 3.83 (1H, apparent t, *J* 11.2, C*H*HO), 3.78-3.73 (2H, m, 2 x dispoke C*H*(CH$_3$)), 3.58 (1H, dd, *J* 11.2, 3.2, CH*H*O), 3.43 (1H, dd, *J* 6.6, 5.0, C*H*OCH$_2$Ar), 3.06 (1H, br.s, O*H*), 1.83-1.71 (4H, m, 2 x dispoke C*H*$_2$), 1.62-1.55 (6H, m, 3 x dispoke C*H*$_2$), 1.46-1.41 (2H, m, 1 x dispoke C*H*$_2$), 1.22 (9H, s, C(C*H*$_3$)$_3$), 1.16 (3H, d, *J* 6.2, 1 x dispoke CH(C*H*$_3$)), 1.13 (3H, d, *J* 6.2, 1 x dispoke CH(C*H*$_3$)); δ_C (100 MHz , CDCl$_3$) 178.77 (*C*=O), 137.66 (Ar(*C*)), 128.47, 128.16, 127.96 (3 x Ar(*C*H)), 97.18, 95.97 (2 x acetal(*C*)), 78.50 (*C*H), 73.63 (*C*H$_2$Ar), 70.98, 67.61, 66.30, 66.04 (4 x *C*H), 65.77, 59.89 (2 x *C*H$_2$), 32.45, 32.42, 27.84, 27.73 (4 x dispoke *C*H$_2$), 27.23 (C(*C*H$_3$)$_3$), 21.85, 21.77 (2 x dispoke CH(*C*H$_3$)), 18.45(*C*(CH$_3$)$_3$); ν_{max} (CHCl$_3$ solution)/cm^{-1}; 3518, 2934, 2871, 1722, 1456, 1382, 1372, 1362, 1150, 1112, 1093, 1020, 989, 961, 902; *m/z* (+FAB) 521 (MH)$^+$, 520 (M)$^+$, 405, 229, 205, 195, 167; Found (MH)$^+$ 521.3112. $C_{29}H_{45}O_8$ requires (MH)$^+$ 521.3114.

To a solution of ester **58** (0.004 g, 0.008 mmol) in dry toluene (0.5 mL), containing triethylamine (0.001 g, 0.009 mmol) and one crystal of DMAP, was added (*R*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.061 g, 0.26 mmol) dropwise. The solution was heated under reflux for 4 hours, under argon, and cooled to room temperature. Ether (10 mL) and NaHCO$_3$ (10mL; sat. aq.) were added and the mixture stirred for 10 minutes before the layers were separated. The aqueous layer was re-extracted with ether (2 x 10 mL). The combined organic fractions were washed sequentially with NaHCO$_3$ (5 mL), NH$_4$Cl (2 x 10 mL), brine (10 mL), dried (MgSO$_4$) and evaporated *in vacuo*. Dry DCM (10 mL) was added and the solution filtered through a plug of Florisil®, eluting with dry DCM (5 mL). The solution was then evaporated *in vacuo* to give the *di-Mosher ester derivative* **59**; δ_H (500 MHz , CDCl$_3$) 7.61-7.36 (10H, m, 10 x Ar-*H*), 5.88 (1H, m, C*H*OCOC(CF$_3$)), 4.70 and 4.45 (2H, 2 x d, *J* 11.1, C*H*$_2$Ar), 4.55 (1H, d, *J* 12.8, C*H*HOCO(CH$_3$)), 4.29 (1H, dd, *J* 12.8, 8.2, CH*H*OCO(CH$_3$)), 4.10 (1H, d, *J* 7.9, C*H*CHOCH$_2$Ar), 3.70-3.60 (3H, m, 1 x dispoke C*H*(CH$_3$), C*H*OCH$_2$Ar, C*H*HOCO), 3.55-3.50 (2H, m, 1 x dispoke C*H*(CH$_3$), CH*H*OCO), 1.80-1.68 (4H, m, 2 x dispoke C*H*$_2$), 1.60-1.54 (4H, m, 2 x dispoke C*H*$_2$), 1 45-1.30 (4H, m, 2 x dispoke C*H*$_2$), 1.17 (9H, s, C(C*H*$_3$)$_3$), 1.12 (3H, d, *J* 6.2, 1 x dispoke CH(C*H*$_3$)), 1.05 (3H, d, *J* 6.2, 1 x dispoke CH(C*H*$_3$)).

