Carbohydrate Research, 97 (1981) C1–C4
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Preliminary communication

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

MAREK CHMIELEWSKI, JAMES N. BeMILLER, and DOUGLAS PAT CERRETTI

Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale, IL 62901 (U.S.A.)

(Received May 12th, 1981; accepted for publication, May 29th, 1981)

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 prepared[1]; 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.

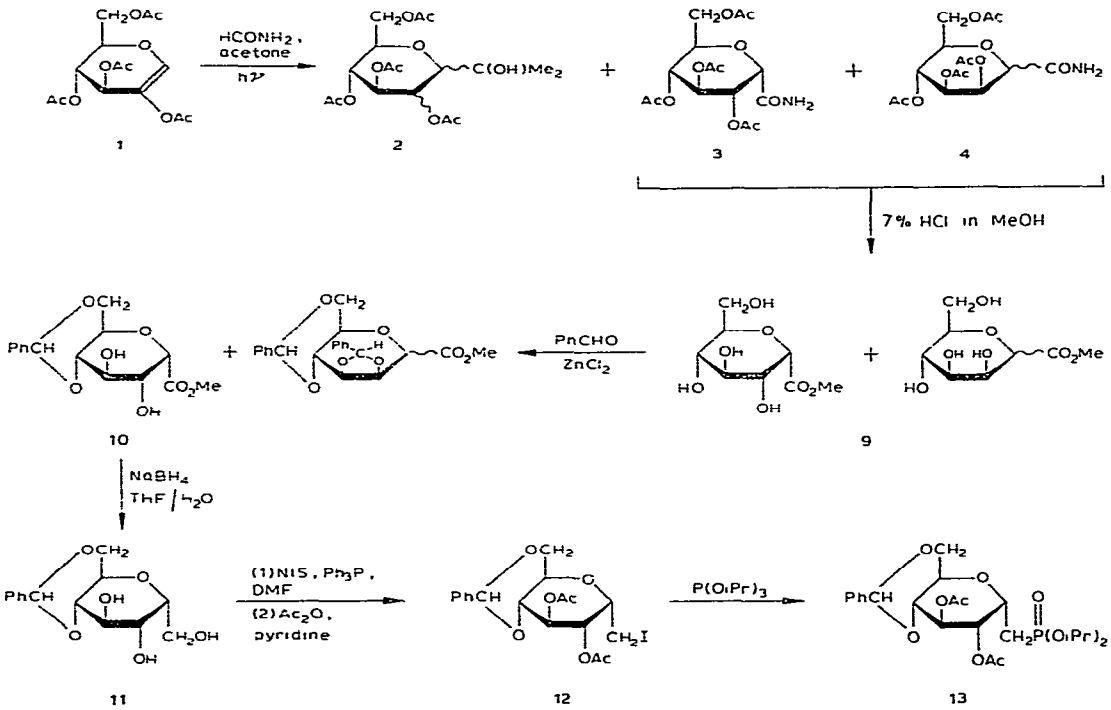
Carbamoylation of 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol ("2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal") (**1**; 0.04 mol) dissolved in formamide (550 mL) and acetone (50 mL) under an atmosphere of oxygen-free argon for 72 h, as described by Rosenthal and Ratcliffe[2], gave a mixture[3] of **2**, **3**, and **4**; the yield of the amide fraction (**3** and **4**) was 50%, from separation by column chromatography[4] 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 afforded[3] **6**, **7**, and **8**; yield of **7**, 53%; m.p. 185–189°, $[\alpha]_D^{25}$ +53.3° (*c* 1.0, $CHCl_3$). N.m.r. analysis of compounds **3** and **7** indicated that they exist primarily in the $^2C_5$(D) conformation [equivalent to the $^1C_4$(D) conformation] in $CDCl_3$, but in the expected $^5C_2$(D) conformation[3] in Me_2SO-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 chromatography[4] with 4:1 (v/v) $CHCl_3$–MeOH; m.p. 130–141°; $[\alpha]_D^{25}$ +110° (*c* 1.0, MeOH); ^{1}H-n.m.r. ($CDCl_3$, tetraacetate of **14**): δ 2.02, 2.06, 2.07, 2.15 (s, 12 H, 4 OAc), 3.78 (s, 3 H, OCH_3), 4.09, 4.15 (pd, 2 H, $J_{6,7}$ 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).

† This paper is a corrected version of that which appeared in *Carbohydr. Res.*, 94 (1981) C10–C13.

