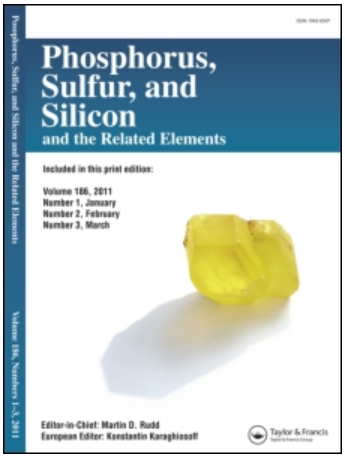

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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 58. SYNTHESIS OF myo-INOSITOL-1,3,5-O-PHOSPHATE AS A NEW TYPE OF CAGE-PHOSPHATE

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Dedicated to Professor Dr. L. Horner on occasion of his 80th Birthday

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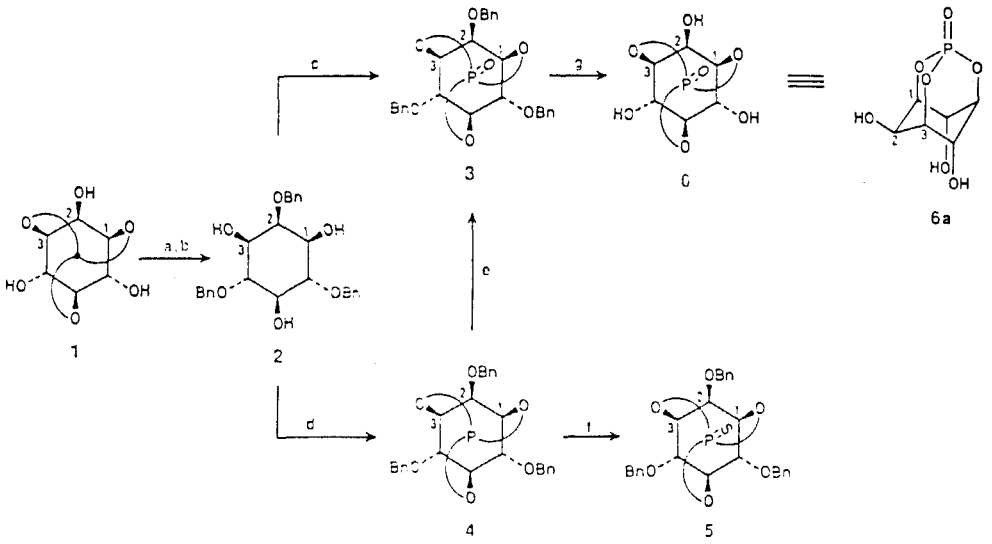
A new type of a cage-phosphate with resemblance to the adamantane structure, namely myo-inositol 1,3,5-O-phosphate was synthesized by debenzylation of 2,4,6-O-trisbenzyl myo-inositol-1,3,5-O-phosphate, which was obtained either by direct phosphorylation of 2,4,6-O-tribenzyl myo-inositol with phosphorus oxychloride or by treatment with phosphorus triamide followed by subsequent oxidation. The structure of the cage-phosphate was confirmed by 2D NMR spectrum.

Key words: myo-inositol phosphate; cage-phosphate; 2D NMR spectrum.

Since myo-inositol-1,4,5-O-trisphosphate (IP_3) behaves as second messenger in cellular signal transduction,[1] synthetic study of myo-inositol phosphate became an area of active investigations.[2] For polyhydroxyl compounds, in the chemistry of inositols in particular, orthoformate is usually applied as a protection grouping for the hydroxyl functions.[3] Investigation on the possibility of using phosphoryl moiety as protecting group in the synthesis of various inositol phosphates is therefore a problem of synthetic importance. Herein we wish to report new synthetic methods leading to myo-inositol-1,3,5-O-phosphate (**6**), a compound with cage-phosphate structure and resemblance to adamantane **6a** by the following sequence of reactions.



Reagents and Conditions

a: NaH, DMF, imidazole, BnBr, r.t, 1 h; b: 36% HCl, MeOH, reflux 1 h; c: $POCl_3$, pyridine, 100°C, 10 h; d: $P(NEt_2)_3$, dioxane, 110°C, 18 h; e: H_2O_2 (30%), THF, reflux, 1 h; f: sulfur, PhOMe, 150°C, 50 h; g: H_2 (17 atm), 10% Pd/C, EtOH-H_2O-HAc, r.t., 24 h.

The conformation of **6** can be expressed as **6a**, a compound with an adamantane skeleton. Since the potential biological activity of bicyclophosphate is well established,[4] it is reasonable to expect a powerful biological activity of the cage-phosphate. Investigation of the chemical reactions of compound **4** and **6** are being carried on in our Laboratory.

