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TETRAHEDRON: *ASYMMETRY*

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

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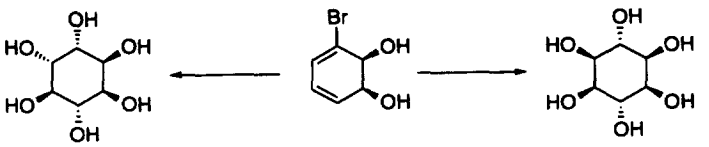
Abstract

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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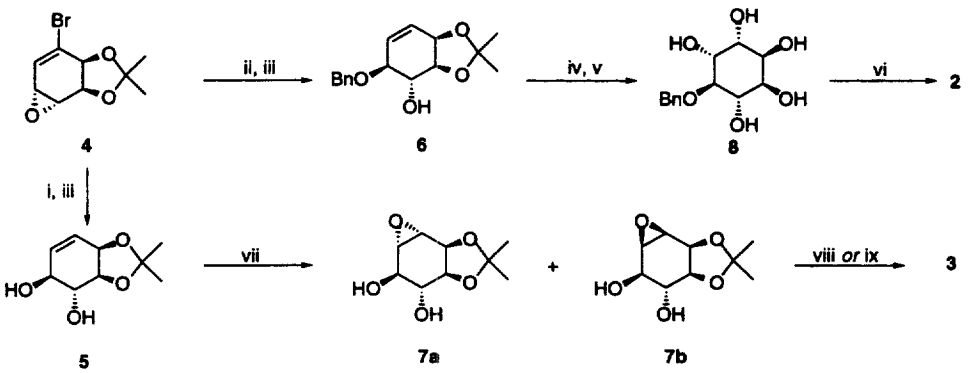
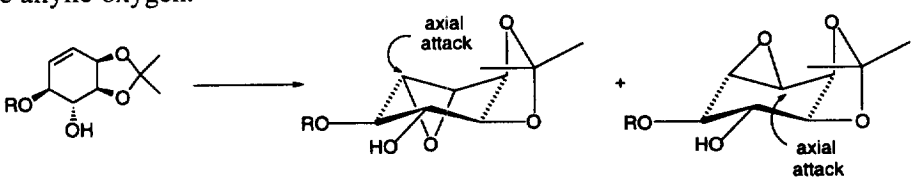
Protection and epoxidation of **1** afforded epoxide **4**[14] in 96% yield from diol **1**, with this sequence performed on a 40 g scale (Scheme 1). Regio- and stereoselective opening was accomplished with dilute aqueous hydroxide in 87% yield (for **5**) and with excess benzyl alcohol in 85% yield (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.

Table 1
Inositol syntheses from aromatic precursors

Compound	Steps	Overall yield*	Date	Ref.
D-*chiro*-inositol	3	25%	1993	4
D-*chiro*-inositol	5	39%	1997	19
allo-inositol	4	21%	1993	6
allo-inositol	5	42%	1997	20
neo-inositol	4	9%	1993	5
muco-inositol	4	10%	1993	5
muco-inositol	6	45%	1998	this work
L-*chiro*-inositol	7	28%	1998	this work

*from halocyclohexadiene diol

Literature precedent,[15] as well as our previous experience in the regiospecific opening of conduritol epoxides of type **7** which are similar to the intermediates employed in the pancratistatin synthesis,[16] indicated that hydrolysis of these diastereomers should proceed in a chemically redundant[17] manner to afford a single isomer of the *trans*-diol by the expected *trans*-diaxial attack of the nucleophile.[18] This finding is of enormous value to the planning and execution of inositol syntheses as it allows for non-stereoselective epoxidations whose final conversions to the desired *trans*-diol proceed to a single isomer. The conditions employed in the hydrolysis of epoxides also led to the concomitant deprotection of the acetonide providing pure *muco*-inositol in 89% yield from **7a** (45% overall yield from **4**) and 78% yield from **7b** (40% overall yield from **4**). The epoxides were not separated during the large-scale (>20 g) synthesis of *muco*-inositol but rather treated as a mixture under conditions identical to those used in the conversion of **7b**. In this fashion a 75% yield of a 16:1 mixture of *muco*- and *myo*-inositol was achieved. These diastereomers were readily separable by recrystallization from mixtures of 2-propanol/water (70/30).

The synthesis of *muco*-inositol described here apparently proceeded without the previously reported Payne rearrangement of hydroxy epoxides of this type.[5] It is superior in yield to the synthesis previously reported in 1993 (45% versus 10%). The current status of our quest for all nine inositols is summarized in Table 1. Further endeavors that include preparation of selected inositol phosphates and various inositol conjugates and oligomers will be reported in due course.

