

Preliminary communication

An approach to the synthesis of aldosl phosphates *via* aldosl phosphites*

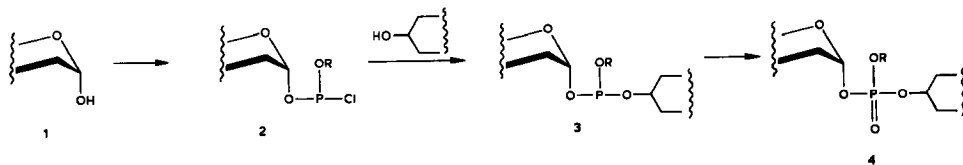
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Phosphates linked to anomeric carbon atoms have been reported to be present at the cell surface of such microbes as *Staphylococcus lactis*², *Saccharomyces cerevisiae*³, *Micrococcus lysodeikticus*⁴, and *Streptococcus pneumoniae*⁵, and to be a part of the structure of glycan chains of glycoproteins⁶. The lipid A moiety of LPS also contains glycosyl phosphate units⁷.

In 1976, Letsinger and Lunsford⁸ reported a new synthetic approach to oligonucleotides *via* phosphorous triester intermediates. As part of a project on studies of the synthesis of oligosaccharides, we report here an approach to the synthesis of aldosl phosphates through the intermediacy of aldosl phosphites. A general synthetic sequence is depicted in Scheme 1. An anomeric hydroxyl group (1) reacts with trivalent phosphorus chloride to give the anomeric phosphorochloridite (2), which then reacts with another hydroxyl group to give the phosphorous triester 3, and oxidation of 3 leads to formation of the aldosl phosphoric triester 4. From the point of view of synthesis, this approach would be expected to be efficient, owing to the high reactivity of phosphorochloridite as a phosphorylating reagent.



Scheme 1

First, we describe an efficient synthesis of aldosl phosphites using phosphorus trichloride as the phosphorylating agent. Treatment of 2,3,4,6-tetra-*O*-acetyl-D-glucose (5) with PCl_3 in oxolane (THF) in the presence of iPr_2NET at -78° gave 6, which was hydrolyzed to give a 53% yield of 7, $[\alpha]_D +86.2^\circ$ (c 2.50, CHCl_3)[†]; R_F 0.65 in 10:5:1 $\text{CHCl}_3\text{--MeOH--H}_2\text{O}$ ^{††}.

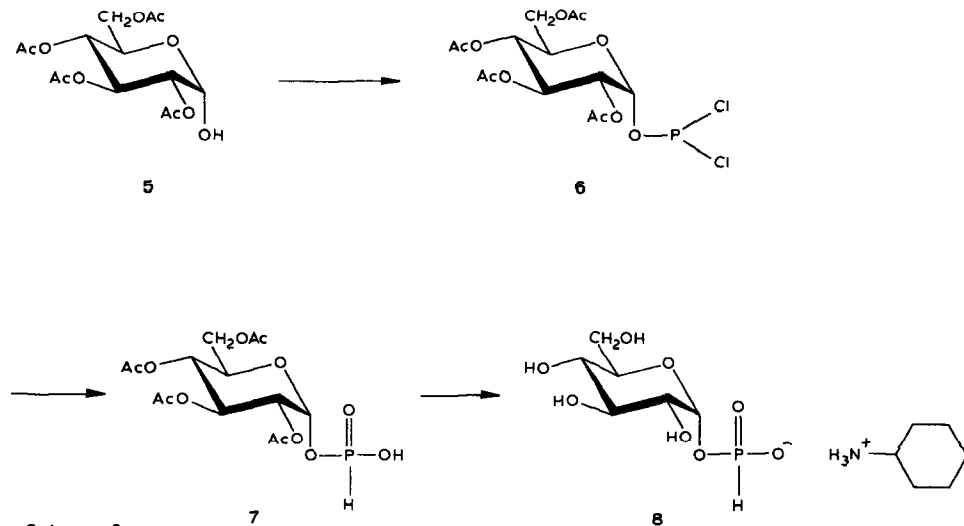
*Synthetic Studies on Cell-Surface Glycans, Part XXI. For Part XX, see ref. 1.

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[†]Compounds with $[\alpha]_D$ recorded gave satisfactory elemental analyses.

^{††}Phosphorus-containing compounds were detected on t.l.c. plates by using the specific spray reported by Dittmer and Lester⁹.

