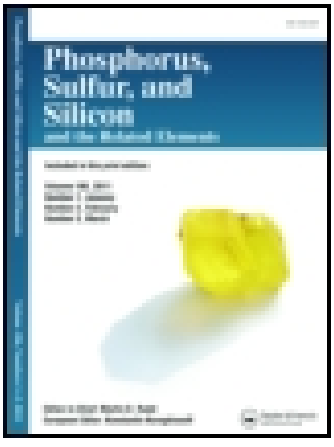

Phosphorus, Sulfur, and Silicon and the Related Elements

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SYNTHESIS OF 5-DEOXY-5,5-DIFLUORO-MYO-INOSITOL-1,2,6-TRIS(PHOSPHATE)

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SYNTHESIS OF 5-DEOXY-5,5-DIFLUORO-*MYO*-INOSITOL-1,2,6-TRIS(PHOSPHATE)

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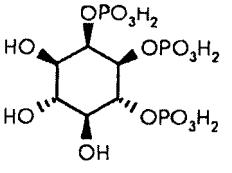
5-deoxy-5,5-difluoro-*myo*-inositol-1,2,6-tris(phosphate), a fluorinated analogue of α-trinositol, (D-*myo*-inositol-1,2,6-tris(phosphate)) was prepared from *myo*-inositol. After selective protection the remaining hydroxyl in position 5 was oxidized by a Swern type reaction and transformed in a *gem*-difluoro derivative by action of DAST. Phosphorylation proceeded through an intermediate phosphite. Mild hydrogenolysis gave the expected final compound.

Keywords: Inositol-phosphates; α-trinositol; fluoro derivative

INTRODUCTION

α-Trinositol, (D-*myo*-inositol-1,2,6-tris(phosphate)), **1** is obtained in large scale by Baker's yeast digestion of phytic acid.[1] This compound possesses interesting analgesic and anti-inflammatory properties.[2,3]



1

The structure-activity relationships have shown the importance of the three charged phosphates. Previous studies have demonstrated that the behavior of the phosphate groups largely depends on the number and relative positions of the functional groups around the inositol cycle.[4–9] Particularly, the ionization state of each phosphate, determined by ^{31}P-NMR, seems to be influenced by the neighboring groups.[6,10] Significant cooperativity is observed between vicinal phosphates[5] and a noticable stabilization seems due to the proximal hydroxyl function involving possible hydrogen bonds.[11,12]

According to these observations it was of interest to prepare fluorinated derivatives of α-trinositol. Such an isosteric replacement leads to compounds which are only able to accept a hydrogen bond compared to the initial hydroxyl which can either accept or donate hydrogen bonds. This isosteric replacement could provide interesting information concerning the type of stabilization induced by the proximal hydroxyl group of α-trinositol.

We wish to report, here, the synthesis of 5-deoxy-5,5-difluoro-*myo*-inositol-1,2,6-tris(phosphate) **2**. Its potentiometric and ^{31}P-NMR analyses were compared with those of the parent α-trinositol **1** (see following article).

SYNTHESIS

The starting material for this synthesis was 1,2–5,6-di-*O*-cyclohexylidene-*myo*-inositol **3**. This derivative was obtained from *myo*-inositol by well known methods.[13,14] The two last free hydroxyls of **3** were protected as benzyl ethers by treatment with NaH and benzyl bromide leading to the totally protected compound **4**. The *trans* cyclohexylidene group in position 5 and 6 was selectively removed by a mild hydrolysis catalyzed by *p*TsOH[15] yielding the derivative **5**. Treatment of **5** with Bu_2SnO generated an intermediate stanyl acetal[16,17] which was opened by means of *p*-methoxybenzyl chlorid to achieve a monoprotection at position 6. Compound **6**, bearing a free hydroxyl in position 5 was oxidized according to a Swern type reaction[18] to give the inosose **7**. The *gem*-difluoro was formed by treatment of the carbonyl group of **7** with DAST[19] (compound **8**). The next step was the simultaneous deprotection of the *cis* acetal in position 1 and 2 and the *p*-methoxybenzyl ether in position 6 in acidic medium.[20] This deprotection furnished derivative **9** with three free hydroxyls in positions 1, 2 and, 6. These hydroxyls were phosphorylated in a two step one pot procedure by initial treatment with diethylamino-1,3,2-benzodioxaphosphepane to give a tris(phosphite) intermediate which was, then, oxidized to tris(phosphate) **10** by means of *m*-CPBA.[21,22]

The final step of the synthesis was the total deprotection of the molecule by mild hydogenolysis catalyzed by Pd on charcoal leading to the expected compound **2** which was stabilized as cyclohexylammonium until usage for physicochemical investigations.

