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Enantiospecific Synthesis of a Differentially Protected L-*chiro*-Inositol from D-Xylose

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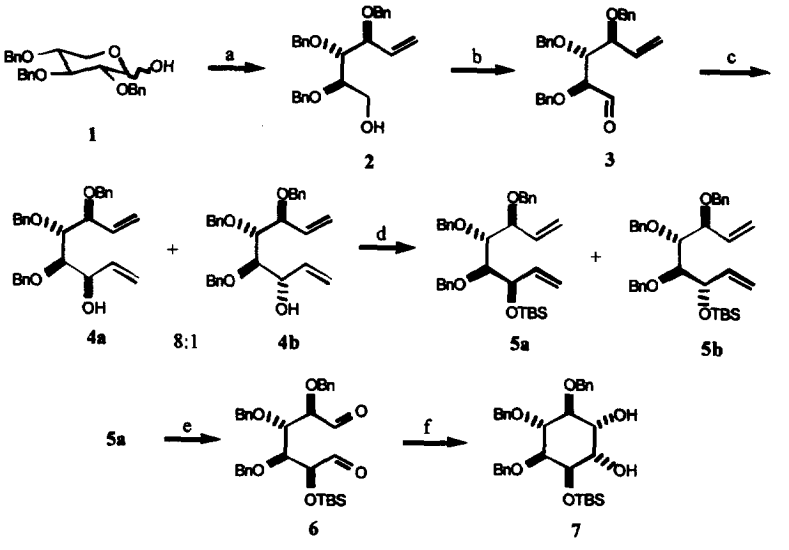
Abstract: A convenient synthesis of differentially protected L-*chiro*-inositol **7** from 2,3,4-tri-*O*-benzyl-D-xylopyranose is described. The structure of **7** was confirmed by its transformation to the pentabenzylated derivative of (-)-quebrachitol. © 1997 Elsevier Science Ltd.

The identification of *chiro*-inositol as an important constituent of certain phosphooligosaccharides believed to be insulin mediators[1] has led to intense research activity aimed at the synthesis of its optically pure, differentially protected derivatives.[2] Underivatized *chiro*-inositol's limited natural availability[3] compounded by the unwieldy nature of the six hydroxyl groups has resulted in utilization of other chiral[2a-e] and achiral[2f-i] sources in these preparations. As part of an ongoing program in our laboratory involving the synthesis of insulin-mimetic oligosaccharides,[4] we have been interested in preparing suitably protected *myo*- and *chiro*-inositol derivatives required for our studies as well as general applications. Herein, we report a convenient synthesis of a differentially protected L-*chiro*-inositol from D-xylose.[5]

2,3,4-Tri-*O*-benzyl-D-xylopyranose **1**, prepared in three steps from D-xylose according to a literature procedure,[6] was subjected to Wittig methylenation at the anomeric center[7] (Scheme 1) by treatment with 3 eq of methylenetriphenylphosphorane at 45 °C. Higher temperatures, though accelerating the reaction, resulted in lower yields. Rapid flash chromatographic purification provided alcohol **2** contaminated with small amounts of benzyl alcohol which was probably formed by competing deprotonation and elimination of benzoxide ion. Swern oxidation[8] of this mixture gave aldehyde **3** which could be isolated and purified. We found it more convenient, however, to continue with the crude material. The addition of vinylmagnesium bromide to crude aldehyde **3** proceeded with high anti-diastereoselectivity (**4a/4b**, 8:1) when the reaction was conducted in methylene chloride at –78 °C in the presence of 3 eq of $MgBr_2 \cdot OEt_2$.[9] Significantly, the opposite sense of diastereoselectivity (**4a/4b**, 1:3) was obtained in the absence of $MgBr_2 \cdot OEt_2$. To establish the stereochemistry of the addition each of the diastereomeric allylic alcohols **4a** and **4b**[10] was converted to its benzylated derivative **8a** and **8b** (Figure 1). The ^1H NMR spectrum of the tetrabenzyloxyoctadiene **8b** derived from the minor Grignard addition product clearly showed the presence of the C_2 axis of symmetry, whereas **8a** was

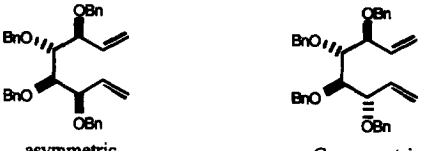
asymmetric. Thus it was concluded that the minor isomer was the syn addition product while the major one was anti.

Scheme 1



Reagents and conditions: (a) $CH_2=PPh_3$, THF, 45°C, 10h; (b) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 20 min; Et_3N, -78°C → r.t.; (c) vinylmagnesium bromide (20 eq), CH_2Cl_2, -78°C, $MgBr_2{\cdot}OEt_2$ (3 eq), 3h; (d) *tert*-butyldimethylsilyl chloride, imidazole, DMF, 12h (42% for **5a** over 4 steps); (e) O_3, MeOH-CH_2Cl_2 (10:1), py (2 eq), -78°C; DMS, -78°C→ r.t.; (f) SmI_2 (3 eq), THF, *t*-BuOH (3 eq), -78°C, 5h (42% over 2 steps).

