Carbohydrate Research, 148 (1986) 168–172
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Synthesis of 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-α- and -β-D-ribopyranose

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(Received April 15th, 1985; accepted for publication in revised form, September 23rd, 1985)

For the chemical modification of sugars to give derivatives having phosphorus in the hemiacetal ring, there has been described a new method for $-CH_2-P$ bond-formation by deoxygenation of a HO-CH-P group at the terminal carbon atom of sugars by 1,1′-(thiocarbonyl)diimidazole (TCDI), followed by treatment with tributyltin hydride, and its use for the synthesis of 1,2,4-tri-*O*-acetyl-5-deoxy-3-*O*-methyl-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-α- and -β-D-xylopyranoses[1] and -β-D-ribopyranoses[2], and 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-α-and -β-D-xylopyranoses[3]. The four title compounds have now been prepared, in the foregoing way, and characterized by 200-MHz, ^{1}H-n.m.r. spectral analysis.

Methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**1**), obtained by oxidation with dicyclohexylcarbodiimide–dimethyl sulfoxide of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[4], was used as the starting material for this synthesis.

Compound **1** was treated in a refrigerator with methyl phenylphosphinate and triethylamine, to give the 5-*C*-[methoxy(phenyl)phosphinyl] adduct (**2**) quantitatively. Treatment of **2** with TCDI afforded the 5-*O*-[imidazol-1-yl-(thiocarbonyl)] compound **3** in 93% yield. Reductive elimination of the imidazol-1-yl-(thiocarbonyl)oxy group of **3** by refluxing with tributyltin hydride produced syrupy, 5-*C*-deoxygenated compound **2**, namely, **4**, in 87% yield; this showed the signals of H-5,5′ at δ 2.1–2.5 in its ^{1}H-n.m.r. spectrum.

Reduction of **4** with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) afforded the 5-*C*-(phenylphosphinyl) compound (**5**) in 72% yield; this showed i.r. absorption at 2330 cm^{-1} (P-H), and a half P-H signal at δ 11.6 in its ^{1}H-n.m.r. spectrum.

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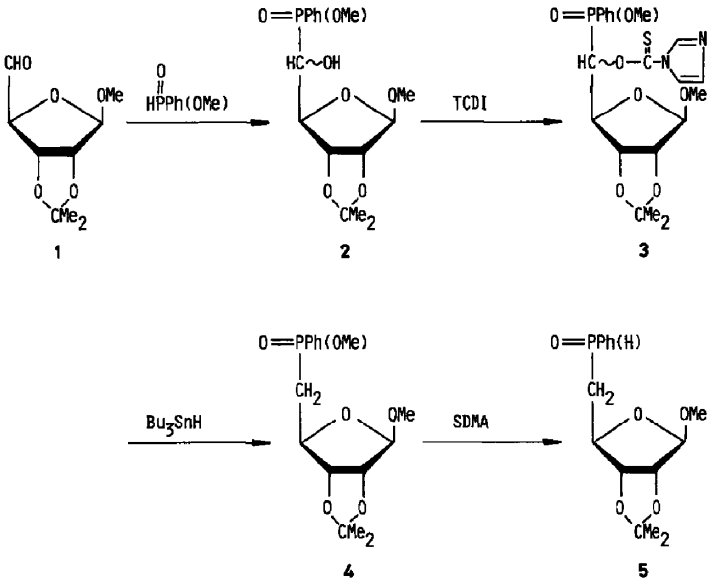
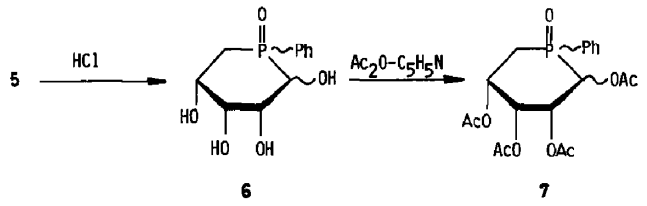


