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Note

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

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Recently, 5-deoxy-3-*O*-methyl-5-*C*-(phenylphosphinyl)-D-ribopyranose[1] (**8**) and 5-deoxy-5-*C*-(isopropylphosphinyl)-D-xylopyranose derivatives[2] (**9**) were prepared; conformational analysis showed that the β anomers of **8** and the (*R*) forms of **9** had been formed preponderantly.

The four title compounds have now been prepared and separated, in order to study the relationship between the repulsive interaction on the axial OH-3 and the steric ones on the bulky *P*-isopropyl group.

RESULTS AND DISCUSSION

The Michaelis–Arbuzov reaction of methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranoside (**1**) with diethyl isopropylphosphonite gave syrupy methyl 5-deoxy-5-*C*-(ethoxyisopropylphosphinyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**2**) in 77% yield. Reduction of **2** with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) in oxolane (THF), and separation by column chromatography on silica gel, afforded methyl 5-deoxy-2,3-*O*-isopropylidene-5-*C*-(isopropylphosphinyl)-β-D-ribofuranoside (**3**) in 31% yield. Compound **3** showed i.r. absorption at 2320 cm^{-1} (P–H), and a P–H signal at δ 6.57 (J_P 455 Hz, disappearing on deuteration).

Hydrolysis of **3** with 0.1M hydrochloric acid under argon for 3 h at 110° (bath), and acetylation of the product (**4**) with acetic anhydride–pyridine, afforded crude, syrupy **5** (89% from **3**). Compound **5** was separated by column chromatography on silica gel (using ethyl acetate–hexane, gradually changed to ethyl acetate, and then to 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 respectively gave colorless prisms, m.p. 204–205° (11% from **3**); colorless needles, m.p. 178–179° (18% from **3**); a colorless syrup (17% from **3**); and a colorless syrup (8% from **3**). Each exhibited four acetoxyl groups in

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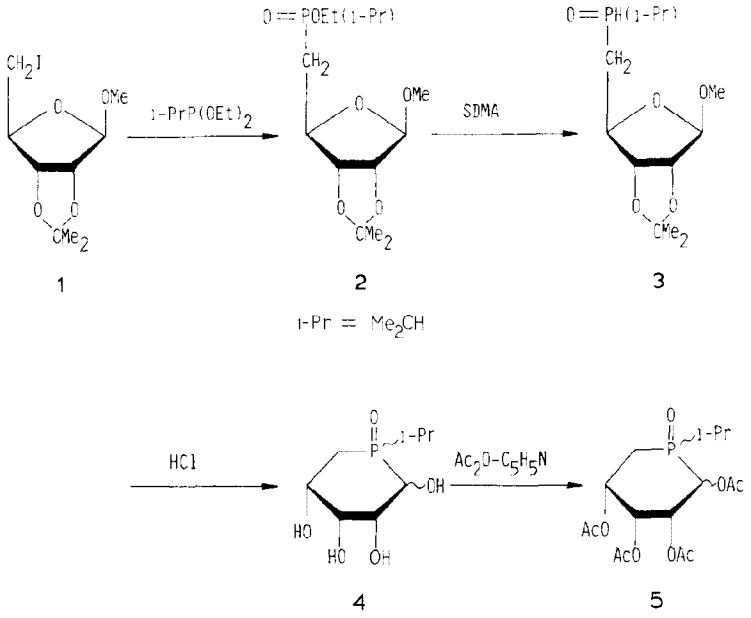
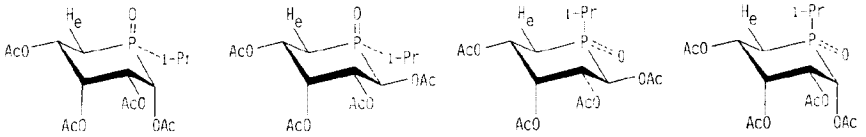


the ^{1}H-n.m.r. spectrum, and the molecular-ion peak at *m/z* 392, corresponding to $C_{16}H_{25}O_9P$, in the high-resolution mass spectrum of each, and this formula was supported by the elemental analysis of fractions A and B.

Structure assignments of these compounds were determined by comparing their ^{1}H-n.m.r. spectra and optical rotations with those of similar analogs whose structures had already been determined, namely, 1,2,4-tri-*O*-acetyl-5-deoxy-5-*C*-[(*R*) and (*S*)-methoxyphosphinyl]-3-*O*-methyl-α- and -β-D-xylopyranose[3] (**6**), 1,2,4-tri-*O*-acetyl-5-deoxy-3-*O*-methyl-5-*C*-[(*R*) and (*S*)-phenylphosphinyl]-α- and -β-D-xylopyranose[4] (**7**) and -β-D-ribopyranose[1] (**8**), and 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*R*) and (*S*)-isopropylphosphinyl]-α- and -β-D-xylopyranose[2] (**9**).

