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Practical Synthesis of Enantiomerically Pure *myo*-Inositol Derivatives

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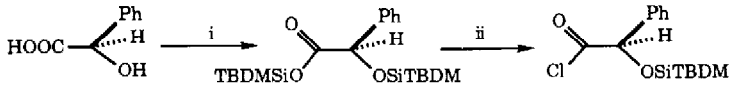
Abstract: *The synthesis of enantiomerically pure myo-inositol derivatives is accomplished using a mandelic acid-derived acyl protecting group.*

A number of synthetic schemes leading to enantiomerically pure, and properly functionalized derivatives of *myo*-inositol start from one of the three positional isomers of di-*O*-cyclohexylidene-*myo*-inositol.[1,2] These derivatives are formed as a mixture, and thus have to be separated by a combination of crystallization and chromatographic techniques,[2] making their availability difficult. In contrast, *cis*-monoacetals of *myo*-inositol are synthesized in one step in good yield.[3] Recently we have found that *cis*-monoacetals can be selectively protected at the 1-hydroxyl group with bulky acylating or silylating reagents.[4] By applying selective protection of the remaining hydroxyl groups a number of useful intermediates for the synthesis of phosphoinositides can be obtained. In this communication we report on the synthesis of novel synthetic precursors of inositol-1,4,5-trisphosphate (IP_3), phosphatidylinositol (PI), and phosphatidylinositol-4,5-bisphosphate (PIP_2). Our approach is to combine the selective protection of 1-hydroxyl group and formation of diastereomeric esters with a chiral auxiliary, and hence to eliminate the need for additional steps to form separable diastereomeric esters of inositol.

Silylation of (R)-(-)-mandelic acid (**1**) with 2 equiv. of *tert*-butyldimethylsilyl chloride (TBDMS-Cl) in pyridine and subsequent chlorination of the resulting silyl ester **2** with oxalyl chloride/DMF[5] afforded 2-(*tert*-butyldimethylsilyloxy)phenylacetyl chloride (**3**).[6]



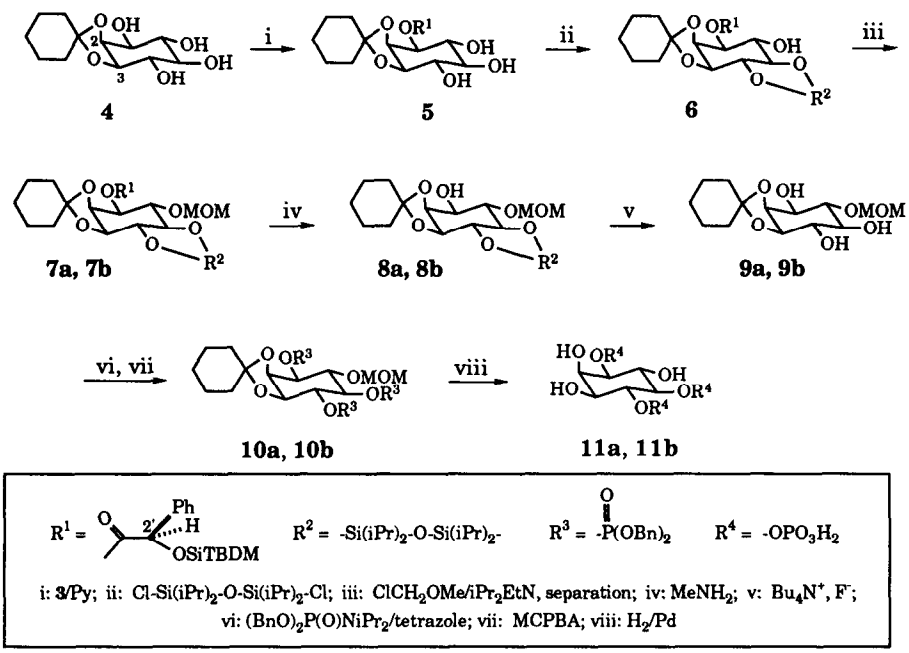
1 **2** **3**

i: $^tBuMe_2SiCl$/Py; ii: $(COCl)_2$/DMF

Reaction of cyclohexylidene-*myo*-inositol (**4**) with **3** in pyridine at -40°C afforded the mixture of 1-protected diastereomeric esters **5** (55%). Formation of other positional isomers could not be detected. The diastereomers **5** proved to be difficult to separate by chromatographic methods.[7a] However, simple precipitation from ether-hexane afforded one of the isomers **5a** with >96% d.e.[7b] The mixture of diastereomers remaining in the mother liquor was chromatographed to remove higher protected

