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PHOSPHORYLATION OF BENZYL-PROTECTED SUGAR DERIVATIVES VIA 1-H-PHOSPHONATE INTERMEDIATES: SYNTHESIS OF DL-MYO-INOSITOL 1,4,5-TRIS-1-H-PHOSPHONATE

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Abstract: The crystalline and easily accessible ammonium salt of benzyl-1-H-phosphonic acid has been used for the formation of intermediate benzyl-1-H-phosphonate diester bonds between primary, secondary and anomerically HO-groups of benzyl-protected (pseudo)sugar derivatives. These intermediates proved to be very suitable for the preparation of modified and non-modified phosphate functions.

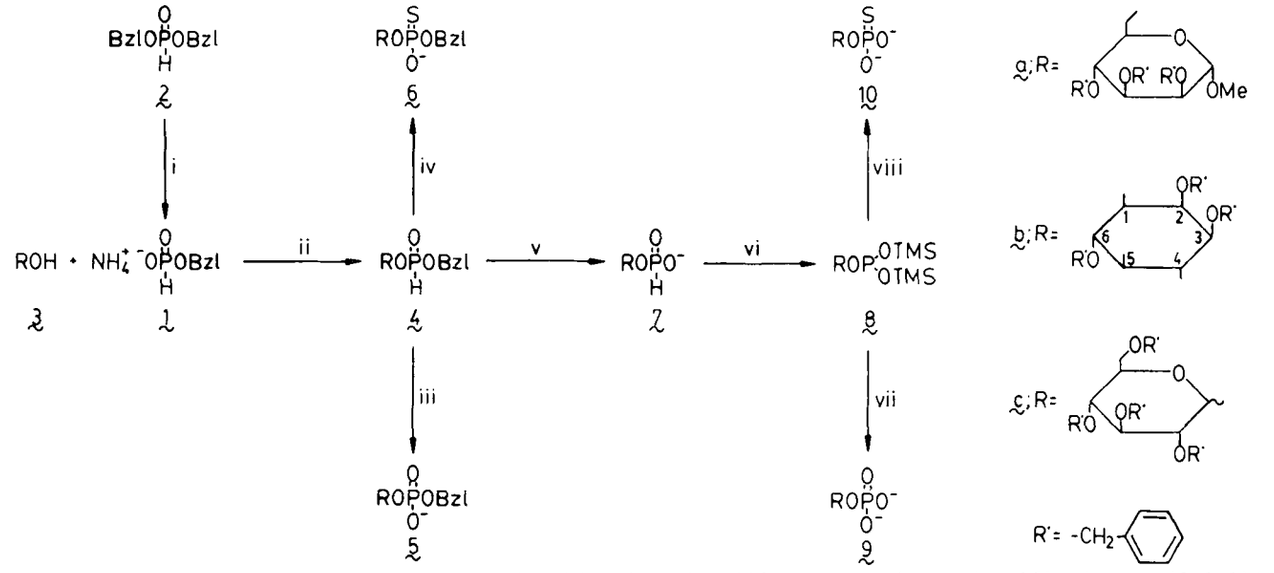
In 1952 Corby et al.[1] showed that an alkyl-benzyl-1-H-phosphonate di-ester (i.e. 4) could be obtained by phosphonylation of an alcohol with O-benzylphosphorous O,O-diphenylphosphoric anhydride. Michelson et al.[2] used this phosphonylation method for the first synthesis in solution of a DNA dimer (i.e. TpT) via an intermediate benzyl phosphotriester, the P(V) benzyl protecting group of which could be removed by anionic debenzylation[3]. Recently it was found that activation of a properly protected nucleoside 3'-H-phosphonate with pivaloyl chloride (PV-Cl), instead of diphenyl phosphorochloridate (Todd's reagent), resulted in a phosphonylating species which proved to be very suitable for a solid-phase synthesis of DNA[4] and RNA[5].

The above findings, together with our increased knowledge of the activation process of 1-H-phosphonate mono-esters with PV-Cl[6], urged us to examine the feasibility of applying benzyl-1-H-phosphonic acid 1 (NH_4^+-salt) for the phosphonylation of primary, secondary and anomerically HO-groups of benzyl protected (pseudo)sugar derivatives.

In the first instance, we selected the primary hydroxyl in methyl 2,3,4-tri-O-benzyl-α-D-mannopyranoside 3a to study in detail the phosphonylating properties of reagent 1, which is a stable crystalline compound easily accessible by anionic debenzylation[3] of 2 (step i). Thus, PV-Cl (2 mmol) was added to a suspension of 3a (1 mmol) and 1 (2 mmol) in pyridine (5 ml). Hydrolysis, after 15 min, and further work-up afforded crude 4a (δ_p 9.67 p.p.m., J_{P-H} 713 Hz and 8.55 p.p.m., J_{P-H} 710 Hz) not contaminated with 1 or 3a. Anionic debenzylation (step v) of 4a thus obtained gave, after work-up and purification (Sephadex LH-20), homogeneous[7] 7a (δ_p 8.01 p.p.m., J_{P-H} 625 Hz) in a yield of 81% (based on 3a). Conversion of 7a to 9a could easily be realized by silylation[6b] (step vi) of 7a to give intermediate phosphite-triester 8a (δ_p 120.31 p.p.m.) which, after oxidation (step vii) followed by hydrolysis of the intermediate bis(trimethylsilyl)-phosphotriester (δ_p -6.98 p.p.m.), resulted in the formation of 9a. Work-up and purification (Sephadex LH-20) yielded homogeneous[7] 9a (85%, δ_p 2.87 p.p.m).