Zemplén deacetylation of 7, and treatment of the product with Amberlist 15 resin (cyclohexylammonium form), afforded a 76% yield of 8, $[\alpha]_D +82.1^\circ$ (c 1.70, H_2O); R_F 0.26 in 6:6:1:2 EtOAc–AcOH– NH_4OH – H_2O . To the best of our knowledge, this is the first example of the synthesis of a free aldose phosphite[†]. The structure of 8 was determined by means of the following n.m.r. data* (in D_2O), ^{13}C : δ 94.559 (C-1, $^1J_{CH}$ 173.3, $^2J_{CP}$ 6.1 Hz, and 71.532 (C-2, $^3J_{CP}$ 6.1 Hz); ^{31}P : δ +3.863 ($^1J_{PH}$ 649.9, $^3J_{PH}$ 8.3, $^4J_{PH}$ 2.0 Hz); 1H : δ 5.48 (H-1, $^3J_{HH}$ 3.4, $^2J_{HP}$ 8.3 Hz) and 3.53 (H-2, $^3J_{HH}$ 3.4, $^3J_{HP}$ 9.8, $^4J_{HP}$ 2.4 Hz). As it had been reported¹¹ that coupling through four bonds depends on the presence of a *trans*-antiplanar arrangement of the five atoms involved, the observation of four-bond coupling of 2.4 Hz between the H-2 and the P atom strongly indicates that the spatial arrangement of H-2–C-2–C-1–O–P is *trans*-antiplanar, in agreement with the favored conformation due to the *exo*-anomeric effect¹². The same procedure could be applied to other aldohexoses, to give, for example, α -D-mannopyranosyl phosphite: δ_C 95.62 (C-1, $^1J_{CH}$ 172.1, $^2J_{CP}$ 4.9 Hz), δ_H 5.44 (H-1, $^3J_{HH}$ 1.9, $^3J_{HP}$ 8.3 Hz); R_F 0.26, and α -D-galactopyranosyl phosphite: δ_H 5.51 (H-1, $^3J_{HH}$ 4.3, $^3J_{HP}$ 8.3 Hz); R_F 0.26 in 6:6:1:2 EtOAc–AcOH– NH_4OH – H_2O .

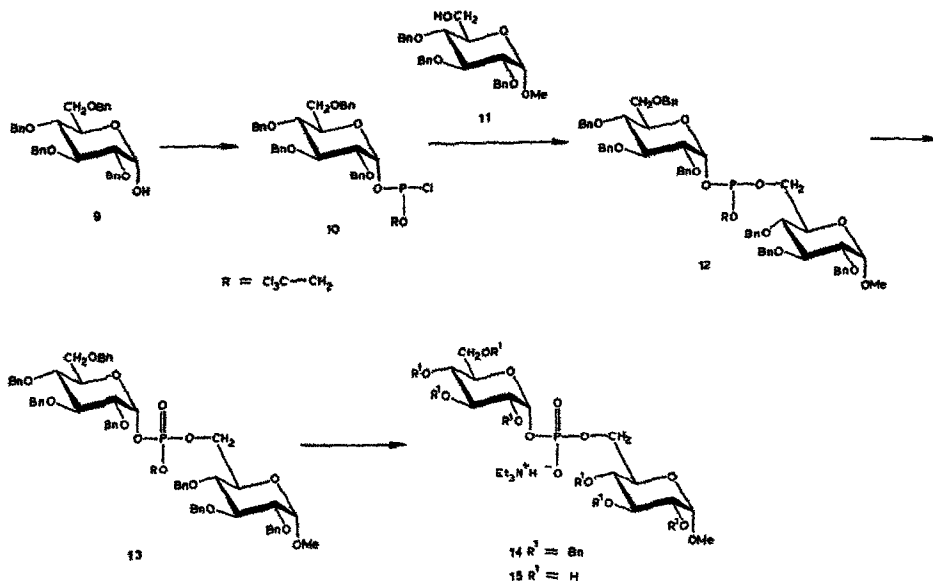


Next, the phosphite approach was employed for the synthesis of hexoside 6-(hexosyl phosphates). Treatment of 2,3,4,6-tetra-*O*-benzyl-D-glucose (9) with 2,2,2-trichloroethylphosphorodichloridite in THF– iPr_2NEt for 1 h at -78° to give 10, and treatment of 10 with 11 at -78° , gave an 81% yield of glycosyl phosphite 12, $[\alpha]_D +30.1^\circ$ (c 2.68, $CHCl_3$); R_F 0.71 in 5:1 toluene–EtOAc. Oxidation of 12 with O_2 –AIBN¹³ in benzene for 14 h

[†]A completely protected α -D-glucopyranosyl phosphite had been reported as an unstable intermediate¹⁰.