EXPERIMENTAL PART

General methods

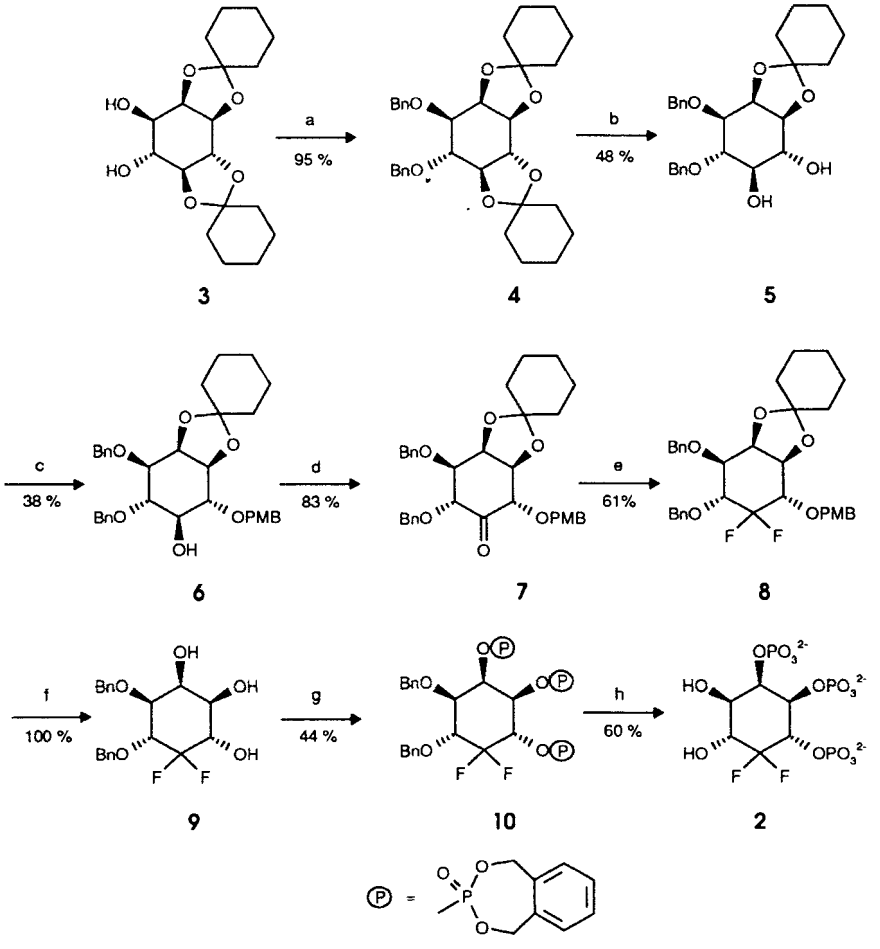
Melting points were measured on a Mettler PF62 apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance DPX 300 MHz spectrometer using the δ scale. Coupling constants are given in Hz. Column chromatographies were performed with silica gel 60 (Merck).