Figure 1



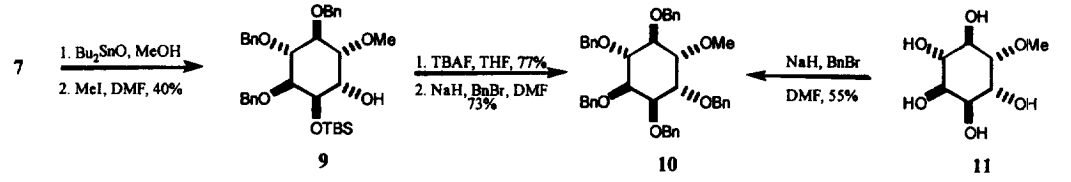
asymmetric **8a**

C_2 symmetric **8b**

The crude mixture of the epimeric alcohols was *tert*-butyldimethylsilylated[11] and the major epimer **5a** was isolated by flash chromatography on silica gel in 42% yield over 4 steps. Ozonolysis of **5a** gave the dialdehyde **6** which was subjected without purification to samarium diiodide reductive coupling.[12] SmI_2 is known to

promote intramolecular pinacol cyclizations with high selectivity for the cis-diol product and the orientation of the two hydroxyl groups opposite to the adjacent alkoxy substituents.[13] Therefore it was no surprise that the only product isolated from pinacol cyclization of **6** was the cis-diol **7** with the arrangement of oxy substituents corresponding to L-*chiro*-inositol in 42% unoptimized yield from **5a**.[14] The stereochemistry of cyclization was established by ^{1}H NMR analysis of the diacetyl derivative of **7**[15] and unequivocally confirmed by transformation of **7** into **10** which was obtained independently by pentabenzylation of naturally occurring (-)-quebrachitol (**11**) as shown in Scheme 2.[16]

Scheme 2



In conclusion, the synthetic sequence described provides an expedient access to differentially protected *chiro*-inositol derivatives of potential value in the synthesis of insulin-mimetic phosphooligosaccharides. It involves eight steps starting from commercially available, inexpensive material with only three facile chromatographic purifications. In addition, this synthesis illustrates another strategy for the preparation of optically pure cyclitol derivatives from non-cyclitol carbohydrate precursors.[17]

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References and Notes:

1. Mato, J.M.; Kelly, K.L.; Alber, A.; Jarett, L.; Corkey, B.E.; Cashel, J.A.; Zopf, D. *Biochem. Biophys. Res. Commun.* **1987**, *146,* 764-770. Larner, J.; Huang, L.C.; Schwartz, C.F.W.; Oswald, A.S.; Shen, T.Y.; Kinter, M.; Tang, G.; Zeller, K. *ibid.* **1988**, *151,* 1416-1426.
2. (a) Tagliaferri, F.; Wang, S.N.; Berlin, W.K.; Outten, R.A.; Shen, T.Y. *Tetrahedron Lett.* **1990**, *31,* 1105-1108. (b) Jaramillo, C.; Martin-Lomas, M. *ibid.* **1991**, *32,* 2501-2504. (c) Reddy, K.K.; Falck, J.R.; Capdevila, J. *ibid.* **1993**, *34,* 7869-7872. (d) Jaramillo, C.; Chiara, J.L.; Martin-Lomas, M. *J. Org. Chem.* **1994**, *59,* 3135-3141. (e) Chiara, J.L.; Valle, N. *Tetrahedron Asymmetry* **1995**, *6,* 1895-1898. (f) Hudlicky, T.; Price, J.D.; Rulin, F.; Tsunoda, T. *J. Amer. Chem. Soc.* **1990**, *112,* 9439-9440. (g) Mandel, M.; Hudlicky, T.; Kwart, L.D.; Whited, G.M. *J. Org. Chem.* **1993**, *58,* 2331-2333. (h) Mandel, M.; Hudlicky, T. *J. Chem. Soc. Perkin Trans. 1* **1993**, 741-743. (i) Hudlicky, T.; Thorpe, A.J. *Synlett* **1994**, 899-901

