Synthesis of (+)-(1*R*,2*R*,4*R*,6*S*)-1,6-epoxy-4-benzyloxycyclohexan-2-ol, a key precursor to inositol monophosphatase inhibitors, from (−)-quinic acid[1]

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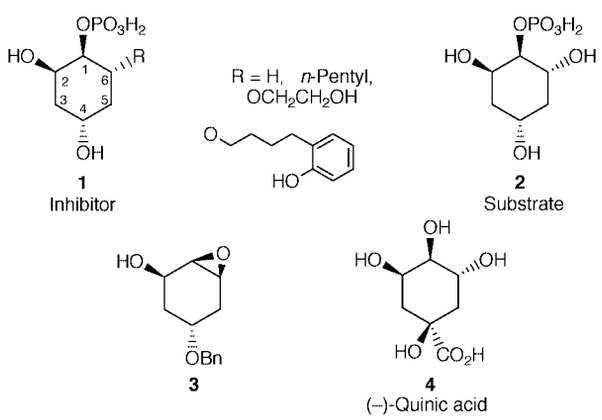
Received (in Cambridge, UK) 24th November 1999, Accepted 3rd February 2000

A new and efficient route to homochiral (+)-(1*R*,2*R*,4*R*,6*S*)-1,6-epoxy-4-benzyloxycyclohexan-2-ol and its 2-benzyl ether derivative is described, starting from (−)-quinic acid. The compounds are key intermediates in the solution-phase and solid-phase synthesis of inhibitors for inositol monophosphatase. The pivotal step involves a La^{3+}-induced reversal of the diastereoselectivity for the borohydride reduction of an intermediate cyclohexan-4-one. (1*R*,2*R*,4*R*,6*R*)-(*O*^{6}-Propyl)cyclohexane-1,2,4,6-tetraol 1-phosphate, predicted to be a submicromolar competitive inhibitor of inositol monophosphatase, was prepared from the title epoxide in 5 steps in good overall yield. The compound proved to be a competitive inhibitor and displayed the expected potency confirming the stereochemical requirements for inhibition. The *O*^{2}-benzylated epoxide derivative could be stereospecifically alcoholysed using either $BF_3{\cdot}(OEt)_2$ or Yb(III)$(OTf)_3$ as catalysts without appreciable levels of benzyl ether protecting group cleavage. The preparation of the alcoholysis products (1*S*,2*R*,4*S*,6*R*)-2,4-bis(benzyloxy)-6-isopropyloxycyclohexanol and (1*S*,2*R*,4*S*,6*R*)-2,4-bis(benzyloxy)-6-(phenethyloxy)cyclohexanol, and the synthesis and evaluation of the inhibitor (1*R*,2*R*,4*R*,6*R*,2′*S*)-6-(1′-hydroxy-3′-phenylpropan-2-yloxy)-2,4-dihydroxycyclohexyl phosphate and its diastereomer (1*R*,2*R*,4*R*,6*R*,2′*R*)-6-(1′-hydroxy-3′-phenylpropan-2-yloxy)-2,4-dihydroxycyclohexyl phosphate are described.

Introduction

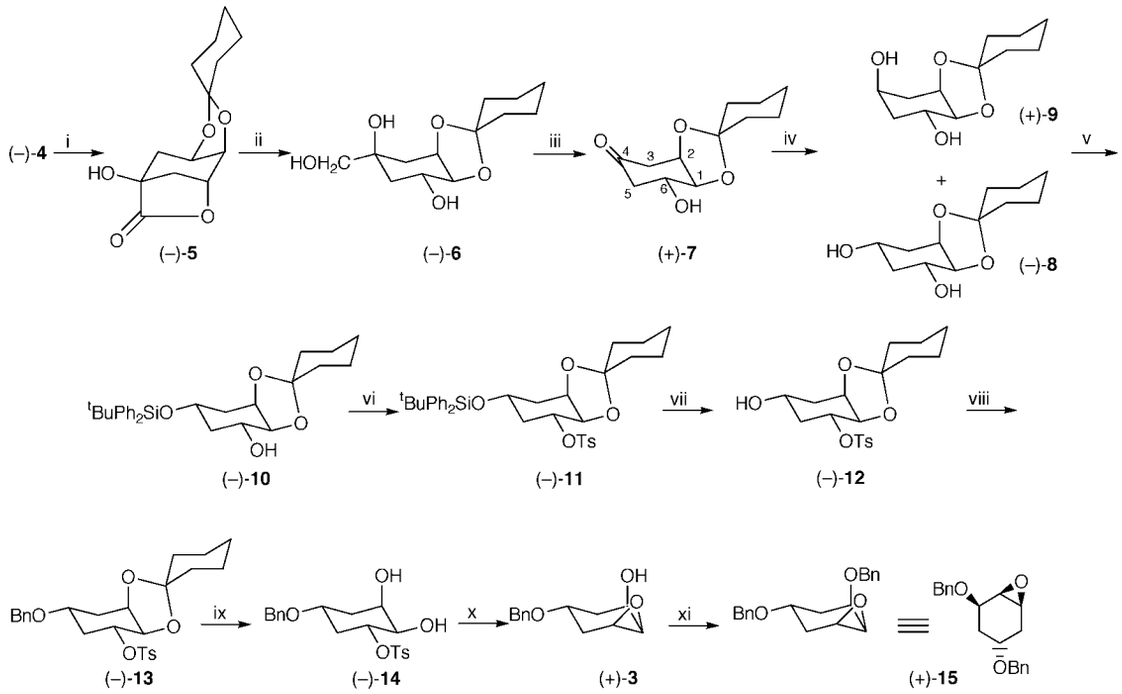
Inositol monophosphatase is a key enzyme in brain secondary messenger systems.[2] The role of the enzyme is to provide free inositol which is used to form the secondary messenger precursor phosphatidylinositol 1,4,5-trisphosphate.[2,3] Over-activity of this cycle is believed to contribute to manic depression in humans, a debilitating chronic condition with no known cure. The current treatment of manic depression with lithium salts has serious drawbacks and thus there has been much interest and research into useful alternatives. Inositol monophosphatase is widely accepted to be the target for lithium ions in manic depression therapy and has been the focus of much research effort over the last twelve years.[4–9]

The enzyme is responsible for the hydrolysis of each of the monophosphates of D-*myo*-inositol phosphorylated in the 1,3,4 or 6 positions.[10] Blocking the enzyme reduces the pool of inositol available for the biosynthesis of the lipid phosphatidylinositol 4,5-bisphosphate which is the precursor for two secondary messengers, diacyl glycerol and inositol 1,4,5-trisphosphate. Lithium ion is now known to inhibit the enzyme by binding to a ternary enzyme·Mg^{2+} phosphate product complex in the site vacated by a second Mg^{2+} ion,[7] see discussion below. This interaction gives rise to uncompetitive inhibition with respect to the substrate[4] in the millimolar range, but is difficult to mimic given the simple structure of the Li^+ cation. Moreover, the action of Li^+ *in vivo* is augmented by the high levels of phosphate dianion, a synergistic product inhibitor, present in the brain.[4] The design of inhibitors, therefore, has focussed on understanding the way in which the cyclitol hydroxy groups and phosphate ester moiety interact with the protein and with the bound magnesium ions. Such interactions within the active site have now been examined and rationalised for a range of substrates and inhibitors.[6,7,11,12] One group of inhibitors shows K_i values of ~1 μM or lower.[11,12] These compounds are based on 6-substituted cyclohexane-1,2,4-triol 1-phosphates **1** whereby the 6-substituent, if large enough, or hydrophobic enough, inhibits by disrupting the coordination sphere of the second of two magnesium cofactors, $Mg^{2+}2$.[7,12] It is now known that $Mg^{2+}2$ should be hydrated in the active complex such that the associated water molecule can H-bond to the 6-OH group in structures that are substrates, *e.g.* cyclitol phosphate **2**.[13] It is also apparent that the terminal hydroxy group of the 6-hydroxyethyloxy side-chain of inhibitor **1** (R = OCH_2CH_2OH) can access the coordination sphere of $Mg^{2+}2$.[7,12] A potential second route to the design of inhibitors lies in taking advantage of a hydrophobic binding pocket formed by Val-40 and Leu-42 which lies near the top of the active site cleft.[7,9] It was reasoned that 6-cyclitol substituents that can interact with both sites should be very tight binding inhibitors and, indeed, some examples are known.[11,12]



The absolute stereochemical requirements of the cyclitol ring for optimal inhibition in 6-substituted cyclohexane-1,2,4-triol 1-phosphate-type inhibitors was already established for a few examples.[11,12] Given that we expected that these requirements should not change with the nature of the 6-substituent, we set out to devise a synthesis of suitable homochiral precursors that would be amenable to simple elaboration to give a range of

DOI: 10.1039/a909292g



Scheme 1 *Reagents and conditions*: i. Cyclohexanone, H_3PO_4 (2 drops), 155 °C, 30 min; ii. $NaBH_4$, EtOH, 0 °C→rt, 12 h; iii. $NaIO_4$, H_2O, pH 5–6, 0 °C→rt, 6 h, 81% over 3 steps; iv. $LaCl_3{\cdot}5H_2O$, $NaBH_4$, MeOH, −78 °C→rt, 12 h, 95%; v. $^tBuSiPh_2Cl$, Et_3N, DMAP, DCM, 0 °C→rt, 16 h, 48%; vi. TsCl, Et_3N, DMAP, 0 °C→rt, 3 days, 67%; vii. TBAF, THF, rt, 6 h, 100%; viii. BnBr, NaH, DMF, −40 °C→rt, 12 h, 80%; ix. $TFA_{(cat.)}$, MeOH, rt, 2 days, 78%; x. K_2CO_3, MeOH, rt, 30 min, 90%; xi. KH, BnBr, DCM, 12 h, −78 °C→rt, 12 h, 93%.

Table 1 Reduction of ketone **7**

Entry	Ketone concn./ mmol dm^{-3}	$NaBH_4$ concn./ mmol dm^{-3}	Solvent	*T*/°C	$LaCl_3{\cdot}7H_2O$ concn./ mmol dm^{-3}	$CaCl_2$ concn./ mmol dm^{-3}	$Ti(O\text{-}^iPr)_4$ concn./ mmol dm^{-3}	Selectivity[a]
1	25	100	Et_2O	reflux	—	—	—	100:0
2	25	100	Et_2O	room temp.	—	—	30	83:17
3	25	100	EtOH	room temp.	—	—	—	75:25
4	200	200	MeOH	0	400	—	—	34:66
5	200	200	EtOH	0	400	—	—	50:50
6	200	200	MeOH	−60	400	—	—	12:88
7	200	200	EtOH	−60	400	—	—	34:66
8	200	200	MeOH	−60	—	400	—	88:12
9	200	400	MeOH	−60	800	—	—	14:86
10	150	150	MeOH	−60	150	—	—	10:90
11	50	50	MeOH	−60	50	—	—	12:88

[a] Selectivity = undesired *trans*-diol **9** : desired *cis*-diol **8**.

homochiral 6-substituted variants.[1] Previous syntheses had utilised the racemic 1,6-epoxy-4-benzyloxycyclohexan-2-ol, (±)-**3**, which was obtained from cyclohexane-1,4-diol in an overall yield of 6.6%. Reaction of the 2-*O*-benzyl derivative with C- and O-nucleophiles gave the racemic 1-alcohols with inversion of configuration at C-6.[11,12] These were resolved as their (−)-(1*S*,4*R*)-camphanate esters, which facilitated X-ray crystallographic analysis of the structures and the determination of the absolute stereochemistry of the cyclitol moieties, prior to saponification and phosphorylation at the O^1-position. In these studies it was, of course, necessary to have access to both enantiomers of each inhibitor in order to probe the geometry of the active site of the enzyme and correlate biological potency with the absolute stereochemistry.[11,12] Since this key epoxide seemed to be an ideal starting point for introducing structural diversity, a synthesis of the homochiral (1*R*,2*R*,4*R*,6*S*)-1,6-epoxy-4-benzyloxycyclohexan-2-ol form starting from (−)-quinic acid was explored.

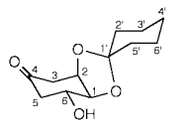
Results and discussion

(−)-Quinic acid **4** was converted to the cyclohexylidene lactone **5** in 85% yield following the procedure of Shing and Tai.[14] Reduction of the lactone **5** with sodium borohydride in ethanol gave the vicinal diol **6** which was, without further purification, converted to the ketone **7** in 95% overall yield using sodium periodate,[15,16] Scheme 1. This sequence was much more efficient than the reported literature preparations of the ketone **7** which used lithium aluminium hydride to reduce the acetylated form of lactone **5**.[14–17]

The diequatorial 4,6-diol (−)-**8** had been required previously for the synthesis of D-(+)-2,6-dideoxystreptamine and it was reported that the reduction of the 4-keto group of (+)-**7** with lithium borohydride in dimethoxyethane gave a 50:50 mixture of the epimeric C-4-equatorial and axial alcohols, (−)-**8** and (+)-**9** respectively.[16] While these could be separated[16,18] we sought conditions to significantly improve the yield of the 4-equatorial alcohol (−)-**8**.

