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A VERSATILE INTERMEDIATE, D-4,5-BIS(DIBENZYL PHOSPHORYL)-MYO-INOSITOL DERIVATIVE FOR SYNTHESIS OF INOSITOL PHOSPHATES. SYNTHESIS OF 1,2-CYCLIC-4,5-, 1,4,5-, AND 2,4,5-TRISPHOSPHATE

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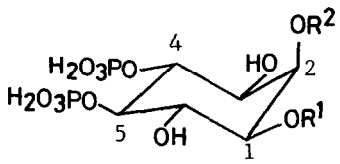
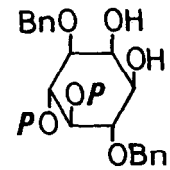
Abstract: Practical synthesis of D-myo-inositol 1,2-cyclic-4,5-, 1,4,5-, and 2,4,5-trisphosphate was accomplished from the key synthetic intermediate, D-3,6-di-O-benzyl-4,5-di-O-(dibenzyl phosphoryl)-myo-inositol.

Chemical synthesis of myo-inositol phosphates which are involved as metabolites in the intracellular signal transduction system[1] have been accomplished during these two years by several groups.[2] Dupont group reported very recently the short-step synthesis of some inositol phosphates.[2i] We have also continuously made efforts to explore practical syntheses of them. As a result, D-3,6-di-O-benzyl-4,5-di-O-(dibenzyl phosphoryl)-myo-inositol 4 have now been found to be a versatile synthetic intermediate which may be converted conveniently into various inositol phosphates. In this communication, we wish to report preparation of optically active 4 and its utility for synthesis of inositol 1,2-cyclic-4,5- 1, 1,4,5- 2, and 2,4,5-trisphosphate 3. There is no report on chemical synthesis of the cyclic derivative 1 which was suggested to have a role as a second messenger.[3]



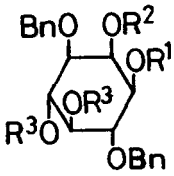
1: R^1~R^2 = P(O)OH
2: R^1 = PO_3H_2, R^2 = H
3: R^1 = H, R^2 = PO_3H_2



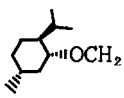
4: P = $(BnO)_2P(O)$
(Bn=benzyl)

Diol 5 which was readily derived from the parent myo-inositol in three steps[2a] was phosphorylated as reported from this laboratory[4] (n-BuLi/tetrabenzyl pyrophosphate, 81% yield for 6) followed by decyclohexylidenation (CF_3CO_2H/MeOH/rt, 85%) to afford racemic 4. Optical resolution of the racemate DL-4 was achieved by two methods, one[2a] of which involved separation of its diastereomeric 1-ℓ-menthoxyacetic esters by means of medium pressure silica gel column chromatography. The other employed a chiral column, Chiralcel OD® as reported in the preceding paper.[2j] The latter method was more convenient than the former in the present case. Optically active D- and L-1,2-diols thus resolved showed specific rotations $[\alpha]_D^{21}$ -21.4 and +21.0° (c=2.0, $CHCl_3$)

respectively and absolute configuration was confirmed by the following chemical transformation technique. Thus, optically pure menthoxyacetic ester 8 which was utilized for the synthesis[2a] of D-Ins(1,4,5)P_3 2 was benzoylated (BzCl/Py, 97% for 9), deallylated ($RhCl(PPh_3)_3$/DABCO, then 1N HCl/MeOH, 97% for 10) and phosphorylated (as above, 70%) to give bisphosphate 11. It should be noted that phosphorylation of 4,5-diol 10 using n-BuLi and pyrophosphate was achieved smoothly without injuring acyl groups at 1 and 2 positions. Ammonolysis (NH_3/MeOH, 71%) to remove two acyl groups gave 1,2-diol 4 which showed $[\alpha]_D^{18}$ -21.1° (c=1.9, $CHCl_3$). Consequently, absolute configuration of 4 thus resolved above was revealed.

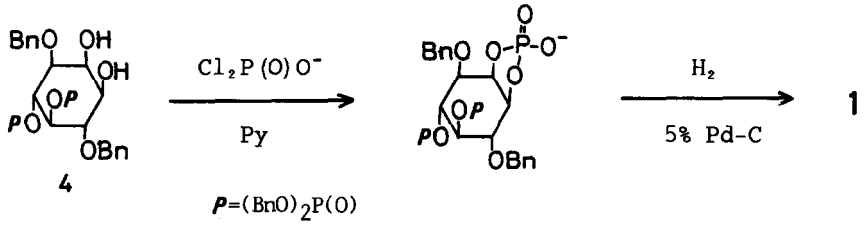


5: R^1~R^2 =  , R^3=H
6: R^1~R^2 = , R^3=$(BnO)_2P(O)$
7: R^1=MntAc, R^2=H, R^3=$(BnO)_2P(O)$
8: R^1=MntAc, R^2=H, R^3=All
9: R^1=MntAc, R^2=Bz, R^3=All
10: R^1=MntAc, R^2=Bz, R^3=H
11: R^1=MntAc, R^2=Bz, R^3=$(BnO)_2P(O)$

