Highly Efficient Protection by the Tetraisopropyldisiloxane-1,3-diyl Group in the Synthesis of *myo*-Inositol Phosphates as Inositol 1,3,4,6-Tetrakisphosphate

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Regioselective introduction of the tetraisopropyldisiloxane-1,3-diyl group onto *myo*-inositol and 1,2-*O*-cyclohexylidene-*myo*-inositol realised the efficient synthesis of various *myo*-inositol phosphates.

In the field of inositol chemistry, the methodology for protection is problematic regarding selectivity and efficiency. In this communication, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPSCl)[1] is a promising protective agent for the synthesis of inositol phosphates which are involved in an intracellular signal transduction system.[2]

Treatment of *myo*-inositol (**1**) with TIPSCl (2.5 equiv.) in pyridine at room temperature afforded the regioselectively symmetrical bis(disiloxane) derivative (**3**) in 66% yield accompanied with no major amounts of other inositol derivatives. A similar type of protected inositol is difficult to obtain by a known method. On the other hand, 1,2-*O*-cyclohexylidene-*myo*-inositol (**2**) which is readily accessible from *myo*-inositol in one step,[3] was allowed to react with TIPSCl (1.2 equiv.) in pyridine at room temperature and product analysis showed exclusive formation of 3,4-TIPS ether (**4**) (90% yield). Thus, employment of TIPSCl realised a convenient and regio-selective protection of *myo*-inositol. The synthetic usefulness of two TIPS derivatives (**3**) and (**4**) is demonstrated by the preparation of some *myo*-inositol phosphates.

Bis(disiloxane) (**3**) was benzoylated in a boiling pyridine solution to give 2,5-dibenzoate (**5**) in 97% yield which was then converted to 1,3,4,6-tetrol (**6**) by treatment with aqueous HF solution in acetonitrile (96% yield). Phosphorylation of (**6**) was successfully carried out with the new reagent (**9**)[4] and subsequent oxidation with 3-chloroperoxybenzoic acid (*m*-CPBA) to afford tetraphosphate (**7**) in 94% yield which was in turn subjected to hydrogenolysis (H_2/5% Pd–C) and ammonolysis to give *myo*-inositol 1,3,4,6-tetrakisphosphate (**8**)[5] in 80% yield. Thus, the first synthesis of (**8**) has been accomplished conveniently.

Next (**4**) was utilised for the synthesis of *myo*-inositol 5-phosphate (**13**), which could not be prepared from the parent *myo*-inositol, by Angyal *et al.*[6] while they obtained it starting from 2-amino-2-deoxy-*neo*-inositol. Thus, selective benzoylation at C-6 in (**4**) was quite easily achieved by the conventional procedure to afford (**10**) in 71% yield. The remaining sterically hindered hydroxy group of (**10**) was then phosphorylated by successive addition of PCl_3, benzyl alcohol, and t-butyl hydroperoxide[7] to give the fully protected derivative (**11**) (quantitative yield) which was deblocked in four steps (ethylene glycol/*p*-$MeC_6H_4SO_2OH$ → Et_3NHF → H_2/5%-Pd–C → NH_3/MeOH) giving rise to (**13**) in 45% yield. On the

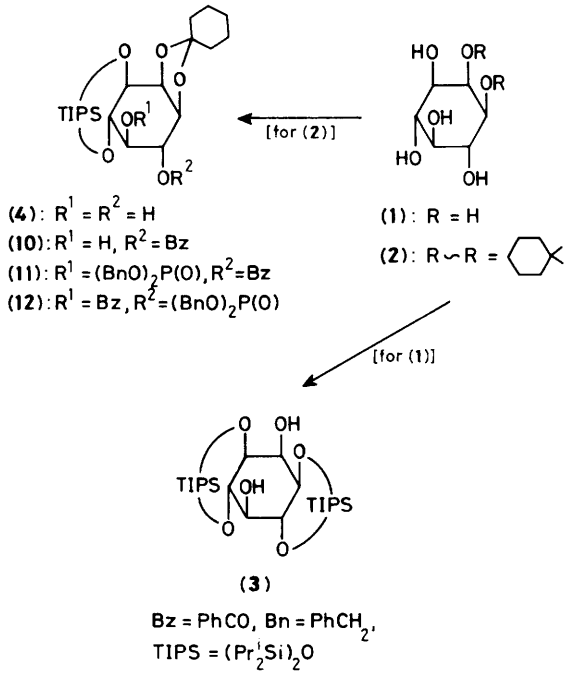

Figure 1

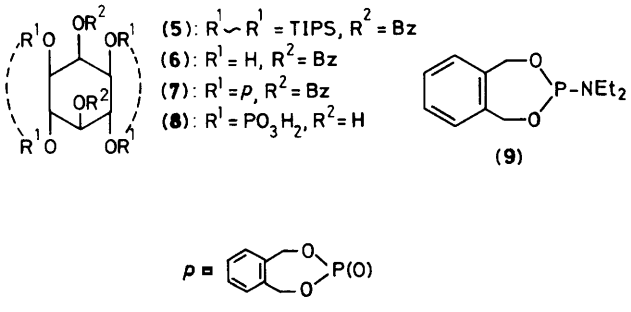

Figure 2

other hand, phosphorylation of monobenzoate (**10**) by the procedure using butyl-lithium and tetrabenzyl pyrophosphate[8] resulted in the formation of 6-phosphate derivative (**12**) (47% yield) which would be derived by migration of the benzoyl group from the C-6 position to C-5 and subsequent phosphorylation. The phosphate (**12**) was deblocked as above to give DL-*myo*-inositol 4-phosphate (**14**) (65% yield).

Dibenzoylation [BzCl/4-dimethylaminopyridine (DMAP), 88% yield] of the pivotal synthetic intermediate (**4**) followed by decyclohexylidenation as above (97% yield) afforded (**15**) which was selectively converted to 1-*l*-methoxyacetic ester (**16**)† in 83% yield. Benzoylation (97% yield) of (**16**) and subsequent removal of the menthoxyacetyl (NH_2NH_2, quantitative yield) and TIPS (Et_3NHF, 51% yield) groups gave 1,3,4-triol (**17**).

† It should be noted that optical resolution of (**15**) in preparative scale by means of a chiral column (Chiralcel OD purchased from Daicel Chemical Industries, Ltd.) was dramatically improved by diastereoisomeric derivatization to (**16**) (retention time: 4 and 24 min). This efficiency may be attributed to double chiral recognition.

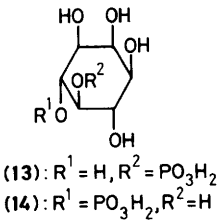

Figure 3

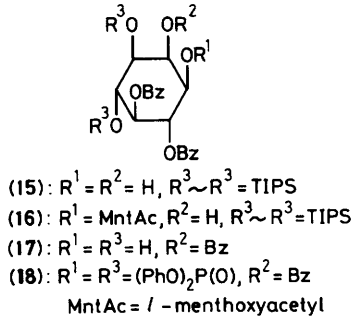

Figure 4

Phosphorylation of (**17**) was accomplished by successive treatment with diphenyl phosphorochloridite[8] in pyridine–tetrahydrofuran (THF) at −78 °C and t-butyl hydroperoxide to afford fully protected inositol 1,3,4-trisphosphate (**18**) in 66% yield.

In summary, the efficiency of TIPS ether derivatives in inositol chemistry was demonstrated.

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