To a solution of ester **58** (0.0018 g, 0.0034 mmol) in dry toluene (0.5 mL), containing triethylamine (0.001 g, 0.009 mmol) and one crystal of DMAP, was added (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.027 g, 0.12 mmol) dropwise. The solution was heated under reflux for 4 hours, under argon, before being cooled to room temperature. Ether (10 mL) and NaHCO$_3$ (10mL; sat. aq.) were added and the mixture stirred for 10 minutes before the layers were separated. The aqueous layer was re-extracted with DCM (2 x 10 mL). The combined organic fractions were washed sequentially with NaHCO$_3$ (5 mL), NH$_4$Cl (2 x 10 mL), brine (10 mL), dried (MgSO$_4$) and evaporated *in vacuo*. Dry DCM (10 mL) was added and the solution filtered through a plug of Florisil®, eluting with dry DCM (5 mL). The solution was then evaporated *in vacuo* to give the *di-Mosher derivative* **60**; δ_H (500 MHz , CDCl$_3$) 7.58-7.28 (10H, m, 10 x Ar-*H*), 5.85 (1H, m, C*H*OCOC(CF$_3$)), 4.58 and 4.33 (2H, 2 x d, *J* 11.3, C*H*$_2$Ar), 4.62-4.60 (1H, dd, *J* 12.9, 1.6, C*H*HOCO), 4.40-4.35 (1H, dd, *J* 12.9, 8.7, CH*H*OCO), 4.00-3.95 (1H, m, C*H*CHOCH$_2$Ar), 3.69-3.66 (1H, m, 1 x dispoke C*H*(CH$_3$)), 3.61-3.53 (4H, m, 1 x dispoke C*H*(CH$_3$), C*H*OCH$_2$Ar, 1 x C*H*$_2$O), 3.57 (3H, s, OC*H*$_3$), 1.80-1.54 (15H, m, 3 x dispoke C*H*$_2$, 1 x C(C*H*$_3$)$_3$); 1.45-1.16 (6H, m, 3 x dispoke C*H*$_2$), 1.12 (3H, d, J 6.2, CH(C*H*$_3$)), 1.05 (3H, d, J 6.2, CH(C*H*$_3$)).

(2*R*,2'*R*,2''*R*,3*R*,4*S*,6'*S*,6''*S*)-1-*O*,5-*O*-Di-(*tert*-butyldiphenylsilyl)-3-*O*,4-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-adonitol 62 and (2*S*,2'*R*,2''*R*,3*S*,4*R*,6'*S*,6''*S*)-1-*O*,5-*O*-Di-(*tert*-butyldiphenylsilyl)-3-*O*,4-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-adonitol 63