The use of sodium borohydride in refluxing ether gave the 4-axial alcohol (+)-**9** exclusively (Table 1, entry 1). Under similar conditions but at 20 °C, either in ether, or in ethanol, or at −60 °C in methanol, the axial alcohol **9** was still the predominant product (Table 1, entries 2, 3 and 8). This is expected because the approach of borohydride from the 4-*re*-face of the ketone (+)-**7** is hindered by the cyclohexylidene moiety. As it seemed possible that the 4-*re*-face of the ketone

Table 2 ^{13}C-NMR shifts of ketone **7** (125 mmol dm^{-3}) in CD_3OD solution and in the presence of $LaCl_3 \cdot H_2O$ (135 mmol dm^{-3})



7

C-Atom	δ with $LaCl_3 \cdot H_2O$	δ without $LaCl_3 \cdot H_2O$	$\Delta\delta$ [a]
4-C	210.70	210.22	+0.48
1′-C	109.08	109.38	−0.30
1-C	74.38	74.88	−0.50
2-C	71.84	72.21	−0.37
6-C	67.31	67.71	−0.40
3-C, 5-C	41.07	41.36	−0.29
	40.05	40.24	−0.19
2′-C, 3′-C, 4′-C 4′-C, 5′-C	35.94	36.28	−0.34
	32.84	33.14	−0.30
	24.89	25.25	−0.36
	23.60	23.92	−0.32
	23.21	23.54	−0.33

[a] $\Delta\delta$ = chemical shift of C-atoms of ketone **7** with $LaCl_3 \cdot H_2O$ − chemical shift without $LaCl_3 \cdot H_2O$.

might be better exposed to the reductant if the 4-carbonyl O-atom and the 6-OH group could be persuaded to occupy axial positions through chelation to a highly charged metal ion, reductions were repeated in the presence of various lanthanide ions.[19]

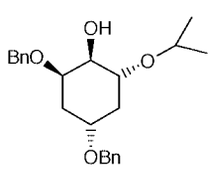
At −60 to −78 °C in methanol in the presence of La^{3+} or Ce^{3+} over a range of conditions and concentrations, borohydride reduction gave a mixture of the required 4-equatorial alcohol **8** and 4-axial alcohol **9** in 95% recovery where the required alcohol **8** constituted up to 80–90% of the total product mixture (as determined by ^{1}H- and ^{13}C-NMR spectroscopy) (see Table 1). On some occasions as much as 95% of the required alcohol **8** was obtained. Similar reductions performed in the presence of Pr^{3+}, Er^{3+} and Nd^{3+} ions were less successful and, interestingly, Ca^{2+} ions were totally ineffective in redirecting the face selectivity of the reduction. The use of Nd^{3+} and Sm^{3+} ions resulted in the formation of extremely viscous slurries at −60 °C which were very difficult to stir. The proportions of the required alcohol **8** obtained in these reactions were lower than for the La^{3+} assisted reduction, as judged by NMR spectroscopy. The use of ethanol in place of methanol also gave higher proportions of the axial alcohol **9**.

Ca^{2+} and La^{3+} ion assisted borohydride reductions have been utilised for the partially selective reduction of other ketones but, as yet, the structures of the transition state complexes for such systems are not well understood.[19,20] Preliminary studies to determine the cause for reversed selectivity for reduction of the ketone **7** observed here were performed in methanol, in the absence and presence of La^{3+} ions. ^{1}H- and ^{13}C-NMR spectroscopic data indicated that the 4-carbonyl O-atom of ketone **7** binds directly to the lanthanide ion and that there are no gross changes in the conformation of the ketone **7** (see Table 2 for ^{13}C-NMR shifts). It would seem quite possible that a small proportion of the equilibrium mixture of bound complexes in methanolic solution exist with the La^{3+} ion bound to the 4-carbonyl O-atom and, simultaneously, with the 6-OH group H-bonded to one of the methanol molecules of solvation, such that the ion resides on the carbonyl 4-*si*-face. An alternative structure might exist as a ketone dimer in which both 4-carbonyl O-atoms bind to a single La^{3+} ion such that the two 6-OH groups interact through an H-bond. Low temperature ^{1}H-NMR spectroscopic analysis at −60 °C did not provide unequivocal evidence in favour of either of these two possibilities but clearly indicated that there is a large and increasing change in the environment of the C-3 and C-5 methylene protons as the temperature is decreased.

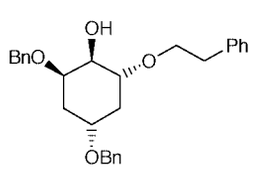
The La^{3+} assisted reduction of ketone **7** to give a 6:1 to 9:1 mixture of alcohols **8** and **9** could be performed successfully on a 20 g scale. Direct separation of the isomers[16,18] was difficult on such a large scale but treatment with TBDPS-Cl (which demands an accessible nucleophile)[21] gave a mixture of monosilylated products, containing predominantly the desired 4-silyl ether **10**. The required silyl ether could be isolated easily in pure form by column chromatography on silica in 46% overall yield from the ketone **7**. [Note that the remaining material could be recycled *via* the sequence: desilylation, reaction with TBDPS-Cl and chromatographic resolution of the isomers to give further quantities of 4-silyl ether **10**.] Tosylation of the free 6-OH group of the 4-silyl ether **10** to give **11** was achieved in 67% yield using tosyl chloride in the presence of a catalytic amount of DMAP. The removal of the silyl group with TBAF gave the 4-hydroxycyclohexane 6-tosylate **12** in quantitative recovery and benzylation of the 6-tosylate afforded the 4-benzyl ether **13** in 80% yield after chromatographic purification on silica. Solvolysis of the cyclohexylidene ketal protection over 2 days in methanol containing a catalytic amount of TFA gave the 1,2-diol **14** in 78% yield together with some recovered starting material. In subsequent reactions the 1,2-diol was not isolated but the solvent methanol and TFA were removed and the diol was redissolved in methanol and then treated with potassium carbonate, in the same "pot", to give the required homochiral 1,6-epoxy-4-benzyloxycyclohexan-2-ol (+)-**3** in 90% yield, 14% overall yield from (−)-quinic acid, Scheme 1. Reaction of the isolated pure diol **14** with methanolic potassium carbonate gave the epoxide **3** in 90% yield after chromatographic purification on silica. Compound (+)-**3** {mp 64–65 °C, $[a]_D$ +56.4 (*c* 0.33 in MeOH), $[a]_D$ +19.2 (*c* 0.21 in $CHCl_3$) {lit.,[22] for 87% ee material obtained as an oil, $[a]_D$ +18.6 (*c* 4.4 in $CHCl_3$)} and all of its synthetic intermediates were fully characterised and showed the expected properties, see Experimental section.

In order to test the stereochemical requirements for inhibition of inositol monophosphatase and verify the validity of the concept, see above, we wished to prepare a single enantiomer of the 6-propyloxycyclohexane-1,2,4-triol 1-phosphate (−)-**19**. We had previously prepared the phosphate ester (±)-**19** in racemic form[12] and had shown that it behaved as a competitive inhibitor and possessed a K_i value of 1.28 μM. Accordingly, using chemistry previously optimised for the synthesis of racemic inhibitors,[12] the epoxy alcohol (+)-**3** was benzylated to give the bis(benzyl ether) (+)-**15** {$[a]_D$ +72.6 (*c* 0.208 in MeOH)} in 93% yield. The fully protected cyclitol epoxide **15** was treated with propanol in the presence of boron trifluoride–diethyl ether to give the 6-propyl ether (−)-**16a** {$[a]_D$ −34.1 (*c* 0.18 in MeOH)} in 60% yield from epoxide (+)-**3**, Scheme 2.

In an attempt to improve the yield of this reaction we also performed the same experiment using ytterbium(III) triflate as a catalyst.[23] A 20% molar equivalent of the Lewis acid in refluxing 1,2-dichloroethane gave an identical product (−)-**16b** to the boron trifluoride–diethyl ether method although in an improved yield of 98%. To explore the practical value of this catalyst the fully protected cyclitol epoxide **15** was also cleaved with two other hindered alcohols, namely isopropanol and 2-phenylethanol. Yields of 99% and 65% were obtained for each of the required isolated products, the isopropyl ether (−)-**20** and the phenethyl ether (−)-**21**, respectively.



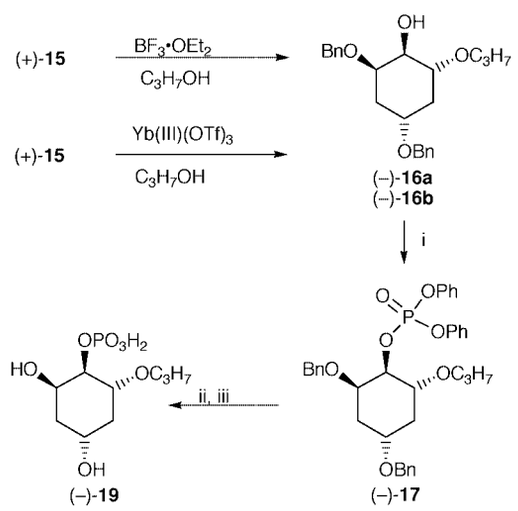
(−)-**20**



(−)-**21**

The 1-hydroxy group of the cyclitol 6-propyl ether **16** was phosphorylated using diphenyl chlorophosphate and the phosphate triester was transesterified, as described previously for the racemic material,[12] to give the dibenzyl phosphate triester (−)-**18**. Deprotection of all four benzyl groups was achieved using sodium in liquid ammonia and the required (1*R*,2*R*,4*R*,6*R*)-6-propyloxycyclohexane-1,2,4-triol 1-phosphate (−)-**19** was isolated as its bis(cyclohexylammonium) salt {mp >200 °C (decomp.), $[\alpha]_D$ −37.8 (*c* 0.53 in H_2O)} after purification by ion exchange chromatography in 40% yield from the cyclitol 6-propyl ether **16**. The compound and all of its intermediates displayed identical spectral properties to those for the racemic material.[12]

In order to access both the coordination sphere of $Mg^{2+}2$ and the hydrophobic pocket it was necessary to conceive of a molecule that possessed a C-6 appended ω-hydroxyalkyl moiety and also, a lipophilic moiety suitably disposed to interact with the side chains of Val-40 and Leu-42 in the protein. Since it was possible that this might be achieved by introducing a lipophilic group at a branched position on a C-6 appended ω-hydroxyalkyl moiety, the effectiveness of such a strategy was examined. (1*R*,2*R*,4*R*,6*R*)-*O*^{6}-(2′-Hydroxyethyl)cyclohexane-1,2,4,6-tetraol 1-phosphate **1** (R = OCH_2CH_2OH) contains a pendant 2-hydroxyethyloxy group attached to C-6 and the synthesis of the parent compound had been previously described.[12] The compound was a submicromolar competitive inhibitor and its interactions with the protein had been modelled.[7,12] Thus, it appeared that the *O*^{6}-(2′-hydroxyethyl)-cyclitol 1-phosphate **1** could be useful in providing a framework for inhibitor design.

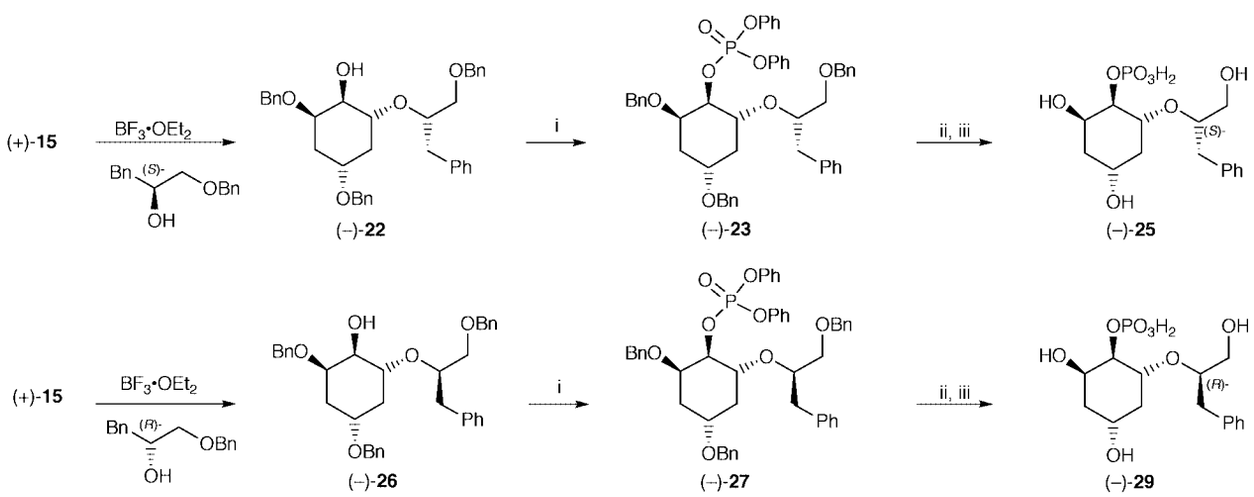


Scheme 2 *Reagents and conditions*: i, $ClP(O)(OPh)_2$, Et_3N, DMAP, DCM, rt, 12 h, 92%; ii, NaH, BnOH, THF, 0 °C→rt, 2 h, 67%; iii, Na, $NH_{3(l)}$, 0 °C→rt, 2 h, 65%.

The introduction of a lipophilic group to create a branch point in the C-6 appended ω-hydroxyalkyl moiety produces a new chiral centre. It was determined that a benzyl group would be first introduced into the 1′-position of the 2′-hydroxyethyl side chain of compound **1** (R = OCH_2CH_2OH) to give the (2′*S*)- and (2′*R*)-epimers **25** and **29**, respectively; Scheme 3.