*The values of δ_C are expressed in p.p.m. downward from tetramethylsilane, referenced indirectly with an internal standard of 1,4-dioxane (δ 66.90). The values of δ_P are expressed in p.p.m. downward from an external standard of 85% H_3PO_4 . The values of δ_H (at 25°) are expressed in p.p.m. downward from sodium 4,4-dimethyl-4-silapentanoate-2,2,3,3- d_4 , referenced indirectly with an internal standard of DOH (δ 4.81).

at 70° afforded a 1:1 diastereomeric mixture of 13 in 61% yield, $[\alpha]_D +34.8^\circ$ (*c* 2.36, CHCl_3) and $+38.7^\circ$ (*c* 4.25, CHCl_3); R_F 0.33 and 0.25, respectively, in 5:1 toluene–EtOAc. Treatment of 13 with Zn–Cu in the presence of 2,4-pentanedione¹⁴ and Et_3N afforded an 84% yield of 14, $[\alpha]_D +35.1^\circ$ (*c* 0.97, CHCl_3); R_F 0.77 in 10:5:1 CHCl_3 –MeOH– H_2O . Birch reduction of 14 with Na– NH_3 –EtOH, and purification of the product with Bio-Gel P-6DG afforded a 46% yield of 15, $[\alpha]_D +61.0^\circ$ (*c* 1.94, H_2O); R_F 0.16 in 6:6:2:1 EtOAc–AcOH– H_2O – NH_4OH . The structure assigned to 15 was supported by the following n.m.r. data (D_2O), δ_C : 99.68 (C-1a, $^1J_{\text{CH}}$ 166.0 Hz), 95.64 (C-1b, $^1J_{\text{CH}}$ 174.5, $^2J_{\text{CP}}$ 6.1 Hz), 72.05 (C-2b, $^3J_{\text{CP}}$ 4.9 Hz), 70.85 (C-5a, $^3J_{\text{CP}}$ 7.3 Hz), and 64.68 (C-6a, $^2J_{\text{CP}}$ 4.9 Hz); δ_P : –0.970; δ_H : 5.50 (H-1b, $^3J_{\text{HH}}$ 3.1, $^3J_{\text{HP}}$ 7.0 Hz), 4.78 (H-1a, $^3J_{\text{HH}}$ 3.1 Hz), and 3.57 (H-2b, $^3J_{\text{HP}}$ 3.4, $^3J_{\text{HH}}$ 10.2, $^4J_{\text{HP}}$ 3.4 Hz).

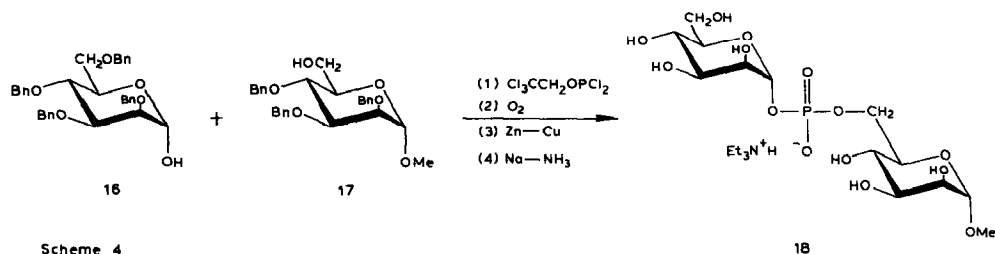


Scheme 3

By employing 2,3,4,6-tetra-*O*-benzyl- α -D-mannopyranose (16) and methyl 2,3,4-tri-*O*-benzyl- α -D-mannopyranoside (17), the same reaction-sequence afforded methyl- α -D-mannopyranoside (α -D-mannopyranosyl phosphate), (18) in 16.0% overall yield; $[\alpha]_D +38.8^\circ$ (*c* 0.825, H_2O); R_F 0.20 in 6:6:2:1 EtOAc–AcOH– H_2O – NH_4OH ; δ_C (D_2O): 101.20 (C-1a, $^1J_{\text{CH}}$ 172.1 Hz), 96.48 (C-1b, $^1J_{\text{CH}}$ 173.1, $^2J_{\text{CP}}$ 4.9 Hz), 71.72 (C-5a, $^3J_{\text{CP}}$ 7.3 Hz), 70.77 (C-2b, $^3J_{\text{CP}}$ 8.5 Hz), and 65.09 (C-6a, $^2J_{\text{CP}}$ 6.1 Hz); δ_H (D_2O): 5.42 (H-1b, $^3J_{\text{HH}}$ 2.3, $^3J_{\text{HP}}$ 7.8 Hz) and 4.74 (H-1a, $^3J_{\text{HH}}$ 1.42 Hz); δ_P (D_2O): –1.731.

It is to be noted that the observation of $^4J_{\text{HP}}$ 3.4 Hz between the H-2b and the P atom in 15 indicates the *trans*-antiplanar arrangement of the five atoms H-2b–C-2b–C-1b–O–P, in agreement with the conformation favored by the *exo*-anomeric effect.

In conclusion, we have developed, for the synthesis of alderyl phosphates through the intermediacy of alderyl phosphites, an efficient approach that complements the available methodology¹⁵.



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