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Synthesis of Optically Active 2,3,6-Tri-O- benzyl-D-*myo*-inositol from D-Glucose

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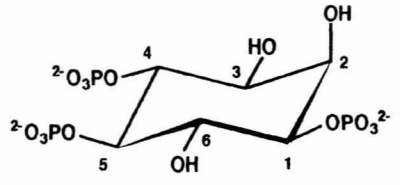
The title compound was synthesized from D-glucose as a key intermediate of D-Inositol-1,4,5-triphosphate synthesis without doing any optical resolution by utilizing C_2 symmetry.

Since the discovery of the role of D-*myo*-inositol 1,4,5-triphosphate(IP_3 ,**1**) as an intracellular second messenger for calcium mobilization,[1] a great biological interest in IP_3 has been increased. In order to explore the biochemical processes, a simple, general, and efficient methodology for chemical syntheses of IP_3, **1** and its derivatives is required. Up to date, for the synthesis of IP_3 and its derivatives, *myo*-inositol has been mainly used as a starting material. But previous methods have required a optical resolution. Here we now report a new strategy for synthesizing the partially-protected key intermediate, 2,3,6-tri-O-benzyl-*myo*-inositol(**2**)[2] from D-glucose.

Methyl 3,4-di-O-methoxymethyl-2,6-di-O-p-tolylsulfonyl-α−D-glucopyranoside(**3**) was prepared from D-glucose in 56 % yield (3 steps) (Scheme 1). 6-Deoxyhex-5-enopyranoside derivative(**4**) was synthesized by treatment of **3** with sodium iodide, tetrabutylammonium iodide, 1,8-diazabicyclo[5,4,0]undec-7-ene(DBU) and molecular sieves 4A in dimethyl sulfoxide(DMSO) at 80-110 °C (one pot reaction,[3] 63% yield). Detosylation of compound **4** followed by protection with benzyl group gave methyl 2-O-benzyl-6-deoxy-3,4-di-O-methoxymethyl-α−D-*xylo*-hex-5-enopyranoside (**5**) in 87% yield. Ferrier reaction [4] of **5** gave partially-protected 2,3,4,5-tetrahydroxycyclohexanone derivative(**6**) which was treated with acetic anhydride in pyridine to give the corresponding enone derivative (**7**) in 77% yield(2 steps). Reduction of **7** with sodium borohydride-celium chloride in ethanol, followed by benzylation of hydroxyl group gave protected cyclohexenol derivative[**8**: NMR ($CDCl_3$); δ 3.79 and 4.17 ppm (each dd, 4H, A_2B_2, J=5.1, 2.4 Hz), 5.73 (s, 2H)] in 89% yield (2 steps). Oxidation of compound **8**, which has C_2 symmetry axis, with osmium tetroxide gave partially protected *myo*-inositol derivative(**9**) in 83% yield. Regioselective protection of vicinal hydroxyl group by use of tris butyl stanyl oxide and methoxymethyl chloride, followed by benzylation of remaining hydroxyl group gave full



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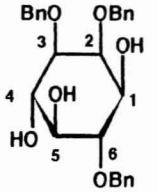