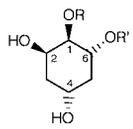
The reason that we wished to examine the introduction of a benzyl group at C-1′ of the parent 2′-hydroxyethyl compound **1** (R = OCH_2CH_2OH) first was because the synthesis of the precursor alcohols (2*R*)- and (2*S*)-1-benzyloxy-3-phenylpropan-2-ol required for the formation of the (2′*R*)- and (2′*S*)-epimers **29** and **25** was much easier, starting from homochiral phenyllactic acids, than the synthesis of the isomeric (2*R*)- and (2*S*)-2-benzyloxy-3-phenylpropan-1-ols. To prepare the 2-benzyloxy-3-phenylpropan-1-ols would require reduction of the carboxy groups, selective protection of the primary OH groups, benzylation of the secondary OH groups and unmasking of the orthogonal primary OH group protection such that the alcohol could serve as a nucleophile in epoxide alcoholysis reactions. The latter primary alcohols were expected to react better with the epoxide (+)-**15** than the secondary alcohols investigated here and, therefore, we did not believe that there would be any additional problems in the synthesis if we could demonstrate that the secondary (2*R*)- and (2*S*)-1-benzyloxy-3-phenylpropan-2-ols could be used as nucleophiles. It should be noted that modelling suggested that the influence of a C-1′-tethered benzyl group in the isomeric (1′*R*)- and (1′*S*)-epimers of compounds **25** and **29** would also be worthy of biological evaluation in the future.

Analysis of the structure of the inhibited complex of *O*^{6}-(2′-hydroxyethyl)cyclitol 1-phosphate **1** had indicated that the 2′-hydroxy group and the phosphate ester O-atoms should interact with $Mg^{2+}2$ to form an eight-membered metallocycle. One face of this fused cyclitol-metallocycle is exposed to the solvent in the upper part of the active site cleft, whereas, the other, lower face (upon which the 2-OH group of the cyclitol ring resides) is buried in the protein. The introduction of a bulky benzyl moiety into the *O*^{6}-(2′-hydroxyethyl) side chain to give the (2′*S*)-epimer **25** was expected to position the benzyl moiety above the metallocycle in solvent-filled space and, therefore, it was expected that the (2′*S*)-epimer **25** should be a better inhibitor than the (2′*R*)-epimer **29**. Indeed, it was expected that the (2′*R*)-epimer **29** would be either a very poor inhibitor, or not active at all.



Scheme 3 *Reagents and conditions*: i, $ClP(O)(OPh)_2$, Et_3N, DMAP, DCM, rt, 12 h, 83–90%; ii, NaH, BnOH, THF, 0 °C→rt, 2 h, 62–67%; iii, Na, $NH_{3(l)}$, 0 °C→rt, 2 h, 60–62%.

Table 3 Inhibition constants for substituted cyclohexane-1,2,4,6-tetraols



Entry	Compound	R	R′	K_i/μmol dm^{-3}	Mode of inhibition
1	(±)	-PO_3^{2-}	-C_2H_4OH	1.8	Competitive [12b]
2	(−)-(1*R*,2*R*,4*R*,6*R*)	-PO_3^{2-}	-C_2H_4OH	0.5	Competitive [12b]
3	(±)	-Cyclic P	-Cyclic P	160.0	Competitive [12b]
4	(±)	-PO_3^{2-}	-CH_3	2.5	Competitive [12b]
5	(±)	-PO_3^{2-}	-C_3H_7	1.2	Competitive [12b]
6	(−)-(1*R*,2*R*,4*R*,6*R*)-**19**	-PO_3^{2-}	-C_3H_7	0.87	Competitive
7	(−)-(1*R*,2*R*,4*R*,6*R*,2′*S*)-**25**	-PO_3^{2-}	-2′-CH-{2′*S*)-2′-CH_2Ph}CH_2OH	100.0	Competitive
8	(−)-(1*R*,2*R*,4*R*,6*R*,2′*R*)-**29**	-PO_3^{2-}	-2′-CH-{2′*R*)-2′-CH_2Ph}CH_2OH	310.0	Competitive
9	(−)-(1*S*,2*R*,4*S*)-**2**	-PO_3^{2-}	-H	3.0	Competitive [12b]
10	(+)-(1*R*,2*S*,4*R*)-**2**	-PO_3^{2-}	-H	Weak substrate	Weak substrate [12b]

The synthesis of the (2′*S*)-epimer **25** started from key epoxide (+)-**15**. Treatment of the epoxide with 1.5 equivalents of (2*S*)-(−)-1-benzyloxy-3-phenylpropan-2-ol (which was itself obtained in two steps from commercially available L-(−)-phenyllactic acid) in the presence of boron trifluoride–diethyl ether [12,24] gave the 1-alcohol **22** in an acceptable 50% yield after chromatographic purification on silica. The use of less than 1.5 equivalents of (2*S*)-(−)-1-benzyloxy-3-phenylpropan-2-ol gave rise to much lower isolated yields. The exclusion of moisture was also found to be particularly important when using lower excesses of the alcohol nucleophile. Phosphorylation of the 1-OH group with diphenyl chlorophosphate, gave the diphenyl phosphate triester **23** in 90% yield. Transesterification in the presence of sodium benzyl oxide gave **24** in 67% yield and reductive deprotection of each of the five benzyloxy groups afforded the required 1-phosphate (−)-**25** in 62% yield after ion exchange chromatographic purification and conversion to the bis(cyclohexylammonium) salt.

Exactly the same methodology was used for the synthesis of the epimeric (−)-(1′*R*)-cyclitol 1-phosphate **29** except the key epoxide [(+)-**15**] was treated, under Lewis acid catalysed conditions, with (2*R*)-(+)-1-benzyloxy-3-phenylpropan-2-ol which was itself obtained in two steps from commercially available D-(+)-phenyllactic acid.

When tested for biological activity using standard enzyme assays [4] compounds (−)-**19**, **25** and **29** behaved as competitive inhibitors for inositol monophosphatase (see Table 3). The observed K_i value of 0.87 μM for (−)-**19** was lower than that for the racemic material [12] indicating that the (1*R*,2*R*,4*R*,6*R*)-antipode is the most active enantiomer. This result is in accord with predictions based upon earlier modelling work [7] and supports the notion that the same absolute (1*R*,2*R*,4*R*,6*R*)-configuration in the cyclitol ring should be optimal for the design of more elaborate inhibitors.

Compounds **25** and **29** were both competitive inhibitors and gave K_i values of 100 μM and 310 μM respectively. These values are much higher than that of 0.5 μM observed for the inhibitor without an additional benzyl moiety (see Table 3; entry 2). The relative potency of the two 2′-epimers is qualitatively consistent with expectations in that the (2′*S*)-epimer **25** binds tighter. The C-2′ branch point in the (2′*S*)-epimer is very close to the position of the side chain carboxylate group of Asp-220 which interacts with $Mg^{2+}2$ and it is quite likely that the position of Asp-220 is disturbed by the benzylic C-atom. Therefore, it may be worthwhile to assess the comparative potency of the (1′*S*)- and (1′*R*)-epimers of the isomeric cyclitol phosphates where the branch point is moved further away from the O^6-atom, see above. The use of the homochiral epoxide **3** will be valuable in the synthesis of such inhibitors and, evidently, will allow access to a wide range of C-6 elaborated inhibitors. The recent finding that 6-aminocyclitol 1-phosphates can serve as substrates and can be prepared using ytterbium triflate catalysed aminolysis of epoxide **3** will help significantly in the design of inhibitors.[13,25] A major objective is now to prepare compounds that can simultaneously recognise both the hydrophilic and hydrophobic binding sites on the enzyme proximal to C-6 of the substrate **2**. The further recent finding that the epoxide can be immobilised on polystyrene resins for the solid-phase synthesis of inhibitors should speed progress in this and related areas considerably.[26,27]

Experimental

Elemental microanalyses were performed in the departmental micro-analytical laboratory. NMR spectra were recorded on a Bruker AM-300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.4 MHz; ^{31}P, 121.5 MHz), Varian Gemini 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.4 MHz) and a Varian Unity Plus 500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125.6 MHz). Chemical shifts are described in parts per million downfield from $SiMe_4$ and are reported consecutively as position (δ_H or δ_C), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double of doublets, sep = septet, m = multiplet, and br = broad), coupling constant (*J*/Hz) and assignment (numbering according to the IUPAC nomenclature for the compound). ^{1}H-NMR spectra were referenced internally on ^{2}HOH (δ 4.68), $CHCl_3$ (δ 7.27) or $(CH_3)_2SO$ (δ 2.47). ^{13}C-NMR spectra were referenced on CH_3OH (δ 49.9), C^2HCl_3 (δ 77.5) or $(CH_3)_2SO$ (δ 39.70) and ^{31}P NMR spectra to external H_3PO_4 (δ 0). IR spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. The samples were prepared as Nujol mulls, solutions in chloroform or thin films between sodium chloride discs. The frequencies (ν) as absorption maxima are given in wavenumbers (cm^{-1}) relative to a polystyrene standard. Mass spectra and accurate mass measurements were recorded on a VG 70-250 SE, a Kratos MS-50 or by the SERC service at Swansea using a VG AZB-E. Fast atom bombardment spectra were recorded using glycerol as a matrix. Major fragments were given as percentages of the base peak intensity (100%). UV–VIS optical densities were measured on a CamSpec M302 spectrophotometer. Flash chromatography was performed according to the method of Still *et al.*[28] using Fluka Kieselgel C60 (40–60 μm mesh) silica gel. Analytical thin layer chromatography was carried out on 0.25 mm precoated silica gel plates (Whatman PE SIL G/UV) and compounds were visualised using UV fluorescence, iodine vapour, ethanolic phosphomolybdic acid, aqueous potassium permanganate or ninhydrin. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were measured at 23 °C on an Optical Activity AA-1000 polarimeter using 10 or 20 cm path length cells and are given in units of 10^{-1} deg cm^2 g^{-1}.

Inositol 1-phosphates were prepared from *myo*-inositol as described previously[29] using the method of Billington *et al.*,[30] while other substrates were prepared as described below. Amberlite IR 118H ion exchange resin was obtained from BDH (Poole, Dorset, UK). Phosphorylating agents were obtained from the Aldrich Chemical Co. Ltd. (Gillingham, Dorset, UK). The solvents used were either distilled or of Analar quality and light petroleum ether refers to that portion boiling between 40–60 °C. Solvents were dried according to literature procedures.[31] Ethanol and methanol were dried using magnesium turnings. DMF, CH_2Cl_2, diisopropylamine and triethylamine, were distilled over CaH_2. THF and diethyl ether were dried over sodium–benzophenone and distilled under nitrogen.

(+)-(1*S*,2*R*,6*R*)-1,2-Cyclohexylidenedioxy-4-oxocyclohexan-6-ol 7[14]

(−)-Quinic acid (−)-**4** (30 g, 156 mmol) and cyclohexanone (48.6 cm^3, 46 g, 470 mmol) were treated with conc. phosphoric acid (3 drops) and heated under reflux for 30 min. The water produced was removed by distillation for 1–2 h and the reaction mixture was allowed to cool to room temperature whereupon it solidified. The crude solid was recrystallised from dichloromethane to remove most of the cyclohexanone and the crude lactone (−)-**5** was collected by filtration. The crude lactone (−)-**5** was dissolved in ethanol (300 cm^3) and the solution cooled in an ice bath. $NaBH_4$ (3.8 g, 100 mmol) was added in 4 batches with vigorous stirring and the mixture was allowed to warm to room temperature with stirring overnight. The solvent was removed under reduced pressure and the residue was dissolved in water (300 cm^3). The pH of the solution was adjusted to pH 6 by the dropwise addition of conc. phosphoric acid. The weakly acidic solution was cooled in an ice bath and $NaIO_4$ (33.4 g, 156 mmol) was added slowly in batches over a period of 30 min with stirring. After a further 5 h, the mixture was extracted with diethyl ether (2 × 150 cm^3) followed by ethyl acetate (150 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil solidified upon drying *in vacuo* and the crude solid was recrystallised (ethyl acetate–petroleum ether; 1:10) to give ketone (+)-**7** as a white solid (27.5 g, 78%); work-up of the mother liquor by chromatography on silica (ethyl acetate–petroleum ether; 1:2) afforded further quantities of the ketone (+)-**7** (1.1 g, 3%), mp 97–98 °C (Found: C, 63.9; H, 8.1. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%); $[\alpha]_D$ +100.3 (*c* 0.44 in MeOH); ν_{max}(Nujol)/cm^{-1} 3775 s, 1720 s, 1471 s, 1386 s and 1092 s; δ_H(300 MHz; C^2HCl_3) 1.30–1.45 (2 H, br s, cyclohexylidene), 1.5–1.70 (8 H, m, cyclohexylidene), 2.00–2.25 (1 H, broad, OH), 2.43 (1 H, ddd, $^2J_{H\text{-}H}$ 17.85, $^3J_{H\text{-}H}$ 3.85 and 1.9, 5-H), 2.63–2.73 (2 H, m, 3-H and 5-H), 2.80 (1 H, dd, $^2J_{H\text{-}H}$ 17.6, $^3J_{H\text{-}H}$ 3.85, 3-H), 4.21–4.26 (1 H, br s, 6-H), 4.27–4.33 (1 H, m, 1-H) and 4.66–4.72 (1 H, m, 2-H); δ_C(75.4 MHz; C^2HCl_3) 23.39, 23.77, 25.01, 33.17, 36.15, 40.17 and 41.59 (5 × C secondary of cyclohexylidene, 3-C and 5-C), 68.21 (6-C), 71.71 (2-C), 74.61 (1-C), 109.52 (C quaternary of cyclohexylidene) and 208.66 (4-C); δ_C(75.4 MHz; $C^2H_3O^2H$) 23.21, 23.59, 24.92, 32.81, 35.95, 39.91 and 41.03 (5 × C secondary of cyclohexylidene, 3-C and 5-C), 67.38 (6-C), 71.89 (2-C), 74.55 (1-C), 109.05 (C quaternary of cyclohexylidene) and 209.89 (4-C); *m*/*z* (CI) 227 (35%, $[M + H]^+$), 129 (56, $[M + H - C_6H_{10}O]^+$) and 99 (100, $C_6H_{11}O^+$).

