Carbohydrate Research, 131 (1984) 180–184
Elsevier Science Publishers B.V , Amsterdam – Printed in The Netherlands

Note

Synthesis of the phosphono analogues of α- and β-D-mannopyranosyl phosphate

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(Received October 27th, 1983; accepted for publication, January 19th, 1984)

Phosphono analogues of naturally occurring phosphates are of interest because of their potential biological activity[1]. In the carbohydrate field, many phosphono analogues of the phosphates involved in metabolism have been synthesised, but analogues in which the methylenephosphonic group is linked to the anomeric centre have been reported only recently[2–4].

We now describe the synthesis of the phosphono analogues of α- and β-D-mannopyranosyl phosphate, which play an important role in carbohydrate metabolism.

The *C*-glycosylation procedure chosen involved the Wittig reaction of 2,3,4,6-tetra-*O*-benzyl-D-mannose[5] (**1**) with methylenetriphenylphosphorane, and the best results were obtained using tetrahydrofuran at 45° for 15 h. The mercuriocyclisation of the olefinic product **2**, effected with mercuric acetate, afforded a mixture of the α- and β-mercurio derivatives (**3** and **4**) which were isolated by chromatography. The anomeric configuration of **3** and **4** was deduced on the basis of ^{1}H-n.m.r. and optical rotation data. The derivative **3** of higher R_F adopts the $^1C_4$ conformation (see *J* values in Table I) with the bulky anomeric substituent in an equatorial orientation; the axial–axial coupling constant for H-1,2 unambiguously establishes the α configuration. The β configuration must therefore be assigned to the derivative **4** of lower R_F, which adopts the $^4C_1$ conformation (see *J* values in Table I) with the bulky anomeric substituent equatorial. Moreover, the two diastereoisomers obey Hudson's rule, which requires the α isomer be more dextrorotatory than the β.

Halogenodemercuriation of **3** using 1 equiv. of bromine in dichloromethane led to partial debenzylation, affording, in addition to the desired bromide, substantial amounts of a bromide lacking one benzyl group. Better results were obtained using iodine, and the iodides **5** and **6** were obtained in yields of 84 and 75%, respectively. Each iodo derivative was submitted to the Arbuzov reaction, to afford the

0008-6215/84/$ 03.00

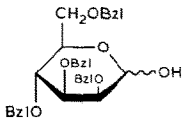
TABLE I

^{1}H-N M R DATA (200 MHz) FOR COMPOUNDS **3** AND **4**

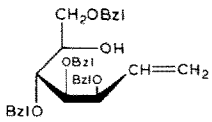
Compound	*Chemical shifts (δ scale)*									
	H-1'a	*H-1'b*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*	*Others*
3 ($CDCl_3$)	1.97(dd)	2.02(dd)	4.08(ddd)	3.30(dd)	3.62(dd)	3.7–3.8(m)	3.98(ddd)	3.54(dd)	3.7–3.8(m)	4.2–4.6 (4 OCH_2Ph); 7.1–7.5 (4 Ph)
3 (C_6D_6)	1.65(dd)	1.79(dd)	4.34(dt)	3.68(dd)	4.1–4.2(m)	4.1–4.2(m)[a]	4.4–4.5(m)[a]	4.07(d)		4.4–4.8 (4 OCH_2Ph); 7.4–7.7 (4 Ph)
4 ($CDCl_3$)	1.35(dd)	2.03(dd)	3.90(ddd)	3.6–3.7(m)	3.73(dd)	3.85(t)	3.53(ddd)	3.6–3.7(m)		4.5–5.1 (4 OCH_2Ph); 7.1–7.5 (4 Ph)
4 (C_6D_6)	0.78(dd)	1.38(dd)	3.24(ddd)	3.12(dd)	3.29(dd)	4.02(t)	3.38(ddd)	3.61(dd)	3.68(dd)	4.2–5.0 (4 OCH_2Ph); 7.1–7.5 (4 Ph)

