

Preliminary communication

Synthesis of phosphonate analogs of α -D-glucopyranosyl and α -D-galactopyranosyl phosphate

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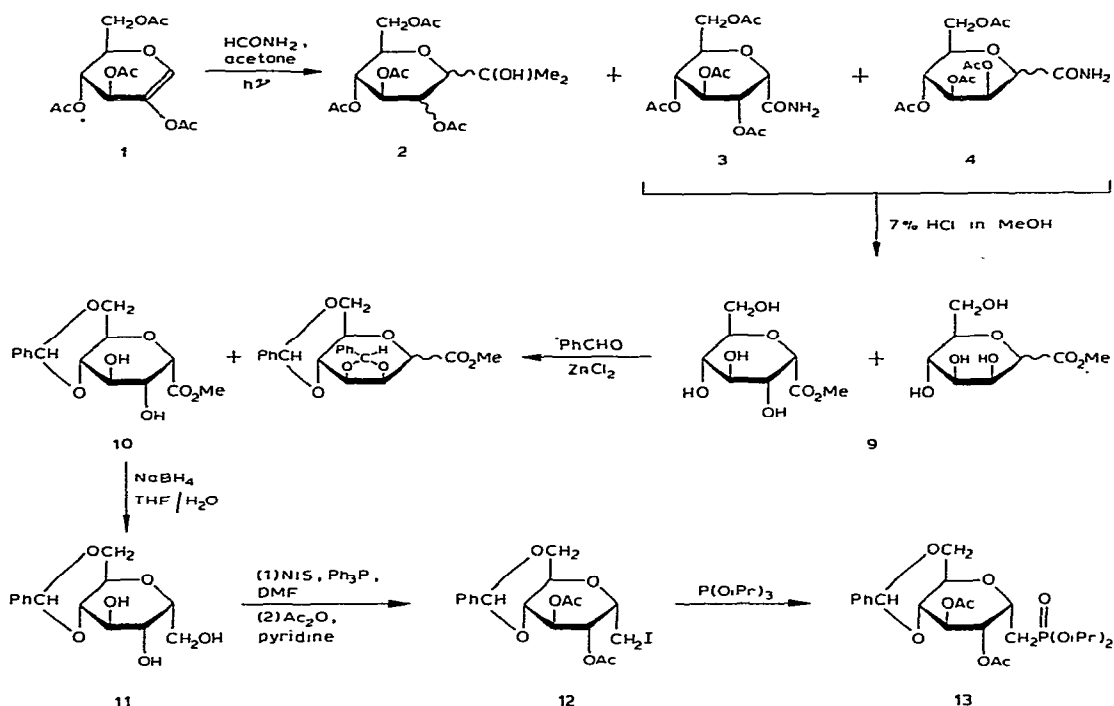
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Phosphonate analogs of amino acids and many naturally occurring phosphoric esters, such as phosphoglycerides, nucleotides, and sugar phosphates, are of interest because of their potential biological activities. *C*-Glycosyl compounds should also be of interest because of their potential biological activities, particularly as inhibitors of glycosyltransferases and glycohydrolases. Phosphonate analogs of most of the intermediates of carbohydrate metabolism have been prepared¹; however, the phosphonate analog of D-glucosyl phosphate has not been reported. We now describe the synthesis of the phosphonate analogs of α -D-glucopyranosyl and α -D-galactopyranosyl phosphate, analogs that are related to *C*-glycosyl compounds having the α -D-configuration, and a general approach to the synthesis of *C*-glycosyl analogs of α -D-gluco- and α -D-galacto-pyranosides

Carbamoylation of 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol (“2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal”) **1**; 0.04 mol) dissolved in formamide (550 mL) and acetone (50 mL) under an atmosphere of oxygen-free argon for 72 h, as described by Rosenthal and Ratcliffe², gave a mixture³ of **2**, **3**, and **4**; the yield of the amide fraction (**3**, + **4**) was 50%, from separation by column chromatography⁴ with 5:5:1 (v/v) petroleum ether–EtOAc–EtOH.

Carbamoylation of 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*lyxo*-hex-1-enitol (“2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-galactal”) (**5**) under the same conditions afforded³ **6**, **7**, and **8**; yield of **7**, 53%; m.p. 185–189°, $[\alpha]_D^{25} +53.3^\circ$ (*c* 1.0, CHCl₃). N.m.r. analysis of compounds **3** and **7** indicated that they exist primarily in the ²C₅(D) conformation [equivalent to the ¹C₄(D) conformation] in CDCl₃, but in the expected ⁵C₂(D) conformation³ in Me₂SO-*d*₆.