1,2-Cyclohexylidenedioxycyclohexane-4,6-diol (−)-(1*S*,2*R*,4*S*,6*R*)-8 and (+)-(1*S*,2*R*,4*R*,6*R*)-9[15,16]

To a stirred solution of the ketone (+)-**7** (13.56 g, 60 mmol) in methanol (700 cm^3) was added $LaCl_3 \cdot 7H_2O$ (22.3 g, 60 mmol) and the suspension was cooled to −78 °C. $NaBH_4$ (2.66 g, 70 mmol) was added in small batches whilst maintaining vigorous stirring. The mixture was allowed to warm slowly to room temperature over 12 h and the solvent was removed under reduced pressure. The residual oil was partitioned between water (100 cm^3) and ethyl acetate (100 cm^3) and the aqueous phase was extracted with ethyl acetate (2 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and then concentrated under reduced pressure to give 13 g of a crude mixture of the *cis*-diol (−)-**8** and the *trans*-diol (+)-**9** in a ratio of 5:1, as judged by ^{1}H-NMR spectroscopy. For analytical purposes a small amount of the diol mixture was chromatographed on silica (ethyl acetate–petroleum ether; 2:1) where the less polar *trans*-4,6 diol (+)-**9** was eluted first.

For the *trans*-diol (+)-**9**: mp 129–130 °C; $[\alpha]_D$ +6 (*c* 0.16 in MeOH); δ_H(300 MHz; C^2HCl_3) 1.33–1.83 (10 H, m, cyclohexylidene), 1.90 (1 H, 'dt', $^2J_{H\text{-}H}$ 15.4, $^3J_{H\text{-}H}$ 4.1, secondary-H), 2.03–2.14 (1 H, m, secondary-H), 2.20–2.30 (1 H, m, secondary-H), 2.58 (1 H, d, $^3J_{H\text{-}H}$ 8.0, OH), 3.30–3.70 (1 H, broad, OH), 3.90 (1 H, 't', $^3J_{H\text{-}H}$ 5.6, 1-H), 4.07–4.20 (2 H, m, 4-H and 6-H) and 4.35–4.44 (1 H, m, 2-H); δ_C(75.4 MHz; C^2HCl_3) 23.56, 23.93, 24.83, 33.07, 34.98, 37.17 and 38.36 (5 × C secondary of cyclohexylidene, 3-C and 5-C), 65.96 (4-C), 68.43 (6-C), 73.98 (2-C), 80.02 (1-C) and 109.75 (C quaternary of cyclohexylidene); *m*/*z* (CI) 229 (100%, $[M + H]^+$), 211 (38, $[M + H - H_2O]^+$) and 99 (4, $C_6H_{11}O^+$).

For *cis*-diol (−)-**8**: mp 119–120 °C (Found: C, 62.65; H, 9.1. $C_{12}H_{20}O_4$ requires C, 63.1; H, 8.8%) (HRMS: found: $[M + H]^+$, 229.1432. $C_{12}H_{21}O_4$ requires 229.1440); $[\alpha]_D$ −70.6 (*c* 0.16 in MeOH); δ_H(300 MHz; C^2HCl_3) 1.30–1.70 (11 H, m, cyclohexylidene and 5-H), 1.75 (1 H, ddd, $^2J_{H\text{-}H}$ 14.3, $^2J_{H\text{-}H}$ 9.33 and 4.7, 3-H), 2.04–2.13 (1 H, m, 5-H), 2.24–2.33 (1 H, m, 3-H), 3.77–3.85 (1 H, m, 6-H), 3.86–3.92 (1 H, 't', $^3J_{H\text{-}H}$ 6.3 and 5.2, 1-H), 4.02–4.14 (1 H, m, 4-H) and 4.34–4.41 (1 H, m, 2-H); δ_C(75.4 MHz; C^2HCl_3) 23.61, 23.94, 24.90 and 35.10 (4 × C secondary of cyclohexylidene), 35.70 (3-C), 38.07 (C secondary of cyclohexylidene), 38.11 (5-C), 65.31 (4-C), 70.8 (6-C), 72.66 (2-C), 79.62 (1-C) and 109.59 (C quaternary of cyclohexylidene); *m*/*z* (CI) 229 (100%, $[M + H]^+$), 211 (44, $[M + H - H_2O]^+$) and 99 (10, $C_6H_{11}O^+$).

(−)-(1*S*,2*R*,4*S*,6*R*)-1,2-Cyclohexylidenedioxy-4-(*tert*-butyldiphenylsilyl)cyclohexan-6-ol 10

The above described crude mixture of *cis*- and *trans*-4,6 diols (−)-**8** and (+)-**9** (10 g, 43.86 mmol) was dissolved in dry dichloromethane (100 cm^3), and DMAP (1.22 g, 10 mmol) and dry TEA (6.26 cm^3, 4.55 g, 45 mmol) were added. The mixture was cooled in an ice bath and *tert*-butyldiphenylsilyl chloride (11.7 cm^3, 12.37 g, 45 mmol) was added dropwise with vigorous stirring. The mixture was stirred for a further 16 h at room temperature and then extracted with water (100 cm^3). The aqueous phase was extracted with dichloromethane (3 × 100 cm^3) and the pooled organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 10:1 and then 5:1) to give the silylated compound (−)-**10** as a white, sticky foam (9.9 g, 48%) (Found: C, 71.9; H, 8.15. $C_{28}H_{38}O_4Si$ requires C, 72.05; H, 8.2%) (HRMS: found: $[M + H]^+$, 467.2608. $C_{28}H_{39}O_4Si$ requires 467.2618); $[\alpha]_D$ −23.0 (*c* 0.398 in MeOH); ν_{max}(Nujol)/cm^{-1} 3404 s; δ_H(300 MHz; C^2HCl_3) 1.06 (9 H, s, ^{t}butyl), 1.30–1.40 (1 H, br s, 3-H), 1.45–1.60 (10 H, m, cyclohexylidene), 1.65–1.75 (1 H, m, 5-H), 1.78–1.93 (2 H, m, 3-H and 5-H), 3.07–3.16 (1 H, br s, 6-OH), 3.73–3.84 (1 H, br s, 6-H), 4.0 (1 H, 't', 1-H, $^3J_{H\text{-}H}$ 5.3), 4.06–4.16 (1 H, m, 4-H), 4.36–4.44 (1 H, m, 2-H), 7.30–7.50 (6 H, m, $SiPh_2$) and 7.60–7.70 (4 H, m, $SiPh_2$); δ_C(75.4 MHz; C^2HCl_3) 18.92 [$C(CH_3)_3$], 23.58, 23.88 and 24.30 (3 × C secondary of cyclohexylidene), 26.84 [$C(CH_3)_3$], 35.19 (C secondary of cyclohexylidene), 35.72 (3-C), 36.55 (5-C), 38.06 (C secondary of cyclohexylidene), 68.02 (4-C), 69.93 (6-C), 71.81 (2-C), 78.79 (1-C), 109.26 (C quaternary of cyclohexylidene) and 127.78, 127.81, 129.89, 129.95, 133.49, 135.78, 135.81 and 135.84 (Ar-CH and Ar-C quaternary of $SiPh_2$); *m*/*z* (CI) 467 (100%, $[M + H]^+$), 369 (33, $[M + H - C_6H_{10}O]^+$), 211 (29, $[M - OSiC_{16}H_{19}]^+$) and 99

(41, $C_6H_{11}O^+$). A mixture of two silylated cyclohexanetetraols (6.1 g, 30% no further characterisation), arising from the presence of an overall three equatorial OH groups and one axial OH group in the mixture of *trans*- and *cis*-diol (+)-**9** and (−)-**8** respectively, which was used for the silylation reaction, was eluted from the column after the desired compound (−)-**10**.

(−)-(1*R*,2*R*,4*S*,6*R*)-1,2-Cyclohexylidenedioxy-4-(*tert*-butyldiphenylsilyl)-6-(4′-methylphenylsulfonyloxy)cyclohexane 11

To a stirred solution of the silylated compound (−)-**10** (9 g, 19.3 mmol) in dry dichloromethane (100 cm^3) was added DMAP (488 mg, 4 mmol) and dry TEA (3.01 cm^3, 2.18 g, 21.6 mmol). The mixture was cooled in an ice bath and 4-methylbenzenesulfonyl chloride (4.78 g, 25.1 mmol) was added with vigorous stirring. Stirring was continued for three days at room temperature and then water (100 cm^3) was added. The two phases were separated and the aqueous phase was extracted with dichloromethane (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 1:10) to give the tosylate (−)-**11** as a white, sticky foam, which solidified upon treatment with MeOH (8 g, 67%), and some unreacted starting material (−)-**10** (710 mg, 8%); mp 98–99 °C (Found: C, 67.75; H, 6.8. $C_{35}H_{44}O_6SSi$ requires C, 67.7; H, 7.1%) (HRMS: found: M^+, 620.2638. $C_{35}H_{44}O_6SSi$ requires 620.2628); $[a]_D$ −51.5 (*c* 0.68 in MeOH); δ_H(300 MHz; C^2HCl_3) 1.0 (9 H, s, ^{t}butyl), 1.10–1.50 (10 H, m, secondary-H of cyclohexylidene), 1.52–1.66 (1 H, m, 5-H), 1.68–1.74 (1 H, m, 3-H), 2.12–2.26 (2 H, m, 3-H and 5-H), 2.4 (3 H, s, tosyl-CH_3), 3.88–4.02 (2 H, m, 1-H and 4-H), 4.08–4.29 (2 H, m, 2-H and 6-H), 7.23–7.28 (2 H, m, Ar-H), 7.33–7.47 (6 H, m, Ar-H), 7.60–7.65 (4 H, m, Ar-H) and 7.72 (2 H, d, $^3J_{H\text{-}H}$ 8.25, tosyl-H); δ_C(75.4 MHz; C^2HCl_3) 18.94 [$C(CH_3)_3$], 21.48 (tosyl-CH_3), 23.39, 23.68 and 24.84 (3 × C secondary of cyclohexylidene), 26.76 [$C(CH_3)_3$], 34.62, 35.34, 37.22 and 38.19 (2 × C secondary of cyclohexylidene, 3-C and 5-C), 65.46 (4-C), 72.94 (2-C), 76.11 (6-C), 81.21 (1-C), 109.51 (C quaternary of cyclohexylidene) and 127.69, 127.76, 128.05, 129.61, 129.77, 129.84, 133.71, 133.94, 135.72, 135.76 and 144.4 (Aryl-CH and Ar-C quaternary); *m*/*z* (EI) 620 (3%, M^+), 353 (100) and 193 (17, $[M - C_7H_7SO_3 - C_{16}H_{19}OSi]^+$).

(−)-(1*R*,2*R*,4*R*,6*R*)-1,2-Cyclohexylidenedioxy-6-(4′-methylphenylsulfonyloxy)cyclohexan-4-ol 12

To a stirred solution of the tosylate (−)-**11** (8 g, 12.9 mmol) in THF was added TBAF (15 cm^3 of a 1 mol dm^{-3} solution in THF, 15 mmol) and the resulting mixture was stirred at room temperature for 16 h. The solvent was concentrated under reduced pressure and the residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 1:1) to give alcohol (−)-**12** as a white solid (dihydrate: 5.39 g, 100%); mp 140–142 °C (Found: C, 55.0; H, 6.6. $C_{19}H_{26}O_6S{\cdot}2H_2O$ requires C, 54.5; H, 6.3%); $[a]_D$ −88.5 (*c* 0.3 in MeOH); ν_{max}(Nujol)/cm^{-1} 3394 s, 1464 s and 1381 s; δ_H(300 MHz; C^2HCl_3) 1.22–1.70 (12 H, m, cyclohexylidene, 3-H and 5-H), 2.32–2.45 (5 H, m, 3-H, 5-H and tosyl-CH_3), 3.95 (1 H, dd, 1-H, $^3J_{H\text{-}H}$ 6.9 and 5.3), 3.99–4.10 (1 H, m, 4-H), 4.30–4.35 (1 H, m, 2-H), 4.45 (1 H, ddd, 6-H, $^3J_{H\text{-}H}$ 11.5, 7.1 and 4.4), 7.29 (2 H, d, $^3J_{H\text{-}H}$ 8.3, Ar-H) and 7.80 (2 H, d, $^3J_{H\text{-}H}$ 8.3, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 21.53 (tosyl-CH_3), 23.49, 23.76, 24.86, 34.72, 35.0, 37.44 and 38.25 (5 × C secondary of cyclohexylidene, 3-C and 5-C), 63.94 (4-C), 73.07 (2-C), 76.16 (6-C), 81.29 (1-C), 109.65 (C quaternary of cyclohexylidene), 128.10 and 129.75 (Ar-CH) and 134.04 and 144.71 (Ar-C quaternary); *m*/*z* (EI) 383 (100%, $[M + H]^+$), 285 (11, $[M + H - C_6H_{10}O]^+$), 211 (33, $[M + H - C_7H_8O_3S]^+$) and 99 (34, $C_6H_{11}O^+$).

