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A stannylene strategy for regioselective acylation and phosphorylation of 1,2-cyclohexylidene-*myo*-inositol. Its convenient resolution and phosphatidylinositol synthesis

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Abstract—The bis(dibutylstannylene) derivative of 1,2-cyclohexylidene-*myo*-inositol reacted with (*S*)-*O*-acetylmandeloyl chloride and diphosphate tetraesters to give 3,6-dimandelate and 3-phosphate, respectively. Using the stannylene methodology for the optical resolution and regioselective phosphorylation of the ketal, a concise synthesis of phosphatidylinositol with the natural configuration was accomplished.

Synthesis of various inositol derivatives including physiologically important inositol phosphates and phosphatidylinositols has been reported.[1] For this purpose, many new synthetic methodologies have been developed.[2] However, synthetic efficiency is still unsatisfactory, mainly because of tedious protection–deprotection procedures. To overcome this drawback, chemo- and regioselective reactions of a minimally protected derivative are required. In light of this consideration, we have investigated selective reactions of 1,2-*O*-cyclohexylidene-*myo*-inositol **1**, which can be readily obtained by ketalization of *myo*-inositol in good yield.[3] According to literatures concerning the reaction of 1,2-ketals (such as **1** and camphor ketal) with electrophiles, selectivity varied with the nature of electrophiles, and often the yields were relatively low.[4] We herein report the optical resolution and phosphorylation of **1** via tin-mediated regioselective acylation with *O*-acetylmandeloyl chloride and phosphorylation with tetraalkyl pyrophosphate. The utility of these results has been exemplified by rapid synthesis of phosphatidylinositol.

The reaction of cyclohexylidene ketal **1** with (*S*)-*O*-acetylmandeloyl chloride **2** (1.2 equiv) in pyridine at −42 °C gave the expected 3-*O*-acylated product **5** as a diastereomeric mixture in 35% yield,[4a,b] accompanied with many other products as analyzed by TLC and NMR. A second mandeloylation of the product did not take place selectively, yielding a complex mixture. The result was different from that obtained by the reaction of camphor ketal with pivaloyl chloride, where the 3,5-diacyl product was obtained in a moderate yield.[4c] We then turned our attention to employ a stannylene derivative, which may be prepared in situ by the reaction of **1** with 2.2 equiv of dibutyltin oxide in toluene under refluxing conditions. A putative distannylene derivative of **1** thus formed was then treated in situ in CH_2Cl_2 with 2.5 equiv of the chloride **2** and subsequently quenched with 3-(dimethylamino)propylamine for easy removal of the remaining chloride. Three diastereomeric products of the reaction were separated easily by a flash silica gel column chromatography, since they had quite different R_f values. One of them was confirmed to be 3,6-diacylated L-*myo*-inositol L-**3** [42% yield, $R_f = 0.35$ (AcOEt/C_6H_6 1:1)] and it was the only product with the L-form.[5] As to a D-series of *myo*-inositol, 3-*O*-monoacyl derivative D-**5** (20%, 0.10) as well as diacyl D-**4** (10%, 0.55) was isolated. When the reaction solvent was toluene, diacylation proceeded smoothly with decrease in yield of mono acylation products. However, the diacyl derivatives obtained were contaminated with small amounts of other positional isomers (Scheme 1).

Di- and monomandelates thus isolated were transformed by hydrazinolysis to optically pure D- and L-1,2-cyclohexylidene ketals D-**1** and L-**1** in quantitative

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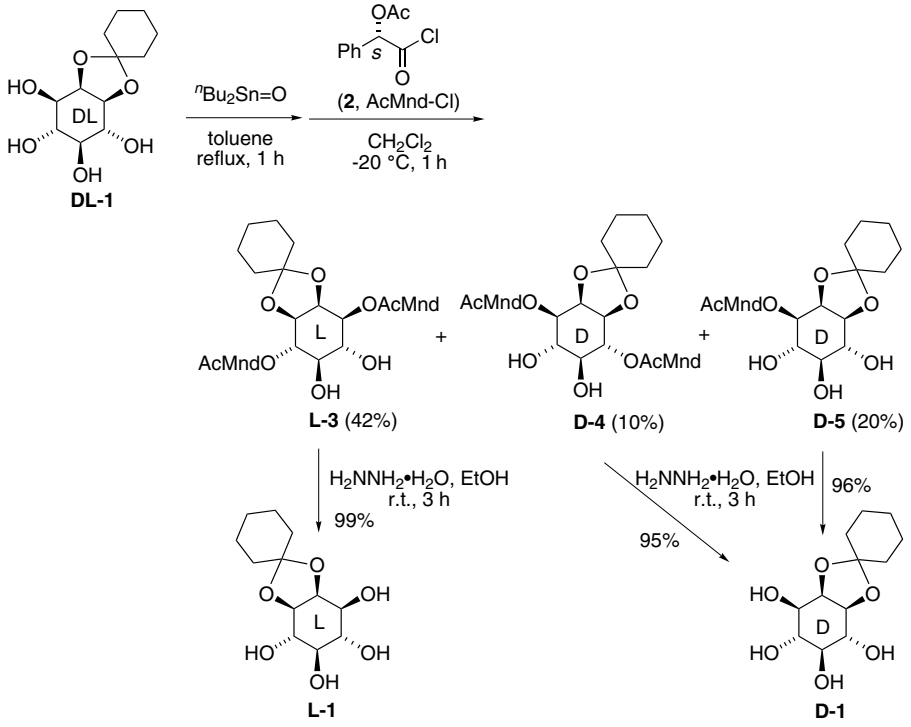
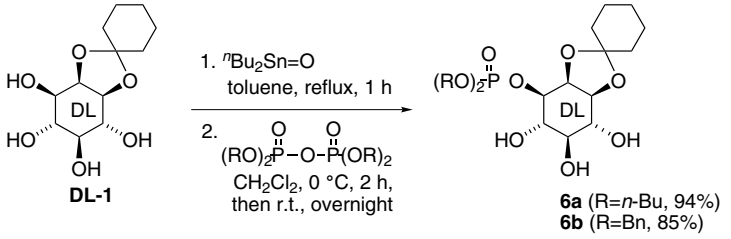


