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-cyclohexyldiene-myoinositol. These derivatives are formed as a mixture, and thus have to be separated by a combination of crystallization and chromatographic techniques, making their availability difficult. In contrast, cis-monoacetals of myo-inositol are synthesized in one step in good yield. Recently we have found that cis-monoacetals can be selectively protected at the 1-hydroxyl group with bulky acylating or silylating reagents. 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 (IP3), phosphatidylinositol (PI), and phosphatidylinositol-4,5-bisphosphate (PIP2). 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 (TBDMSCl) in pyridine and subsequent chlorination of the resulting silyl ester 2 with oxalyl chloride/DMF afforded 2-(tert-butyldimethylsilyloxy)phenylacetyl chloride (3).

\[
\begin{align*}
1 & \xrightarrow{i} \text{Ph} \xrightarrow{\text{Ph}} \text{HOOC} \xrightarrow{\text{H}} \text{OH} \\
& \text{TBDMSCl} \xrightarrow{\text{Py}} \text{Ph} \xrightarrow{\text{OSi/TBDM}} \text{H} \\
& \text{Cl} \xrightarrow{\text{OSi/TBDM}} \text{Ph} \\
\end{align*}
\]

Reaction of cyclohexylidene-myoinositol (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. However, simple precipitation from ether-hexane afforded one of the isomers 5a with >96% d.e. 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-diisopropylsiloxane 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: Rp 0.18; 7b: Rp 0.13).8 The isomers of 7 were converted into functionally useful enantiomeric alcohols 89 by deacylation at the 1-position with methylamine (83%), and subsequently into triols 910 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 and 8), 6-glycosylated phosphatidylinositol (from 6), and PIP2 (from 8), in addition to the synthesis of IP3 described below. The synthesis of various phosphorothioate analogs, and unsaturated fatty acid-containing inositol phospholipids should also be possible.

\[
\begin{align*}
\text{4} & \xrightarrow{i} \text{5} & \xrightarrow{ii} \text{6} \\
\text{7a, 7b} & \xrightarrow{iv} \text{8a, 8b} & \xrightarrow{v} \text{9a, 9b} \\
\text{10a, 10b} & \xrightarrow{vi, vii} \xrightarrow{viii} \text{11a, 11b}
\end{align*}
\]

\[
\begin{align*}
R^1 & = \text{OSiTBDMS} & R^2 & = \text{-Si(iPr)}_2-O-Si(iPr)_2 \quad R^3 & = \text{-PO(OBn)}_2 & R^4 & = \text{-OPO}_3H_2 \\
i & : 3\text{Py} & ii & : \text{Cl-Si(iPr)}_2-O-Si(iPr)_2-Cl & iii & : \text{ClCH}_2\text{OMe/iPr}_2\text{EtN, separation; iv: MeNH}_2 & v & : \text{Bu}_4\text{N}^+, F^- & vi & : \text{(BnO)}_2\text{P(O)NiPr}_2\text{tetrazole; vii: MCPBA; viii: H}_2\text{Pd}
\end{align*}
\]

The utility of synthesized compounds as phosphoinositides precursors was demonstrated by the synthesis of L- and D-IP3 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 IP3. 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 H₂/Pd in methanol and subsequent spontaneous cleavage of inositol protecting groups during hydrolysis afforded IP₃ (11). The synthesis starting from the crystalline triol 5a produced enantiomerically pure L-myoinositol-1,4,5-trisphosphate (11a). D-IP₃ (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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References and Notes:


6. Reagent 3 was sufficiently pure in a crude form; ¹H NMR (CDCl₃) 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: ¹H NMR (CD₃OD) 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, CH₂, 10H), 0.92 (s, Bu, 9H), 0.14, 0.05 (s, Me, 3H).

8. 7a: ¹H NMR (CDCl₃) 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, CH₂, 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, CH₂, 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, CH₂, 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, CH₂, iPr, 38H), 0.92 (s, Bu, 9H), 0.13, 0.02 (each s, Me, 3H).

9. 8a: ¹H NMR (CDCl₃) δ 4.86, 4.76 (each d, CH₂, 2H), 4.43 (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); ¹³C NMR (CDCl₃) δ 110.4 (Cq), 98.3 (OCH₂), 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, CH₂), 12.7, 12.6,
12.8, 11.8 (Me); [α]D$^20$ +7.5° (c 4.2, CHCl$_3$); 8b: [α]D$^20$ -7.9° (c 4.2, CHCl$_3$).

10. 9a: [α]D$^20$ -20.5° (c 4.4, MeOH); $^1$H NMR (CD$_3$OD) δ 4.85 (m, CH$_2$O), 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: [α]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), [α]D$^20$ +31.3° (c 2.6, H$_2$O, as pentahydrate of hexasodium salt, calculated for acid form), lit.$^{13}$ +35°; $^{31}$P NMR (D$_2$O, acid form) δ -0.6, -1.0, -1.7 ppm; $^1$H NMR (D$_2$O, 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: [α]D$^20$ -30.5° (c 1.3, H$_2$O), lit.$^{13}$ -30°; $^1$H and $^{31}$P NMR spectra were essentially the same as those of 11a.


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