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Synthesis of (-)-(1R,2R,4R,6S)-1,6-Epoxy-4-benzyloxycyclohexan-2-ol, A Key Precursor to Inositol Monophosphatase Inhibitors, from (-)-Quinic Acid.

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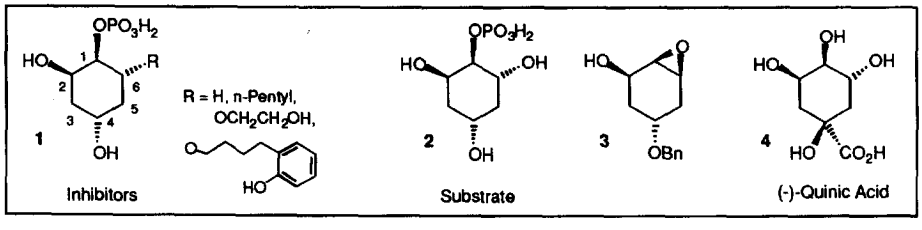
Abstract. A new and efficient route to (-)-(1R,2R,4R,6S)-1,6-epoxy-4-benzyloxycyclohexan-2-ol is described starting from (-)-quinic acid. The pivotal step involves a La^{3+}-induced reversal of the diastereoselectivity for the borohydride reduction of an intermediate cyclohexan-4-one. (1R,2R,4R,6R)-6-Propyloxycyclohexan-1,2,4-triol 1-phosphate, predicted to be a submicromolar inhibitor of inositol monophosphatase, was prepared from the epoxide in 20% yield and displayed the expected potency.

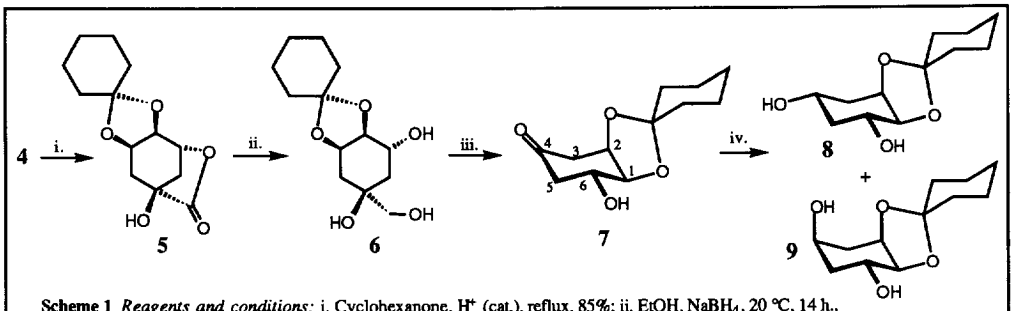
Inositol monophosphatase plays a central role in providing free inositol for the biosynthesis of the secondary messenger precursor phosphatidylinositol 4,5-trisphosphate in brain cells and is widely held to be the target for lithium ion therapy in the treatment of manic depression.[1,2] Since 1994 details of the interactions of the active-site with various enzyme-bound substrates and inhibitors have begun to emerge[3,4] and it is now possible to rationalise the mode of binding of all reported inhibitors. One particularly potent group of inhibitors display K_i values of ~1 μmol dm^{-3} or lower.[5,6] These compounds are 6-substituted cyclohexan-1,2,4-triol 1-phosphates (**1**) of the same relative stereochemistry and are derived from the substrate, 1,2,4,6-tetraol 1-phosphate (**2**),[5] where the substituent, it is believed, prevents catalysis by modifying the coordination sphere of the second of two cofactor Mg^{2+} ions.[3] The 6-substituent in individual compounds can access both the hydrophilic coordination sphere of the second Mg^{2+} ion[6] and a hydrophobic binding pocket[5] (formed by Val-40 and Leu-42) but, as yet, substituents that can access both sites simultaneously have not been described.