The versatility of the benzyl-H-phosphonate approach is further exemplified by the preparation of the two phosphorothioate derivatives 6a and 10a, as well as the phosphodiester 5a. Thus in situ sulfurization of 4a (step iv) and 8a (step viii) afforded, after work-up and purification (Sephadex LH-20), 6a[7] (δ_p 58.69 and 58.39 p.p.m.) and 10a[7] (δ_p 56.00 p.p.m.), respectively, in excellent yields. On the other hand, oxidation[8] of 4a (step iii) with iodine gave, after purification, 5a[7] (δ_p -1.51 p.p.m.).

The reactivity of the above described benzyl-1-H-phosphonate method was further illustrated by the preparation of the racemic myo-inositol 1,4,5-tris-H-phosphonate 7b. Monitoring of the phosphonylation of DL-2,3,6 -tri-O-benzyl-myo-inositol 3b[9], as described earlier for the preparation of 3a, by ^{31}P-NMR-spectroscopy revealed rapid formation of inter-



Scheme: i NH_4I/butanone/reflux 1 h; ii PV-Cl/pyridine/15 min; iii 0.2 M I_2 in THF/pyridine/water (8:1:1)/ 10 min; iv elemental sulfur in pyridine/16 h; V NaI/acetone/reflux 16 h; vi N,O-bis(trimethylsilyl)-acetamide/triethylamine/CH_3CN/10 min; vii t-BuOOH/CH_3CN/10 min followed by hydrolysis; viii elemental sulfur in pyridine/2 h followed by hydrolysis.

mediate 4b (δ_p 9.61-8.25 p.p.m.) which, after work-up, was immediately subjected to anionic debenzylation (step v). Purification (Sephadex LH-20) of the crude product gave homogeneous[7] 7b [yield (Na^+-salt) 75%; δ_p 7.22 p.p.m., $^1J_{P-H}$ 649 Hz and $^3J_{P-H}$ 9.77 Hz; 6.71 p.p.m., $^1J_{P-H}$ 649 Hz and $^3J_{P-H}$ 9.77 Hz; 5.29 p.p.m., $^1J_{P-H}$ 630 Hz and $^3J_{P-H}$ 12.20 Hz; see also Figure].

Finally, the introduction of a phosphate function at the anomeric centre of a sugar was demonstrated by the phosphonylation of 2,3,4,6-tetra-O-benzyl-α(β)-D-glucopyranose 3c. Thus phosphonylation of 3c (step ii) followed by oxidation (step iii) of intermediate 4c resulted in the formation of 5c which was isolated, after purification (Sephadex LH-20), as a mixture of α- and β-isomers[7] (δ_p -0.03 and -2.24 p.p.m.).

In conclusion, the 1-H-phosphonate method presented in this paper may become a general approach to the introduction of modified and non-modified phosphate functions at the primary, secondary and anomerically hydroxyl groups of sugars. It is also interesting to note that the introduction of an extra benzyl protective group at P(V), by our phosphonate approach, is in line with the commonly accepted strategy of using permanent protective groups (e.g. benzyl) which can be deblocked, together with P(V)-benzyl, by hydrogenolysis. Apart form this, it is also possible to remove the benzyl separately from phosphor by anionic debenzylation. Finally, compound 7b gave, after hydrogenolysis, 7b (R'=H)[7] which represents the first chemically prepared analogue of DL-myo-inositol 1,4,5-trisphosphate.

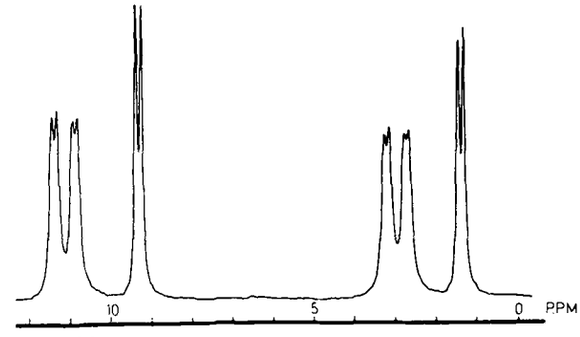


Figure: ^{31}P NMR-spectrum (80.7 MHz) of compound 7b without ^1H-hetero-nuclear decoupling.

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