0008-6215/81/0000–0000/$02.50 © 1981 Elsevier Scientific Publishing Company



NIS = *N*-iodosuccinimide
DMF = $HCONMe_2$
THF = oxolane
iPr = Me_2CH

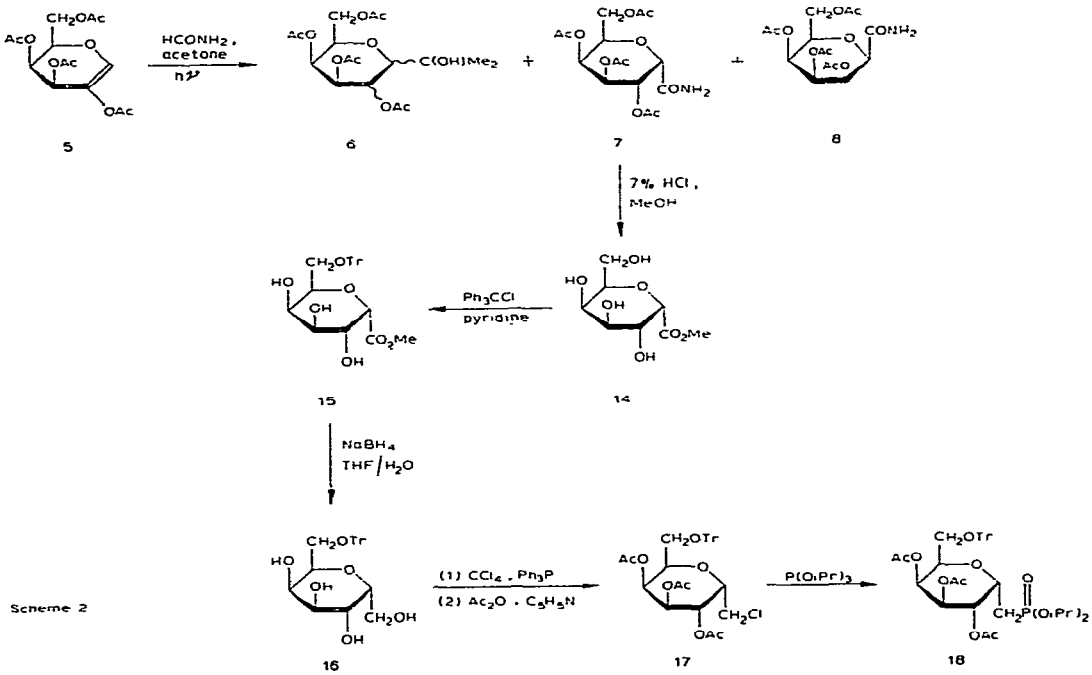
Scheme 1

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 chromatography[4] with 7:3 (v/v) EtOAc–petroleum ether; yield 64%; m.p. 127–129°, $[\alpha]_D^{25}$ +45.0° (*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° (*c* 1.0, $HCONMe_2$).

Triol **11** was then treated[5] with *N*-iodosuccinimide and triphenylphosphine in $HCONMe_2$ during 24 h at 50°. The crude product (**12**) was partially purified by column chromatography[4] with 7:3 (v/v) EtOAc–petroleum ether, then acetylated with acetic anhydride–pyridine; the product was purified by column chromatography[4] with 7:3 (v/v) petroleum ether–EtOAc, to give **12**; yield 30%; m.p. 134–137°, $[\alpha]_D^{25}$ +21.3° (*c* 1.0, $CHCl_3$); ^{1}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, PhC*H*), 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



Scheme 2

α-D-glucopyranosyl phosphate, which was purified by column chromatography[4] with 30:30:1 (v/v) petroleum ether–Et_2O–EtOH; yield 43%; syrup; $[\alpha]_D^{25}$ +9.0° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.32 [d, 12 H, 2 CH(CH_3)$_2$], 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 C*H*(CH_3)$_2$], 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, PhC*H*), 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 monobenzylidene derivatives (the 4,5-*O*- and the 5,7-*O*-monobenzylidene derivatives) were formed. Ester **14** was treated for 48 h with chlorotriphenylmethane in pyridine, to give **15**, which was purified by column chromatography[4] with 50:1 (v/v) $CHCl_3$–MeOH; yield 85%; syrup; $[\alpha]_D^{25}$ +28.2° (*c* 1.0, $CHCl_3$).

Compound **15** was reduced to **16**, as described for compound **10**. Compound **16** was isolated by extraction with $CHCl_3$ after addition of a saturated aqueous solution of $(NH_4)_2SO_4$; yield 91%; m.p. 104–105°, $[\alpha]_D^{25}$ +23.6° (*c* 1.0, $CHCl_3$).

Replacement of the unblocked, primary hydroxyl group with a chlorine atom was achieved by treatment of **16** with CCl_4 and triphenylphosphine in pyridine[6] for 24 h at 50°. The monochloro derivative was partially purified by column chromatography[4] (EtOAc), and then acetylated, to give **17**, which was purified by column chromatography[4] with 7:3 (v/v) petroleum ether–EtOAc; overall yield of **17**, 32%; m.p. 166–167°, $[\alpha]_D^{25}$ –4.0° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): 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 chromatography[4] (EtOAc); yield 26%; syrup; $[\alpha]_D^{25}$ + 12.5° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$); δ 1.13–1.40 [m, 12 H, 2 $CH(CH_3)_2$], 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 $CH(CH_3)_2$], 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

This work was supported by a grant (GM26193) from the National Institutes of Health.

REFERENCES

1 R. Engle, *Chem. Rev.*, 77 (1977) 349–367.
2 A. Rosenthal and M. Ratcliffe, *Can. J. Chem.*, 54 (1976) 91–96.
3 M. Chmielewski, J. N. BeMiller, and D. P. Cerretti, *J. Org. Chem.*, in press.
4 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 43 (1978) 2923–2925.
5 S. Hanessian and P. Lavallée, *Methods Carbohydr. Chem.*, 7 (1976) 49–55.
6 R. L. Whistler and A. K. M. Anisuzzaman, *Methods Carbohydr. Chem.*, 8 (1980) 227–231.