In order to prepare such compounds, we required the (1R,2R,4R,6S)-enantiomer of 1,6-epoxy-4-benzyloxycyclohexan-2-ol (**3**) as a key intermediate. In reported syntheses of the inhibitors (**1**) racemic (**3**) had been prepared in 6.6% yield from cyclohexan-1,4-diol and the 2-O-benzyl derivative reacted with C- and O-nucleophiles to give the racemic 1-alcohols which were resolved as their (-)-(1S,4R)-camphanate esters.[5,6]



In this work it was neccessary to have access to both enantiomers of each inhibitor in order to correlate biological potency with the absolute stereochemistry.[5,6] However, for our present purposes, yields were too low to consider resolving racemic (**3**) and, thus, alternatives starting from (-)-quinic acid (**4**) were examined.

(-)-Quinic acid (**4**) was converted to the cyclohexylidene lactone (**5**) in 85% yield following a literature procedure.[7] Reduction of the lactone (**5**) with sodium borohydride in ethanol gave the primary alcohol (**6**) which was, without further purification, converted to the ketone (**7**) in 95% overall yield using sodium periodate.[8,9] This sequence was much more efficient than reported literature preparations of the ketone (**7**) which used lithium aluminium hydride to reduce the acetylated form of lactone (**5**).[7-10]



Scheme 1 *Reagents and conditions:* i. Cyclohexanone, H^+ (cat.), reflux, 85%; ii. EtOH, $NaBH_4$, 20 °C, 14 h., then; iii. Water, pH 6, $NaIO_4$, 20 °C, 95% over both steps; iv. MeOH, $LaCl_3 7H_2O$, $NaBH_4$, -78 °C, 95%.

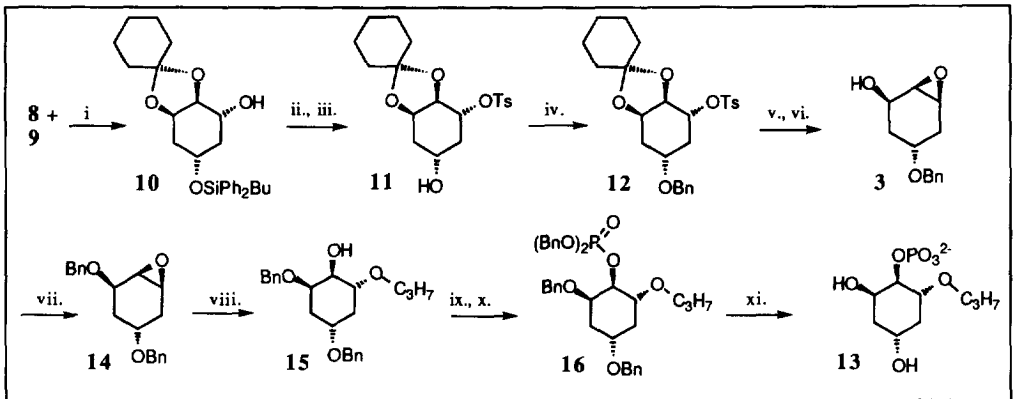
The diol (**8**) had been required previously for the synthesis of D-(+)-2,6-dideoxystreptamine and it was reported that the reduction of the 4-keto group of (**7**) with lithium borohydride in dimethoxyethane gave a 50:50 mixture of the C-4-equatorial and axial alcohols, (**8**) and (**9**) respectively.[9] While these could be separated[9,11] we sought conditions to significantly improve the yield of the equatorial alcohol (**8**).

The use of sodium borohydride in refluxing ether gave the 4-axial alcohol (**9**) exclusively. Under similar conditions but at 20 °C, in either ether, or, in ethanol, or, at -60 °C in methanol, the axial alcohol (**9**) was still the predominant product. 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 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.[12]

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 the 4-equatorial alcohol (**8**) and 4-axial alcohol (**9**) in 95% yield of which the desired alcohol (**8**) constituted to 83-90% of the total product mixture (as determined by ^{1}H- and ^{13}C-NMR spectroscopy). Similar reductions performed in the presence of Pr^{3+}, Er^{3+} and Nd^{3+} were less successful, Ca^{2+} was totally ineffective and Nd^{3+} and Sm^{3+} gave viscous slurries at -60 °C. The use of ethanol in place of methanol also gave higher proportions of the axial alcohol (**9**). Note that Ca^{2+} and Ln^{3+} 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.[12,13] Preliminary studies on 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+}. ^{1}H- and ^{13}C-NMR spectroscopic data indicate 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**). Further details will be reported in due course.