(−)-(1*R*,2*R*,4*R*,6*R*)-1,2-Cyclohexylidenedioxy-4-benzyl-6-(4′-methylphenylsulfonyloxy)cyclohexane 13

Under an atmosphere of N_2, a solution of alcohol (−)-**12** (5 g, 12 mmol) in dry DMF (100 cm^3) was treated with benzyl bromide (2.8 cm^3, 4.1 g, 24 mmol). The solution was cooled to −50 °C and NaH (600 mg, 15 mmol; 60% dispersion in oil) was added with continued stirring. The mixture was allowed to slowly warm up to room temperature and then water (100 cm^3) was cautiously added. The mixture was extracted with diethyl ether (2 × 100 cm^3) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 1:5) to give, after recrystallisation from methanol, the benzyl ether (−)-**13** as a white solid (4.53 g, 80%); mp 83–84 °C (Found: C, 65.8; H, 6.9. $C_{26}H_{32}O_6S$ requires C, 66.1; H, 6.8%) (HRMS: found: M^+, 472.1927. $C_{26}H_{32}O_6S$ requires 472.1920); $[a]_D$ −85.3 (*c* 0.214 in MeOH); ν_{max}-(CH_2Cl_2)/cm^{-1} 3063 s, 2946 s, 1605 s, 1444 s, 1346 s, 1273 s, 1183 s, 942 s, 816 s and 742 s; δ_H(300 MHz; C^2HCl_3) 1.25–1.52 (10 H, m, cyclohexylidene), 1.52–1.61 (1 H, m, 5-H), 1.71 (1 H, ddd, $^2J_{H\text{-}H}$ 13.6, $^3J_{H\text{-}H}$ 10.4 and 4.7, 3-H), 2.43 (3 H, m, tosyl-CH_3), 2.46–2.56 (1 H, m, 3-H and 5-H), 3.70–3.81 (1 H, m, 4-H), 3.97 (1 H, dd, $^3J_{H\text{-}H}$ 5.5 and 7.1, 1-H), 4.32–4.37 (1 H, m, 2-H), 4.46 (1 H, ddd, $^3J_{H\text{-}H}$ 11.8, 7.1 and 4.4, 6-H), 4.49 (1 H, d, $^2J_{H\text{-}H}$ 11.5, one of OCH_2Ph), 4.55 (1 H, d, $^2J_{H\text{-}H}$ 11.5, one of OCH_2Ph), 7.20–7.30 (7 H, m, Ar-H) and 7.82 (2 H, d, $^3J_{H\text{-}H}$ 8.3, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 21.47 (tosyl-CH_3), 23.44, 23.72, 24.83, 32.5, 34.71, 35.18 and 37.41 (5 × C secondary of cyclohexylidene, 3-C and 5-C), 70.71 (OCH_2Ph), 70.97 (4-C), 72.98 (2-C), 76.42 (6-C), 81.43 (1-C), 109.72 (C quaternary of cyclohexylidene), 127.52, 127.69, 128.05, 128.45 and 129.64 (Ar-CH) and 134.10, 138.2 and 144.56 (Ar-C quaternary); *m*/*z* (EI) 472 (31%, M^+), 382 (7, $[M + H - C_7H_7]^+$) and 91 (100, $C_7H_7^+$).

(−)-(1*R*,2*R*,4*R*,6*R*)-4-Benzyloxy-6-(4′-methylphenylsulfonyloxy)cyclohexane-1,2-diol 14

To a stirred solution of the ketal (−)-**13** (4 g, 8.5 mmol) in MeOH (50 cm^3) was added TFA (0.1 cm^3). After 2 days, the solvent was removed under reduced pressure and the residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 2:1) to give diol (−)-**14** as a colourless oil (2.6 g, 78%) and some unreacted starting material (−)-**13** (0.6 g, 15%) (Found: C, 60.8; H, 6.6. $C_{20}H_{24}O_6S$ requires C, 61.2; H, 6.2%) (HRMS: found: $[M + H]^+$, 393.1382. $C_{20}H_{25}O_6S$ requires 393.1372); $[a]_D$ −42.0 (*c* 0.67 in MeOH); ν_{max}(neat)/cm^{-1} 3472, 2926, 1600, 1444, 1361 and 1084; δ_H(300 MHz; C^2HCl_3) 1.37–1.48 (1 H, m, 3-H), 1.49–1.61 (1 H, m, 5-H), 2.24–2.39 (2 H, m, 3-H, 5-H), 2.46 (3 H, m, tosyl-CH_3), 2.54–2.62 (1 H, broad, OH), 3.06–3.14 (1 H, broad, OH), 3.63 (1-H, dd, $^3J_{H\text{-}H}$ 8.8 and 2.8, 1-H), 3.75–3.86 (1 H, m, 4-H), 4.12–4.17 (1 H, m, 2-H), 4.46 (2 H, s, OCH_2Ph), 4.70 (1 H, ddd, $^3J_{H\text{-}H}$ 11.8, 9.05 and 4.95, 6-H) and 7.20–7.30 (7 H, m, Ar-H) and 7.82 (2 H, d, $^3J_{H\text{-}H}$ 8.3, tosyl-H); δ_C(75.4 MHz; C^2HCl_3) 21.62 (tosyl-CH_3), 35.48 (3-C), 36.16 (5-C), 68.59 (2-C), 70.86 (OCH_2Ph), 70.95 (4-C), 73.61 (1-C), 80.42 (6-C), 127.59, 127.75, 127.94, 128.48 and 130.05 (Ar-CH) and 133.42, 138.25 and 145.34 (Ar-C quaternary); *m*/*z* (CI) 393 (67%, $[M + H]^+$), 221 (63, $[M + H - C_7H_8O_3S]^+$), 203 (51, $[MH - C_7H_8O_3S - H_2O]^+$), 113 (100) and 91 (22, $C_7H_7^+$).

(+)-(1*S*,2*R*,4*R*,6*R*)-4-Benzyloxy-1,6-epoxycyclohexan-2-ol 3[22]

To a stirred solution of the diol (−)-**14** (2.5 g, 6.4 mmol) in MeOH (30 cm^3) was added K_2CO_3 (1.77 g, 12.8 mmol) in small portions. The viscous reaction mixture was stirred at room temperature for 30 min, filtered, and the pad washed thoroughly with diethyl ether followed by ethyl acetate. The combined organic solutions were concentrated under reduced pressure

and the residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 1:1) to give epoxy alcohol (+)-**3** as a white solid (1.27 g, 90%), mp 64–65 °C (Found: C, 70.7; H, 7.2. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%); $[a]_D$ +56.4 (*c* 0.329 in MeOH); δ_H(300 MHz; C^2HCl_3) 1.56 (1 H, ddd, $^2J_{H\text{-}H}$ 13.7, $^3J_{H\text{-}H}$ 9.3 and 2.0, 3-H), 1.90–2.10 (3 H, m, 2 × 5-H and 3-H), 3.32–3.42 (2 H, m, 1-H and 6-H), 3.62–3.71 (1 H, m, 4-H), 4.26–4.38 (1 H, br s, 2-H), 4.42 (1 H, d, $^2J_{H\text{-}H}$ 11.7, one of OCH_2Ph), 4.50 (1 H, d, $^2J_{H\text{-}H}$ 11.7, one of OCH_2Ph) and 7.25–7.50 (5 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 29.14 and 32.50 (3-C and 5-C), 54.05 and 55.40 (1-C and 6-C), 64.83 (2-C), 70.13 (O*C*H_2Ph), 71.63 (4-C), 127.51, 127.70 and 128.49 (Ar-CH) and 138.39 (Ar-C quaternary); *m*/*z* (CI) 221 (65%, $[M + H]^+$), 203 (100, $[M + H - H_2O]$). Epoxy alcohol (+)-**3** was also obtained directly from compound (−)-**13** in a one-pot reaction, simply by adding K_2CO_3 (2.5 equivalents) to the reaction mixture of compound (−)-**13** in methanol, following the treatment with TFA, after 3 days. An overall yield of 78% of (+)-**11** was obtained together with 6% of recovered (−)-**13**. [Note that the synthesis of racemic epoxy alcohol (±)-**3**[11,12] and spectroscopic data thereof have been reported previously,[12] and limited data of (+)-**3** have also been reported previously.[22]]

(+)-(1*S*,2*R*,4*R*,6*R*)-2,4-Bis(benzyloxy)-1,6-epoxycyclohexane 15

Under an atmosphere of N_2, a solution of epoxy alcohol (+)-**3** (1.1 g, 5 mmol) in dry THF (50 cm^3) was cooled in an ice bath and benzyl bromide (0.66 cm^3, 940 mg, 5.5 mmol) and then KH (washed with petroleum ether prior to use, 220 mg, 5.5 mmol) were added with stirring. Stirring was continued at room temperature for 3 h and then water was added cautiously. The mixture was extracted with diethyl ether (2 × 50 cm^3), and the organic phases were combined, dried ($MgSO_4$) and then concentrated under reduced pressure. The residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 1:5) to give epoxide (+)-**15** as a colourless oil (1.44 g, 93%); $[a]_D$ +72.6 (*c* 0.208 in MeOH); δ_H(300 MHz; C^2HCl_3) 1.68–1.72 (1H, m, 3-H), 2.00–2.10 (3 H, m, 3-H and 2 × 5-H), 3.29–3.32 (1 H, m, 6-H), 3.42–3.46 (1 H, m, 1-H), 3.70–3.77 (1 H, m, 4-H), 4.15–4.23 (1 H, m, 2-H), 4.45 (2 H, s, OCH_2Ph), 4.70 (1 H, d, $^2J_{H\text{-}H}$ 12.1, OCH_2Ph), 4.74 (1 H, d, $^2J_{H\text{-}H}$ 12.1, OCH_2Ph) and 7.25–7.50 (10 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 28.60 and 29.09 (3-C and 5-C), 52.25 and 53.12 (1-C and 6-C), 70.04 and 70.50 (O*C*H_2Ph), 71.12 (4-C), 72.09 (2-C), 127.48, 127.62, 127.75 and 128.39 (Ar-CH) and 138.36 and 138.58 (Ar-C quaternary); *m*/*z* (CI) 221 (8%, $[M + 2H - C_7H_7]^+$) and 91 (100, $C_7H_7^+$).

(−)-(1*S*,2*R*,4*S*,6*R*)-2,4-Bis(benzyloxy)-6-propyloxycyclohexanol 16a

To an ice cooled, stirred solution of the epoxide (+)-**15** (620 mg, 2 mmol) and propan-1-ol (0.37 cm^3, 300 mg, 5 mmol) in dry toluene (5 cm^3) was added $BF_3{\cdot}OEt_2$ (3 drops of a 1:15 mixture in dry toluene). After stirring at room temperature for 3 h the solvent was removed under reduced pressure and the residual oil chromatographed on silica (ethyl acetate–petroleum ether; 1:2) to give alcohol (−)-**16** as a colourless oil (380 mg, 65%) (HRMS: found: $[M + H]^+$ 371.2214. $C_{23}H_{31}O_4$ requires 371.2222); $[a]_D$ −34.1 (*c* 0.18 in MeOH); δ_H(300 MHz; C^2HCl_3) 0.92 (3 H, t, $^3J_{H\text{-}H}$ 7.4, $OCH_2CH_2CH_3$), 1.23–1.43 (2 H, m, 3-H and 5-H), 1.54–1.67 (2 H, m, $OCH_2CH_2CH_3$), 2.31–2.40 (1 H, m, secondary-H), 2.45–2.53 (1 H, m, secondary-H), 3.39–3.61 (4 H, m, $OCH_2CH_2CH_3$, 1-H and 6-H), 3.68–3.8 (1 H, m, 4-H), 3.93–3.98 (1 H, m, tertiary-H), 4.46 (1 H, d, $^2J_{H\text{-}H}$ 12.8, OCH_2Ph), 4.53 (1 H, d, $^2J_{H\text{-}H}$ 12.8, OCH_2Ph), 4.60 (2 H, s, OCH_2Ph) and 7.20–7.50 (10 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 10.49 ($OCH_2CH_2CH_3$), 23.24 ($OCH_2CH_2CH_3$), 34.05 and 35.31 (3-C and 5-C), 70.60 (O*C*H_2Ph), 71.17 (OCH_2-CH_2CH_3), 71.67 (4-C), 72.02 (O*C*H_2Ph), 75.59 and 76.18 (2-C and 6-C), 76.73 (1-C), 127.67 and 128.46 (Ar-CH) and 138.62 (Ar-C quaternary); *m*/*z* (CI) 371 (26%, $[M + H]^+$) and 107 (100). [Note that synthesis of racemic **16** has previously been reported.[12]]

(−)-(1*S*,2*R*,4*S*,6*R*)-1-(Diphenoxyphosphoryloxy)-2,4-bis(benzyloxy)-6-propyloxycyclohexane 17

Under an atmosphere of N_2, a stirred solution of alcohol (−)-**16** (340 mg, 0.92 mmol) in dry dichloromethane (50 cm^3) was treated with DMAP (37 mg, 0.3 mmol) and dry TEA (0.17 cm^3, 121 mg, 1.2 mmol) followed by diphenyl chlorophosphate (0.31 cm^3, 403 mg, 1.5 mmol). After stirring at room temperature for 3 h, water (50 cm^3) was added and the two phases separated. The aqueous phase was extracted with dichloromethane (50 cm^3) and the combined organic phases were dried ($MgSO_4$) and then concentrated under reduced pressure. The residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 1:5) to give phosphate triester (−)-**17** as a colourless oil (510 mg, 92%) (HRMS: found: $[M + H]^+$, 603.2504. $C_{35}H_{40}O_7P$ requires 603.2512); $[a]_D$ −37.7 (*c* 0.17 in MeOH); δ_H(300 MHz; C^2HCl_3) 0.84 (3 H, t, $^3J_{H\text{-}H}$ 7.8, OCH_2-CH_2CH_3), 1.38–1.55 (4 H, m, $OCH_2CH_2CH_3$, 3-H and 5-H), 2.22–2.32 (1 H, m, secondary-H), 2.40–2.49 (1 H, m, secondary-H), 3.36–3.50 (2 H, m, $OCH_2CH_2CH_3$), 3.72–3.82 (2 H, m, 4-H and 6-H), 3.07–4.12 (1 H, m, 2-H), 4.41 (1 H, d, $^2J_{H\text{-}H}$ 11.4, OCH_2Ph), 4.45 (1 H, d, $^2J_{H\text{-}H}$ 12.3, OCH_2Ph), 4.46 (1 H, d, $^2J_{H\text{-}H}$ 11.4, OCH_2Ph), 4.52 (1 H, d, $^2J_{H\text{-}H}$ 12.3, OCH_2Ph), 4.51–4.59 (1 H, m, 1-H) and 7.10–7.40 (20 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 10.35 ($OCH_2CH_2CH_3$), 23.09 ($OCH_2CH_2CH_3$), 33.89 and 35.53 (3-C and 5-C), 70.60 (O*C*H_2Ph), 71.07 (4-C), 71.78 ($OCH_2CH_2CH_3$), 72.19 (O*C*H_2Ph), 74.47 (C tertiary, $^3J_{C\text{-}P}$ 6.6), 75.35 (C tertiary, $^3J_{C\text{-}P}$ 2.8), 82.85 (1-C, $^2J_{C\text{-}P}$ 7.6), 120.12, 120.18, 120.20, 120.28, 125.15, 125.22, 127.55, 127.58, 127.61, 127.67, 128.35, 128.39, 128.44, 128.47 and 129.70 (Ar-CH), 138.51 and 138.59 (Ar-C quaternary) and 150.87 (Ar-C quaternary); δ_P(121.5 MHz; C^2HCl_3) −12.32; *m*/*z* (EI) 603 (16), 341 (13), 251 (56), 140 (43) and 91 (100). [Note that synthesis of racemic **17** has previously been reported.[12]]