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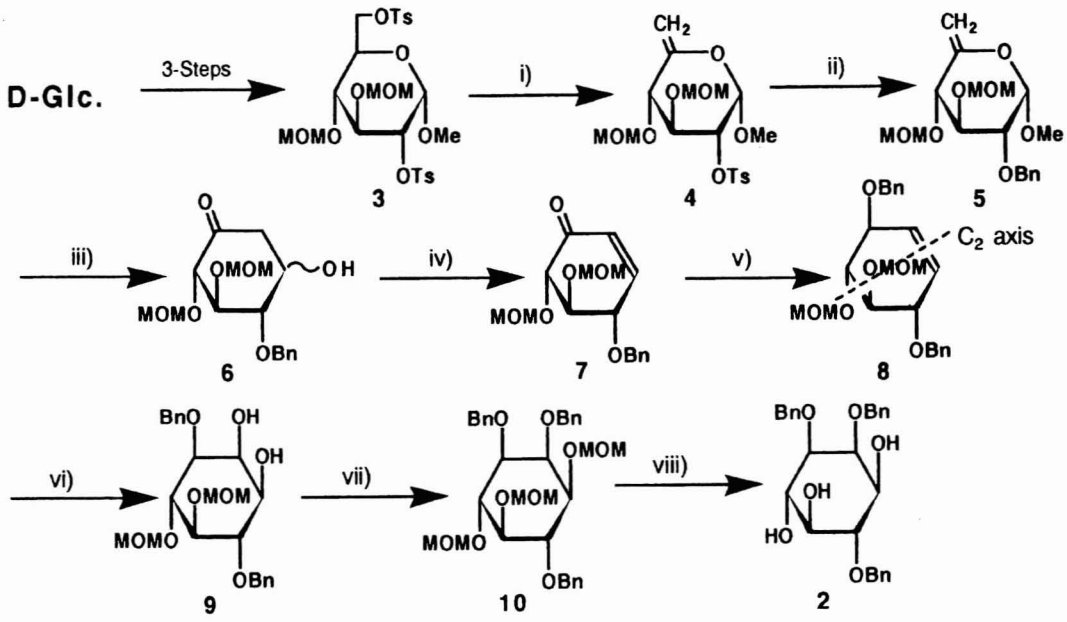
protected *myo*-inositol derivative [**10**: mp 70-72 °C (EtOH-hexane), $[\alpha]_D$ +8.6° (c 0.3, $CHCl_3$), NMR: δ 7.38-7.27(m, 15H, 3xPh), 4.94-4.58(m, 12H, 6x-CH_2-), 4.07(dd, $J_{4,3}$=$J_{4,5}$=9.5 Hz, H-4), 3.96(dd, $J_{2,1}$=2.4, $J_{2,3}$=2.0 Hz, H-2), 3.94(dd, $J_{6,1}$=$J_{6,5}$=9.8 Hz, H-6), 3.48(dd, H-1), 3.47(dd, H-5), 3.35(dd, H-3), 3.41, 3.39, and 3.30(each s, 3xOMe)] in 79% yield (2 steps). Hydrolytic removal of methoxymethyl group of **10** gave title compound 2,3,6-tri-O-benzyl-D-*myo*-inositol [**2**: mp 117-119 °C (EtOH-H_2O), $[\alpha]_D$ +12.4° (c 0.8,$CHCl_3$), lit.,[2] mp 117-119 °C, $[\alpha]_D$ + 15.5° ($CHCl_3$), NMR($CHCl_3$): δ 7.40-7.29(m, 15H, 3xPh), 4.97-4.55(m,6H, 3x-CH_2-), 4.08(dd, $J_{2,1}$=$J_{2,3}$=2.7, H-2), 4.01(ddd, $J_{4,3}$=$J_{4,5}$=9.8, $J_{4,OH}$=2.7 Hz, H-4), 3.68(dd, $J_{6,5}$=$J_{6,1}$=9.2 Hz, H-6), 3.52(ddd, $J_{1,OH}$=6.6 Hz, H-1), 3.47(ddd, $J_{5,OH}$=2.7 Hz, H-5), 3.29(dd, H-3), 2.65 and 2.61(each d, 2xOH), 2.34(d, OH)] in 90% yield. Thus the method proposed herein may promise a wide application to the preparation of inositol phosphate derivatives.



i) NaI,Bu_4NI,DBU / DMSO, 90 °C, 63%. ii) NaOMe / MeOH, NaH,BnBr / DMF 87%. iii) $Hg(OAc)_2$ / acetone-H_2O, reflux, 77%. iv) Ac_2O / pyridine, quantitative. $NaBH_4$, $CeCl_3$·$7H_2O$ / CH_2Cl_2-EtOH, -78 °C, 91% v) NaH,BnBr/ DMF, 98%. vi) OsO_4,NMO (4-methylmorpholine N-oxide) / acetone- H_2O, r.t 83%. vii) n-Bu_2SnO / C_6H_6, reflux, then MOMCl,Et_3N /C_6H_6, r.t, NaH,BnBr / DMF, 79%. viii) 0.1M HCl-MeOH, 63 °C, 90%

Scheme 1.

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