Compound	*Coupling constants (Hz)*									
	$J_{1'a,1'b}$	$J_{1'a,1}$	$J_{1'b,1}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
3 ($CDCl_3$)	12	7	6	9	2.5	2	<1	6	6	10
3 (C_6D_6)	12	7	7	8	2.5	—	—	6.5		—
4 ($CDCl_3$)	12	2.5	6	1	3	9	9	4.5	2.5	—
4 (C_6D_6)	12	3	6	1	2.5	9.5	9.5	2.5	4	12

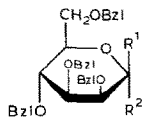
[a]These assignments may be interchanged.



1

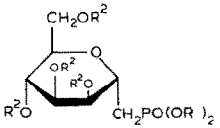


2

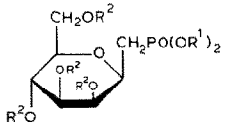


3 R^1 = H, R^2 = CH_2HgCl
4 R^1 = CH_2HgCl, R^2 = H
5 R^1 = H, R^2 = CH_2I
6 R^1 = CH_2I, R^2 = H

corresponding phosphonic esters **7** and **8**. Removal of the protecting groups, effected in one step employing 6 equiv. of iodotrimethylsilane, afforded the phosphono analogues (**9** and **10**) of α- and β-D-mannopyranosyl phosphate, isolated as monoammonium salts.



7 R^1 = Et, R^2 = Bzl
9 R^1 = R^2 = H



8 R^1 = Et, R^2 = Bzl
10 R^1 = R^2 = H

Previous reports[6,7] indicated that the chemical shift of the carbon linked to the anomeric centre of a sugar is at higher field when this atom is *cis* to the substituent at C-2, than when it is *trans*. Although **3** and **4** possess different conformations, they obey this rule. However, the pairs **7/8** and **9/10** show the opposite relationship, indicating that this rule cannot be fully extended to *C*-mannopyranosyl derivatives.

EXPERIMENTAL

General. — N.m.r. spectra were recorded with Varian XL-100 (^{13}C), Bruker WP-80, or Varian XL-200 (^{31}P, ^{1}H) spectrometers. Chromatography was carried out on Silica Gel S (Riedel-De Haen AG) using the flash procedure. The usual work-up refers to dilution with water, extraction with an organic solvent, washing the extract with water to neutrality, drying (Na_2SO_4), and evaporation of the solvent.

Reaction of 2,3,4,6-tetra-O-benzyl-D-mannose (**1**) *with methylenetriphenylphosphorane.* — To a suspension of methyltriphenylphosphonium iodide (28 g, 69 mmol) in tetrahydrofuran (140 mL) under dry nitrogen was added, dropwise, butyl-lithium (69 mmol). After 30 min of vigorous stirring, a solution of **1** (17.8 g) in tetrahydrofuran (160 mL) was added, the mixture was kept at 45° for 15 h, cooled to −10°, filtered, and worked-up in the usual manner. The resulting syrup was subjected to chromatography, to afford 1,2-dideoxy-3,4,5,7-tetra-*O*-benzyl-D-

manno-hept-1-enitol (**2**) as an oil (6.1 g, 34%), $[\alpha]_D^{20}$ +5° (*c* 3, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 2.68 (d, 1 H, *J* 5 Hz, OH), 3.5–4.9 (14 H, HC-O), 5.39 (m, 2 H, $=CH_2$), 5.98 (ddd, 1 H, *J* 17, 10, and 7.5 Hz, HC=), and 7.4 (20 H, 4 Ph); ^{13}C, 119.5 ($=CH_2$) and 136.0 (HC=) p.p.m.

Anal. Calc. for $C_{35}H_{38}O_5$: C, 78.04; H, 7.11. Found: C, 77.55; H, 6.76.

