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SYNTHESIS OF FLUORODEOXYSCYLLOINOSITOL AND PHOSPHATIDYLFLUORODEOXYSCYLLOINOSITOL

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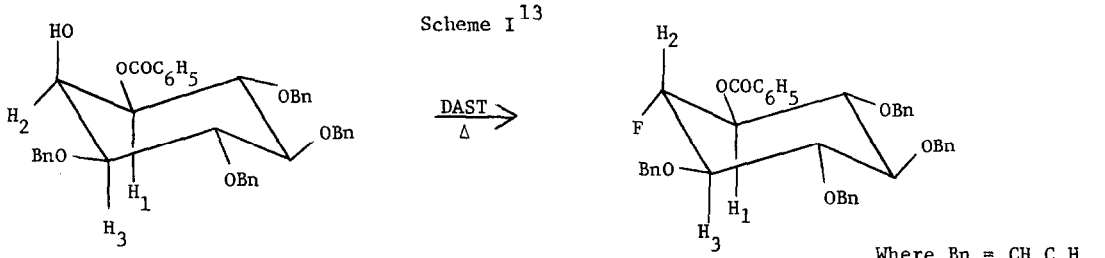
Summary: Synthesis of 1-fluoro-1-deoxyscylloinositol and 2-fluoro-2-deoxy-1-phosphatidylscylloinositol from myoinositol is described.

Inositol and phosphatidylinositol (PI) are receiving increasing attention as their role of importance in cellular metabolism[1] becomes more clearly recognized. PI has been implicated in playing specific roles in various cellular processes[2] such as Ca^{++}-mediated control of cell function, cell proliferation, initiation of the arachidonic acid cascade[3] and attachment of enzymes to plasma membranes. As was the case with carbohydrates where modified analogs were important in delineating functions of the parent substances in metabolism,[4,5] so too can the same be expected for inositol and PI. In contrast to the considerable interest directed toward synthesis and chemistry of fluorinated carbohydrates,[6,7] no fluoroinositols and phosphatidylfluoroinositols have been reported. We have synthesized 1-fluoro-1-deoxyscylloinositol (4) and 2-fluoro-2-deoxy-1-phosphatidylscylloinositol (6), molecules of similar steric bulk to myoinositol and PI but with significant polarity differences, as the first examples of fluorinated inositol and PI for biochemical studies.

DL-1-O-Benzoyl-3,4,5,6-tetra-O-benzylmyoinositol (1) was prepared from myoinositol in four steps as described previously.[8] When 1 was treated with diethylaminosulfur trifluoride (DAST)[9,10,11] under conventional conditions (CH_2Cl_2 solution, 0-25°C, aqueous workup), starting material was recovered intact despite formation of two labile esters before aqueous workup. However, under more drastic conditions (toluene solution, 70-80°C, aqueous workup), 1-O-benzoyl-2-fluoro-2-deoxy-3,4,5,6-tetra-O-benzylscylloinositol (2)[12] [mp 134.5-135.5°; m/e 646 (M^+), 555 ($M^+-CH_2C_6H_5$)] was isolated in 86% yield.

Scheme I[13]