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[9,11] was difficult on such a large scale but treatment with TBDPS-Cl (which demands an accessible nucleophile)[14] gave a mixture of mono-silylated products, containing predominantly the desired 4-silyl ether (**10**), which could be isolated easily by column chromatography on silica in 38% 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 followed by removal of the silyl group with TBAF gave the 4-alcohol 6-tosylate (**11**) in excellent yield and benzylation afforded the 4-benzylether (**12**). Solvolysis of the cyclohexylidene protection in methanol containing a catalytic amount of TFA gave the diol which was treated with potassium carbonate, in the same "pot", to give the required homochiral 1,6-epoxy-4-benzyloxycyclohexan-2-ol (**3**) in 80% yield, 16% overall yield from (-)-quinic acid, Scheme 2. Compound (**3**){mp 64-65 °C, $[\alpha]_D$ +56.4° (c. 0.33 in MeOH), $[\alpha]_D$ +19.2° (c. 0.21 in $CHCl_3$) {lit.[15] for the 87% ee material obtained as an oil, $[\alpha]_D$ +18.6° (c. 4.4 in $CHCl_3$)} and all of its intermediates were fully characterised and showed the expected properties.

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-propyloxycyclohexan-1,2,4-triol 1-phosphate (**13**). We had previously prepared the phosphate ester (**13**) in racemic form[6] 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,[6] the epoxy alcohol (**3**) was benzylated to give the *bis*-benzylether (**14**) {$[\alpha]_D$ +72.6° (c. 0.208 in MeOH)} which was treated with propan-1-ol in the presence of borontrifluoride etherate to give the 1-hydroxy-6-propyl ether (**15**) {$[\alpha]_D$ -34.1° (c. 0.18 in MeOH)}in 60% yield from epoxide (**3**), Scheme 2.



Scheme 2 *Reagents and conditions:* i. DCM, TBDPS-Cl, DMAP, TEA, chromat. on SiO_2, 38%; ii. DCM, Ts-Cl, DMAP, TEA, 90%; iii. THF, TBAF, 100%; iv. DMF, Bn-Br, NaH, -50 °C -> 20 °C, 78%; v. MeOH, TFA (cat.), 72 h, then vi. K_2CO_3, 80%; vii. THF, KH, Bn-Br, 95%; viii. 1-PrOH, $BF_3{\cdot}OEt_2$, 65%; ix. $ClPO(OPh)_2$, TEA, DMAP, DCM, 95%; x. 2 eq. BnONa, THF, 60%; xi. Na, $NH_{3(liq)}$, -78 °C, then Amberlite IR 118H and cyclohexylamine, 60%

The 1-hydroxy group was phosphorylated using diphenyl chlorophosphate and the phosphate triester was transesterified, as described previously for the racemic material,[6] to give the dibenzyl phosphate triester (**16**). Deprotection of all four benzyl groups was achieved using sodium in liquid ammonia and the required (1R,2R,4R,6R)-6-propyloxycyclohexan-1,2,4-triol 1-phosphate (**13**) 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 34% yield from the 1-hydroxy-6-propyl ether (**15**). The compound and all of its intermediates displayed identical spectral properties to those of the racemic material.[6]

When tested[16] for biological activity, compound (**13**) behaved as a competitive inhibitor for inositol monophosphatase. The observed K_i value of 0.87 μM was lower than that for the racemic material[6] showing that the (1R,2R,4R,6R)-antipode is the most active enantiomer, in accord with predictions based upon earlier modelling work.[3] Homochiral epoxide (**3**) is, therefore, suitable for the synthesis of structurally diverse inhibitors, including those described by structures (**1**). The route to the key epoxide intermediate (**3**) described here will allow access to C-6 elaborated inhibitors that are designed to simultaneously recognise both the hydrophilic and hydrophobic binding sites on the enzyme proximal to C-6 of the substrate (**2**), see above.

Acknowledgements

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