The ^{1}H-n.m.r. spectra of fractions C and D showed relatively high values of δ for the H-2 and H-4 signals (compared with those of fractions A and B). The H-1 signal of the β-acetate **5c** consisted of a triplet at δ 5.90, with $J_{1,2}$ and $J_{1,P}$ 11.0 Hz, whereas that of the α anomer **5d** showed a triple doublet at δ 5.70, with a large $J_{1,P}$ (8.0 Hz) and a small $J_{1,2}$ (2.8 Hz) value, and $J_{1,5}$ 1.1 Hz, due to 1,5 W coupling. Such remarkable shift and splitting patterns of fractions C and D were observed in the case of compounds **6** [(S), α and β; ref. 3], **7** [(S), α and β; ref. 4], **8** [(S), β; ref. 1], and **9** [(S), α; ref. 2]. Therefore, fractions C and D were respectively identified as 5-deoxy-5-*C*-[(*S*)-isopropylphosphinyl]-β-D-ribopyranose (structure **5c**) and 5-deoxy-5-*C*-[(*S*)-isopropylphosphinyl]-α-D-ribopyranose (structure **5d**), 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 low δ values for the H-2 and H-4 signals, com-



5a 5b 5c 5d

pared with those for **5c** and **5d**, and a half H-1 signal of the α-acetate **5a** showed a double doublet at δ 5.71, with $J_{1,2}$ (3.1 Hz) and $J_{1,5}$ (1.0 Hz) due to 1,5 W coupling. The optical rotation of fraction A was larger than that of fraction B. Therefore, fractions A and B were respectively considered to be 5-deoxy-5-*C*-[(*R*)-isopropylphosphinyl]-α-D-ribopyranose (structure **5a**) and 5-deoxy-5-*C*-[(*R*)-isopropylphosphinyl]-β-D-ribopyranose (structure **5b**), both in the $^4C_1$(D) conformation.

α Anomers (**5a** and **5d**) were obtained in low yield, compared with β anomers (**5b** and **5c**). An explanation of this result is that β anomers of precursor **4** are more stable than α anomers thereof, because the repulsive interaction between axial OH-1 and OH-3 of α anomers is stronger than the steric interaction (as is seen for compound **9**; ref. 2) between the bulky *P*-isopropyl and β-hydroxyl group (or axial H-2 and H-4).

EXPERIMENTAL

The general experimental methods have been reported[2].

*Methyl 5-deoxy-5-*C*-(ethoxyisopropylphosphinyl)-2,3-*O*-isopropylidene-β-*D*-ribofuranoside* (**2**). — Compound **1** (4.05 g) was treated with diethyl isopropylphosphonite (20 mL) as previously described[2], to give syrupy **2** (3.21 g, 77%); $[\alpha]_D^{18}$ −48.0° (*c* 2.45, $CHCl_3$); ^{1}H-n.m.r. data: δ 0.9–1.5 (m, 15 H, CMe_2, P-CMe_2, P-OCMe), 1.5–2.2 (m, 3 H, H-5,5′, P-CH-), 3.25, 3.31 (2 s, 3 H, OMe-1), 3.8–4.35 (m, 2 H, P-OCH_2-), 4.35–4.7 (m, 3 H, H-2,3,4), and 4.90 (s, 1 H, H-1); *m/z* 322 (M^+).

*Methyl 5-deoxy-2,3-*O*-isopropylidene-5-*C*-(isopropylphosphinyl)-*D*-ribofuranoside* (**3**). — Compound **2** (1.56 g) was treated with SDMA (2.5 g, 70% solution in benzene) as described, to give a crude mixture that afforded colorless, syrupy **3** (0.42 g, 31%) by chromatography on a column of silica gel with 20:1 EtOAc–methanol as the eluant; $[\alpha]_D^{18}$ −29.2° (*c* 1.71, $CHCl_3$); ν_{max}^{KBr} 2320 cm^{-1} (P–H); ^{1}H-n.m.r. data: δ 0.8–1.5 (m, 12 H, CMe_2), 1.6–2.5 (m, 3 H, H-5,5′, P-CH-), 3.37, 3.39 (2 s, 3 H, OMe-1), 4.4–4.8 (m, 3 H, H-2,3,4), 4.94 (s, 1 H, H-1), and 6.57 (dm, 1 H, J_P 455 Hz, P-H); *m/z* 278 (M^+).

