

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

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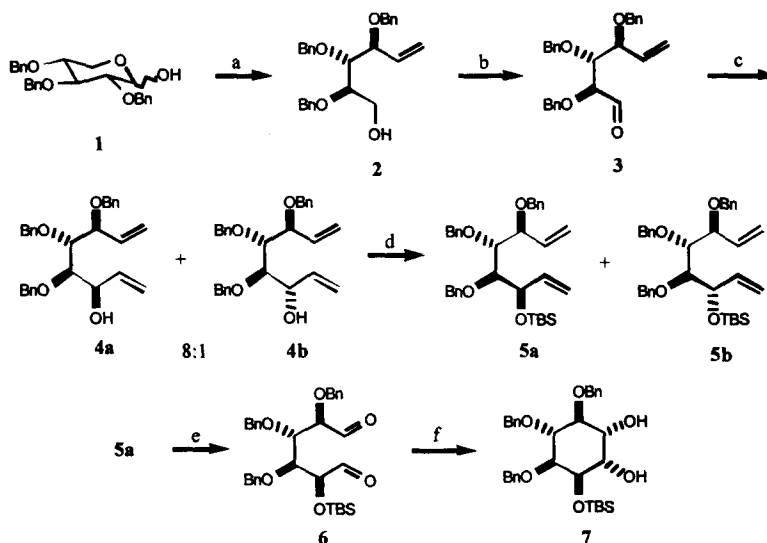
Abstract: A convenient synthesis of differentially protected *L-chiro*-inositol **7** from 2,3,4-tri-*O*-benzyl-*D*-xylopyranose is described. The structure of **7** was confirmed by its transformation to the pentabenzylated derivative of (-)-quebrachitol. © 1997 Elsevier Science Ltd.

The identification of *chiro*-inositol as an important constituent of certain phosphooligosaccharides believed to be insulin mediators¹ has led to intense research activity aimed at the synthesis of its optically pure, differentially protected derivatives.² Underivatized *chiro*-inositol's limited natural availability³ compounded by the unwieldy nature of the six hydroxyl groups has resulted in utilization of other chiral^{2a-c} 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 center⁷ (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 benzoate ion. Swern oxidation⁸ 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 MgBr₂·OEt₂.⁹ Significantly, the opposite sense of diastereoselectivity (**4a/4b**, 1:3) was obtained in the absence of MgBr₂·OEt₂. 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 tetrabenzylxylooctadiene **8b** derived from the minor Grignard addition product clearly showed the presence of the C₂ axis of symmetry, whereas **8a** was

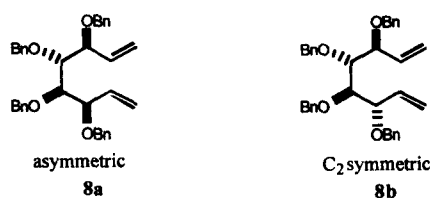
asymmetric. Thus it was concluded that the minor isomer was the syn addition product while the major one was anti.

Scheme 1



Reagents and conditions: (a) $\text{CH}_2=\text{PPh}_3$, THF, 45°C , 10h; (b) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C , 20 min; Et_3N , $-78^\circ\text{C} \rightarrow \text{r.t.}$; (c) vinylmagnesium bromide (20 eq), CH_2Cl_2 , -78°C , $\text{MgBr}_2\cdot\text{OEt}_2$ (3 eq), 3h; (d) *tert*-butyldimethylsilyl chloride, imidazole, DMF, 12h (42% for 5a over 4 steps); (e) O_3 , $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (10:1), py (2 eq), -78°C ; DMS, $-78^\circ\text{C} \rightarrow \text{r.t.}$; (f) SmI_2 (3 eq), THF, *t*-BuOH (3 eq), -78°C , 5h (42% over 2 steps).

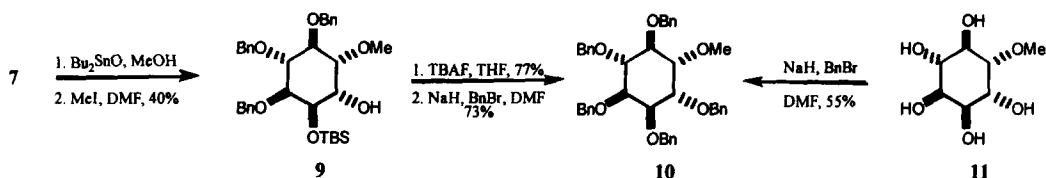
Figure 1



The crude mixture of the epimeric alcohols was *tert*-butyldimethylsilylated¹¹ 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 ¹H NMR analysis of the diacetyl derivative of **7**¹⁵ and unequivocally confirmed by transformation of **7** into **10** which was obtained independently by pentabenzoylation 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

Acknowledgment: We thank the National Institutes of Health for financial support.

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14. ¹H NMR of **7** (CDCl₃): 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, *ψ*t, 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 C₃₃H₄₄O₆Si: C, 70.18; H, 7.85. Found: C, 70.21; H, 7.95.
15. ¹H NMR data for the ring hydrogens of diacetyl **7** (CDCl₃): 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 (*ψ*t, 9.8 Hz, H3), 3.80 (*ψ*t, 9.8 Hz, H4), 3.63 (dd, 9.8; 2.8 Hz, H2).
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(Received in USA 24 June 1997; revised 10 July 1997; accepted 14 July 1997)