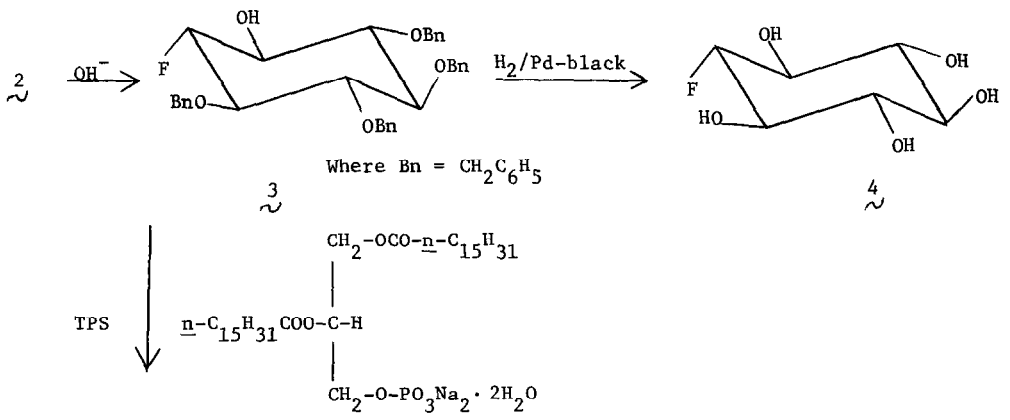


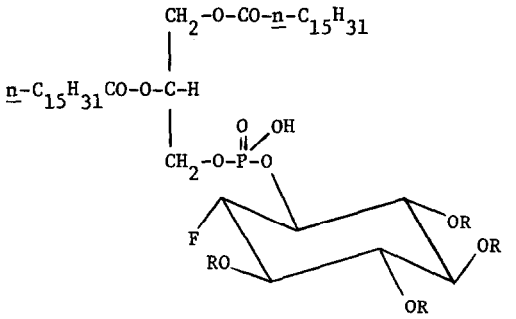
1 2

The structural assignment of 2 was based on analysis of its 300 MHz ^{1}H NMR spectrum and mass spectral data. That fluorination at C-2 resulted in inversion of configuration was readily shown by the coupling constants of vicinal protons at C-1 and C-3. The axial H-1 proton was observed at δ5.55 ppm (dt) with vicinal equatorial F-axial H coupling constant (13.5 Hz) and diaxial H-H coupling (9.5 Hz). The axial H-3 proton was centered at 3.82 ppm (dt) also with vicinal equatorial F-axial H coupling (13.0 Hz) and diaxial H-H coupling (9.2 Hz). The H-2 proton (4.62 ppm, dt) was judged to be axial on the basis of vicinal H-H coupling (9.2 Hz) and geminal F-H coupling (51 Hz).

Mild hydrolysis of 2 gave the fluorohydrin 3[12] [mp 113.5-114.5°; m/e 542 (M^+), 451 (M^+-$CH_2C_6H_5$)] in 95% yield. Debenzylation of 3 in aqueous ethanol in the presence of palladium black afforded 1-fluoro-1-deoxyscylloinositol (4)[12] [mp 250-253°; m/e 542 (penta-trimethylsilyl M^+), 527 (penta-TMS M^+-CH_3), 507 (penta-TMS M^+-CH_3-HF)] in quantitative yield after cation resin purification.

Scheme II





5: R = $CH_2C_6H_5$

6: R = H

Condensation of 3 with dipalmitoyl-L-α-phosphatidic acid disodium salt dihydrate in dry pyridine in the presence of large excess of triisopropylbenzenesulfonyl chloride (TPS) gave, after preparative tlc purification, a 72% yield of 5[14,15] [mp 90-93°; FD MS m/e 1211 (M^+ + K), 1195 (M^+ + Na), 1172 (M^+); Rf = 0.63 (silica gel; $CHCl_3$:MeOH:NH_4OH = 170:30:3)]. Hydrogenolysis of 5 gave 2-fluoro-2-deoxy-1-phosphatidylscyllоinositol (6)[15] [mp 191.5-194.5° (dec); m/e 1157 (penta-TMS M^+-CH_3); Rf = 0.36 for 6 and 0.24 for natural PI (silica gel; $CHCl_3$:MeOH:NH_4OH = 65:25:4)] in 80% yield.

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12. The 300 MHz NMR spectra of ring protons of 1, 2, and 3 ($CDCl_3$) as well as 4 (D_2O) were tabulated as follows:

	1	2	3	4
H-1	5.12 ppm (dd) 10; 2 Hz	5.55 (dt) 13; 9.5	3.74 (dtd) 13; 9; 2	3.67 (dt) 13; 9
H-2	4.43 (t) 2	4.62 (dt) 51; 9.2	4.42 (dt) 52; 9	4.29 (dt) 52; 10
H-3	3.63 (dd) 9.5; 2	3.82 (dt) 13; 9.2	3.57 (dt) 13; 9	3.67 (dt) 13; 9
H-4	4.01 (t) 9.5	3.64 (t) 9.0	3.57 (t) ~8	3.39 (m)
H-5	3.61 (t) 9.5	3.61 (t) 9.4	3.40 (t) 9.5	3.39 (m)
H-6	4.24 (t) 10.0	3.67 (t) 9.5	3.57 (t) ~8	3.39 (m)

13. For convenience, 1 is drawn with D-configuration for actual DL-form.

14. 5: 60 MHz NMR ($CDCl_3$) δ0.4-2.4 (m, 62 H, 2 x C_{15} H_{31}-), 3.0-5.6 (m, 19 H, CH_2-CH-CH_2, 6 x CH-ring, and 4 x $OCH_2C_6H_5$), and 7.2 ppm (s, 20 H, 4 x C_6H_5).

15. Successful mass spectral data were obtained only by field-desorption from 5 and only by low voltage electron impact on persilylated 6. We were not always successful in obtaining mass spectral data of PI and PI-tetrabenzyl ether analogs by conventional EI and/or FD means.

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