Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2783–2786

TETRAHEDRON: *ASYMMETRY*

Practical synthesis of a differentially protected *myo*-inositol

Alexander Kornienko, David I. Turner, Christine H. Jaworek and Marc d'Alarcao *

Michael Chemistry Laboratory, Department of Chemistry, Tufts University, Medford, MA 02155, USA

Received 8 July 1998; accepted 20 July 1998

Abstract

An enantiospecific synthesis of 3,4,5-tri-*O*-benzyl-6-*O*-triisopropylsilyl-D-*myo*-inositol from D-xylose is reported. The synthesis features a diastereofacially selective SmI_2-promoted pinacol cyclization.

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.[1] Consequently, extensive efforts have been made toward the preparation of differentially protected, enantiomerically pure *myo*-inositol derivatives. Of these, D-*myo*-inositol 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 glycans (IPGs) implicated in insulin signal transduction.[2]

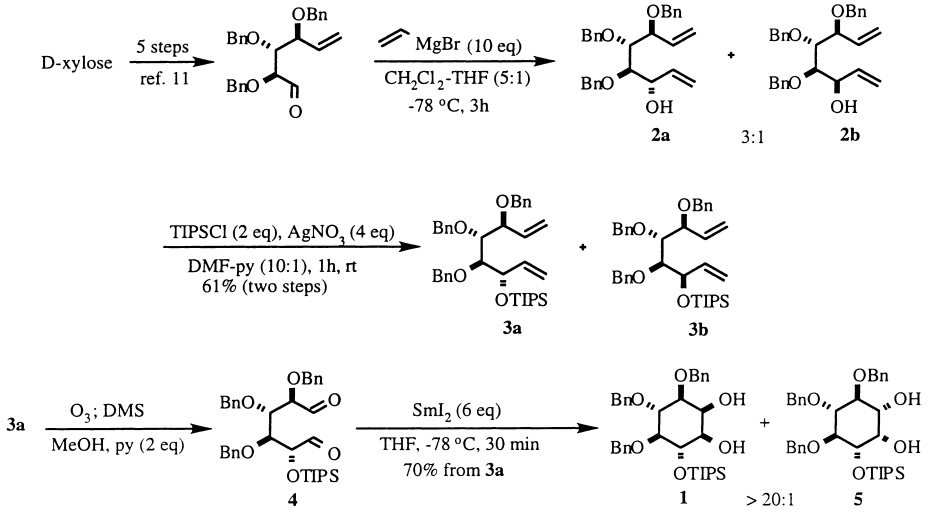
Four general synthetic strategies have been employed in the synthesis of differentially protected *myo*-inositols. The most frequently used are the procedures starting from parent achiral *myo*-inositol.[3] Although this strategy provides a wide array of differential protection schemes, the major drawbacks 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[4] and derivatization of naturally occurring enantiomerically pure cyclitols.[5] In addition, approaches utilizing other readily available, enantiomerically pure starting materials such as glucose,[6] mannitol,[7] diethyltartrate,[8] quinic acid[9] and dehydroshikimic acid[10] 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[11] wherein 2(*S*),3(*R*),4(*S*)-tribenzyloxyhex-5-enal, prepared in five steps from D-xylose, was treated with vinylmagnesium bromide in the presence of 3 equiv. of $MgBr_2 \cdot OEt_2$ in CH_2Cl_2 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 $MgBr_2 \cdot OEt_2$ in CH_2Cl_2:THF (5:1) solvent pair. The

* Corresponding author.

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00302-4

crude mixture of the diastereomeric alcohols was treated with triisopropylsilyl chloride in DMF–py in the presence of $AgNO_3$ 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 SmI_2-mediated reductive ring closure to produce *myo*-inositol derivatives **1** and **5** in >20:1 ratio.[12] The diols could be conveniently separated by column chromatography eluting with CH_2Cl_2: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 C_2-symmetric dialdehydes similar to **6**[7,8,14a–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 SmI_2 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 **11**[15] by mixed TLC, ^1H and ^{19}F NMR.