Stetter and Steinacker[5] reported the synthesis of cyclohexan-1,3,5-O-phosphite in 20% yield by treating cis-1,3,5-cyclohexantriol with phosphorus trichloride in the presence of pyridine. Wadsworth[6] synthesized the bicyclic phosphite in 79–98% yield by transesterification of a trialkyl phosphite with a trimethylolalkane. However, our trials on the preparation of myo-inositol-1,3,5-O-phosphite by treating directly myo-inositol with phosphorus trichloride and/or trialkyl phosphite failed. We supposed that the reaction of P(III) with myo-inositol containing six hydroxyl groups are much more difficult and complicated. Then we try to synthesize 2,4,6-O-protected myo-inositol. Starting from a myo-inositol derivatives 1,3,5-O-orthoformate myo-inositol (**1**),[3] in which the three hydroxyl groups at position 1,3,5 were blocked by orthoformate, we obtained 2,4,6-O-tribenzyl myo-inositol (**2**) by benzylation and subsequent hydrolysis. The resultant **2** is easily converted to **4** by heating with hexaethyl phosphorus triamide and/or phosphorus trichloride in the presence of pyridine. Treatment of **2** with sulfur gave 2,4,6-O-tribenzyl myo-inositol-1,3,5-O-thiophosphate (**5**) in 70% yield. Compound **4** is easily transformed to **3** in 95% yield upon oxidation with hydrogen peroxide. Reaction of **2** with phosphorus oxychloride in the presence of pyridine afforded **3** in 60% yield. The latter was then hydrogenated on 10% Pd/C to give myo-inositol-1,3,5-O-phosphate

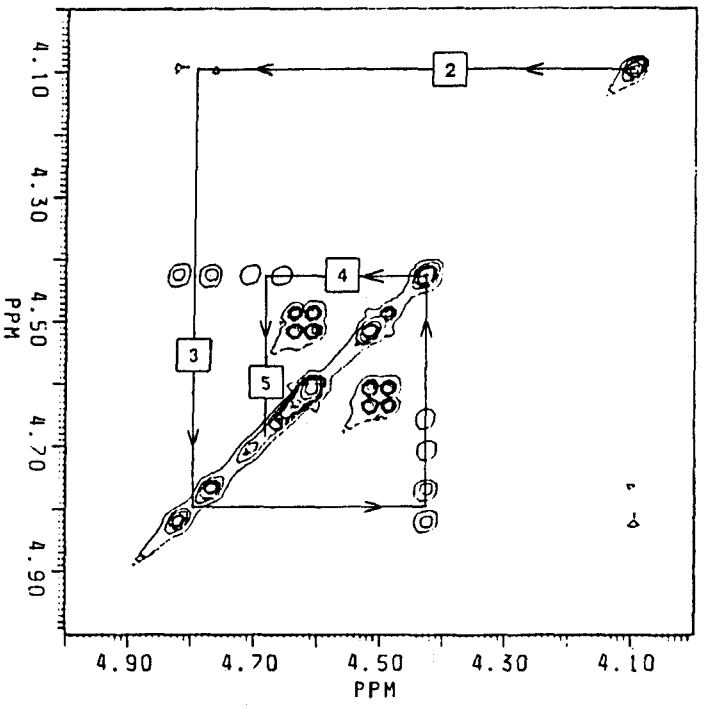


FIGURE 1 2D NMR Spectrum of Compound 3.

in 77% yield. The structure of **3** was confirmed by means of 2D NMR method. ^{1}H-^{1}H COSY is shown in Figure 1. Upon phosphorylation, the resonance of the phosphorylated position is downfield and the value of $^3J_{H,P}$(19–20 Hz) is large(10–12 Hz in general). ^{1}H signal in the NMR spectrum indicated the position which is phosphorylated. In the chair conformation of compound **3** only H-2 is an axial proton and the other five are equatorial protons. So H-2 in the spectrum is upfield. The signals for H-1,3 and/or H-4,6 are doublets. It shows that they are at the phosphorylated position. Compound **3** has a mirror symmetry. The signal of H-1 in the spectrum is similar to H-3 and consequently H-4 is similar to H-6.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR were recorded on a Varian XL-200 and 2D NMR was recorded on Brucker AM-400 spectrometer. Chemical shifts are reported as values relative to Me_4Si as internal standard. ^{13}C and ^{31}P NMR were recorded on a Varian FX-90Q spectrometer and the chemical shifts of ^{31}P NMR are reported relative to 85% H_3PO_4 as standard. Mass spectra were recorded with a Finnigan MAT 8430 or a Finnigan 4021 spectrometer.