derivatives, and was further treated with 1,3-dichloro-1,1,3,3-diisopropyldisiloxane in pyridine at room temperature. The resulting diastereomeric mixture of 6-alcohols (**6a** and **6b**) was reacted with methoxymethylene chloride - diisopropylethylamine in THF at 55°C during 12 h (62%). Fully protected compounds **7a,b** were easily separated into individual isomers by chromatography on silica gel (hexane-ether, 40:1, **7a**: R_F 0.18; **7b**: R_F 0.13).[8] The isomers of **7** were converted into functionally useful enantiomeric alcohols **8**[9] by deacylation at the 1-position with methylamine (83%), and subsequently into triols **9**[10] by desilylation of **8** with tetra-*n*-butylammonium fluoride (100%).

The combination of acyl, silyl and acetal protective groups in **5-9** make these compounds versatile starting materials for the synthesis of phosphatidylinositol, inositol-1-phosphate (from **5**[11] and **8**), 6-glycosylated phosphatidylinositols (from **6**), and PIP_2 (from **8**), in addition to the synthesis of IP_3 described below. The synthesis of various phosphorothioate analogs, and unsaturated fatty acid-containing inositol phospholipids should also be possible.



The utility of synthesized compounds as phosphoinositides precursors was demonstrated by the synthesis of L- and D-IP_3 starting from enantiomers **9a** and **9b**, respectively.[12] This synthesis also enabled determination of the inositol configurations in **5-9** on the basis of configurations of IP_3. Thus, triols **9** were treated with *N,N*-diisopropyl-*O,O*-dibenzylphosphoramidite/tetrazole, and the resulting trisphosphites were oxidized with *m*-chloroperbenzoic acid to give the corresponding tris(dibenzyl-

phosphates) **10a,b**. Deprotection of the phosphate groups in **10** with H_2/Pd in methanol and subsequent spontaneous cleavage of inositol protecting groups during hydrogenolysis afforded IP_3 (**11**). The synthesis starting from the crystalline triol **5a** produced enantiomerically pure L-*myo*-inositol-1,4,5-trisphosphate (**11a**). D-IP_3 (**11b**) was synthesized in a reaction sequence starting from the more polar isomer **7b**.

The advantage of our method is in its brevity, versatility of intermediates and in a fewer number of chromatographic purifications required along the synthesis of phosphoinositides precursors.

