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SYNTHESIS OF OPTICALLY ACTIVE PENTABENZYL ETHERS OF MYOINOSITOL. TOTAL SYNTHESIS OF PHOSPHATIDYLINOSITOL WITH NATURAL STRUCTURE

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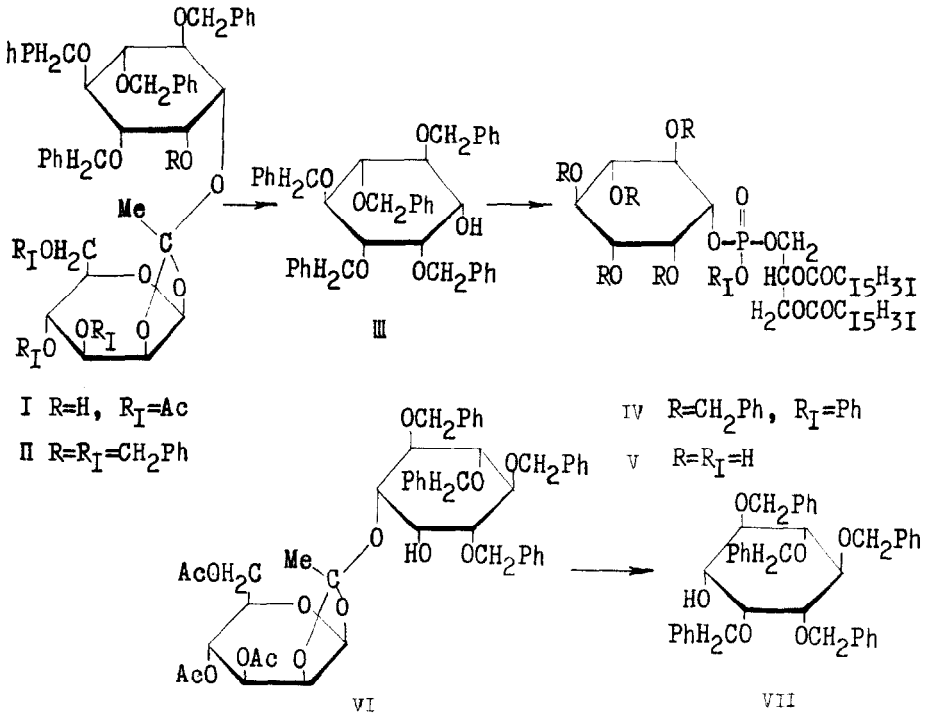
The structure, properties and biological functions of phosphoinositides are being extensively studied (1). Yet their chemical synthesis could not be effected owing to the lack of optically active derivatives of selectively protected myoinositol. The 1,2,4,5,6 - penta-O-benzoyl-sn-myoinositol (2) recently synthesized from quebrachitol (3) is only the enantiomer of the compound needed for the synthesis of phosphatidylinositol with natural structure whose phosphatidyl group is in the position 1 of myoinositol (4).

We have proposed a method for resolution of the asymmetrically substituted myoinositols to antipodes via diastereomeric orthoesters with D-mannose (5) and synthesized 3,4,5,6 - and 1,4,5,6 - tetra-O-benzyl-sn-myoinositols through corresponding orthoesters (I) and (VI). The introduction of the phosphate group into position 1 of 3,4,5,6 - tetra-O-benzyl-sn-myoinositol was hindered by the vicinal cis-OH group. The 2,3,4,5,6 - penta-O-benzyl-sn-myoinositol

(III) previously obtained (6) by resolution of the racemic 1,2,4,5, 6 - penta-O-benzylmyoinositol (7) proved to be more suitable for the synthesis of phosphatidylinositol. Starting from III we synthesized sn-myoinositol 1-phosphate (7), the structural component of natural phosphoinositides, identical to sn-myoinositol 1-phosphate from soy--bean (8).

This report deals with a novel synthesis of pentabenzyl ether III and its antipode (VII) using D-mannose orthoacetate both as an asymmetric reagent for resolution of 1,4,5,6 - tetra-O-benzylmyoinositol and as a temporary protection of the 1-OH group of the myoinositol molecule. The availability of III made it possible to use it in the unambiguous synthesis of optically active phosphatidylinositol (V).



Orthoester I, previously obtained on resolution of 1,4,5,6 - -tetra-O-benzylmyoinositol (5) was benzylated by benzyl chloride in the presence of alkali (100°, 8 hr) to obtain orthoester (II). Yield 71.4%, m.p.112-113° (ethanol) (9), $[\alpha]_D^{20}$ + 47.1° (c 0.15, chloroform). In IR spectrum of II absorption bands disappeared at 3560 cm^{-1} (OH) and 1750, 1730 cm^{-1} (C=O in acetates) whereas in NMR spectrum a proton singlet of the $C-CH_3$-group remained at δ 1.78 pointing to the retention of the orthoester group on benzylation. Hydrolysis of II (0.1N H_2SO_4 in 90% aqueous acetone, 2 hr, 20°) resulted in pentabenzyl ether III. Yield 91.6%, m.p. 59.2-60.2° (petroleum ether), $[\alpha]_D^{20}$ - 13.5° (c 0.3 chloroform). When the experiment was carried out without isolation of intermediate orthoester II the yield of III reached 75% on the starting orthoacetate I. Similarly orthoester VI (5) gave 1,2,4,5,6 - penta-O-benzyl-sn- -myoinositol (VII). Yield 50.3%, m.p. 58.8-60.0° (petroleum ether), $[\alpha]_D^{20}$ + 13.9° (c 0.3, chloroform). The melting point of the sample involving III and VII in equal amounts was 92-93.5°[that of the racemic modification being 93-94° (7)] . The evidence provided by TLC, IR spectra and optical rotatory dispersion curves of III and VII left no doubt about these substances being enantiomorphs.

The reaction of pentabenzyl ether III with dichlorophenylphosphate and 1,2-dipalmytoyl-sn-glycerol led to 1-O-[1',2'-dipalmytoyl- -sn- glyceryl-3'-(phenyl)-phosphoryl] -2,3,4,5,6-penta-O-benzyl- -sn-myoinositol (IV). Yield 32.2%, m.p. 53-54° (ethanol), $[\alpha]_D^{20}$ - 7.76° (c 1.4 chloroform). IR spectrum: 3090, 3060, 3030, 1590, 1490 cm^{-1} (benzene rings), 1740 cm^{-1} (C=O in COOR), 1210 cm^{-1} (P=O), 1025 cm^{-1} (C-O in P-O-C).

Hydrogenolysis of tertiary phosphate IV in the presence of Adams catalyst and palladium black gave 1-O-(1', 2'-dipalmytoyl-sn- -glyceryl-3'-phosphoryl)-sn-myoinositol (V) isolated in the form

of ammonium salt. Yield 48.5%, m.p. 169-172° (chloroform-acetone), $[\alpha]_D^{20}$ + 7.48° (c 0.3, chloroform). The chromatographic characteristics, the optical rotatory dispersion curve and the IR spectrum of V were rather similar to these of natural monophosphoinositides (10).

Compound V is the first synthetic optically active phosphatidylinositol with natural structure.

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