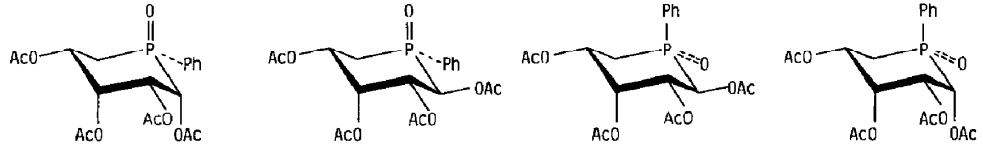
Hydrolysis of **5** with 0.1M hydrochloric acid, and acetylation of the product (**6**) with acetic anhydride–pyridine gave crude, syrupy **7** (60% from **5**). The mixture of compounds **7** was separated by column chromatography on silica gel, using ethyl acetate–methanol as the eluant, into four major fractions, which will be referred to as A, B, C, and D (according to their decreasing R_F values).

Fractions A, B, C, and D were respectively obtained in yields of 2.7, 21, 21, and 4.3% from **5**; each exhibited four acetoxyl groups in the ^{1}H-n.m.r. spectrum, and the molecular-ion peak at *m/z* 426 (M^+), corresponding to $C_{19}H_{23}O_9P$, in the high-resolution mass-spectrum of each; and this formula was supported by elemental analysis of fractions B, C, and D.

The 200-MHz, ^{1}H-n.m.r. spectra of fractions C and D showed relatively low values of δ for the H-2 and H-4 signals, compared with those of fractions A and B. The upfield shift of the H-2 and H-4 signals can be explained in terms of the shielding effect of the phenyl group linked axially to the ring-P atom. The H-1 signal of fraction C showed a triplet at δ 6.15, with $J_{1,2} = J_{1,P} = 11.9$ Hz, whereas that of fraction D showed a triple doublet at 6.09, with $J_{1,2}$ 3.6, $J_{1,P}$ 9.6, and $J_{1,5}$ 0.9 Hz (probably due to 1,5 W coupling). These splitting patterns for fractions C and



D resembled those of structurally similar analogs, namely, 5-deoxy-3-*O*-methyl-5-*C*-[(*S*)-phenylphosphinyl]-β-D-ribopyranose triacetate[2] (**8**), 5-deoxy-5-*C*-[(*S*)-isopropylphosphinyl]-α- and -β-D-ribopyranose tetraacetate[5] (**9**), and 5-deoxy-5-*C*-[(*S*)-methoxyphosphinyl]-β-D-ribopyranose tetraacetate[6] (**10**). The optical rotation of fraction C was more negative than that of fraction D. Therefore, fractions C and D were respectively identified as 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*S*)-phenylphosphinyl]-β-D-ribopyranose (**7c**) and 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*S*)-phenylphosphinyl]-α-D-ribopyranose (**7d**), both in the $^4C_1$(D) conformation.



The shift patterns in the ^{1}H-n.m.r. spectra of fractions A and B were somewhat similar, and showed relatively high δ values for the H-2 and H-4 signals (compared with those of **7c** and **7d**). The H-1 signal of fraction B showed a double doublet at δ 5.83, with $J_{1,2}$ 11.4 and $J_{1,P}$ 2.9 Hz; this splitting pattern resembled those of the *R* and β anomer of **8**, and the *R* and β anomer of **10**. The H-1 signal of fraction A was overlapped by the H-2,3,4 signals. The optical rotation of fraction A was more positive than that of fraction B. Therefore, fractions A and B were respectively considered to be 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*R*)-phenylphosphinyl]-α-D-ribopyranose (**7a**) and 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*R*)-phenylphosphinyl]-β-D-ribopyranose (**7b**), both in the $^4C_1$(D) conformation.

The β anomers **7b** and **7c** preponderate in the formation of the D-ribopyranoses, most probably owing to the thermodynamic stabilities of the anomers of the precursor **6**, α anomers being destabilized because of the axial–axial interaction between OH-1 and OH-3.

