General Synthesis of Inositols by Hydrolysis of Conduritol Epoxides Obtained Biocatalytically from Halogenobenzenes: (+)-D-*chiro*-Inositol, *allo*-Inositol, *muco*-Inositol and *neo*-Inositol

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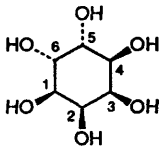
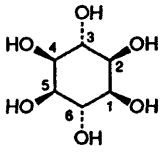
Four of the nine isomeric inositols have been prepared by hydrolytic opening of epoxides derived from 3-halogenocyclohexa-3,5-diene-1,2-diol by further oxidation with potassium permanganate or by reduction of *chiro*-3-inosose (2L-2,3,6/4,5-pentahydroxycyclohexanone).

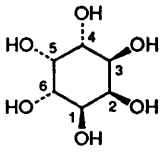
Inositols, or hexahydroxycyclohexanes, belong to an important class of biologically active compounds, the cyclitols.[1] These carbocyclic sugar derivatives and their phosphates are responsible for cellular communication[2] and have been linked to antiglycosidic and therefore antiviral activity.[3] Some of them have shown promise as antidiabetic agents[4] or insulin mimics.[5] The broad range of their physiological activities has been reviewed,[6] and the syntheses of these compounds have been summarized[7] and continue to attract the attention of organic chemists.[8] The synthetic achievements include the preparation of most of the tetra-, penta- and hexa-hydroxycyclohexanes and many of their phosphates.[7,9] Of the nine stereoisomeric inositols, only three are commercially available.‡ In this manuscript we report the preparation of four of the nine isomers by a brief and potentially general method.



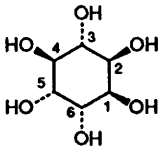
allo-Inositol **1**



muco-Inositol **2**



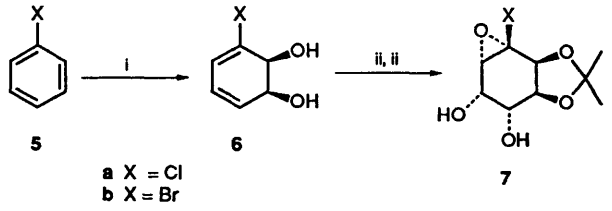
neo-Inositol **3**



(+)-D-*chiro*-Inositol **4**

(Note: the numbering reflects the current version in Chemical Abstracts).[10]

The oxidation of aromatic hydrocarbons with mutant bacterial strains has been discovered by Gibson[11] and made popular in the synthesis of homochiral oxygenated compounds by several research groups[12] including ours.[13] The traditional methods of synthesis of oxygenated compounds have relied on sometimes tedious transformations of simple carbohydrates[14] or by oxidation of olefinic compounds *via* catalytic asymmetric induction processes that, while being highly stereo- and enantioselective, use environmentally unacceptable components.[15] In contrast, the biocatalytic conversion of aromatics to the corresponding homochiral cyclohexadiene *cis*-diols allows, through careful symmetry-based planning, for an efficient and fully environmentally benign protocol that promises to eventually supplant the carbohydrate chiral pool. We recently reported on the unique oxidation of halogenocyclohexadienediols **6**§ to halogeno epoxides **7** (Scheme 1) with potassium permanganate and a prefatory synthesis of the most important of the inositols, D-*chiro*-inositol **4**, from the latter useful synthon.[16] The rich functionality content of **7** and the ease of the preparation of these compounds (generation of six contiguous chiral centres with complete stereocontrol in two steps!) prompted us to address the synthesis of several of the title compounds by further manipulation of the oxygenation state of **7**.



a X = Cl
b X = Br

Scheme 1 Synthesis of halogeno epoxides by $KMnO_4$ oxidation of diene diols. *Reagents:* i, Pp 39 D; ii, DMP–PTSA–acetone; iii, $KMnO_4$–$MgSO_4$–H_2O–acetone.

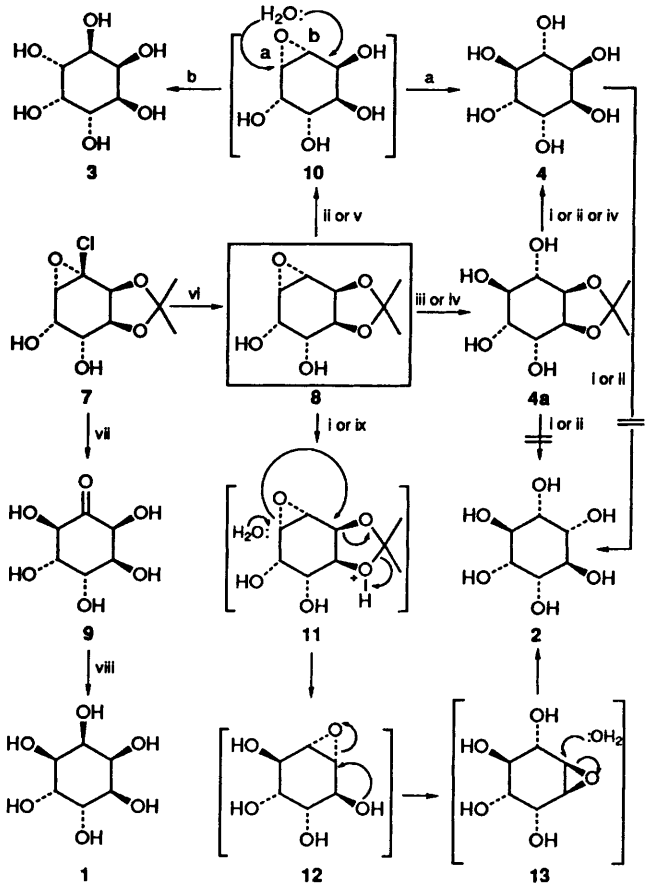
We now wish to report that precise tuning of conditions for the hydrolysis of epoxides **7** and **8** leads effectively to the general preparation of all four title inositols as single compounds requiring only recrystallization as means of further purification. In mechanistic terms, the possibility of acid- or base-catalysed Payne rearrangements[12k,17] leads to several options in the final configuration of the six hydroxy groups.