(±)-3,4-Di-O-benzyl-1,2–5,6-di-O-isopropylidene-myo-inositol 4

Diol **3** (3.0 g; 9.36 mmol) was dissolved in anhydrous DMF (50 ml) and cooled to 0°C. NaH suspension (1.12 g; 60%; 28.1 mmol) and benzyl bromide (3.34 ml; 28.1 mmol) were added. The reaction mixture was kept at room temperature overnight, precipitated in water and extracted with ethyl acetate (2 × 50 ml). The organic layer was washed with water (3 × 20 ml), dried over Na_2SO_4, filtered and the solvent was evaporated. The crude product was purified by column chromatography eluted with ether/hexane, 1:6. The dibenzylated compound was obtained in 95% yield (4.63 g). ^{1}H-NMR ($CDCl_3$): 7.5–7.1 (*m*, 10H, -(C_6H_5)$_2$); $\overline{4.68}$ (*AB*, $\Delta\delta$= 0.06, J_{AB} = 12.0, 2H, -CH_2-C_6H_5); $\overline{4.60}$ (*AB*, $\Delta\delta$ = 0.14, J_{AB} = 12.0, 2H, -CH_2-C_6H_5); 4.38 (*dd*, ^{3}J = 6.9 and ^{3}J = 3.7, 1H, H_2); 4.31 (*t*, ^{3}J = 6.6, 1H, H_3); 4.13 (*dd*, ^{3}J = 10.6 and ^{3}J = 6.9, 1H, H_4); 3.88 (*dd*, ^{3}J = 7.8 and ^{3}J = 2.7, 1H, H_6); 3.77 (*t*, ^{3}J = 3.1, 1H, H_1); 3.51 (*dd*, ^{3}J = 10.6 and ^{3}J = 7.7, 1H, H_5); 2.0–1.2 (*m*, 20H, -(C_6H_{10})$_2$).

(±)-3,4-Di-O-benzyl-1,2-O-cyclohexylidene-myo-inositol 5

The di-*O*-cyclohexylidene (3.75 g; 11.7 mmol) was dissolved in a mixture of acetone (60 ml) and water (2 ml). *p*TSOH was added till pH = 1. After 45 min stirring at room temperature the reaction mixture was neutralized with triethylamine. The solvents were evaporated. The residue was redissolved in CH_2Cl_2 and filtered in vacuo. The expected diol was precipitated in a mixture of ether/petrol ether (1.53 g, yield = 48%). mp 117°C. ^{1}H-NMR ($CDCl_3$/C_6D_6, 4:1): 7.5–7.1 (*m*, 10H, -(C_6H_5)$_2$); $\overline{4.86}$ (*AB*, $\Delta\delta$ = 0.30, J_{AB} = 11.3, 2H, -CH_2-C_6H_5);



SCHEME 1 Bn = $CH_2C_6h_5$; PMB = *p*-methoxybenzyl; **a**: NaH, BnBr, DMF; **b**: *p*TsOH, acetone, H_2O; **c**: Bu_2SnO, $BrNBu_4$, ClPMB; **d**: DMSO-acetic anhydride (3:2); **e**: DAST, toluene; **f**: EtOH-HCl 1N (2:1), reflux; **g**: 3-diethylamino-2,4,3-benzodioxaphosphepane, tetrazole, CH_3CN-CH_2Cl_2 then, *m*CPBA, CH_2Cl_2; **h**: h_2, Pd/C 10%, ethanol-CH_2Cl_2-water (2:2:1), then, $C_6H_{11}NH_2$.

4.77 (*s*, 2H, -CH_2-C_6H_5); 4.22 (*dd*, ^3J = 4.9 and ^3J = 3.7, 1H, H_2); 3.83 (*dd*, ^3J = 7.4 and ^3J = 5.2, 1H, H_3); 3.71 (*t*, ^3J = 8.3, 1H, H_4); 3.69 (*ddd*, ^3J = 9.8, ^3J = 7.1 and ^3J = 2.3, 1H, H_5); 3.61 (*dd*, ^3J = 8.3 and ^3J = 4.1, 1H, H_1); 3.23 (*ddd*, ^3J = 10.2, ^3J = 8.3 and ^3J = 2.3, 1H, H_6); 2.54 (*d*, ^3J = 2.3, 1H, OH_6); 2.52 (*d*, ^3J = 2.3, 1H, OH_5); 2.0–1.0 (*m*, 10H, -C_6H_{10}).