EXPERIMENTAL

The general experimental methods have been reported[1]. The ^{1}H-n.m.r. spectra were recorded with a Hitachi R-600 (60 MHz) spectrometer or a Varian XL-200 (200 MHz) spectrometer, with $CDCl_3$ as the solvent and Me_4Si as the internal standard.

Methyl 2,3-O-isopropylidene-5-C-[methoxy(phenyl)phosphinyl]-β-D-allo- and α-L-talo-pentofuranoside (**2**). — Compound **1** (2.0 g) was treated with methyl phenylphosphinate (2 mL) and triethylamine (3 mL) in a refrigerator overnight, as previously described[1], to give **2** as colorless crystals (mixture of diastereoisomers) in quantitative yield; m.p. 151–152° (a part consisting of plates), 170–171° (a part consisting of needles) (recrystallized from ethanol); $[\alpha]_D^{27}$ −32.7° (*c* 2.45, $CHCl_3$); ^{1}H-n.m.r. data: δ 1.18, 1.24, 1.40 (3 s, 6 H, CMe_2), 3.29 (s, 3 H, OMe-1), 3.68, 3.70

(2 d, 3 H, J_P 11 Hz, P-OMe), 4.0 (m, 1 H, H-5), 4.35–6.0 (m, 5 H, one proton disappearing on deuteration, H-1,2,3,4, and OH-5), and 7.25–7.95 (m, 5 H, C_6H_5); *m/z* 359 ($M^+ + 1$).

Anal. Calc. for $C_{16}H_{23}O_7P$: C, 53.36; H, 6.74. Found: C, 53.34; H, 6.61.

Reaction of **2** *with TCDI.* — Compound **2** (1.50 g) was treated with TCDI (1.20 g) in 1,2-dichloroethane for 30 min at 90° (bath), as described[1], to give yellow, syrupy *methyl 5-*O*-[imidazol-1-yl-(thiocarbonyl)]-2,3-*O*-isopropylidene-5-*C*-[methoxy(phenyl)phosphinyl]-β-*D*-allo- and α-*L*-talo-pentofuranoside* (**3**) (1.83 g, 93%); R_F 0.5 (50:1 EtOAc–MeOH); $[\alpha]_D^{27}$ −3.2° (*c* 2.35, $CHCl_3$); ^{1}H-n.m.r. data: δ 1.24, 1.29, 1.43 (3 s, 6 H, CMe_2), 2.98, 3.14 (2 s, 3 H, OMe-1), 3.71, 3.77 (2 d, 3 H, J_P 11 Hz, P-OMe), 4.35–5.0 (m, 4 H, H-1,2,3,4), 6.3 (m, 1 H, H-5), and 6.9–8.2 (m, 8 H, C_6H_5 and imidazolyl H).

Deoxygenation of **3**. — Compound **3** (1.66 g) was treated with tributyltin hydride (1.5 mL) in toluene for 1 h at 120° (bath), as described[1], to give colorless, syrupy *methyl 5-deoxy-2,3-*O*-isopropylidene-5-*C*-[methoxy(phenyl)phosphinyl]-β-*D*-ribofuranoside* (**4**) (1.05 g, 87%); R_F 0.38 (50:1 EtOAc–MeOH); $[\alpha]_D^{27}$ −2.7° (*c* 3.17, $CHCl_3$); ^{1}H-n.m.r. data: δ 1.31, 1.45 (2 s, 6 H, CMe_2), 2.1–2.5 [m, 2 H, H-5,5′ (overlapped)], 3.13, 3.22 (2 s, 3 H, OMe-1), 3.61 (d, 3 H, J_P 11 Hz, P-OMe), 4.5–4.9 (m, 4 H, H-1,2,3,4), and 7.2–7.95 (m, 5 H, C_6H_5); *m/z* 343 ($M^+ + 1$).