To a solution of diene **1** (0.133 g, 0.68 mmol), triol **61**[29] (0.363 g, 0.50 mmol) in dry $CHCl_3$ (5 mL; passed through a plug of alumina) was added CSA (0.016 g, 0.069 mmol). The solution was refluxed, under argon, for 29 hours and cooled to room temperature. After evaporation of the solvent, *in vacuo*, the residue was subjected to flash column chromatography, using ether/petrol (9:1) as eluent, to give, in order of elution, *alcohol* **63** (0.032 g, 0.040 mmol, 7%) as a colourless oil; $[\alpha]_D^{23}$ - 4.26 (c = 0.40 in $CHCl_3$); δ_H (500 MHz , $CDCl_3$) 7.75-7.68 (8H, m, 8 x *o*-Ar -*H*), 7.42-7.36 (12H, m, 8 x *m*-Ar -*H*, 4 x *p*-Ar -*H*), 4.37 (1H, d, *J* 10.3, C*H*CH(OH)), 4.31 (1H, dt, *J* 10.2, 3.2, C*H*CH_2OSi), 4.21 (1H, m, 1 x dispoke C*H*(CH_3)), 3.98 (1H, m, 1 x dispoke C*H*(CH_3)), 3.97-3.87 (2H, m, C*H*(OH), C*H*HOSi), 3.83-3.81 (3H, m, CH*H*OSi, CH(OH)CH_2OSi), 1.90-1.80 (4H, 2 x dispoke CH_2), 1.64-1.48 (6H, 3 x dispoke CH_2) 1.13-1.05 (26H, m, 2 x (C(CH_3)$_3$), 2 x dispoke CH(CH_3), 1 x dispoke CH_2); δ_C (100 MHz , $CDCl_3$) 135.60 (Ar(*C*H)), 133.40, 133.28 (2 x Ar(*C*)), 129.72, 129.65, 129.56, 127.74, 127.66 (5 x Ar(*C*H)), 98.46, 98.36 (2 x acetal(*C*)), 71.75, 70.88, 70.26, 66.47, 66.07 (5 x *C*H), 64.75, 63.88 (2 x *C*H_2), 32.79, 32.72 (2 x dispoke *C*H_2), 29.68, 29.12 (2 x *C*(CH_3)$_3$), 27.26, 27.12 (2 x dispoke *C*H_2), 26.86, 26.84 (2 x C(*C*H_3)$_3$), 22.13, 21.95 (2 x dispoke CH(*C*H_3)), 19.21, 19.17 (2 x dispoke *C*H_2); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3314, 1590, 1353, 1318, 1112, 974, 896; *m/z* (+FAB) 822 (M)$^+$, 821 (M-H)$^+$, 756, 737, 725, 705, 651, 599, 535, 515, 379, 353, 319, 295, 259, 239, 195, 163, 135; Found (M)$^+$ 822.4280. $C_{49}H_{66}O_7Si_2$ requires (M)$^+$ 822.4347. Together with *alcohol* **62** (0.269 g, 0.38 mmol, 57%) as a colourless oil; $[\alpha]_D^{23}$ - 23.5 (c = 2.14 in $CHCl_3$); δ_H (500 MHz , $CDCl_3$) 7.80-7.74 (4H, 2 x overlapping d, *J* 7.8, 6.6, 4 x *o*-Ar-*H*), 7.68-7.64 (4H, 2 x