(−)-(1*S*,2*R*,4*S*,6*R*)-1-[Bis(benzyloxy)phosphoryloxy]-2,4-bis-(benzyloxy)-6-propyloxycyclohexane 18

Under an atmosphere of N_2, a stirred, cooled solution of the phosphate triester (−)-**17** (480 mg, 0.8 mmol) and benzyl alcohol (0.165 cm^3, 172 mg, 1.6 mmol) in dry THF (50 cm^3) was treated with NaH (60% dispersion in oil, 76 mg, 1.9 mmol). The solution was allowed to warm to room temperature over 3 h and then water (50 cm^3) was added with caution. The mixture was extracted with diethyl ether (2 × 50 cm^3) and the organic phases were combined and then dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was chromatographed on silica (ethyl acetate–petroleum ether) to give phosphate triester (−)-**18** as a white solid (340 mg, 67%), mp 68–69 °C (Found: C, 70.9; H, 7.1. $C_{37}H_{43}O_7P$ requires C, 70.5; H, 6.9%) (HRMS: found: $[M - C_7H_7]^+$, 539.2204. $C_{30}H_{36}O_7P$ requires 539.2199); $[a]_D$ −33.4 (*c* 0.155 in MeOH); δ_H(300 MHz; C^2HCl_3) 0.86 (3 H, t, $^3J_{H\text{-}H}$ 7.4, $OCH_2CH_2CH_3$), 1.34–1.46 (2 H, m, 3-H and 5-H), 1.48–1.58 (2 H, m, $OCH_2CH_2CH_3$), 2.09–2.29 (1 H, m, secondary-H), 2.38–2.47 (1 H, m, secondary-H), 3.4–3.54 (2 H, m, $OCH_2CH_2CH_3$), 3.70–3.82 (2 H, m, 4-H and 6-H), 4.07–4.12 (1 H, m, 2-H), 4.28–4.36 (1 H, m, 1-H), 4.45 (1 H, d, $^2J_{H\text{-}H}$ 11.5, OCH_2Ph), 4.49 (1 H, d, $^2J_{H\text{-}H}$ 11.8, OCH_2Ph), 4.52 (1 H, d, $^2J_{H\text{-}H}$ 11.8, OCH_2Ph), 4.58 (1 H, d, $^2J_{H\text{-}H}$ 11.8, OCH_2Ph), 5.03–5.12 (4 H, m, 2 × POCH_2Ph) and 7.20–7.40 (20 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 10.40 (OCH_2-CH_2CH_3), 23.22 ($OCH_2CH_2CH_3$), 33.95 and 35.37 (3-C and 5-C), 69.00 (POCH_2Ph, $^2J_{C\text{-}P}$ 5.4), 69.11 (POCH_2Ph, $^2J_{C\text{-}P}$ 6.5), 70.59 (O*C*H_2Ph), 71.20 (4-C), 71.65 ($OCH_2CH_2CH_3$), 72.31 (O*C*H_2Ph), 74.65 (C tertiary, $^3J_{C\text{-}P}$ 6.5), 75.24 (C tertiary), 81.36 (1-C, $^2J_{C\text{-}P}$ 6.6), 127.56, 127.61, 127.65, 127.82, 127.89, 128.32,

128.38, 128.41, 128.45, 128.54 and 128.60 (Ar-CH) and 138.64 (Ar-C quaternary); δ_P(121.5 MHz; C^2HCl_3) −1.55; *m/z* (EI) 539 (21), 279 (26), 261 (25) and 91 (100). [Note that synthesis of racemic **18** has previously been reported.[12]]

(−)-(1*R*,2*R*,4*R*,6*R*)-6-Propoxy-2,4-dihydroxycyclohexyl bis-(cyclohexylammonium) phosphate [bis(cyclohexylammonium) salt of 19]

Under an atmosphere of N_2, gaseous ammonia (15–20 cm^3) was condensed at −78 °C, and sodium metal (110 mg, 4.8 mmol) was added. A solution of phosphate triester (−)-**19** (300 mg, 0.48 mmol) in dry THF (0.5 cm^3) was added to the blue solution through a septum. After stirring at −78 °C for 30 min, methanol (2 cm^3) was added and the mixture allowed to warm up to room temperature. The solvents were removed under reduced pressure and the residual white solid was subjected to ion exchange chromatography (Amberlite IR-118H), eluting with water. The acidic fractions containing the product were collected and an excess of freshly distilled cyclohexylamine was added and stirring at room temperature continued for 4 h. The aqueous layer was extracted with diethyl ether (3 × 50 cm^3) to remove the excess of cyclohexylamine, and lyophilised. The crude white solid was recrystallised from water–acetone to give phosphate (−)-**19** as a white solid (84 mg, 65%); mp >200 °C (decomp.); $[a]_D$ −37.7 (*c* 0.526 in MeOH); δ_H(500 MHz; ^2H_2O) 0.74 (3 H, t, $^3J_{H\text{-}H}$ 7.41, $OCH_2CH_2CH_3$), 0.94–1.12 (2 H, m, 2 × 4-H of Cha†), 1.12–1.30 (9 H, m, 2 × {2 × 2-H and 3-H of Cha} and 5-H), 1.36–1.54 (5 H, m, $OCH_2CH_2CH_3$, 2 × 4-H of Cha and 3-H), 1.58–1.70 [4 H, m, 2 × (2 × 3-H of Cha)], 1.79–1.88 [4 H, m, 2 × (2 × 2-H of Cha)], 1.9–2.0 (1 H, m, 3-H), 2.12–2.20 (1 H, m, 5-H), 2.94–3.06 (2 H, m, 2 × 1-H of Cha), 3.40–3.60 (3 H, m, OCH_2-CH_2CH_3 and 6-H), 3.80–3.91 (2 H, m, 1-H and 4-H) and 4.16–4.22 (1 H, m, 2-H); δ_C(75.4 MHz; ^2H_2O) 9.40 (OCH_2-CH_2CH_3), 22.08 ($OCH_2CH_2CH_3$), 23.42 (3-C of Cha), 23.91 (4-C of Cha), 29.97 (2-C of Cha), 36.68 (5-C), 36.95 (3-C), 50.0 (1-C of Cha), 64.08 (4-C), 67.13 (2-C), 71.72 ($OCH_2CH_2CH_3$), 75.12 (1-C, $^2J_{C\text{-}P}$ 6.6) and 77.29 (6-C, broad); δ_P(121.4 MHz; ^2H_2O) +3.11. [Note that synthesis of racemic **19** has previously been reported.[12]]

(−)-(1*S*,2*R*,4*S*,6*R*)-2,4-Bis(benzyloxy)-6-propyloxycyclohexanol 16b

To a stirred solution of the epoxide (+)-**15** (180 mg, 0.58 mmol) in 1,2-dichloroethane (25 cm^3) was added Yb(III)$(OTf)_3$ (128 mg, 0.08 mmol) followed by propan-1-ol (1.28 mmol, 80 mg, 0.1 cm^3). The mixture was refluxed for 3 h, and then the solvent was removed under reduced pressure. The residue was then washed with water (10 cm^3) and then extracted with ethyl acetate (2 × 10 cm^3). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure to give a light coloured oil (0.21 g, 98%) (HRMS: found: $[M + H]^+$, 371.2229. $C_{36}H_{41}O_5$ requires 371.2222); $[a]_D$ −25.0 (*c* 1.1 in EtOAc); ν_{max}(neat)/cm^{-1} 3490 s, 2975 s, 1728 s and 1090 s; δ_H(300 MHz; C^2HCl_3) 0.85 (3 H, t, $J_{H\text{-}H}$ 7.42, $OCH_2CH_2CH_3$), 1.16–1.34 (2 H, m, secondary-H), 1.47–1.58 (2 H, qt, $OCH_2CH_2CH_3$), 2.25–2.49 (3 H, m, 2 × secondary-H and OH), 3.32–3.63 (4 H, m, $OCH_2CH_2CH_3$, 4-H and 6-H), 3.64–3.88 (2 H, m, 1-H and 2-H), 4.37–4.60 (4 H, m, 2 × OCH_2Ph), 7.17–7.27 (10 H, m, Ar-H); δ_C(75 MHz; C^2HCl_3) 23.33 (CH_3), 34.10 (3-C), 35.38 (5-C), 70.67 (OCH_2Ph), 71.24 (7-CH_2), 71.74 (4-C), 72.10 (OCH_2Ph), 75.66 (6-C), 76.26 (2-CH), 76.82 (1-C), 76.01 (2-C), 77.01 (1-C), 127.80, 128.57 and 138.76 (Ar-CH), 138.73 (Ar-C quaternary); *m/z* (CI) 371 (100%, $[M + H]^+$), 281 (49), 263 (31), 107 (78) and 91 (20).

† Cha = cyclohexylammonium.

(−)-(1*S*,2*R*,4*S*,6*R*)-2,4-Bis(benzyloxy)-6-isopropoxycyclohexanol 20

This compound was prepared in a manner identical with that described for the 6-propoxy compound **16b** using isopropanol (40 mg, 0.05 cm^3, 0.64 mmol) to give the protected tetraol **20** as a light brown oil which did not require any further purification (110 mg, 99%) (HRMS: found: $[M + H]^+$, 370.2157. $C_{23}H_{30}O_4$ requires 370.2144); $[a]_D$ −25.6 (*c* 0.31 in EtOAc); ν_{max}(neat)/cm^{-1} 3481 s, 2935 s, 1731 s and 1080 s; δ_H(300 MHz; C^2HCl_3) 1.00–1.15 (6 H, m, 2 × CH_3), 1.17–1.97 (2 H, m, secondary-H), 2.22–2.42 (3 H, m, secondary-H and OH), 3.37–3.40 (1 H, m, 6-H), 3.46–3.57 (1 H, m, 1-H), 3.61–3.76 (2 H, m, 1′-CH and 4-H), 3.86–3.89 (1 H, m, 2-H), 4.36–4.60 (4 H, m, 2 × CH_2Ph) and 7.17–7.37 (10 H, m, Ar-H); δ_C(75 MHz; C^2HCl_3) 22.33 and 23.35 (CH_3), 34.12 (3-C), 36.51 (5-C), 70.44 (1′-C), 70.53 (OCH_2Ph), 71.66 (4-C), 72.09 (OCH_2Ph), 74.49 (6-C), 75.64 (2-C), 75.28 (2-C), 76.14 (1-C), 127.62, 127.65 and 128.44 (Ar-CH) and 138.68 and 138.71 (Ar-C quaternary); *m/z* (EI) 370 (3%, $[M + H]^+$), 279 (23), 205 (11) and 91 (100).

(−)-(1*S*,2*R*,4*S*,6*R*)-2,4-Bis(benzyloxy)-6-(2-phenylethoxy)-cyclohexanol 21

This compound was prepared in a manner identical with that described for the 6-propoxy compound **16b** using 2-phenylethanol (0.04 g, 0.04 cm^3, 0.32 mmol) to give a light brown oil which was purified by silica column chromatography (ethyl acetate–petroleum ether; 1:5) to afford the 6-(2-phenylethyl) protected tetraol **21** as a colourless oil (90 mg, 65%); $[a]_D$ −70.6 (*c* 0.34 in EtOAc); δ_H(300 MHz; C^2HCl_3) 1.19–1.29 and 2.18–2.41 (4 H, m, 2 × secondary-H), 2.80 (2 H, m, CH_2Ph), 3.34–3.42 (2 H, m, 1-H and 6-H), 4.03–4.06 (1 H, m, 2-H), 3.58–3.80 (3 H, m, 4-H and -OCH_2CH_2), 3.83 (1 H, m, 2-H), 4.33–4.57 (4 H, m, 2 × OCH_2Ph) and 7.03–7.35 (15 H, m, Ar-H); δ_C(75 MHz; C^2HCl_3) 33.91 (3-C), 35.11 (5-C), 36.53 (8-CH_2), 70.20 (7-CH_2), 70.49 (OCH_2Ph), 71.51 (4-CH), 71.92 (OCH_2Ph), 75.42 (6-C), 76.01 (2-C), 77.01 (1-C), 126.26, 127.55, 127.61, 127.63, 128.38, 128.41 and 128.90 (Ar-CH) and 138.54 and 138.91 (Ar-C quaternary).

