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Inositol synthesis: concise preparation of L-*chiro*-inositol and *muco*-inositol from a common intermediate

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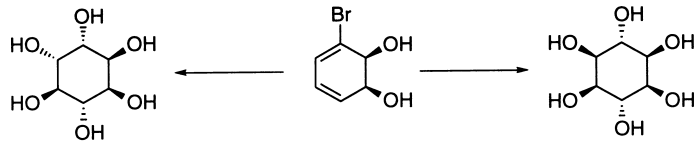
Abstract

Fully stereoselective large-scale syntheses have been attained for L-*chiro*-inositol (**2**) and *muco*-inositol (**3**) by means of controlled peripheral oxygenation of cyclohexadiene diol **1**.

Developing a general protocol for the preparation of all nine isomeric inositols in a practical fashion has comprised a significant part of our program for the last few years. Motivated by the medicinal value of certain inositol phosphates,[1] for which the parent compounds or, more importantly, their homochiral precursors would serve as intermediates, we formulated a general strategy of synthesis based on the peripheral oxygenation of the diene diol **1**[2] derived from the biooxidation of bromobenzene.[3]



2 L-*chiro*-inositol **1** **3** *muco*-inositol

Previous efforts in this area from our laboratory included a medium-scale three-step synthesis of D-*chiro*-[4] and *allo*-inositol,[5] as well as the preparation of *neo*-inositol[6] and both enantiomers of pinitol.[3] In addition to several conduritols[7] and conduramines[8,9] many other syntheses of natural products have been attained; these are summarized in several recent reviews.[10] In this communication we report a fully stereoselective total synthesis of L-*chiro*-inositol[11] and an efficient total synthesis of *muco*-inositol.[12] For the preparation of the latter compound we have taken advantage of 'chemically redundant' opening of diastereomeric epoxides leading to the same isomer of a *trans*-diol.

Diol **1** was obtained in a yield of 10 g/L by exposing bromobenzene in a 15 L fermentor to *E. coli* JM109 (pDTG601) cells grown on a glucose medium with *i*-propylthiogalactopyranoside as an inducer.[13]

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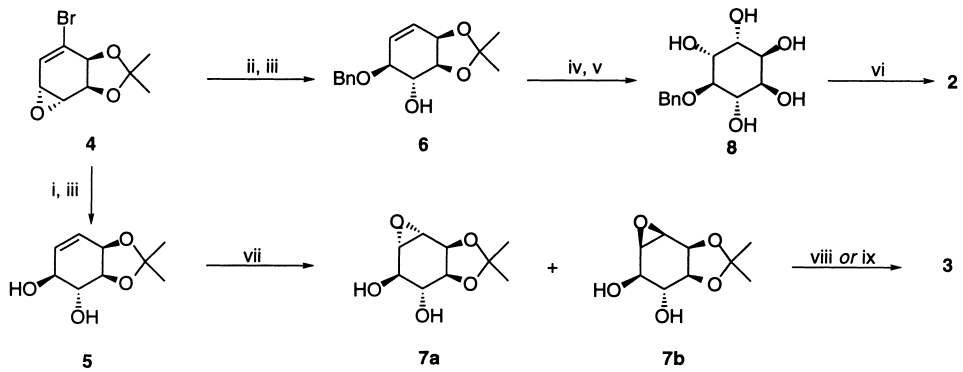
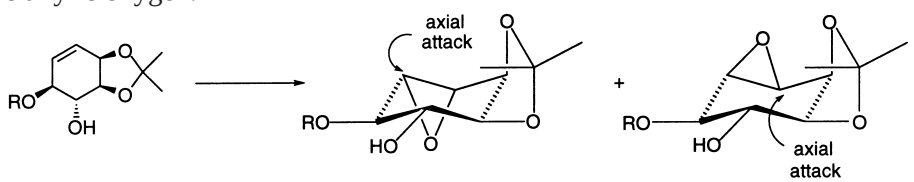
Protection and epoxidation of **1** afforded epoxide **4**[14] in 96% yield from diol **1**, with this sequence performed on a 40 g scale (Scheme 1). Regio- and stereoselective opening was accomplished with dilute aqueous hydroxide in 87% yield (for **5**) and with excess benzyl alcohol in 85% yield (for **6**), respectively. In both cases the crude reaction mixtures were subjected to dehalogenation (*n*-Bu_3SnH/AIBN) to provide *trans*-diol **5** and benzyl ether **6** in 90% and 78% yield, respectively. Benzyl ether **6** was subjected to osmylation (75%) followed by acid-catalyzed deprotection to furnish pentol **8** in 79% yield. Hydrogenation of this material on 10% Pd(C) furnished L-*chiro*-inositol in 81% yield (30% overall from **4** for the five-step sequence). The entire sequence was carried out on a scale of 40 g of diol **1**, with only two purifications necessary, chromatography following osmylation and recrystallization of the final product.



Reagents: (i) 10% aqueous KOH, H_2O, DME; (ii) $PhCH_2OH$, BF_3Et_2O, –10 °C; (iii) *n*-Bu_3SnH, AIBN, THF, D; (iv) OsO_4, acetone, H_2O, NMO; (v) HCl, EtOH, r.t.; (vi) 10% Pd(C), H_2, H_2O; (vii) *m*-CPBA, CH_2Cl_2; (viii) for **7a**: Amberlyst A-27, H_2O; (ix) for **7b**: 10% aqueous H_2SO_4.

Scheme 1.

The *trans*-diol **5** was subjected to epoxidation with *m*-CPBA to provide a mixture of α- and β-epoxides **7a** and **7b** in a 1:1.8 ratio and in 71% yield. In contrast, oxidation of benzyl ether **6** under the same conditions produced a 53% yield of α- and β-epoxides **9a** and **9b** in a 3.6:1 ratio. The contrasting product ratios resulting from the epoxidations of **5** and **6** can be explained based on the nature of the substituent present on the allylic oxygen.



5, R = H
6, R = BnO

7a, R = H
9a, R = BnO

7b, R = H
9b, R = BnO

7a : **7b** = 1 : 1.8 (71%)
9a : **9b** = 3.6 : 1 (53%)

The mixture of epoxides produced from the oxidation of **5** resulted from the apparent competition between the *syn*-directing effect of the free allylic hydroxyl and the hindering effect of the acetonide moiety, with the former predominantly controlling the ratio of epoxides. The *syn*-directing effect is eliminated in **6** through replacement of the allylic hydroxyl group with a benzyl ether. Steric hindrance thus becomes the determining factor in the ratio of α- and β-epoxides produced and results in predominance of the α-epoxide.