3. Modest amounts of D-*chiro*-inositol can be obtained by demethylation of (+)-pinitol found in the extracts of sugar pine (Pinas lambertiana Dougl) wood dust: Anderson, A.B. *Ind. Eng. Chem.* **1953**, 593-596. It is also accessible by ether cleavage of the natural antibiotic kasugamycin: Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M.; Takeuchi, T. *J. Antibiot. (Tokyo) Ser. A* **1965**, *18*, 101-103. For a synthesis of D-*chiro*-inositol using a biocatalytic approach see: ref. 2g.
4. Plourde, R.; d'Alarcao, M. *Tetrahedron Lett.* **1990**, *31*, 2693-2696. Plourde, R.; d'Alarcao, M.; Saltiel, A.R. *J. Org. Chem.* **1992**, *57*, 2606-2610.
5. It is understood that the enantiomeric derivatized D-*chiro*-inositol could be prepared in a similar manner from inexpensive L-xylose.
6. Tejima, S.; Ness, R.K.; Kaufman, R.L.; Fletcher, H.G. *Carbohydr. Res.* **1968**, *7*, 485-490. Tsuda, Y.; Nunozawa, T.; Yoshimoto, K. *Chem. Pharm. Bull.* **1980**, *28*, 3223-3231.
7. For other examples of methylenation of an anomeric position see: Nicotra, F.; Perego, R.; Ronchetti, F.; Russo, G.; Toma, L. *Gazzetta Chimica Italiana*, **1984**, *114*, 193-195. Nicotra, F.; Perego, R.; Ronchetti, F.; Russo, G.; Toma, L. *Carbohydr. Res.* **1984**, *131*, 180-184. Lancelin, J.-M.; Pougny, J.-R.; Sinay, P. *ibid.* **1985**, *136*, 369-374. Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *ibid.* **1987**, *171*, 49-57.
8. Mancuso, A.J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.
9. The solution of vinylmagnesium bromide in CH_2Cl_2 was prepared by two freeze, evaporation, dilution cycles of the commercial 1M solution of the reagent in THF. For a related protocol utilizing $MgBr_2{\cdot}OEt_2$ in a chelation controlled Grignard addition see: Keck, G.E.; Andrus, M.B.; Romer, D.R. *J. Org. Chem.* **1991**, *56*, 417-420.
10. Alcohols **4a** and **4b** were not completely separable by column chromatography. Mixtures enriched in either **4a** or **4b** were used in this experiment.
11. Corey, E.J.; Venkateswarlu, A. *J. Amer. Chem. Soc.* **1972**, *94*, 6190-6191.
12. For the use of SmI_2 pinacol coupling in the synthesis of cyclitols see: Chiara, J.L.; Martin-Lomas, M. *Tetrahedron Lett.* **1994**, *35*, 2969-2972. Guidot, J.P.; Gall, T.L.; Mioskowski, C. *ibid.* **1994**, *35*, 6671-6672. Sawada, T.; Shirai, R.; Iwasaki, S. *ibid.* **1996**, *37*, 885-886. Carpintero, M.; Fernandez-Mayoralas, A.; Jaramillo, C. *J. Org. Chem.* **1997**, *62*, 1916-1917. See also ref. 2e.
13. Chiara, J.L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125-1128.
14. ^{1}H NMR of **7** ($CDCl_3$): δ 7.37-7.2 (15H, m), 5.01 (1H, d, 11.4 Hz), 4.95 (1H, d, 10.9 Hz), 4.8 (1H, d, 10.9 Hz), 4.71 (2H, s), 4.63 (1H, d, 11.4 Hz), 4.17 (1H, dd, 3.8; 2.7 Hz), 3.95-3.87 (3H, m), 3.79 (1H, dd, 10; 2.6 Hz), 3.62 (1H, ψt, 9.2 Hz), 2.46 (1H, br s), 2.35 (1H, br s), 0.87 (9H, s), 0.08 (3H, s), 0.03 (3H, s). MALDI-TOF: 587.7 ($M+Na^+$), 603.7 ($M+K^+$). Anal. Calcd for $C_{33}H_{44}O_6Si$: C, 70.18; H, 7.85. Found: C, 70.21; H, 7.95.
15. ^{1}H NMR data for the ring hydrogens of diacetyl **7** ($CDCl_3$): δ 5.34 (dd, 9.8; 3.4 Hz, H5), 5.17 (dd, 4.3; 3.4 Hz, H6), 3.98 (dd, 4.3; 2.8 Hz, H1), 3.95 (ψt, 9.8 Hz, H3), 3.80 (ψt, 9.8 Hz, H4), 3.63 (dd, 9.8; 2.8 Hz, H2).
16. The ^{1}H NMR spectra of **10** obtained from the two different sources were indistinguishable.
17. For some other strategies see: Watanabe, Y.; Mitani, M.; Ozaki, S. *Chemistry Lett.* **1987**, 123-126. Sato, K.; Sakuma, S.; Muramatsu, S.; Bokura, M. *ibid.* **1991**, 1473-1474. Bender, S.L.; Budhu, R. *J. Amer. Chem. Soc.* **1991**, *113*, 9883-9885. Sato, K.; Bokura, M.; Taniguchi, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1633-1640. See also ref. 12, 2b,d.

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