Reduction of **4**. — Compound **4** (1.01 g) was treated with SDMA (2.0 g) in THF under argon for 1 h at 0°, as described[1], to give colorless, syrupy *methyl 5-deoxy-2,3-*O*-isopropylidene-5-*C*-(phenylphosphinyl)-β-*D*-ribofuranoside* (**5**) (0.66 g, 72%); R_F 0.15 (EtOAc); $[\alpha]_D^{27}$ −18.9° (*c* 2.51, $CHCl_3$); ν_{max}^{KBr} 2330 cm^{-1} (P–H); ^{1}H-n.m.r. data: δ 1.26, 1.37, 1.42 (3 s, 6 H, CMe_2), 2.0–2.6 (m, 2 H, H-5,5′), 3.29, 3.33 (2 s, 3 H, OMe-1), 4.0–4.95 (m, 4 H, H-1,2,3,4), 7.1–7.9 (m, 5 H, C_6H_5), and 11.6 (m, ½ H, a half of P-H; the signal of another half-proton usually appears at δ 2–3.5 (J_{P-H} 400–500 Hz)[5,7,8], but, in this spectrum, its signal was not detected, owing to overlapping with H-5,5′ or OMe-1).

Hydrolysis of **5**, *and 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(R)- and (S)-phenylphosphinyl]-α- and -β-*D*-ribopyranoses* (**7a–d**). — Compound **5** (634 mg) was treated with 0.1M HCl (30 mL) under argon for 3 h at 110° (bath), as described[1], to give syrupy **6** (446 g), which was treated with acetic anhydride (9 mL) in dry pyridine (30 mL), to afford the crude mixture **7** as a syrup (521 mg, 60% from **5**); this was separated by chromatography on a column of silica gel with 25:1 EtOAc–methanol as the eluant, to give, separately, **7a–d**, having the following properties.

*5-[(R)-Phenylphosphinyl]-α-*D*-ribopyranose derivative* (**7a**). R_F 0.55 (25:1 EtOAc–MeOH); colorless solid (23 mg, 2.7% from **5**); $[\alpha]_D^{25}$ +28.2° (*c* 0.71, $CHCl_3$); ^{1}H-n.m.r. (200 MHz) data: δ 1.86, 1.92, 1.99, 2.15 (4 s, 12 H, OAc-1,2,3,4), 2.1–2.4, 2.7–2.9 (m, 2 H, H-5,5′), 5.6–5.75 (m, 4 H, H-1,2,3,4), and 7.45–7.85 (m, 5 H, C_6H_5); *m/z* 427 (0.60, $M^+ + 1$), 426 (0.52, M^+), 385 (13, $M^+ + 1 - CH_2CO$), 368 (30, $M^+ - CH_3CO_2H$), 325 (100, $M^+ + 1 - CH_2CO - CH_3CO_2H$), 282 (49, $M^+ - 2\ CH_2CO - CH_3CO_2H$), 265 (30, $M^+ + 1 - CH_2CO - 2\ CH_3CO_2H$), and 223 (75, $M^+ + 1 - 2\ CH_2CO - 2\ CH_3CO_2H$).

5-C-[(R)-*Phenylphosphinyl*]-β-D-*ribopyranose derivative* (**7b**). R_F 0.54 (25:1 EtOAc–MeOH); colorless plates (184 mg, 21% from **5**); m.p. 209–210° (recrystallized from ethanol–hexane), $[\alpha]_D^{25}$ +11.7° (*c* 3.0, $CHCl_3$); ^{1}H-n.m.r. (200 MHz) data: δ 1.19, 1.94, 1.96, 2.22 (4 s, 12 H, OAc-1,2,3,4), 2.40–2.55 (m, 2 H, H-5,5′), 5.68 (ddd, 1 H, $J_{1,2}$ 11.4, $J_{2,3}$ 3.2, $J_{2,P}$ 2.4 Hz, H-2, overlapping with H-4), 5.77 (dd, 1 H, $J_{2,3}$ 3.2, $J_{3,4}$ 2.6 Hz, H-3), 5.83 (dd, 1 H, $J_{1,2}$ 11.4, $J_{1,P}$ 2.9 Hz, H-1), and 7.45–7.81 (m, 5 H, C_6H_5); *m/z* 426 (M^+).