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2. a) Garegg, P. J., Lindberg, B., Kvarnstrom, I. and Svensson, C. T. *Carbohydr. Res.* **1985**, *139*, 209; (b) Garegg. P. J., Iversen, T., Johansson, R. and Lindberg, B. *Carbohydr. Res.* **1984**, *130*, 322.
3. Jiang, C. and Baker, D. C. *J. Carbohydr. Chem.*, **1986**, *5*, 615.
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6. Reagent **3** was sufficiently pure in a crude form; ^{1}H NMR ($CDCl_3$) δ 7.6-7.45, (m, Ph, 5H), 5.52 (s, H-2, 1H), 1.04 (s, Bu, 9H), 0.14, 0.05 (each s, Me, 3H).
7. (a) Chromatographic separation was attempted for triols **5**, and the corresponding exhaustively acetylated and methoxymethylated derivatives. (b) **5a**: ^{1}H NMR (CD_3OD) δ 7.5-7.3 (m, Ph, 5H), 5.41 (s, H-2', 1H), 4.93 (dd, H-1, J 4.3, 9.8 Hz, 1H), 4.26 (dd, H-2, J 4.4, 5.0 Hz, 1H), 3.91 (dd, H-3, J 5.2, 7.5 Hz, 1H), 3.75 (tr, H-6, J 9.6 Hz, 1H), 3.47 (dd, H-4, J 7.5, 9.9 Hz, 1H), 3.19 (dd, H-5, J 9.9, 9.6 Hz,1H), 1.6-1.2 (m, CH_2, 10H), 0.92 (s, Bu, 9H), 0.14, 0.05 (s, Me, 3H).
8. **7a**: ^{1}H NMR ($CDCl_3$) δ 7.45, 7.3 (m, Ph, 5H), 5.24 (s, H-2', 1H), 4.98 (dd, H-1, J 3.9, 10.2 Hz, 1H), 4.51, 4.45 (d, CH_2, 2H), 4.42 (dd, H-2, J 4.0, 5.3 Hz, 1H), 3.98 (dd, H-3, J 5.3, 6.8 Hz, 1H), 3.84 (tr, H-6, J 9.0 Hz, 1H), 3.76 (dd, H-4, J 6.8, 9.4 Hz, 1H), 3.52 (tr, H-5, 9.2 Hz, 1H), 3.12 (s, Me, 3H), 1.7-1.0 (m, CH_2, iPr, 38H), 0.89 (s, Bu, 9H), 0.10, 0.02 (s, Me, 6H); Compound **7a** had the same inositol configuration as triol **5a**. **7b**: 7.45, 7.3 (m, Ph, 5H), 5.32 (s, H-2', 1H), 4. 96 (dd, H-1, J 4.0, 10.0 Hz, 1H), 4.91, 4.71 (d, CH_2, 2H), 4.28 (tr, H-2, J 4.2 Hz, 1H), 3.98 (tr, H-6, J 9.2 Hz, 1H), 3.91 (dd, H-3, J 5.0, 6.8 Hz, 1H), 3.72 (dd, H-4, J 6.8, 9.3 Hz, 1H), 3.53 (tr, H-5, 9.2 Hz, 1H), 1.6-1.0 (m, CH_2, iPr, 38H), 0.92 (s, Bu, 9H), 0.13, 0.02 (each s, Me, 3H)
9. **8a**: ^{1}H NMR ($CDCl_3$) δ 4.86, 4.76 (each d, CH_2, 2H), 4.43 (dd, 1H, H-2, J 3.5, 5.1 Hz), 3.99 (dd, H-1, J 5.2, 6.8 Hz, 1H), 3.74 (m, 3H), 3.50 (tr, H-5, J 6.8 Hz, 1H), 3.45 (s, Me, 3H), 1.6 (br m), 1.40 (br m), 1.25 (m, 2H), 1.05 (m, 38H); ^{13}C NMR ($CDCl_3$) δ 110.4 (C_q), 98.3 (OCH_2), 80.9, 79.6, 79.3, 77.1, 75.1, 69.3 (CH-inositol), 55.7 (OMe), 37.9, 35.2, 24.9, 23.9 (CH-isopropyl), 17.3-16.9 (5 peaks, CH_2), 12.7, 12.6,

12.8, 11.8 (Me); $[\alpha]_D^{20}$ +7.5° (c 4.2, $CHCl_3$); **8b**: $[\alpha]_D^{20}$ -7.9° (c 4.2, $CHCl_3$).

10. **9a**: $[\alpha]_D^{20}$ -20.5° (c 4.4, MeOH); ^1H NMR (CD_3OD) δ 4.85 (m, CH_2O), 4.35 (dd, H-2, J 4.0, 5.2 Hz, 1H), 3.93 (dd, H-1, J 5.2, 7.5 Hz, 1H), 3.78 (dd, H-3, J 4.0, 9.2 Hz, 1H), 3.61 (tr, H-4, J 9.0 Hz, 1H), 3.58 (dd, H-6, J 7.5, 9.9 Hz, 1H), 3.45 (s, Me, 3H), 3.22 (dd, H-5, J 9.0, 9.9 Hz, 1H), 1.8-1.55 (m, CH_2, 10H); **9b**: $[\alpha]_D^{20}$ +15.5° (c 2.5, MeOH).
11. Exhaustive methoxymethylation of **5a** followed by deacylation produces enantiomerically pure 1-alcohol suitable for phosphorylation.
12. **11a** (from **7a**), $[\alpha]_D^{20}$ +31.3° (c 2.6, H_2O, as pentahydrate of hexasodium salt, calculated for acid form), lit.[13] +35°; ^{31}P NMR (D_2O, acid form) δ -0.6, -1.0, -1.7 ppm; ^1H NMR (D_2O, acid form) δ 4.23 (dtr, H-4, J 9.1Hz, 1H), 4.15 (tr, H-2, J 2.8 Hz, 1H), 3.96 (m, H-1, H-5, 2H), 3.76 (tr, H-6, J 9.5 Hz, 1H), 3.59 (dd, H-3, J 2.7, 9.8 Hz, 1H); **11b**: $[\alpha]_D^{20}$ -30.5° (c 1.3, H_2O), lit. [13] -30°; ^1H and ^{31}P NMR spectra were essentially the same as those of **11a**.
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