Scheme 1. Optical resolution of cyclohexylidene-*myo*-inositol via mandeloylation of the stannylene intermediate.

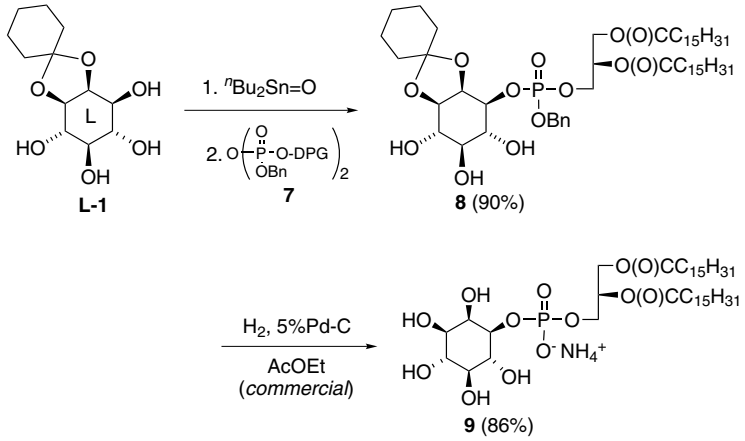
yields, respectively. A mixture of D-series of the diacyl and monoacyl derivatives was also converted to the homochiral ketal D-**1**.[5] Consequently, this chemical procedure provides a facile method for the preparation of the synthetically important intermediate, chiral monoketal. An optical resolution of the ketal **1** itself has been only accomplished so far by the enzymatic process[6] and chemical method.[4a]

Regioselective phosphorylation of cyclohexylidene ketal **1** via the same strategy as above was investigated. The reaction of the stannylene derivative with dibutyl phosphorobromidate yielded messy products consisting of mono-, bis-, and trisphosphates, contrary to the case of the mandeloylation using the acid chloride. According to the literature, stannylene dialkoxide and tin alkoxide derived from vicinal triol or tetrol in a trisaccharide reacted regioselectively with dibenzyl phosphoriodidate.[7] In order to decrease the reactivity of the phosphorylation reagent, we then chose a phosphoric anhydride. The reaction employing tetrabutyl and tetrabenzyl diphosphates (pyrophosphates) was dramatically regulated and selectively gave 3-*O*-phosphates **6** in high yields. It should be noted that, even though 4 M equiv of tetrabutyl pyrophosphate were used, the monophosphate **6a** was also obtained in very good yield (95%), accompanied with no other products. The phosphorylation position was confirmed by the coupling multiplicity of the H-3 methine proton (Scheme 2).[8]

The tin-mediated electrophilic substitutions, mainly alkylation, acylation, and silylation are synthetically useful tools.[9] The stannylene intermediate has been often utilized for the mono-substitution of a vicinal diol derivative, however, polyols are little used.[10] The stannylene strategy has now been shown to be satisfactory for regioselective and high yield substitution reactions such as acylation and phosphorylation of tetrol, 1,2-cyclohexylidene-*myo*-inositol, while, in general, the selective reaction of vicinal polyols are difficult. Indeed, direct phosphorylation of the 1,2-ketal derived from *myo*-inositol and camphor with diethyl phosphorochloridate (1.1 equiv) in pyridine gave 3-*O*-phosphate in poor yield



Scheme 2. Selective phosphorylation via a stannylene route.



Scheme 3. Synthesis of phosphatidylinositol.

(20%).[4c] We also found that the reaction of **1** with dibutyl phosphorobromidate (1.5 equiv) in pyridine and CH_2Cl_2 (1:1) gave a mixture of 3-*O*-phosphate (42%) and 3,6-bisphosphate (11%).