(±)-3,4-Di-O-benzyl-6-O-p-methoxybenzyl-1,2-O-cyclohexylidene-myo-inositol 6

Using a soxhlet filled with 3 Å molecular sieves, the diol (1.0 g; 2.27 mmol), dibutyltinoxide (850 mg; 3.4 mmol) and tetrabutylammonium bromide (732 mg; 2.27 mmol) in toluene were refluxed for 1 h. *p*-Methoxybenzylchloride (1.54 ml; 11.35 mmol) was slowly added and reflux was maintained for 48 h. After cooling to room temperature the reaction mixture was evaporated to dryness and dissolved in a mixture of, CH_2Cl_2 /H_2O, washed with saturated $NaHCO_3$ water. The tin salts were filtered of. The organic layer was dried over Na_2SO_4, filtered and the solvents were evaporated. The crude product was purified by column chromatography eluted with ether/hexane 2:3 giving 491 mg of **6** as an oil (yield = 38%) ^{1}H-NMR ($CDCl_3$): 7.5–6.7 (*m*, 14H, -(CH_2-C_6H_5)$_2$ and -CH_2-(C_6H_4)-OCH_3); 5.0–4.6 (*m*, 6H, -(CH_2-C_6H_5)$_2$ and -CH_2-(C_6H_4)-OCH_3); 4.34 (*dd*, ^{3}J = 6.0 and ^{3}J = 3.8, 1H, H_2); 4.12 (*dd*, ^{3}J = 7.0 and ^{3}J = 5.8, 1H, H_1); 3.9–3.8 (*m*, 4H, containing at 3.82 (*s*, 3H, -OCH_3) and 1H, H_4); 3.73 (*dd*, ^{3}J = 7.9 and ^{3}J = 3.8, 1H, H_3); 3.72 (*dd*, ^{3}J = 9.8 and ^{3}J = 7.0, 1H, H_6); 3.52 (*dd*, ^{3}J = 9.8 and ^{3}J = 7.9, 1H, H_5); 2.52 (*s*, ^{3}J = 2.3, 1H, O*H*); 2.0–1.0 (*m*, 10H, C_6H_{10}).

(±)-3,4-Di-O-benzyl-6-O-p-methoxybenzyl-1,2-O-cyclohexylidene-myo-inosose 7

The alcohol **6** (490 mg; 0.874 mmol), dried in high vacum was dissolved in a mixture of acetic anhydride (5 ml) and anhydrous DMSO (7.5 ml). The flask was kept under an argon atmosphere. After 20 h at room temperature a saturated $NaHCO_3$ water solution was added and the mixture was extracted with ether (2 × 50 ml). Ether layers were dried over Na_2SO_4, filtered and evaporated to dryness. Column chromatography (ether/hexane/dichloromethane, 1:4:1) gave 405 mg of ketone **7** (yield = 83%). ^{1}H-NMR ($CDCl_3$) (cosy 45): 7.5–6.7 (*m*, 14H, containing at $\overline{7.03}$ ($(AB)_2$, $\Delta\delta$ = 0.39, J_{AB} = 8.8, 4H, -C_6H_4-OCH_3) and 10H, -C_6H_5); $\overline{4.82}$ (*AB*, $\Delta\delta$ = 0.21, J_{AB} = 11.3, 2H, -CH_2-(C_6H_5)$_2$); 4.80 (*s*, 2H, -CH_2-C_6H_5); $\overline{4.54}$ (*AB*, $\Delta\delta$ = 0.24, J_{AB} = 11.0, 2H, -CH_2-C_6H_4-OCH_3); 4.53 (*dd*, ^{3}J = 6.2 and ^{3}J = 2.2, 1H, H_2); 4.28 (*dd*, ^{3}J = 6.2 and ^{3}J = 4.7, 1H, H_1); $\overline{4.17}$ (*AB* part of an ABX, $\Delta\delta$ = 0.05, J_{AB} = 8.3, J_{BX} = 2.3 $H_{4''}$, $H_{3''}$); 4.00 (*d*, ^{3}J = 4.7, 1H, H_6); 1.8–1.1 (*m*, 10H, C_6H_{10}).

