Practical synthesis of a differentially protected myo-inositol
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Abstract

An enantiospecific synthesis of 3,4,5-tri-O-benzyl-6-O-triisopropylsilyl-D-myoinositol from D-xylose is reported. The synthesis features a diastereofacially selective SmI2-promoted pinacol cyclization. © 1998 Elsevier Science Ltd. All rights reserved.

The rich biochemistry of inositol phosphates identified as second messengers in a variety of cellular signal transduction systems has stimulated intense interest in these compounds and their analogs. Consequently, extensive efforts have been made toward the preparation of differentially protected, enantiomerically pure myo-inositol derivatives. Of these, D-myoinositol derivatives orthogonally protected at positions (1,2), (6), and (3,4,5) as in compound 1 are of special interest for the synthesis of inositol phosphate glycols (IPGs) implicated in insulin signal transduction.

Four general synthetic strategies have been employed in the synthesis of differentially protected myo-inositols. The most frequently used are the procedures starting from parent achiral myo-inositol. Although this strategy provides a wide array of differential protection schemes, the major drawbacks include tedious manipulations of the many hydroxyl groups and the necessity of enantiomeric resolution. Other strategies which circumvent some of these difficulties are the syntheses based on microbial oxidation of aromatic compounds and derivatization of naturally occurring enantiomerically pure cyclitols.

In addition, approaches utilizing other readily available, enantiomerically pure starting materials such as glucose, mannitol, diethyltartrate, quinic acid and dehydroshikimic acid have been reported. In view of the practicality of the latter, we sought to utilize this strategy for the preparation of an inositol precursor suitable for use in the synthesis of IPGs. We report herein a new enantiospecific synthesis of compound 1 from D-xylose.

We recently reported a synthesis of a differentially protected L-chiro-inositol wherein 2(S),3(R),4(S)-tribenzylxyoxyhex-5-enal, prepared in five steps from D-xylose, was treated with vinylmagnesium bromide in the presence of 3 equiv. of MgBr2·OEt2 in CH2Cl2 to give a 1:8 mixture of syn and anti alcohols 2a and 2b (Scheme 1). Further experimentation allowed us to reverse the selectivity to 3:1 favoring 2a by performing the reaction in the absence of MgBr2·OEt2 in CH2Cl2:THF (5:1) solvent pair. The

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crude mixture of the diastereomeric alcohols was treated with triisopropylsilyl chloride in DMF–py in the presence of AgNO₃ and the resulting TIPS-protected derivatives 3a and 3b were separated by silica gel chromatography eluting with hexane:ether, 24:1 (61% for 3a over two steps).

Scheme 1.

Ozonolysis of 3a gave 4, which was subjected to SmI₂-mediated reductive ring closure to produce myo-inositol derivatives 1 and 5 in >20:1 ratio.² The diols could be conveniently separated by column chromatography eluting with CH₂Cl₂:benzene:ethyl acetate (50:50:3)¹³ providing 1 in 67% isolated yield (from 3a).

The exclusive formation of cis-diols in this reaction is not surprising and has been amply precedented in cyclitol syntheses utilizing this technology in a six-membered ring construction step.⁷,⁸,¹⁴ However, the face selectivity is noteworthy. The previously reported methodologies have employed either C₂-symmetric dialdehydes similar to 6⁷,⁸,¹⁴a-c (Fig. 1), where the face discrimination is inconsequential, or asymmetric dialdehydes similar to 8,¹¹,¹⁴c,d where the face selection is controlled by the two adjacent alkoxy substituents both oriented trans to the incipient hydroxyl groups. Type 8 dialdehydes do not produce myo-inositols, whereas the dialdehydes of type 6 result in less versatile protection schemes. The SmI₂ reaction of 4 is, to the best of our knowledge, the first example of a face-selective pinacol coupling resulting in a myo-inositol.

The structure of 1 was established by ¹H NMR and confirmed by an independent synthesis of 10 starting from unprotected myo-inositol. The enantiomeric identity of 10 from each source was demonstrated by conversion to the Mosher ester 12 (Scheme 2). Compound 12 prepared via 1 was identical to that prepared via 11¹⁵ by mixed TLC, ¹H and ¹⁹F NMR.

To confirm unequivocally the structure of 5, the mixture of 5 and 1 obtained in a reaction quenched at room temperature¹² was desilylated (TBAF, THF, 2 h, 90%) and exhaustively benzylated (BnBr, DMF, NaH, rt, 2 days, 85%) to give a single compound, hexabenzyl-myosinositol (established by TLC and

![Diagram](https://example.com/diagram.png)

**Fig. 1.**
\[^{1}H\text{ NMR analyses}.\] The preparation of a single mono-Mosher ester of 5 demonstrated its enantiomeric integrity.

The synthesis of the differentially protected and enantiomerically pure myo-inositol derivative 1 is relatively short and requires only three facile chromatographic purifications starting from inexpensive D-xylose. It could be further extended for the preparation of the enantiomer of 1 provided that commercially available L-xylose is used as a starting material. We believe that this method will be applicable for the preparation of a variety of myo-inositol containing compounds.

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**References**


12. The conditions are critical to the diastereoselectivity. When the reaction was performed with 6 equiv. SmI₂ at −78°C in THF for 30 min followed by slow dropwise addition of aqueous NaHCO₃ to the reaction mixture at −78°C, diols 1 and 5 were produced in >20:1 ratio (70% yield). However, if the reaction was performed under standard conditions¹²c (2 equiv. SmI₂, 3 equiv. t-BuOH, −78°C to 20°C) prior to quenching, compounds 1 and 5 were formed in 1:2:3 ratio (63% yield).

13. R₁ (1)=0.18, R₂ (5)=0.12. 'H NMR of 1: δ 7.33–7.18 (15H, m), 4.95 (1H, d, 11.5 Hz), 4.83 (1H, d, 10.8 Hz), 4.74–4.62 (4H, m), 4.16 (1H, dd, 4.2, 2.8 Hz), 4.11 (1H, ωτ, 9.0 Hz), 3.94 (1H, ωτ, 9.0 Hz), 3.53 (1H, dd, 9.0, 2.8 Hz), 3.43 (1H, ddd, 9.0, 6.8, 4.2 Hz), 3.33 (1H, ωτ, 9.0 Hz), 2.55 (1H, s), 2.48 (1H, d, 6.8 Hz), 1.08 (21H, m). 5 (CDCl₃): δ 7.35–7.18 (15H, m), 4.94 (1H, d, 11.2 Hz), 4.91 (1H, d, 10.3 Hz), 4.87 (1H, d, 10.3 Hz), 4.80 (2H, d, 10.3 Hz), 4.77 (1H, d, 11.2 Hz), 4.09 (1H, ωτ, 2.4 Hz), 3.89–3.76 (3H, m), 3.54 (1H, dd, 8.0, 4.7 Hz), 3.47 (1H, ωτ, 9.2 Hz), 2.54 (1H, s), 2.41 (1H, d, 5.1 Hz), 1.07 (21H, m).