The hydrolysis of epoxide **7** to *chiro*-3-inosose (2L-2,3,6/4,5-pentahydroxycyclohexanone) **9** proceeds best in water or under alumina catalysis and provides this compound in 85% yield. The hydride reduction of the carbonyl affords a mixture of *allo*-inositol and D-*chiro*-inositol in the ratio of about 3:1 (not separated), while Raney nickel hydrogenation gives essentially a single product, *allo*-inositol **1**, in greater than 90% yield.

Stereospecific hydrolysis of epoxide **8** occurs at 90–100 °C in water containing trace amounts of weak base and leads to D-*chiro*-inositol **4** with greater than 95% selectivity and in 98% yield.[16] With diligent monitoring of this reaction, the acetonide **4a** can be observed as an intermediate, and in the presence of a stronger base (Amberlite IRA 904 and Amberlyst A 21, 1:1) it is isolated as the sole product in 85% yield, Scheme 2. Acid hydrolysis of D-*chiro*-inositol acetonide **4a** furnishes, with more than 95% selectivity, D-*chiro*-inositol **4** accompanied by small amount of *neo*-inositol **3** (up to 5%).

† Recipient of the American Cyanamid Faculty Research Award, 1992.
‡ Sigma Chem. prices (1992): *epi*-inositol (95%), 100 mg/$ 131.20; *myo*-inositol, 1 kg/$ 85.25; *c scyllo*-inositol 100 mg/$ 154.00.

§ For the preparation of diols **6a**, **b** on a laboratory scale see ref. 13(*f*).



Scheme 2 Synthesis of four inositols: D-*chiro*-inositol **4**, *neo*-inositol **3**, *muco*-inositol **2** and *allo*-inositol **1** from halogeno epoxide **7**. *Reagents and conditions:* i, H_2O–Amberlyst 15/25 °C; ii, H_2O–Amberlite IR 118/110 °C; iii, Amberlyst A 21 and Amberlite IRA 904 (1 : 1), 100 °C; iv, H_2O–sodium benzoate; v, H_2O, 100 °C; vi, TTMSS–AIBN–toluene, 110 °C; vii, H_2O–Al_2O_3, 80 °C; viii, H_2–RaNi–MeOH; ix, 10% AcOH, 80 °C.

Hydrolysis of epoxide **8** catalysed by Amberlite IR 118 (acidic resin) at 100 °C for 1 h, as well as non-catalysed hydrolysis (*i.e.*, refluxing epoxide **8** in water for 64 h) yields **4** and *neo*-inositol **3** in the ratio of about 7:3. *neo*-Inositol **3**, because of its significantly lower solubility in water–alcohol mixtures, is easily separable from D-*chiro*-inositol by recrystallization with about 60% recovery.

Acid hydrolysis of epoxide **8** at ambient temperature by means of Amberlyst 15 (acidic resin) for 20 h or exposure to 10% acetic acid for 2 h at 80 °C leads to *muco*-inositol **2** with 95% selectivity and in greater than 80% yield. Under these conditions D-*chiro*-inositol **4** does not undergo further rearrangements and is recovered unchanged. The absence of *muco*-inositol **2** in the reaction mixtures resulting from the exposure of either **4** or **4a** to acidic conditions lends credence to the proposed mechanism invoking the Payne rearrangement to explain the formation of *muco*-inositol **2** from **8** *via* epoxides **12** and **13**, Scheme 2.

At higher temperature the selectivity of epoxide opening is compromised by the rapid hydrolysis of the acetonide and competing opening of epoxide *syn* to the C-2 hydroxy in epoxide **10**, leading to *neo*-inositol **3** (path b, Scheme 2; the numbering refers to the assignment of epoxide **8**, not to the inositol nomenclature). While these mechanistic explanations are rather speculative, considering the possibility of total stereochemical scrambling through degenerate Payne rearrangements, they do account for the observed results. Noteworthy is the observation that the protonated acetonide **11** appears to suffer a fate radically different from that of the free tetrol **10**. The synthesis of epoxides of type **8**[12b] and their nucleophilic opening has recently been reported by Carless and Malik.[12k]

These results further underscore the merit of biocatalytic conversion of aromatic compounds to oxygenated products in short sequences. Seven of nine of the inositols are now available and L-*chiro*-inositol is potentially accessible through a simple adaptation of our enantiodivergent synthesis of (+)- and (−)-pinitols.[13b,c] We will report on details of further transformations in this series in the near future.[18]

Experimental

allo-*Inositol* **1**.—The mixture of inosose (2L-2,3,6/4,5-pentahydroxycyclohexanone) **9** (1.15 g, 6.45 mmol), Raney nickel (0.5 g) and methanol (15 cm^3) was hydrogenated at 60 psi* for 24 h. The reaction mixture was then diluted with water, filtered with charcoal and evaporated to dryness to furnish 1.06 g (91%) of the crude yellow product containing >90% of the title compound **1**. Recrystallization of this product (0.626 g) from aqueous ethanol gave 0.24 g of pure compound **1**; $\delta_H(D_2O$ 3.92 (m, 4 H) and 3.80 (br s, 2 H); GCMS was identical with an authentic sample.

Acknowledgements

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* 1 psi = 6.895 × 10^3 Pa.

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