Acknowledgements

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References

1. (a) *Inositol Phosphates and Derivatives: Synthesis, Biochemistry, and Therapeutic Potential*; Reitz, A. B., Ed., American Chemical Society: Washington, 1991; (b) Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197; (c) Cosgrove, D. J. In *Inositol Phosphates: Their Chemistry, Biochemistry, and Physiology*; Elsevier: Amsterdam, 1980; (d) Wells, W. W.; Eisenbrg, F. In *Cyclitols and Phosphoinositides I*; Academic Press: New York, 1978.
2. Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439.

3. (a) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J. *Biochemistry* **1970**, *9*, 1626; (b) Gibson, D. T.; Koch, G. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653.
4. Mandel, M.; Hudlicky, T.; Kwart, K. D.; Whited, G. M. *J. Org. Chem.* **1993**, *58*, 2331.
5. (a) Mandel, M.; Hudlicky, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 741; corrigendum: Mandel, M.; Hudlicky, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1537.
6. Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachman, B.; Dudding, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553.
7. Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907.
8. Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077.
9. Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108.
10. For comprehensive reviews of arene *cis*-diol chemistry see: (a) Prestwich, G. D. *Acc. Chem. Res.* **1996**, *29*, 503; (b) Reddy, K. K.; Rizo, J.; Falck, J. R. *Tetrahedron Lett.* **1997**, *38*, 4729; (c) Cobb, J. E.; Johnson, M. R. *Tetrahedron* **1991**, *47*, 21; (d) Roemer, S.; Stadler, C.; Rudolf, M. T.; Jastorff, B.; Schultz, C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 741; (e) Brown, S. M.; Hudlicky, T. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed., JAI Press: Greenwich, CT, 1993; Vol. 2, pp. 113–176; (f) Widdowson, D. A.; Ribbons, D. W.; Thomas, S. D. *Janssen Chim. Acta* **1990**, *8*, 3; (g) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795; (h) Hudlicky, T.; Reed, J. W. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed., JAI Press: Greenwich, CT, 1995; p. 271; (i) Hudlicky, T. In *Green Chemistry: Designing Chemistry for the Environment*; Anastas, P. T.; Williamson, T., Eds.; ACS Symposium Series 626, American Chemical Society: Washington, DC, 1996; Chapter 14; (j) Hudlicky, T.; Thorpe, A. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1993; (k) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3; (l) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195; (m) Grund, A. D. *SIM News* **1995**, *45*, 59; (n) Sheldrake, G. N. In *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds.; Wiley: Chichester, 1992, Chapter 6, pp. 128–165.
11. For previous syntheses see: (a) Kornienko, A.; d'Alarcao, M. *Tetrahedron Lett.* **1997**, *38*, 6497 (asymmetric synthesis from D-xylose); (b) Chiara, J. L.; Valle, N. *Tetrahedron: Asymmetry* **1995**, *6*, 1895 (asymmetric synthesis from D-sorbitol); (c) Carless, H. A. J.; Busia, K.; Oak, O. Z. *Synlett* **1993**, 672 (racemic); (d) Angyal, S. J.; MacDonald, C. G. *J. Chem. Soc.* **1952**, 686 (asymmetric synthesis from quebrachitol).
12. For previous syntheses see: (a) Nakajima, M.; Tomida, I.; Kurihara, N.; Takai, S. *Chem. Ber.* **1959**, *92*, 173; (b) Angyal, S. J.; Bender, V.; Curtin, J. H. *J. Chem. Soc.* **1966**, 798; (c) Dangschat, G; Fisher, H. O. L. *Carbohyd. Res.* **1987**, *164*, 343; (d) Carless, H. A. J.; Busia, K.; Oak, O. Z. *Synlett* **1993**, 672 (racemic).
13. Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.* **1989**, *264*, 14940.
14. Hudlicky, T.; Tian, X.; Konigsberger, K.; Rouden, J. *J. Org. Chem.* **1994**, *59*, 4037.
15. Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221.
16. (a) Tian, X.; Hudlicky, T.; Konigsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643; (b) Hudlicky, T.; Tian, X.; Konigsberger, K.; Maurya, R.; Rouden, J.; Boreas, F. *J. Am. Chem. Soc.* **1996**, *118*, 10752; (c) Tian, X.; Maurya, R.; Konigsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125.
17. For definition of this term see Ref. 10(k), p. 10.
18. Deslongschamps, P. In *Stereoselective Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.
19. Unpublished results from this laboratory.
20. Desjardins, M.; Brammer Jr., L. E.; Hudlicky, T. *Carbohyd. Res.* **1997**, *340*, 39.