overlapping d, *J* 7.7, 6.7, 4 x *o*-Ar-*H*), 7.45-7.31 (12H, m, 8 x *m*-Ar-*H*, 4 x *p*-Ar-*H*), 4.16 (1H, d, *J* 9.8, C*H*CH(OH)), 4.08 (1H, m, C*H*CH_2OSi), 3.99 (1H, m, C*H*(OH)), 3.90-3.88 (1H, m, C*H*HOSi), 3.84 (2H, m, CH*H*OSi, CH(OH)C*H*HOSi), 3.78-3.75 (2H, m, 1 x dispoke C*H*(CH_3), CH(OH)CH*H*OSi), 3.74-3.67 (1H, m, 1 x dispoke C*H*(CH_3)), 2.38 (1H, br.s, O*H*), 1.88-1.64 (6H, m, 3 x dispoke CH_2), 1.57-1.36 (6H, m, 3 x dispoke CH_2), 1.09 (3H, d, *J* 6.3, 1 x dispoke CH(CH_3)), 1.06 (21H, 2 x apparent d, *J* 2.9, 1 x dispoke CH(CH_3), 2 x C(CH_3)$_3$); δ_H (500 MHz , D_6-DMSO) 7.78-7.76 (2H, d, *J* 6.8, 2 x *o*-Ar -*H*), 7.69-7.68 (2H, d, *J* 6.6, 2 x *o*-Ar -*H*), 7.64-7.61 (2H, d, *J* 9.8, 2 x *o*-Ar -*H*), 7.59-7.58 (2H, d, *J* 8.0, 2 x *o*-Ar -*H*), 7.46-7.34 (12H, m, 8 x *m*-Ar-*H*, 4 x *p*-Ar-*H*), 4.68 (1H, d, *J* 6.4, C*H*O), 4.26 (1H, d, *J* 9.3, C*H*O), 3.98-3.91 (4H, m, 1 x dispoke C*H*(CH_3), 3 x C*H*O), 3.76-3.74 (1H, m, 1 x C*H*O), 3.66-3.62 (1H, m, 1 x dispoke C*H*(CH_3)), 3.50-3.47 (1H, m, 1 x C*H*O), 1.78-1.73 (2H, m, 1 x dispoke CH_2), 1.65-1.63 (2H, m, 1 x dispoke CH_2), 1.56-1.48 (4H, m, 2 x dispoke CH_2), 1.46-1.32 (2H, m, 1 x dispoke CH_2), 1.29-1.18 (2H, m, 1 x dispoke CH_2), 0.98-0.94 (24H, m, 2 x dispoke CH(CH_3), 2 x C(CH_3)$_3$); δ_C (100 MHz , $CDCl_3$) 135.88, 135.62, 135.58, 135.50 (4 x Ar(*C*H)), 133.79, 133.59, 133.31, 133.28 (4 x Ar(*C*)), 129.72, 129.69, 129.63, 127.71, 127.64 (5 x Ar(*C*H)), 96.63, 96.51 (2 x acetal(*C*)), 70.49, 67.76, 67.02, 65.91, 65.75 (5 x *C*H), 64.18, 63.92 (2 x *C*H_2), 32.68, 32.59, (2 x dispoke *C*H_2), 26.88, 26.75 (2 x C(*C*H_3)$_3$), 22.09, 21.87 (2 x dispoke CH(*C*H_3)), 19.29, 19.21, 18.58, 18.54 (4 x dispoke *C*H_2); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3328, 2931, 2857, 1589, 1461, 1380, 1361, 1112, 999, 968, 898, 613; *m/z* (+FAB) 822 (M)$^+$, 821 (M-H)$^+$, 765, 705, 651, 535, 515, 379, 337, 319, 295, 281, 259, 239, 221, 135; Found (M)$^+$ 822.4377. $C_{49}H_{66}O_7Si_2$ requires (M)$^+$822.4347.