*(2,3,4,6-Tetra-*O*-benzyl-α-*D*-mannopyranosyl)methylmercury chloride* (**3**) *and its β anomer* (**4**). — A solution of **2** (6 g, 11 mmol) in tetrahydrofuran (50 mL) was stirred overnight with mercuric acetate (3.53 g, 11 mmol). A solution of potassium chloride (1.35 g, 18 mmol) in water (4 mL) was then added and the mixture was stirred for 30 min. The usual work-up afforded a yellow syrup which was subjected to chromatography to afford (95% combined yield) **3** (2.25 g) and **4** (5.85 g).

Compound **3** had m.p. 76–77° (from ether–hexane), $[\alpha]_D^{20}$ +40° (*c* 0.8, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): 34.0 p.p.m. (CH_2HgCl).

Anal. Calc. for $C_{35}H_{37}ClHgO_5$: C, 54.33; H, 4.82. Found: C, 54.59; H, 4.62.

Compound **4** had m.p. 65–66° (from ether–hexane), $[\alpha]_D^{20}$ −32° (*c* 0.4, chloroform). ^{13}C-N.m.r. data ($CDCl_3$): 31.5 p.p.m. (CH_2HgCl).

Anal. Found: C, 54.61; H, 5.10.

*(2,3,4,6-Tetra-*O*-benzyl-α-*D*-mannopyranosyl)methyl iodide* (**5**) *and its β anomer* (**6**). — To a solution of **3** (2 g, 2.5 mmol) in dichloromethane (20 mL) was added a solution of iodine (715 mg, 2.8 mmol) in dichloromethane (35 mL). The mixture was stirred for 1 h, washed with aqueous 10% sodium sulfite and then aqueous 5% potassium iodide, and worked-up as usual to afford, after filtration through silica gel, **5** as an oil (1.53 g, 84%), $[\alpha]_D^{20}$ +12° (*c* 2.5, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 3.4–4.3 (9 H, HC-O and CH_2I), 4.6 (8 H, 4 PhCH_2O), and 7.4 (20 H, 4 Ph); ^{13}C, 7.0 (t, CH_2I), 68.6 (t), 70.6 (d), 71.1 (t), 72.3 (t), 72.5 (t), 73.2 (t), 74.3 (2 d), 74.8 (d), 75.7 (d), and 127–138 p.p.m. (Ph).

Anal. Calc. for $C_{35}H_{37}IO_5$: C, 63.25; H, 5.61. Found: C, 62.89; H, 5.47.

Treatment of **4** (2 g, 2.5 mmol), as described for **3**, afforded **6** as an oil (1.28 g, 75%), $[\alpha]_D^{20}$ −3° (*c* 2.7, chloroform), N.m.r. data ($CDCl_3$): ^1H, δ 3.1–5.2 (17 H) and 7.4 (20 H, 4 Ph); ^{13}C, 4.0 (t, CH_2I), 69.8 (t), 72.6 (t), 73.7 (t), 75.1 (t), 75.1 (d), 75.3 (d), 75.3 (t), 79.0 (d), 80.4 (d), 85.2 (d), and 126.9–139.3 p.p.m. (Ph).

Anal. Found: C, 62.82; H, 5.52.

*Diethyl (2,3,4,6-tetra-*O*-benzyl-α-*D*-mannopyranosyl)methylphosphonate* (**7**) *and its β anomer* (**8**). — The iodo derivative **5** (1.3 g, 2 mmol) was treated for 3 h with boiling triethyl phosphite (15 mL). The excess of reagent was removed under reduced pressure and the residue was subjected to chromatography, to afford **7** as an oil (1.14 g, 84%), $[\alpha]_D^{20}$ −6° (*c* 2.4, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.25 and 1.26 (2 t, 6 H, *J* 7 Hz, Me), 2.02 (ddd, 1 H, $J_{1'a,1}$ 7, $J_{1'a,1'b}$ 15, $J_{H,P}$ 19 Hz, H-1'a), 2.13 (ddd, 1 H, $J_{1'b,1}$ 7, $J_{1'b,1'a}$ 15, $J_{H,P}$ 19, H-1'b), 3.7–4.8 (19 H, HC-O), and 7.4 (20 H, Ph); ^{13}C, 27.2 p.p.m. ($J_{C,P}$ 123 Hz, CH_2P); ^{31}P, 28.1 p.p.m.