Using these results, preparation of optically active phosphatidylinositol was explored. Thus, the stannylene derivative of L-**1** reacted smoothly with 1,2-di-*O*-palmitoyl-*sn*-glycerol diphosphate **7** to furnish 1-*O*-phosphate **8** in 90% yield. Hydrogenolysis of **8** by 5% Pd/C in commercial-grade ethyl acetate under a hydrogen atmosphere resulted in the global deprotection to form the final product **9**.[11] A trace of water in the AcOEt and its nonprotic medium is likely to promote the deketalization under co-operation with an acid catalyst of the deprotected phosphate group, as demonstrated in a similar compound where MeOH or aq MeOH in place of AcOEt retarded the deketalization and the debenzylated product was formed (Scheme 3).[12]

In conclusion, the stannylene strategy has been shown to provide a useful tool for the optical resolution and regioselective phosphorylation of a synthetically versatile intermediate, 1,2-cyclohexylidene-*myo*-inositol. These methodologies have enabled a practical synthesis of phosphatidylinositol. Transformation of the phosphorylation products such as **6** and **8** to phosphatidylinositol phosphates and inositol phosphates is now under investigation.

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Supplementary data

Experimental procedures and characterization data (partial) for compounds L-**3**, D-**4**, D-**5**, and **6a** (PDF). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.055.

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5. Optical purity and absolute configuration of all the three mandeloylation products were confirmed by transforming them individually to 1,4,5,6-tetra-*O*-benzoyl-*myo*-inositol via hydrazinolysis, benzoylation, and deketalization.[6a,b] The acylation products were shown to be isolated without contamination of other products.
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8. NMR Data of **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (6H, t, J = 6.8 Hz, CH_3), 1.39–1.47 (4H, complex, *n*-BuH_3), 1.50–1.75 (4H, complex, *n*-BuH_2), 1.22–1.75 (10H, m, cyclohexylidene H), 3.33 (1H, t, J_{H5-H6}=J_{H6-H5} = 9.6 Hz, $InsH_5$), 3.68 (1H, dd, J_{H6-H1} = 7.6 Hz, J_{H6-H5} = 9.6 Hz, $InsH_6$), 3.92 (1H, t, J_{H4-H3} = J_{H4-H5} = 9.6 Hz, $InsH_4$), 4.04 (1H, dd, J_{H1-H6} = 7.6 Hz, J_{H1-H2} = 4.4 Hz, $InsH_1$), 4.16–4.19 (4H, complex, *n*-BuH_1), 4.44 (1H, td, J_{H3-H4} = J_{H3-P} = 9.6 Hz, J_{H3-H2} = 4.4 Hz, $InsH_3$), 4.47 (1H, t, J_{H2-H3} = J_{H3-H2} = 4.4 Hz, $InsH_2$); ^{31}P NMR (162 MHz, $CDCl_3$) δ −0.24. NMR data of **6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (2H, br), 1.55 (6H, br), 1.78 (2H, br) (cyclohexylidene H), 3.26 (1H, t, J_{H5-H6} = J_{H5-H4} = 9.6 Hz,

$InsH_5$), 3.64 (1H, dd, J_{H6-H5} = 9.6 Hz, J_{H6-H1} = 7.6 Hz, $InsH_6$), 3.90 (1H, t, $J_{H4-H5} = J_{H4-H3}$ = 9.6 Hz, $InsH_4$), 4.02 (1H, dd, J_{H1-H6} = 7.6 Hz, J_{H1-H2} = 4.4 Hz, $InsH_1$), 4.47 (1H, td, $J_{H3-H4} = J_{H3-P}$ = 9.6 Hz, J_{H3-H2} = 3.6 Hz, $InsH_3$), 4.50 (1H, dd, J_{H2-H3} = 3.6 Hz, J_{H2-H1} = 4.4 Hz, $InsH_2$), 5.09–5.22 (4H, complex, benzylic H), 7.32–7.45 (10H, complex, aromatic H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −1.25.

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11. Data of **9** (white solid): R_f = 0.61 ($CHCl_3$/MeOH/AcOH/acetone/H_2O, 60:15:13:12:8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (6H, t, J = 6.6 Hz, CH_3), 1.27 (48H, br s, CH_2), 1.50–1.68 (4H, complex, acyl H_β), 2.24–2.40 (4H, complex, acyl H_α), 3.39 (H, br, $InsH_5$), 3.59 (H, br, $InsH_4$), 3.66(H, br, $InsH_6$), 3.79 (H, br, $InsH_3$), 3.86–4.13 (4H, complex, Gly H_α and H_γ), 4.41 (H, br, $InsH_2$, $InsH_1$), 5.25 (H, complex, Gly H_β); ^{31}P NMR (162 MHz, $CDCl_3$) δ −0.09 (1P, br); MS-FAB(−) [glycerol/diethanolamine 1:1, M (free form of **9**) = $C_{41}H_{79}O_{13}P$] *m*/*z* 810 (M−H); $[\alpha]_D^{27}$ +62.2 (*c* 2.09, $CHCl_3$) {lit.[13] $[\alpha]_D^{20}$ +7.48 (*c* 0.3, $CHCl_3$)}.
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