MntAc= 

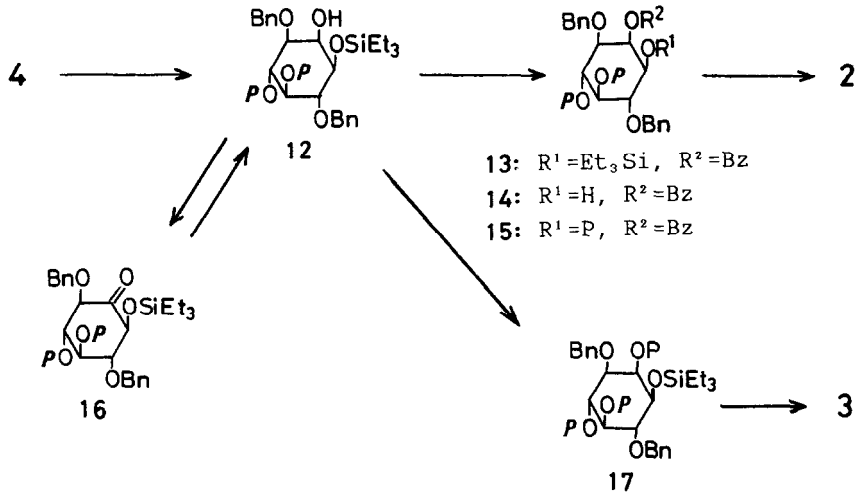
All=allyl, Bz=benzoyl

For the first time, the key intermediate 4 was utilized for the synthesis of cyclic trisphosphate 1. Thus, treatment of 4 at room temperature for 1h with N-methylpyridinium phosphorodichloridate[5] prepared in situ from methyl phosphorodichloridate and pyridine afforded 1,2-cyclic derivative in quantitative yield which was then subjected to deprotection at once (H_2/5% Pd-C/$AcONH_4$/rt/24h, quant.) to give the expected 1, $[\alpha]_D^{23}$ -11° (c=1.0, H_2O). The structure was confirmed by analysis of ^{1}H-, ^{13}C-, and ^{31}P-NMR. Synthetic 1 proved to be identical with natural 1 by HPLC analysis.[6]



Difference in reactivity of equatorially and axially disposed 1,2-cis hydroxyl groups of 4 enables selective introduction of the phosphoryl function at either position leading to Ins(1,4,5)P_3 2 or Ins(2,4,5)P_3 3. Thus, the intermediate 4 was utilized next for the synthesis of 2. Selective silylation at the C-1 position of racemic 4 (Et_3SiCl/Py, 95% for 12) followed by benzoylation (BzCl/DMAP/Py, 97% for 13) and desilylation (80% aq AcOH/TsOH/$CHCl_3$, 90%) gave 1-hydroxy derivative 14 which was then phosphorylated by the procedure using PCl_3, BnOH and t-BuO_2H successively to give the fully protected trisphosphate 15 in 85% yield. Deprotection in two steps (H_2/5% Pd-C then NH_4OH) gave Ins(1,4,5)P_3 2 quantitatively.

A radioactive substance is employed frequently for biological



investigation. In particular, isotopically labeled inositol phosphates are useful for detection of them since the corresponding natural phosphates are difficult to detect by usual methods.[7] As a preliminary experiment aiming at preparation of tritium-labeled inositol phosphates, oxidation and regeneration of the hydroxyl group on C-2 were examined. Thus, 12 was treated with DMSO and acetic anhydride in benzene under reflux to afford 2-oxo derivative 16 in 86% yield. Reduction of 16 with lithium borohydride in THF at -78 ℃ took place smoothly and 12 was obtained as a sole stereoisomer in 78% yield. The known methods using $LiAlH_4$[8] and $NaBH_4$[9] for reduction of the myo-inosose-2 derivatives gave the corresponding scyllo-inositol derivatives as a minor component. The present result suggests that the use of tritiated lithium borohydride might provide a convenient way to produce radio active inositol phosphates such as labeled 1 and 2.

Finally, 1,2-diol 4 was transformed to inositol 2,4,5-trisphosphate 3 by way of 1-triethylsilylated derivative 12 used for the synthesis of 2. Thus, 12 was phosphorylated by the method using PCl_3 described above to afford 17 in 84% yield which was then hydrogenolyzed by H_2/Pd-C in the presence of ammonium acetate in MeOH-H_2O (4:1) to give spontaneously Ins(2,4,5)P_3 3 as a result of concomitant removal of the silyl group under the hydrogenolysis conditions.

In conclusion, 3,6-di-O-benzyl-4,5-bis(dibenzyl phosphoryl)-myo-inositol 4 was shown to be a useful intermediate for the synthesis of myo-inositol phosphates. Further utilization of 4 for the synthesis of phospholipids is now under investigation.

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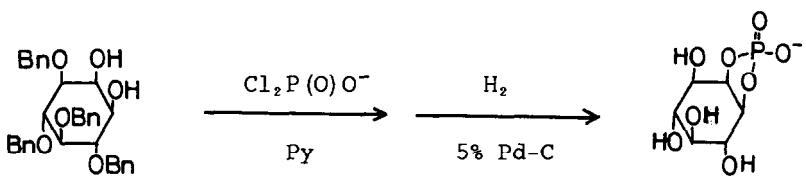

$[\alpha]_D^{23}$ -17° (c=1.0, H_2O)

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