Synthesis of 2,4,6-O-tribenzyl myo-inositol-1,3,5-O-phosphite (**4**). *Method A*: Hexaethyl phosphorus triamide (6 mL) was mixed with 1.5 g (3.3 mmol) of 2 under N_2. The mixture was heated at 120°C for 24 h and then the lower boiling fraction was removed under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel using EtoAc-petroleum ether (1:5) as eluent. **4** was obtained as an oily liquid 0.5 g (31.4%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.09 (1H, d, J = 2.2Hz), 4.28–4.32 (2H, m), 4.37 (2H, t, J = 3.2Hz), 4.47–4.66 (7H, m), 7.16–7.37 (15H, m) ^{31}P NMR (90MHz·$CDCl_3$) δ: +112.9 MS (m/e), 478 (M).

Anal. Calcd. for $C_{27}H_{27}O_6P$ C, 67.78; H, 5.65; P, 6.48. Found: C, 67.63; H 5.49; P 6.0.

Method B: To a mixture of 0.3 g (0.67 mmol) of **2**, 2 mL of pyridine and 10 mg of 4-dimethylamine pyridine (DMAP) was added 0.1 g (0.7 mmol) of phosphorus trichloride. The mixture was heated at 80°C for 4 h and then pyridine was removed under reduced pressure. The resulting residue was extracted with EtOAc and the organic layer was washed successively with dilute hydrochloric acid, water, saturated aqueous sodium chloride solution and then dried over anhydrous sodium sulfate. Yield of **4**: 190 mg (60%).

Synthesis of 2,4,6-O-trisbenzyl myo-inositol-1,3,5-O-phosphate (**3**). *Method A*: A mixture of 98 mg (0.2 mmol) **4**, aqueous H_2O_2 (30% 1 mL) and THF (5 mL) was heated at 100°C for 30 min and then extracted with EtOAc (2 10mL). The organic layer was dried over anhydrous $MgSO_4$. After removal of EtOAc the residue was recrystallized from dioxane-petroleum ether. Yield of **3**, 96 mg (95%), m.p. 109–110°C. ^{1}H NMr (400MHz $CDCl_3$) δ: 4.11 (1H, d, J = 1.44Hz); 4.44 (2H, s); 4.50–4.64 (1H, d, J = 19.8Hz); 4.80 (2H, d, J = 20.2 Hz); 7.18–7.37 (15H, m) ^{31}P NMR (90 MHz $CDCl_3$) δ: −9.20. MS (m/e) 495 (M + 1).

Anal. Calcd. for $C_{27}H_{27}O_7P$ C, 65.58; H, 5.46; P, 6.28. Found: C, 65.01; H, 5.71; P, 5.84.

Method B: The synthetic procedure of **3** was similar to method B for compound **4** except PCl_3 was used in place of $POCl_3$ and the reaction was heated at 100°C for 10 h. Yield 60%.

Synthesis of 2,4,6-O-tribenzyl myo-inositol-1,3,5-O-thiophosphate (**5**). The mixture of 0.2 g (0.44 mmol) **4**, sulfur (15 mg 0.45 mmol) and 5 mL of anisole was heated at 150°C for 50 h. The reaction mixture was concentrated and chromatographed (silica gel, EtOAc: petroleum ether = 1:1) to give a colorless solid. Recrystallization from EtOAc-petroleum ether yielded **5**, 0.12 g (70%), m.p. 116-7°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.11 (1H, t, J = 2Hz); 4.46 (3H m); 4.54–4.70 (7H, m); 4.76 (1H, t, J = 2.2Hz); 7.16–7.36 (15H, m). ^{31}P NMR (90MHz, $CDCl_3$) δ: 57.26. MS (FAB): 511 (M + 1).

Anal. Calcd. for $C_{27}H_{27}O_6PS$; C, 63.5; H, 5.29; P, 6.08; S, 6.27. Found: C, 63.46; H, 5 35; P, 5.77; S, 6.57.

Synthesis of myo-inositol-1,3,5-O-phosphate (**6**). A mixture of 0.1 g (0.2 mmol) **3**, 0.11 g 10% Pd/C, EtOH (3 mL), H_2O (0.2 mL) and 2 drops of HAc was hydrogenated under 17 atm for 24 h at room temperature. The catalyst was filtered off. After concentration of the filtrate, **6** (35 mg) was obtained in 77% yield. m.p. 278°C (decomp.) ^{1}H NMR (200MHz DMSO-d_6) δ: 4.19 (1H, t, J = 3Hz), 4.41–4.58 (4H, m); 4.64 (1H, t, J = 2.3Hz); 5.75 (2H, d, J = 4Hz, disappeared after exchange with D_2O); 5.83 (1H, d, J = 4Hz, disappeared after exchange with D_2O). ^{31}P NMR (90MHz, DMSO-d_6) δ: −10.6. ^{13}C NMR (90MHz DMSO-d_6) δ: 58.27 (1C C-2), 66.92 (2C, C-4 and C-6); 76.11 (1C, C-5); 83.23 (2C, C-1 and C-3). MS (FAB) 225 (m + 1).

Anal. Calcd. for $C_6H_9O_7P$ C 32.14; H 4.02. Found: C, 32.46; H, 3.95.

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