The mixture of amides (**3** + **4**), or pure amide **7**, subjected to methanolysis with 7% HCl in MeOH for 24 h at the reflux temperature, gave, respectively, a mixture of esters (**9**), or **14**. Mixture **9** was purified by column chromatography⁴ with 4:1 (v/v) CHCl₃–MeOH; m.p. 130–141°. $[\alpha]_D^{25} +110^\circ$ (*c* 1.0, MeOH); ¹H-n.m.r. (CDCl₃, tetraacetate of **14**): δ 2.02, 2.06, 2.07, 2.15 (s, 12 H, 4 OAc), 3.78 (s, 3 H, OCH₃), 4.09, 4.15 (pd, 2H, *J*_{6,7} 6.5, *J*_{6,7'} 6.4, *J*_{7,7'} 11.5 Hz, H-7, 7'), 4.86 (d, 1 H, *J*_{2,3} 6.2 Hz, H-2), 4.89 (pd, 1 H, *J*_{5,6} 2.1 Hz, H-6), 5.34 (pd, 1 H, *J*_{3,4} 10 Hz, H-3), 5.44 (pd, 1 H, *J*_{4,5} 3.0 Hz, H-4), and 5.52 (pd, 1 H, H-5).

NIS = *N*-iodosuccinimideDMF = HCONMe_2

THF = oxolane

 $i\text{Pr} = \text{Me}_2\text{CH}$

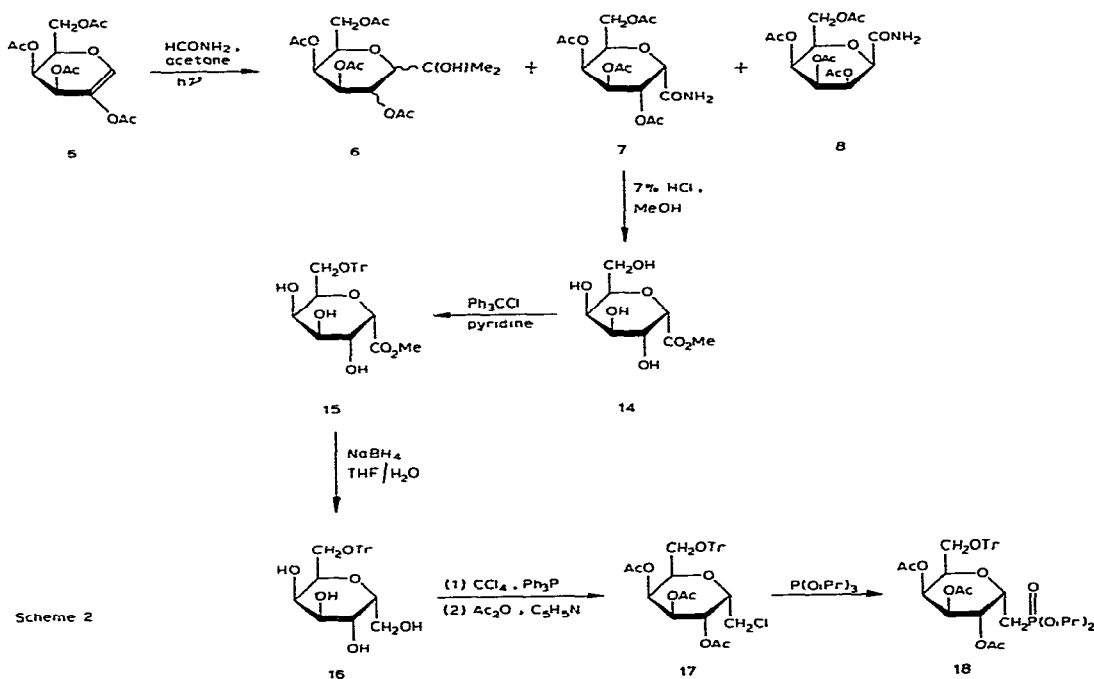
Scheme 1

Mixture **9** was shaken for 48 h with benzaldehyde and ZnCl_2 to block the primary and a secondary hydroxyl group. The solution was diluted with CHCl_3 made neutral and evaporated under diminished pressure. Isolation of the mono-*O*-benzylidene derivative (**10**) was accomplished by column chromatography⁴ with 7:3 (v/v) EtOAc–petroleum ether; yield 64%; m.p. 127–129°, $[\alpha]_D^{25} +45.0^\circ$ (c 1.0, CHCl_3).

Compound **10** in 2:1 (v/v) oxolane– H_2O was reduced with NaBH_4 to compound **11**, which was isolated by extraction with EtOAc; m.p. 205–208°, $[\alpha]_D^{25} +6.7^\circ$ (c 1.0, HCONMe_2).

Triol **11** was then treated⁵ with *N*-iodosuccinimide and triphenylphosphine in HCONMe_2 during 24 h at 50°. The crude product (**12**) was partially purified by column chromatography⁴ with 7:3 (v/v) EtOAc–petroleum ether, then acetylated with acetic anhydride–pyridine, and the product purified by column chromatography⁴ with 7:3 (v/v) petroleum ether–EtOAc, to give **12**; yield 30%; m.p. 134–137°, $[\alpha]_D^{25} +21.3^\circ$ (c 1.0, CHCl_3); $^1\text{H-n.m.r.}$ (CDCl_3): δ 2.1 (s, 6 H, 2 OAc), 3.20–3.80 (m, 5 H, H-1), 5.6, 1'' 7'), 4.26–4.46 (m, 2 H, H-2, 7), 5.17 (pd, 1 H, $J_{2,3}$ 6.0 Hz, H-3), 5.40 (t, 1 H, $J_{3,4}$ 9.7, $J_{4,5}$ 9.0 Hz, H-4), 5.51 (s, 1 H, PhCH), and 7.20–7.60 (m, 5 H, Ph).