(±)-5-Deoxy-5,5-difluoro-3,4-di-O-benzyl-6-O-p-methoxybenzyl-1,2-O-cyclohexylidene-myo-inositol 8

Ketone **7** (405 mg; 0.725 mmol), dried in vacuo, was dissolved in anhydrous toluene (10 ml) and kept under argon. DAST (0.96 ml; 7.25 mmol) was slowly added. After 72 h stirring at room temperature, an additional 150 μl de DAST

was added and the mixture stirred again for 24 h at room temperature. A saturated $NaHCO_3$ aqueous solution was added (10 ml). The product was extracted with ethylacetate (2 × 25 ml). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. Column chromatography (ether/hexane/dichloromethane, 1:6:1) gave 255 mg of **8** as an oil (yield = 61%). ^{1}H-NMR ($CDCl_3$ /C_6D_6, 4:6): 7.4–6.6 (*m*, 14H, -(C_6H_5)$_2$ and -C_6H_4-OCH_3); 4.80 (*AB*, $\Delta\delta$ = 0.04, J_{AB} = 11.3, 2H, -CH_2- Ar); 4.77 (*AB*, $\Delta\delta$ = 0.13, J_{AB} = 10.9, 2H, -CH_2- Ar); 4.59 (*AB*, $\Delta\delta$ = 0.09, J_{AB} = 12.1, 2H, -CH_2- Ar); 4.09 (*t*, ^3J = 4.5, 1H, H_2); 4.01 (*t*, ^3J = 5.8, 1H, H_1); 3.99 (*ddd*, $^3J_{HFtrans}$ = 19.6, ^3J = 9.4, $^3J_{HFcis}$ = 3.8, 1H, H_4); 3.77 (*ddd*, ^3J = 9.4, ^3J = 4.1, $^4J_{HFcis}$ = 2.3, 1H, H_3); 3.72 (*ddd*, $^3J_{HFtrans}$ = 23.7, ^3J = 7.2, $^3J_{HFcis}$ = 3.4, 1H, H_6); 3.46 (*s*, 3H, -OCH_3); 1.8–1.2 (*m*, 10H, C_6H_{10}).

(±)-5-Deoxy-5,5-difluoro-3,4-di-O-benzyl-myo-inositol 9

(±)-5-Deoxy-5,5-difluoro-3,4-di-*O*-benzyl-6-*O*-*p*-methoxybenzyl-1,2-*O*-cyclohexylidene-*myo*-inositol **8** (255 mg; 0.44 mmol) was dissolved in a mixture of ethanol/HCl 1N (2:1; 30 ml) and refluxed for 5h. The reaction mixture was evaporated to dryness and chromatographied (EtOAc/hexane, 1:1). The triol was obtained in quantitative yield (167 mg). ^{1}H-NMR ($CDCl_3$): 7.5–7.2 (*m*, 10H, -(C_6H_5)$_2$); 4.83 (*AB*, $\Delta\delta$ = 0.07, J_{AB} = 11.3, 2H, -CH_2- Ar); 4.71 (*AB*, $\Delta\delta$ = 0.08, J_{AB} = 11.7, 2H, -CH_2- Ar); 4.18 (*t*, ^3J = 2.6, 1H, H_2); 4.06 (*ddd*, $^3J_{HFtrans}$ = 20.7, ^3J = 10.2, $^3J_{HFcis}$ = 4.1, 1H, H_4); 3.94 (*ddd*, $^3J_{HFtrans}$ = 21.1, ^3J = 10.2, $^3J_{HFcis}$ = 4.9, 1H, H_6); 3.55 (*dt*, ^3J = 10.2, ^3J = 2.1, $^4J_{HFcis}$ = 2.1, 1H, H_3); 3.52 (*dt*, ^3J = 10.2, ^3J = 2.3, $^4J_{HFcis}$ = 2.3, 1H, H_1).