Anal. Calc. for $C_{19}H_{23}O_9P$: C, 53.52; H, 5.44. Found: C, 53.38; H, 5.41.

5-C-[(S)-*Phenylphosphinyl*]-β-D-*ribopyranose derivative* (**7c**). R_F 0.51 (25:1 EtOAc–MeOH); colorless needles (183 mg, 21% from **5**); m.p. 219.5–220° (recrystallized from ethanol–hexane), $[\alpha]_D^{25}$ −64.1° (*c* 3.04, $CHCl_3$); ^{1}H-n.m.r. (200 MHz) data: δ 1.92, 2.00, 2.07, 2.19 (4 s, 12 H, OAc-1,2,3,4), 2.73 (ddd, 1 H, $J_{4,5a}$ 12.2, $J_{5a,5e}$ 14.6, $J_{5a,P}$ 18.2 Hz, H-5*a*), 2.82 (dddd, 1 H, $J_{3,5e}$ 1.1, $J_{4,5e}$ 5.0, $J_{5a,5e}$ 14.6, $J_{5e,P}$ 33.4 Hz, H-5*e*), 4.91 (ddd, 1 H, $J_{1,2}$ 11.9, $J_{2,3}$ 3.5, $J_{2,P}$ 2.3 Hz, H-2), 5.03 (dddd, 1 H, $J_{3,4}$ 2.4, $J_{4,5a}$ 12.2, $J_{4,5e}$ 5.0, $J_{4,P}$ 2.4 Hz, H-4), 5.56 (ddd, 1 H, $J_{2,3}$ 3.5, $J_{3,4}$ 2.4, $J_{3,5e}$ 1.1 Hz, H-3), 6.15 (t, 1 H, $J_{1,2} = J_{1,P}$ = 11.9 Hz, H-1), and 7.5–8.0 (m, 5 H, C_6H_5); *m/z* 426 (M^+).

Anal. Calc. for $C_{19}H_{23}O_9P$: C, 53.52; H, 5.44. Found: C, 53.41; H, 5.45.

5-C-[(S)-*Phenylphosphinyl*]-α-D-*ribopyranose derivative* (**7d**). R_F 0.48 (25:1 EtOAc–MeOH); colorless plates (37 mg, 4.3% from **5**); m.p. 211.5–212.5° (recrystallized from ethanol–hexane), $[\alpha]_D^{25}$ −29.0° (*c* 1.12, $CHCl_3$); ^{1}H-n.m.r. (200 MHz) data: δ 1.95, 2.03, 2.14, 2.22 (4 s, 12 H, OAc-1,2,3,4), 2.7–2.9 (m, 2 H, H-5,5′), 4.77 (ddd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 2.4, $J_{2,P}$ 1.8 Hz, H-2), 4.92 (m, 1 H, H-4), 5.41 (ddd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 2.1, $J_{3,5e}$ 0.9 Hz, H-3), 6.09 (ddd, 1 H, $J_{1,2}$ 3.6, $J_{1,5e}$ (probably) 0.9, $J_{1,P}$ 9.6 Hz, H-1), and 7.5–8.0 (m, 5 H, C_6H_5); *m/z* 426 (M^+).

Anal. Calc. for $C_{19}H_{23}O_9P$: C, 53.52; H, 5.44. Found: C, 53.38; H, 5.52.

ACKNOWLEDGMENTS

The authors thank Dr. T. Hirabayashi (Nagoya Institute of Technology, Japan) for recording the 200-MHz, ^{1}H-n.m.r. spectra.

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