When heated for 24 h at 180° with triisopropyl phosphite compound **12** underwent the Arbuzov reaction, to give the substituted phosphonate analog (**13**) of



α -D-glucopyranosyl phosphate, which was purified by column chromatography⁴ with 30:30:1 (v/v) petroleum ether—Et₂O—EtOH; yield 43%; syrup; $[\alpha]_D^{25} +9.0^\circ$ (c 1.0, CHCl₃); ¹H-n.m.r. (CDCl₃): δ 1.32 [d, 12 H, 2 CH(CH₃)₂], 1.70–2.90 (m, 2 H, H-1, 1'), 2.06 (s, 3 H, 2 OAc), 3.50–3.90 (m, 3 H, H-5, 6, 7'), 4.32 (m, 1 H, H-2), 4.50–4.90 [m, 3 H, H-7, 2 CH(CH₃)₂], 5.16 (m, 1 H, $J_{2,3}$ 5.9, $J_{3,p}$ 2.4 Hz, H-3), 5.39 (t, 1 H, $J_{3,4}$ 9.7, $J_{4,5}$ 9.0 Hz, H-4), 5.50 (s, 1 H, PhCH), and 7.20–7.60 (m, 5 H, Ph).

Benzylidenation was not used to block the primary hydroxyl group in compound 14, because, in this case, two monobenzyldene derivatives (the 4,5-*O*- and the 5,7-*O*-monobenzyldene derivatives) were formed. Ester 14 was treated for 48 h with chlorotriphenylmethane in pyridine, to give 15, which was purified by column chromatography⁴ with 50:1 (v/v) CHCl₃—MeOH; yield 85%; syrup; $[\alpha]_D^{25} +28.2^\circ$ (c 1.0, CHCl₃).

Compound 15 was reduced to 16, as described for compound 10. Compound 16 was isolated by extraction with CHCl₃ after addition of a saturated aqueous solution of (NH₄)₂SO₄; yield 91%; m.p. 104–105°, $[\alpha]_D^{25} +23.6^\circ$ (c 1.0, CHCl₃).

Replacement of the unblocked, primary hydroxyl group with a chlorine atom was achieved by treatment of 16 with CCl₄ and triphenylphosphine in pyridine⁶ for 24 h at 50°. The monochloro derivative was partially purified by column chromatography⁴ (EtOAc), and then acetylated, to give 17, which was purified by column chromatography⁴ with 7:3 (v/v) petroleum ether—EtOAc; overall yield of 17, 32%; m.p. 166–167°, $[\alpha]_D^{25} -4.0^\circ$ (c 1.0, CHCl₃); ¹H-n.m.r. (CDCl₃): δ 1.88, 1.92, 2.02 (s, 9 H, 3 OAc), 3.08 (pd, 1 H, $J_{6,7'}$ 6.7, $J_{7,7'}$ 9.4 Hz, H-7'), 3.28–4.40 (m, 5 H, H-1, 2, 6, 7, 1'), 5.12 (pd, 1 H, $J_{3,4}$ 9.4, $J_{4,5}$ 3.0 Hz, H-4), 5.30 (pd, 1 H, $J_{2,3}$ 4.7 Hz, H-3), 5.53 (pd, 1 H, $J_{5,6}$ 3.0 Hz, H-5), and 7.15–7.52 (m, 15 H, trityl).

When heated with triisopropyl phosphite, compound 17 underwent the Arbuzov reaction, to give the substituted phosphonate analog 18 of α -D-galactopyranosyl phosphate, which was purified by column chromatography⁴ (EyOAc); yield 26%; syrup; $[\alpha]_D^{25} + 12.5^\circ$ (c 1.0, CHCl_3); $^1\text{H-n.m.r.}$ (CDCl_3); δ 1.13–1.40 [m, 12 H, 2 $\text{CH}(\text{CH}_3)_2$] 1.50–2.50 (m, 2 H, H-1, 1'), 1.87, 1.95, 2.04 (s, 9 H, 3 OAc), 3.13, 3.39 (pd, 2 H, $J_{6,7}$ 5.4, $J_{6,7'}$ 8.7, $J_{7,7'}$ 8.7 Hz, H-7, 7'), 3.90–4.19 (m, 1 H, H-6), 4.40–4.80 [m, 2 H, 2 $\text{CH}(\text{CH}_3)_2$], 5.13 (pd, 1 H, $J_{3,4}$ 9.4, $J_{4,5}$ 2.4 Hz, H-4), 5.28 (pd, 1 H, $J_{2,3}$ 4.0 Hz, H-3), 5.63 (pd, 1 H, $J_{5,6}$ 2.0 Hz), and 7.16–7.56 (m, 15 H, trityl).

ACKNOWLEDGMENT

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