(−)-(1*R*,2*R*,4*S*,6*S*,2′*S*)-2,4-Bis(benzyloxy)-6-(1′-benzyloxy-3′-phenylpropan-2-yloxy)cyclohexanol 22

A stirred solution of the epoxide (+)-**15** (620 mg, 2 mmol) and (2*S*)-1-benzyloxy-3-phenylpropan-2-ol (726 mg, 3 mmol) in dry toluene (5 cm^3) was cooled in an ice bath. $BF_3{\cdot}Et_2O$ (0.1 cm^3 of a 1:15 mixture of $BF_3{\cdot}Et_2O$ in dry toluene) was added dropwise, and stirring at room temperature was continued for 1 h. The solvent was then removed under reduced pressure and the residual oil chromatographed on silica (ethyl acetate–petroleum ether; 1:2) to give alcohol (−)-**22** as a colourless oil (550 mg, 50%) (HRMS: found: $[M + H]^+$, 553.2947. $C_{36}H_{41}O_5$ requires 553.2954); $[a]_D$ −24.0 (*c* 0.14 in MeOH); ν_{max}(neat)/cm^{-1} 3462 s, 2916 s, 1463 s and 1093 s; δ_H(300 MHz; C^2HCl_3) 1.08–1.21 (1 H, m, 5-H), 1.21–1.34 (1 H, m, 3-H), 1.85–1.95 (1 H, m, 5-H), 2.18–2.28 (1 H, m, 3-H), 2.72 (1 H, dd, $^2J_{H\text{-}H}$ 13.6, $^3J_{H\text{-}H}$ 7.7, 3′-H), 2.80 (1 H, dd, $^2J_{H\text{-}H}$ 13.6, $^3J_{H\text{-}H}$ 5.5, 3′-H), 3.47–3.64 (5 H, m, 1-H, 4-H, 6-H and 2 × 1′-H), 3.91 (1 H, br s, 2-H), 3.95–4.5 (1 H, m, 2′-H), 4.31 (1 H, d, $^2J_{H\text{-}H}$ 11.7, one of OCH_2Ph), 4.40 (1 H, d, $^2J_{H\text{-}H}$ 11.7, one of OCH_2Ph), 4.53 (1 H, d, $^2J_{H\text{-}H}$ 12.3, one of OCH_2Ph), 4.56 (2 H, s, OCH_2Ph), 4.71 (1 H, d, $^2J_{H\text{-}H}$ 12.3, one of OCH_2Ph) and 7.20–7.50 (20 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 34.86 and 36.92 (3-C and 5-C), 39.55 (3′-C), 70.39 (OCH_2Ph), 71.87 (4-C), 72.42 (OCH_2Ph), 73.04 (1′-C), 73.50 (OCH_2Ph), 76.25 (C tertiary), 77.10 (C tertiary), 78.75 (2′-C), 81.26 (1-C), 126.49, 127.36, 127.45, 127.58, 127.68, 127.92, 127.97, 128.28, 128.38, 128.42, 128.53 and 129.70 (Ar-CH) and 137.46, 138.21, 138.78 and 139.32 (Ar-C quaternary); *m/z* (CI) 553 (100%, $[M + H]^+$) and 462 (8, $[MH - C_7H_7]^+$); *m/z* (FAB-MS) 553 (16%, $(M + H]^+$) and 181 (100).

(−)-(1*R*,2*R*,4*S*,6*S*,2′*S*)-1-(Diphenoxyphenylphosphoryloxy)-2,4-bis(benzyloxy)-6-(1′-benzyloxy-3′-phenylpropan-2-yloxy)-cyclohexane 23

Alcohol (−)-**22** (500 mg, 0.9 mmol), DMAP (244 mg, 0.2 mmol) and dry TEA (0.14 cm^3, 101 mg, 1 mmol) were dissolved in dry dichloromethane (50 cm^3) under an atmosphere of N_2, and cooled in an ice bath. Diphenyl chlorophosphate (0.31 cm^3, 403 mg, 1.5 mmol) was added dropwise and stirring at room temperature was continued for 16 hours. Water (50 cm^3) was added and the two phases separated. The aqueous phase was extracted with dichloromethane (50 cm^3) and the combined organic phases were dried ($MgSO_4$) and then concentrated under reduced pressure. The residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 1:2) to give phosphate triester (−)-**23** as a colourless oil (660 mg, 90%); $[\alpha]_D$ −22.6 (*c* 0.2825 in MeOH); ν_{max}(neat)/cm^{-1} 2936 s, 1600 s, 1498 s, 1463 s, 1361 s, 1283 s, 1190 s, 1059 s and 957 s; δ_H(300 MHz; C^2HCl_3) 0.98–1.12 (1 H, m, 5-H), 1.34–1.45 (1 H, 't', $^3J_{H\text{-}H}$ 13.8, 3-H), 1.94–2.04 (1 H, m, 5-H), 2.15–2.25 (1 H, m, 3-H), 2.61 (1 H, dd, $^2J_{H\text{-}H}$ 16.5, $^3J_{H\text{-}H}$ 9.3, 3′-H), 2.90 (1 H, dd, $^2J_{H\text{-}H}$ 16.5, $^3J_{H\text{-}H}$ 6.0, 3′-H), 3.34 (1 H, dd, $^2J_{H\text{-}H}$ 9.6, $^3J_{H\text{-}H}$ 5.8, 1′-H), 3.50 (1 H, dd, $^2J_{H\text{-}H}$ 9.6, $^3J_{H\text{-}H}$ 4.7, 3′-H), 3.55–3.65 (1 H, m, 4-H), 3.72–3.82 (1 H, m, 2′-H), 3.85–3.94 (1 H, m, 6-H), 4.09–4.15 (1 H, m, 2-H), 4.28 (1 H, d, $^2J_{H\text{-}H}$ 11.5, one of OCH_2Ph), 4.38 (1 H, d, $^2J_{H\text{-}H}$ 11.5, one of OCH_2Ph), 4.37–4.44 (4 H, m, 2 × OCH_2Ph), 4.45–4.56 (1 H, m, 1-H) and 7.20–7.50 (20 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 33.88 (3-C), 35.16 (5-C), 39.17 (3′-C), 70.3 (OCH_2Ph), 70.79 (4-C), 71.95 (OCH_2Ph), 72.25 (1′-C), 73.27 (OCH_2Ph), 73.89 (6-C, $^3J_{C\text{-}P}$ 7.5), 75.12 (2-C), 78.89 (2′-C), 82.46 (1-C, $^3J_{C\text{-}P}$ 6.0), 120.10, 120.18, 120.26, 125.14, 125.22, 126.16, 127.48, 127.61, 127.67, 128.14, 128.29, 128.32, 128.39, 129.71 and 129.79 (Ar-CH), 138.42, 138.54 and 138.92 (Ar-C quaternary), 150.70 (Ar-C quaternary, $^2J_{C\text{-}P}$ 6.5) and 150.90 (Ar-C quaternary, $^2J_{C\text{-}P}$ 7.0); δ_P(121.5 MHz; C^2HCl_3) −12.29.

(−)-(1*R*,2*R*,4*S*,6*S*,2′*S*)-1-[Bis(benzyloxy)phosphoryloxy]-2,4-bis(benzyloxy)-6-(1′-benzyloxy-3′-phenylpropan-2-yloxy)cyclohexane 24

Under an atmosphere of N_2, a stirred, cooled solution of the phosphate triester (−)-**23** (610 mg, 0.69 mmol) and benzyl alcohol (0.14 cm^3, 151 mg, 1.4 mmol) in dry THF (50 cm^3) was treated with NaH (60% dispersion in oil, 60 mg, 1.5 mmol). The mixture was stirred at room temperature for a further 2 h and then quenched with water (20 cm^3). The mixture was extracted with diethyl ether (2 × 50 cm^3) and the organic phases were combined, dried ($MgSO_4$), and then concentrated under reduced pressure. The residual oil was chromatographed on silica (ethyl acetate–petroleum ether; 1:1) to give phosphate triester (−)-**24** as a colourless oil (375 mg, 67%) (Found: C, 73.6; H, 6.45. $C_{50}H_{53}O_8P$ requires C, 73.9; H, 6.6%); $[\alpha]_D$ −27.1 (*c* 0.3425 in MeOH); δ_H(300 MHz; C^2HCl_3) 1.00–1.11 (1 H, m, 5-H), 1.27–1.40 (1 H, m, 3-H), 1.95–2.04 (1 H, m, 5-H), 2.12–2.42 (1 H, m, 3-H), 2.67 (1 H, dd, $^2J_{H\text{-}H}$ 12.7, $^3J_{H\text{-}H}$ 8.0, 3′-H), 2.92 (1 H, dd, $^2J_{H\text{-}H}$ 13.5, $^3J_{H\text{-}H}$ 4.7, 3′-H), 3.43 (1 H, dd, $^2J_{H\text{-}H}$ 9.9, $^3J_{H\text{-}H}$ 5.75, 1′-H), 3.53 (1 H, dd, $^2J_{H\text{-}H}$ 9.9, $^3J_{H\text{-}H}$ 5.4, 1′-H), 3.57–3.65 (1 H, m, 4-H), 3.72–3.88 (2 H, m, 2′-H and 6-H), 4.10–4.15 (1 H, m, 2-H), 4.22–4.29 (1 H, m, 1-H), 4.30 (1 H, d, $^2J_{H\text{-}H}$ 11.4, one of OCH_2Ph), 4.38 (1 H, d, $^2J_{H\text{-}H}$ 11.4, one of OCH_2Ph), 4.42 (2 H, s, OCH_2Ph), 4.47 (1 H, d, $^2J_{H\text{-}H}$ 12.0, one of OCH_2Ph), 4.56 (1 H, d, $^2J_{H\text{-}H}$ 12.0, one of OCH_2Ph), 4.97–5.12 (4 H, m, 2 × POCH_2Ph) and 7.15–7.45 (30 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 34.0 and 35.21 (3-C and 5-C), 39.16 (3′-C), 68.97 (POCH_2Ph, $^2J_{C\text{-}P}$ 5.4), 69.08 (POCH_2Ph, $^2J_{C\text{-}P}$ 5.4), 70.31 (OCH_2Ph), 70.90 (4-C), 71.93 (OCH_2Ph), 72.18 (1′-C), 73.24 (OCH_2Ph), 74.05 (6-C, $^3J_{C\text{-}P}$ 7.5), 75.06 (2-C), 78.93 (2′-C), 81.10 (1-C), 126.18, 127.49, 127.60, 127.66, 127.78, 127.82, 127.85, 127.98, 128.14, 128.29, 128.32, 128.36, 128.41, 128.51, 128.57, 128.59, 128.6 and 129.78 (Ar-CH) and 138.42, 138.58, 138.68 and 138.85 (Ar-C quaternary); δ_P(121.5 MHz; C^2HCl_3) −1.49; *m/z* (FAB-MS) 813 (5%, $[M + H]^+$), 279 {25, $[(PhCH_2O)_2PO_2H_2]^+$} and 181 (100).

(−)-(1*R*,2*R*,4*R*,6*R*,2′*S*)-2,4-Dihydroxy-6-(1-hydroxy-3-phenylpropan-2-yloxy)cyclohexyl bis(cyclohexylammonium) phosphate [bis(cyclohexylammonium) salt of 25]

Under an atmosphere of nitrogen, ammonia gas was condensed (15–20 cm^3) at −78 °C and sodium metal (103.5 mg, 4.5 mmol) was added. A solution of phosphate triester (−)-**24** (350 mg, 0.43 mmol) in dry THF (1 cm^3) was added to the blue solution through a septum. After stirring at −78 °C for 30 minutes, methanol (5 cm^3) was added to quench the reaction, followed by water (2 cm^3) and the mixture allowed to warm up to room temperature. The solvents were removed under reduced pressure and the residual solid was subjected to ion exchange chromatography (Amberlite IR-118H), eluting with water. The acidic fractions containing the product were collected and an excess of cyclohexylamine was added and stirring at room temperature continued for 1 h. The aqueous solution was then lyophilised and the residual white solid was dissolved in water (5 cm^3). Dichloromethane (10 cm^3) was added to the mixture and after stirring for 15 min, the aqueous phase was pipetted off and lyophilised to give phosphate (−)-**25** as a white solid (149 mg, 62%); mp >200 °C (decomp.) (HRMS: found: $[MH_2 - C_6H_{14}N]^+$, 462.2243. $C_{21}H_{37}NO_8P$ requires 462.2257); $[\alpha]_D$ −40.9 (*c* 0.3535 in MeOH); δ_H(500 MHz; ^2H_2O) 0.99–1.08 (1 H, m, 5-H), 1.08–1.70 (2 H, m, 2 × 4-H of Cha), 1.22–1.34 [8 H, m, 2 × (2 × 2-H and 2 × 3-H of Cha)], 1.38–1.44 (1 H, m, 3-H), 1.56–1.62 (2 H, m, 2 × 4-H of Cha), 1.70–1.79 [5 H, m, 2 × (2 × 3-H of Cha) and 5-H], 1.89–1.96 [4 H, m, 2 × (2 × 2-H of Cha)], 1.95–2.0 (1 H, m, 3-H), 2.76 (1 H, dd, $^2J_{H\text{-}H}$ 13.4, $^3J_{H\text{-}H}$ 7.8, 3′-H), 2.81 (1 H, dd, $^2J_{H\text{-}H}$ 14.5, $^3J_{H\text{-}H}$ 5.6, 3′-H), 3.00–3.14 (2 H, m, 2 × 1-H of Cha), 3.49 (1 H, dd, $^2J_{H\text{-}H}$ 12.2, $^3J_{H\text{-}H}$ 4.45, 1′-H), 3.55–3.62 (1 H, m, 6-H), 3.71 (1 H, dd, $^2J_{H\text{-}H}$ 12.2, $^3J_{H\text{-}H}$ 3.3, 1′-H), 3.73–3.79 (1 H, m, 4-H), 3.82–3.88 (2 H, m, 2′-H and 1-H), 4.19–4.24 (1 H, m, 2-H) and 7.10–7.30 (5 H, m, Ar-H); δ_C(75.4 MHz; ^2H_2O) 24.41 and 24.91 (3-C and 4-C of Cha), 30.96 (2-C of Cha), 38.21 (3-C), 38.31 (3-C), 39.17 (5′-C), 51.0 (1-C of Cha), 63.75 (1′-C), 64.5 (4-C), 68.54 (2-C), 76.19 (6-C, $^3J_{C\text{-}P}$ 5.4), 78.96 (1-C, $^2J_{C\text{-}P}$ 5.4), 83.08 (2′-C), 127.24, 129.29 and 130.34 (Ar-CH) and 139.41 (Ar-C quaternary); δ_P(121.5 MHz; ^2H_2O) 1.16; *m/z* (FAB-MS) 462 (72%, $[MH_2 - C_6H_{14}N]^+$), 385 (40, $[MH_2 - C_6H_{14}N - C_7H_7]^+$), 363 (15, $[MH_3 - 2 \times C_6H_{14}N]^+$) and 105 (100).