(±)-5-Deoxy-5,5-difluoro-3,4-di-O-benzyl-myo-inositol-1,2,6-tri-O-(orthoxylilene)-phosphate 10

Triol **9** (164 mg; 0.44 mmol) and tetrazole (277 mg; 3.95 mmol) were dissolved in anhydrous CH_3CN (10 ml) and CH_2Cl_2 (10 ml). *N,N*-Diethyl-*O*-xylylene phosphoramidite (0.63 g; 2.6 mmol) dissolved in anhydrous CH_2Cl_2 (20 ml) was added. The mixture was stirred overnight at room temperature. The reaction was cooled to 0°C and *m*CPBA (1.04 g; 4.21 mmol) in CH_2Cl_2 (10 ml) was rapidly added. After 1 h stirring at 0°C the solvents were evaporated and the crude material redissolved in a mixture of ether/dichloromethane (2:1). The organic layer was washed with 10% $Na_2S_2O_5$ water solution (2 × 30 ml), 5% $NaHCO_3$ aqueous solution (2 × 30 ml) and NaCl saturated water (2 × 30 ml), dried over Na_2SO_4 and evaporated to dryness. The residue was purified, first, by col-

umn chromatography eluted with ether/AcOEt (9:1). The main fraction (300 mg) was eluted on a layer chromatography eluted with AcOEt/ether (3:1). giving 180 mg of pure **10** (yield = 44%). ^{1}H-NMR ($CDCl_3$): 7.5–7.1 (*m*, 22H, Ar); 5.9–4.6 (m, 19H containing at 5.44 (*t*, ^{3}J = 2.6, 1H, H_2), at $\overline{5.41}$ (*AB*, $\Delta\delta$ = 0.70, J_{AB} = 13.6, 2H, -CH_2- Ar), at $\overline{5.36}$ (*AB*, $\Delta\delta$ = 0.53, J_{AB} = 13.6, 2H, -CH_2- Ar), at $\overline{5.35}$ (*AB*, $\Delta\delta$ = 0.61, J_{AB} = 13.6, 2H, -CH_2- Ar), at $\overline{5.29}$ (*AB*, $\Delta\delta$ = 0.43, J_{AB} = 13.6, 2H, -CH_2- Ar), at 5.04 (1H, H_6), at 4.96 (1H, H_1), at $\overline{4.87}$ (*AB*, $\Delta\delta$ = 0.11, J_{AB} = 11.1, 2H, -CH_2- Ar), at $\overline{4.78}$ (*AB*, $\Delta\delta$ = 0.22, J_{AB} = 10.9, 2H, -CH_2- Ar)); 3.91 (*ddd*, $^3J_{HFtrans}$ = 20.1, ^{3}J = 9.7, $^3J_{HFcis}$ = 3.2, 1H, H_4); 3.76 (*d*, ^{3}J = 9.2, 1H, H_3).

(±)-5-Deoxy-5,5-difluoro-myo-inositol-1,2,6-tris(phosphate) 2

The protected tris(phosphate) **10** (80 mg; 0.086 mmol) dissolved in a mixture of ethanol/CH_2Cl_2 /eau (2:2:1; 25 ml) was hydrogenolysed in the presence of Pd/C 10 % (0.2 g) at 5 Atm for 24 heures at 20°C. After filtration, the solvents were evaporated and the residue redissolved in water (1 ml) and placed at 0°C. Cyclohexylamine (0.5 ml) was slowly added. The cyclohexylammonium salts were precipitated in acetone. The solid was washed twice with acetone and dried in vacuo giving 31 mg white salt (yield = 60 %). Analyses calculated for $C_6H_{13}F_2O_4P_3$; $4C_6H_{13}N$; H_2O: C 42.15, H 7.90, N 6.55 P 10.87, F 4.45; found: C 41.86, H 8.08, N 6.59, P 9.89, F 4.58. MS (FAB), $C_6H_{13}O_{14}F_2P_3$: 438.9 (MH^-). ^{1}H-NMR (D_2O): 4.90 (*broad s*, 1H, H_2); 4.8–4.6 (*m*, 1H, H_6); 4.27 (*ddd*, $^3J_{HFtrans}$ = 21.5, ^{3}J = 10.4, $^3J_{HFcis}$ = 5.3, 1H, H_4); 4.16 (*d*, ^{3}J = 10.4, 1H, H_1); 3.69 (*d*, ^{3}J = 10.4, 1H, H_3); 3.6–3.3 (*m*, 3H, [H_2-C(*H*)C_5H_{10}]$_3$); 2.5–1.3 (*m*, 30H, [H_2N-C(H)C_5H_{10}]$_3$).

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