To confirm unequivocally the structure of **5**, the mixture of **5** and **1** obtained in a reaction quenched at room temperature[12] was desilylated (TBAF, THF, 2 h, 90%) and exhaustively benzylated (BnBr, DMF, NaH, rt, 2 days, 85%) to give a single compound, hexabenzyl-*myo*-inositol (established by TLC and

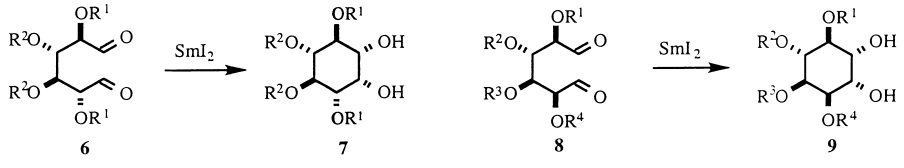
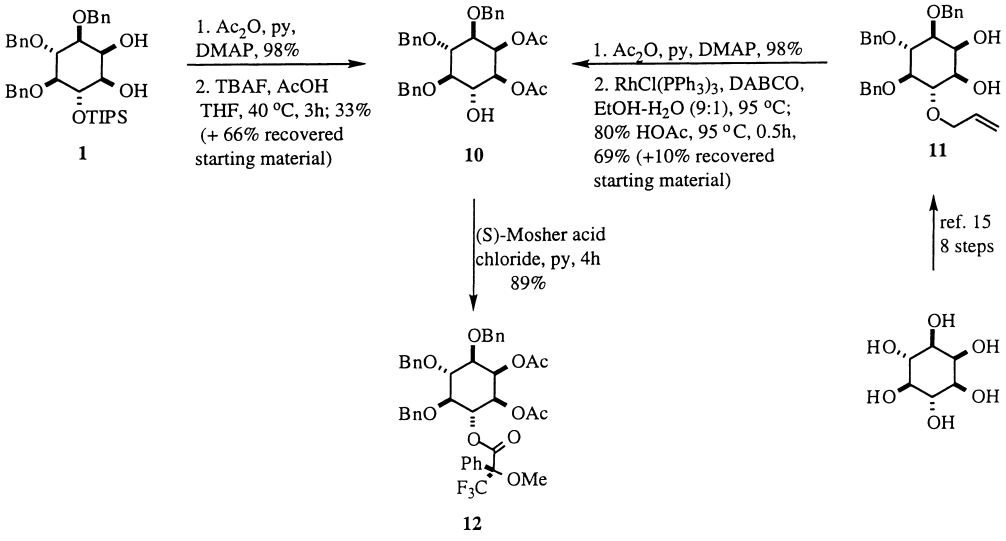


Fig. 1.



Scheme 2.

^{1}H 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.

Acknowledgements

We are grateful to Professor James Panek and his group for assistance with the ozonolysis reaction and to the National Institutes of Health for financial support.

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12. The conditions are critical to the diastereoselectivity. When the reaction was performed with 6 equiv. SmI_2 at −78°C in THF for 30 min followed by slow dropwise addition of aqueous $NaHCO_3$ 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 conditions[14c] (2 equiv. SmI_2 , 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. R_f (**1**)=0.18, R_f (**5**)=0.12. ^{1}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), 4.74–4.64 (4H, m), 4.16 (1H, dd, 4.2; 2.8 Hz), 4.11 (1H, ψt, 9.0 Hz), 3.94 (1H, ψt, 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, ψt, 9.0 Hz), 2.55 (1H, s), 2.48 (1H, d, 6.8 Hz), 1.08 (21H, m). **5** ($CDCl_3$): 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, ψt, 2.4 Hz), 3.89–3.76 (3H, m), 3.54 (1H, dd, 8.0; 4.7 Hz), 3.47 (1H, ψt, 9.2 Hz), 2.54 (1H, s), 2.41 (1H, d, 5.1 Hz), 1.07 (21H, m).
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