A repetition of this experiment using boiling toluene as solvent gave exclusively adduct **62** in 54% yield with identical spectral data to that given above.

(2*R*,2'*R*,2''*R*,3*S*,4*S*,6'*S*,6''*S*)-1-*O*,5-*O*-Di-(*tert*-butyldiphenylsilyl)-3-*O*,4-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-2-*O*-((*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl)-adonitol 64

To a solution of alcohol **62** (0.011 g, 0.014 mmol) in dry DCM (0.2 mL), containing triethylamine (0.004 g, 0.04 mmol) and one crystal of DMAP, was added (*R*)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.0096 g, 0.04 mmol) dropwise. The solution was stirred, under argon, for 41 hours before being heated to reflux for 8 hours and then cooled to room temperature. DCM (10 mL) and $NaHCO_3$ (10 mL; sat. aq.) were added and the mixture stirred for 30 minutes before the layers were separated. The aqueous layer was re-extracted with DCM (2 x 10 mL). The combined organic fractions were washed sequentially with $NaHCO_3$ (5 mL), NH_4Cl (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Dry DCM (10 mL) was added and the solution filtered through a plug of Florisil®, eluting with dry DCM (5 mL). The solution was then evaporated *in vacuo* to give the *di-Mosher ester derivative* **64**; δ_H (500 MHz , $CDCl_3$) 7.82-7.81 (1H, d, *J* 6.6, 1 x *o*-Ar-*H*), 7.77-7.75 (1H, dd, *J* 7.7, 1.6, 1 x *o*-Ar-*H*), 7.60-7.57 (2H, m, 2 x *o*-Ar-*H*), 7.47-7.22 (21H, m, 21 x Ar-*H*), 5.50 (1H, apparent t, *J* 6.1, C*H*OCOC(CF_3)), 4.38 (1H, d, *J* 10.0, C*H*COCOC(CF_3)), 3.98 (1H, dd, *J* 11.7, 4.2, C*H*HOSi), 3.90 (1H, dd, *J* 10.6, 6.2, C*H*HCHOCOC(CF_3)), 3.82 (1H, d, *J* 11.7, CH*H*OSi), 3.80 (1H, m, C*H*CH_2OSi), 3.73 (1H, d, *J* 6.2, CH*H*CHOCOC(CF_3)), 3.72-3.65 (1H, m, 1 x dispoke C*H*(CH_3)), 3.60-3.58 (1H, m, 1 x dispoke C*H*(CH_3)), 3.55 (3H, s, OCH_3), 1.85-1.82 (2H, m, 1 x dispoke CH_2), 1.70-1.68 (2H, m, 1 x dispoke CH_2), 1.49-1.46 (2H, m, 1 x dispoke CH_2), 1.38-1.34 (2H, m, 1 x dispoke CH_2), 1.10-1.02 (28H, m, 2 x dispoke (CH_2), 2 x C(CH_3)$_3$), 2 x dispoke CH(CH_3)).

(2*R*,2'*R*,2''*R*,3*S*,4*S*,6'*S*,6''*S*)-1-*O*,5-*O*-Di-(*tert*-butyldiphenylsilyl)-3-*O*,4-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-2-*O*-((*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl)-adonitol 65

To a solution of ester **62** (0.018 g, 0.022 mmol) in dry DCM (0.2 mL), containing triethylamine (0.007 g, 0.066 mmol) and one crystal of DMAP, was added (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (0.016 g, 0.066 mmol) dropwise. The solution was stirred, under argon, for 28 hours before the addition of DCM (10 mL) and $NaHCO_3$ (10 mL; sat. aq.) and the mixture stirred for 30 minutes. The layers were then separated and the aqueous layer was re-extracted with DCM (2 x 10 mL). The combined organic fractions were washed sequentially with $NaHCO_3$ (5 mL), NH_4Cl (2 x 10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. Dry DCM (10 mL) was added and the solution filtered through a plug of Florisil®, eluting with dry DCM (5 mL). The solution was then evaporated *in vacuo* to give the *di-Mosher ester derivative* **65**; δ_H (500 MHz , $CDCl_3$) 7.82 (1H, d, *J* 6.7, 1 x *o*-Ar-*H*), 7.76 (1H, d, *J* 5.7, 1 x *o*-Ar-*H*), 7.65-7.68 (2H, m, 2 x *o*-Ar-*H*), 7.54 (1H, d, *J* 7.7, 1 x *o*-Ar-*H*), 7.47-7.21 (20H, m, 20 x Ar-*H*), 5.61 (1H, m, C*H*OCOC(CF_3)), 4.32 (1H, dd, *J* 9.6, 1.4, C*H*COCOC(CF_3)), 3.96 (2H, m, CH_2COCOC(CF_3)), 3.77 (1H, dd, *J* 11.6, 3.9, C*H*HOSi), 3.67 (1H, dd, *J* 11.6, 1.9, CH*H*OSi), 3.54 (1H, m, C*H*CH_2OSi), 3.52 (1H, m, 1 x dispoke C*H*(CH_3)), 3.50 (3H, s, OCH_3), 3.43 (1H, m, 1 x dispoke C*H*(CH_3)), 1.79-1.74 (2H, m, 1 x dispoke CH_2), 1.69-1.66 (2H, m, 1 x dispoke CH_2), 1.53-1.29 (8H, m, 4 x dispoke CH_2), 1.06 (9H, s, C(CH_3)$_3$), 1.05 (9H, s, C(CH_3)$_3$), 1.04 (3H, d, *J* 7.6, 1 x dispoke CH(CH_3)), 0.79 (3H, d, J 6.2, 1 x dispoke CH(CH_3)).