Treatment of the iodo derivative **6** (1.0 g, 1.6 mmol), as described for **5**, afforded **8** as an oil (943 mg, 88%), $[\alpha]_D^{20}$ −22° (*c* 2, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.25 and 1.26 (2 t, 6 H, *J* 7 Hz, Me), 2.06 (ddd, 1 H, $J_{1'a,1}$ 7, $J_{1'a,1'b}$

16, $J_{H,P}$ 18 Hz, H-1'a), 2.17 (ddd, 1 H, $J_{1'b,1}$ 6, $J_{1'b,1'a}$ 16, $J_{H,P}$ 18 Hz, H-1'b), 3.4–5.2 (19 H, HC-O), and 7.4 (20 H, 4 Ph); ^{13}C, 28.5 p.p.m. ($J_{C,P}$ 141 Hz, CH_2P); ^{31}P, 28.3 p.p.m.

(α-D-Mannopyranosyl)methylphosphonic acid (**9**) *and its β isomer* (**10**). — A solution of **7** (1 g, 1.5 mmol) in carbon tetrachloride (1.5 mL) was treated at 0° under dry nitrogen with iodotrimethylsilane (2.31 g, 11.6 mmol). After 30 min, the reaction was quenched with water (0.5 mL), the solvent was evaporated under reduced pressure, and the residue was subjected to chromatography on cellulose (1-propanol–ammonia–water, 6:3:1), to afford hygroscopic, crystalline **9** as the monoammonium salt (346 mg, 80%), $[\alpha]_D^{20}$ +21° (*c* 0.3, water). N.m.r. data (D_2O): ^1H, δ 2.00 (dd, 2 H, $J_{H,P}$ 18, $J_{1',1}$ 7 Hz, CH_2P), and 3.3–4.0 (7 H, HC-O); ^{13}C, 30.0 ($J_{C,P}$ 130 Hz, CH_2P), 62.7 (t, C-6), 73.0 ($J_{C,P}$ 8.7 Hz, C-1), 68.8, 71.8, 75.3, and 76.2 p.p.m. (d, C-2,3,4,5); ^{31}P, 19.9 p.p.m.

Anal. Calc. for $C_7H_{18}NO_8P \cdot H_2O$: C, 28.67; H, 6.87; N, 4.80. Found: C, 27.39; H, 7.07; N. 4.43.

Treatment of **8** (0.8 g, 1.2 mmol), as described for **7**, afforded hygroscopic, crystalline **10** as the monoammonium salt (242 mg, 70%), $[\alpha]_D^{20}$ −12° (*c* 0.6, water). N.m.r. data (D_2O): ^1H, δ 1.96 (dd, 2 H, $J_{H,P}$ 18 Hz, $J_{1',1}$ 7 Hz, CH_2P), and 3.5–4.5 (7 H, HC-O); ^{13}C, 31.6 ($J_{C,P}$ 133 Hz, CH_2P), 62.9 (t, C-6), 72.7 ($J_{C,P}$ 8 Hz, C-1), 68.6, 75.6, 76.0, and 81.4 p.p.m. (d, C-2,3,4,5); ^{31}P, 21.07 p.p.m.

Anal. Found: C, 27.47; H, 7.11; N, 3.97.

ACKNOWLEDGMENTS

This contribution is part of the "Progetto Finalizzato Chimica Fine e Secondaria", CNR, Italy. We thank Farmitalia–Carlo Erba S.P.A. Milano for a scholarship (to R.P.).

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