(−)-(1*R*,2*R*,4*S*,6*S*,2′*R*)-2,4-Bis(benzyloxy)-6-(1′-benzyloxy-3′-phenylpropan-2-yloxy)cyclohexanol 26

This compound was prepared in a manner identical with that described for the alcohol (−)-(1*R*,2*R*,4*S*,6*S*,2′*S*)-**22**, using epoxide (+)-**15** (620 mg, 2 mmol) and (2*R*)-1-benzyloxy-3-phenylpropan-2-ol (726 mg, 3 mmol) to give alcohol (−)-**26** as a colourless oil (500 mg, 45%) (HRMS: found: $[M + H]^+$, 553.2959. $C_{36}H_{41}O_5$ requires 553.2954); $[\alpha]_D$ −12.7 (*c* 0.5 in MeOH); ν_{max}(neat)/cm^{-1} 3570 s, 3472 s, 2935 s, 2868 s, 1610 s, 1502 s, 1449 s, 1347 s, 1244 s, 1093 s and 918 s; δ_H(300 MHz; C^2HCl_3) 1.26–1.43 (2 H, m, 3-H and 5-H), 2.07 (1 H, d, $^3J_{H\text{-}H}$ 4.5, OH), 2.22–2.32 (1 H, m, 3-H), 2.38–2.47 (1 H, m, 5-H), 2.84 (1 H, dd, $^2J_{H\text{-}H}$ 12.7, $^3J_{H\text{-}H}$ 7.7, 3′-H), 2.92 (1 H, dd, $^2J_{H\text{-}H}$ 14.0, $^3J_{H\text{-}H}$ 5.8, 3′-H), 3.36–3.43 (1 H, m, 1-H), 3.5 (2 H, 'd', $J_{H\text{-}H}$ 5.5, 2 × 1′-H), 3.54–3.64 (1 H, m, 6-H), 3.65–3.73 (1 H, m, 4-H), 3.82–3.87 (1 H, m, 2-H), 3.88–3.97 (1 H, m, 2′-H), 4.36 (1 H, d, $^2J_{H\text{-}H}$ 11.8, one of OCH_2Ph), 4.45 (1 H, d, $^2J_{H\text{-}H}$ 11.5, one of OCH_2Ph), 4.50 (1 H, d, $^2J_{H\text{-}H}$ 12.1, one of OCH_2Ph), 4.55 (2 H, s, OCH_2Ph), 4.58 (1 H, d, $^2J_{HH}$ 12.1, one of OCH_2Ph) and 7.20–7.50 (20 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 34.40 and 36.91 (3-C and 5-C), 38.97 (3′-C), 70.52 (OCH_2Ph), 71.88 (4-C), 72.12 (OCH_2Ph), 72.83 (1′-C), 73.37 (OCH_2Ph), 75.93 (C tertiary), 76.18 (C tertiary), 77.16 (2′-C), 79.55 (1-C), 126.50, 127.51, 127.54, 127.57, 127.62, 127.68, 128.33, 128.40, 128.43, 128.51

and 129.57 (Ar-CH) and 138.21, 138.61, 138.75 and 138.91 (Ar-C quaternary); *m/z* (CI) 553 (44%, $[M + H]^+$), 463 (100, $[MH_2 - C_7H_7]^+$), 373 (64, $[MH_3 - 2 \times C_7H_7]^+$) and 91 (20, $[C_7H_7]^+$).

(−)-(1*R*,2*R*,4*S*,6*S*,2′*R*)-1-(Diphenoxyphosphoryloxy)-2,4-bis-(benzyloxy)-6-(1′-benzyloxy-3′-phenylpropan-2-yloxy)cyclohexane 27

This compound was prepared in a manner identical with that described for the phosphate triester (−)-(1*R*,2*R*,4*S*,6*S*,2′*S*)-**23**, using alcohol (−)-**26** (450 mg, 0.82 mmol) to give phosphate triester (−)-**27** as a colourless oil (530 mg, 83%) (HRMS: found: $[M + H]^+$, 785.3253. $C_{48}H_{50}O_8P$ requires 785.3243); $[a]_D$ −2.1 (*c* 0.6125 in MeOH); δ_H(300 MHz; C^2HCl_3) 1.45–1.61 (2 H, m, 3-H and 5-H), 2.19–2.29 (1 H, m, secondary-H), 2.36–2.46 (1 H, m, secondary-H), 2.74 (1 H, dd, $^2J_{H\text{-}H}$ 13.7, $^3J_{H\text{-}H}$ 8.2, 3′-H), 2.94 (1 H, dd, $^2J_{H\text{-}H}$ 13.7, $^3J_{H\text{-}H}$ 5.2, 3′-H), 3.35 (1 H, dd, $^2J_{H\text{-}H}$ 10.2, $^3J_{H\text{-}H}$ 6.0, 1′-H), 3.43 (1 H, dd, $^2J_{H\text{-}H}$ 10.2, $^3J_{H\text{-}H}$ 3.6, 1′-H), 3.67–3.78 (1 H, m, 4-H), 3.87–3.96 (1 H, m, 2′-H), 3.98–4.08 (1 H, m, 6-H), 4.04–4.20 (1 H, m, 2-H), 4.33 (1 H, d, $^2J_{H\text{-}H}$ 11.8, one of OCH_2Ph), 4.39–4.45 (3 H, m, 1.5 of OCH_2Ph), 4.48 (2 H, s, OCH_2Ph), 4.52–4.60 (1 H, m, 1-H) and 7.2–7.5 (20 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 33.71 (3-C), 35.84 (5-C, broad), 38.27 (3′-C), 70.47 (OCH$_2$Ph), 71.26 (4-C), 71.88 (OCH$_2$Ph), 72.12 (1′-C), 73.23 (OCH$_2$Ph), 73.80 (6-C, $^3J_{C\text{-}P}$ 6.5), 74.92 (2-C), 79.94 (2′-C), 82.59 (1-C, broad), 120.11, 120.19, 120.25, 120.30, 125.27, 126.11, 127.49, 127.52, 127.55, 127.58, 127.6, 128.29, 128.35, 128.39, 129.53, 129.63, 129.71 and 129.76 (Ar-CH), 138.36, 138.43, 138.55 and 138.66 (Ar-C quaternary), 150.73 (Ar-C quaternary, $^2J_{C\text{-}P}$ 7.6) and 150.8 (Ar-C quaternary, $^2J_{C\text{-}P}$ 2.1); δ_P(121.5 MHz; C^2HCl_3) −12.22; *m/z* (FAB-MS) 785 (15%, $[M + H]^+$) and 251 (100, $[(PhO)_2PO_2H_2]^+$).

(−)-(1*R*,2*R*,4*S*,6*S*,2′*R*)-1-[Bis(benzyloxy)phosphoryloxy]-2,4-bis(benzyloxy)-6-(1′-benzyloxy-3′-phenylpropan-2-yloxy)cyclohexane 28

This compound was prepared in a manner identical with that described for the phosphate triester (−)-(1*R*,2*R*,4*S*,6*S*,2′*S*)-**24**, using the phosphate triester (−)-**27** (500 mg, 0.64 mmol) to give phosphate triester (−)-**28** as a colourless oil (322 mg, 62%) (Found: C, 73.65; H, 7.25. $C_{50}H_{53}O_8P$ requires C, 73.9; H, 6.6%); $[a]_D$ −3.5 (*c* 0.405 in MeOH); δ_H(300 MHz; C^2HCl_3) 1.38–1.55 (2 H, m, 3-H and 5-H), 2.13–2.23 (1 H, m, secondary-H), 2.32–2.42 (1 H, m, secondary-H), 2.78 (1 H, dd, $^2J_{H\text{-}H}$ 13.7, $^3J_{H\text{-}H}$ 8.0, 3′-H), 2.96 (1 H, dd, $^2J_{H\text{-}H}$ 13.7, $^3J_{H\text{-}H}$ 4.9, 3′-H), 3.32 (1 H, dd, $^2J_{H\text{-}H}$ 10.2, $^3J_{H\text{-}H}$ 5.8, 1′-H), 3.40 (1 H, dd, $^2J_{H\text{-}H}$ 10.2, $^3J_{H\text{-}H}$ 3.6, 1′-H), 3.66–3.76 (1 H, m, 4-H), 3.83–3.91 (1 H, m, 2′-H), 3.92–3.42 (1 H, m, 6-H), 4.09–4.15 (1 H, m, 2-H), 4.24–4.32 (1 H, m, 1-H), 4.33 (1 H, d, $^2J_{H\text{-}H}$ 11.8, one of OCH_2Ph), 4.41–4.48 (3 H, m, 1.5 of OCH_2Ph), 4.53 (1 H, d, $^2J_{H\text{-}H}$ 11.5, one of OCH_2Ph), 5.00–5.10 (4 H, m, 2 × POCH_2Ph) and 7.10–7.40 (30 H, m, Ar-H); δ_C(75.4 MHz; C^2HCl_3) 33.82 (3-C), 35.60 (5-C, broad), 38.21 (3′-C), 69.09 (POCH$_2$Ph, $^2J_{C\text{-}P}$ 5.4), 69.23 (POCH$_2$Ph, $^2J_{C\text{-}P}$ 5.4), 70.48 (OCH$_2$Ph), 71.42 (4-C), 72.0 (OCH$_2$Ph), 72.11 (1′-C), 73.23 (OCH$_2$Ph), 74.34 (6-C, $^3J_{C\text{-}P}$ 7.5), 74.85 (2-C), 79.59 (2′-C), 81.18 (1-C, broad), 126.12, 127.53, 127.57, 127.63, 127.92, 128.32, 128.36, 128.42, 128.46, 128.50, 128.56, 129.67 and 129.77 (Ar-CH) and 138.32, 138.45 and 138.72 (Ar-C quaternary); δ_P(121.5 MHz; C^2HCl_3) −1.33.

(−)-(1*R*,2*R*,4*R*,6*R*,2′*R*)-2,4-Dihydroxy-6-(1-hydroxy-3-phenylpropan-2-yloxy)cyclohexyl bis(cyclohexylammonium) phosphate [bis(cyclohexylammonium) salt of 29]

This compound was prepared in a manner identical with that described for the phosphate (−)-(1*R*,2*R*,4*R*,6*R*,2′*S*)-**25**, using the triester (−)-**28** (300 mg, 0.37 mmol) to give phosphate (−)-**29** as a white solid (124 mg, 60%); mp >200 °C (decomp.); $[a]_D$ −12.4 (*c* 0.335 in MeOH); δ_H(500 MHz; ^2H_2O) 0.87–0.98 (2 H, m, 2 × 4-H of Cha), 1.02–1.15 [8 H, m, 2 × (2 × 2-H and 2 × 3-H of Cha)], 1.30–1.43 (4 H, m, 2 × 4-H of Cha, 3-H, 5-H), 1.50–1.59 [4 H, m, 2 × (2 × 3-H of Cha)], 1.65–1.76 [5 H, m, 2 × (2 × 2-H of Cha) and 5-H], 1.81–1.89 (1 H, m, 3-H), 2.80 (1 H, dd, $^2J_{H\text{-}H}$ 13.5, $^3J_{H\text{-}H}$ 7.5, 3′-H), 2.92 (1 H, dd, $^2J_{H\text{-}H}$ 13.5, $^3J_{H\text{-}H}$ 6.0, 3′-H), 3.07–3.13 (2 H, m, 2 × 1-H of Cha), 3.46 (1 H, dd, $^2J_{H\text{-}H}$ 11.5, $^3J_{H\text{-}H}$ 6.0, 1′-H), 3.59–3.65 (1 H, m, 1′-H), 3.76–3.81 (1 H, br s, 2-H), 3.86–3.92 (1 H, m, 2′-H), 3.92–4.04 (3 H, m, 4-H, 2-H and 1-H) and 7.10–7.30 (5 H, m, Ar-H); δ_C(75.4 MHz; ^2H_2O) 24.40 and 24.90 (3-C and 4-C of Cha), 30.96 (2-C of Cha), 34.60 (3-C, broad), 36.82 (5-C), 37.58 (3′-C), 51.01 (1-C of Cha), 62.85 (1′-C), 66.36 (C tertiary), 66.63 (C tertiary), 75.30 (1-C, broad), 75.37 (6-C, $^3J_{C\text{-}P}$ 5.4), 80.02 (2′-C), 127.25, 129.45 and 130.26 (Ar-CH) and 139.29 (Ar-C quaternary); δ_P(121.5 MHz; ^2H_2O) 3.0.

Acknowledgements

The authors thank the BBSRC and EPSRC for grants J29893 and K35792, the Wellcome Trust for grant 040331, the EPSRC for a studentship for M. W. B. and Dr Mahmoud Akhtar for scientific support.

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Paper a909292g