(2*S*,2'*R*,2''*R*,3*R*,4*R*,5*S*,6'*S*,6''*S*)-1-*O*,6-*O*-Di-(*tert*-butyldiphenylsilyl)-2-*O*,3-*O*-(6,6'-dimethyl-3,3',4,4',5,5',6,6'-octahydro-2,2'-bi-2*H*-pyran-2,2'-diyl)-dulcitol 67

To a solution of tetrol **66**[27] (0.14 g, 0.21 mmol) and diene **1** (0.046 g, 0.23 mmol) in dry $CHCl_3$ (2 mL; passed through a plug of alumina) was added CSA (0.009 g, 0.037 mmol). The solution was heated to reflux, under argon, for 24 hours. After cooling to room temperature, the solution was evaporated, *in vacuo*, and the residue subjected to flash column chromatography on silica gel, using ether/petrol (1:9) as eluent, to give *diol* **67** (0.062 g, 0.073 mmol, 35%) as a colourless oil; $[\alpha]_D^{23}$ -28.9 (c = 0.63 in $CHCl_3$); δ_H (500 MHz , $CDCl_3$) 7.76-7.68 (8H, m, 8 x Ar-*H*), 7.44-7.34 (12H, m, 12 x Ar-*H*), 4.17-4.13 (2H, m, C*H*(OH)CH_2OSi, C*H*CH(OH)CH(OH)), 3.96-3.92 (2H, m, 1 x dispoke C*H*(CH_3), C*H*HOSi), 3.89-3.87 (2H, m, CH*H*OSi, C*H*(OH)CH(OH)CH_2), 3.83-3.81 (3H, m, 1 x O*H*, 1 x CH(OH)C*H*$_2$OSi), 3.76-3.73 (1H, dd, *J* 9.1, 4.3, C*H*CH_2OSi), 3.59-3.56 (1H, m, 1 x dispoke C*H*(CH_3)), 2.90 (1H, d, *J* 4.7, 1 x O*H*), 1.81-1.71 (4H, m, 2 x dispoke C*H*$_2$), 1.60-1.52 (4H, m, 2 x dispoke C*H*$_2$), 1.47-1.38 (4H, m, 2 x dispoke C*H*$_2$), 1.12 (3H, d, *J* 6.2, 1 x dispoke CH(C*H*$_3$)), 1.09 (3H, d, *J* 6.2, 1 x dispoke CH(C*H*$_3$)), 1.06 (9H, s, 1 x C(C*H*$_3$)$_3$), 1.05 (9H, s, 1 x C(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 135.80, 135.62, 135.59, 134.82 (4 x Ar(*C*H)), 133.32, 133.24, 133.21, 132.83 (4 x Ar(*C*)), 129.77, 129.68, 127.76, 127.68 (4 x Ar(*C*H)), 96.71, 96.62 (2 x acetal(*C*)), 70.69, 69.90, 69.87, 69.66, 66.03, 65.88 (6 x *C*HO), 65.61, 64.74 (2 x *C*H_2O), 32.54 (1 x dispoke *C*H$_2$), 27.83, 27.71 (2 x *C*(CH$_3$)$_3$), 26.89, 26.70 (2 x C(*C*H$_3$)$_3$), 21.99, 21.84 (2 x dispoke CH(*C*H$_3$)), 19.24, 18.82, 18.45 (3 x dispoke *C*H$_2$); ν_{max} ($CHCl_3$ solution)/cm^{-1}; 3420, 3072, 3019, 2933, 2834, 2859, 1590, 1522, 1472, 1444, 1428, 1383, 1362, 1343 1218, 1113, 1048, 1028, 998, 968, 929, 850, 823, 768, 704, 669, 614; *m/z* (+FAB) 853 (MH)$^+$, 852 (M)$^+$, 796, 776, 756, 289, 259, 241, 221, 213, 195; Found (MH)$^+$ 853.4605. $C_{50}H_{69}Si_2O_8$ requires (MH)$^+$ 853.4531.

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