Hydrolysis of **3**, *and 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(R) and (S)-isopropylphosphinyl]-α- and -β-*D*-ribopyranose* (**5a–d**). — Compound **3** (390 mg) was treated with 0.1M HCl (15 mL) as described, to give syrupy **4** (295 mg), which was treated with acetic anhydride (6 mL) in dry pyridine (20 mL), to afford crude mixture **5** as a syrup (489 mg, 89% from **3**); this was separated by chromatography on

a column of silica gel with 10:1 EtOAc–hexane, gradually changed to EtOAc, and then 20:1 EtOAc–methanol, as the eluant, to give **5a–d**, having the following properties.

5-C-[(R)-Isopropylphosphinyl]-α-D-ribopyranose (**5a**); R_F 0.62 (20:1 EtOAc–methanol); colorless prisms (63 mg, 11% from **3**); m.p. 204–205° (recrystallized from ethanol–hexane), $[\alpha]_D^{28}$ +20.8° (*c* 1.20, $CHCl_3$); ^{1}H-n.m.r. data: δ 0.9–1.5 (m, 6 H, P-CMe_2), 1.95, 1.99, 2.13 (3 s, 12 H, OAc-1,2,3,4), 1.5–2.55 (m, 3 H, H-5,5′, P-CH-), 5.0–5.35 (m, 0.5 H, 1/2 H-4), 5.35–5.65 (m, 3 H, 1/2 H-1, H-2,3, 1/2 H-4), and 5.71 (dd, 0.5 H, $J_{1,2}$ 3.1, $J_{1,5}$ 1.0 Hz, 1/2 H-1); *m/z* 392 (M^+).

Anal. Calc. for $C_{16}H_{25}O_9P$: C, 48.98; H, 6.42; 392.1235 (M). Found: C, 48.74; H, 6.42; 392.1253 (M).

5-C-[(R)-Isopropylphosphinyl]-β-D-ribopyranose (**5b**); R_F 0.58 (20:1 EtOAc–methanol); colorless needles (101 mg, 18% from **3**); m.p. 178–179° (recrystallized from EtOAc–hexane), $[\alpha]_D^{28}$ −22.0° (*c* 1.82, $CHCl_3$); ^{1}H-n.m.r. data: δ 1.0–1.5 (m, 6 H, P-CMe_2), 1.93, 1.95, 2.08, 2.12 (4 s, 12 H, OAc-1,2,3,4), 1.55–2.6 (m, 3 H, overlapping with OAc, H-5,5′, P-CH-), 5.05–5.35 (m, 0.5 H, 1/2 H-4), and 5.4–5.7 (m, 3.5 H, H-1,2,3, 1/2 H-4); *m/z* 392 (M^+).

Anal. Calc. for $C_{16}H_{25}O_9P$: C, 48.98; H, 6.42; 392.1235 (M). Found: C, 48.83; H, 6.42; 392.1254 (M).

5-C-[(S)-Isopropylphosphinyl]-β-D-ribopyranose (**5c**); R_F 0.56 (20:1 EtOAc–methanol); colorless syrup (95 mg, 17% from **3**); $[\alpha]_D^{28}$ −10.9° (*c* 1.37, $CHCl_3$); ^{1}H-n.m.r. data: δ 1.0–1.65 (m, 6 H, P-CMe_2), 1.96, 2.00, 2.09, 2.17 (4 s, 12 H, OAc-1,2,3,4), 2.25–2.7 (m, 3 H, H-5,5′, P-CH-), 5.17 (dt, 1 H, $J_{1,2}$ 11.0, $J_{2,3} = J_{2,P}$ = 2.3 Hz, H-2), 4.7–5.35 (m, 1 H, overlapping with H-2, H-4), 5.53 (t, 1 H, $J_{2,3} = J_{3,4}$ = 2.3 Hz, H-3), and 5.90 (t, 1 H, $J_{1,2} = J_{1,P}$ = 11.0 Hz, H-1); *m/z* 392 (M^+).

Anal. Calc. for $C_{16}H_{25}O_9P$: (M): 392.1235. Found: 392.1238.

5-C-[(S)-Isopropylphosphinyl]-α-D-ribopyranose (**5d**); R_F 0.55 (20:1 EtOAc–methanol); colorless syrup (45 mg, 8% from **3**); $[\alpha]_D^{28}$ +4.4° (*c* 1.14, $CHCl_3$); ^{1}H-n.m.r. data: δ 0.85–1.65 (m, 6 H, P-CMe_2), 1.98, 2.00, 2.13, 2.15 (4 s, 12 H, OAc-1,2,3,4), 1.7–2.95 (m, 3 H, overlapping with OAc, H-5,5′, P-CH-), 5.07 (t, 1 H, $J_{1,2} = J_{2,3}$ = 2.8, $J_{2,P}$ 0.7 Hz, H-2), 4.75–5.3 (m, 1 H, overlapping with H-2, H-4), 5.42 (t, 1 H, $J_{2,3} = J_{3,4}$ = 2.8 Hz, H-3), and 5.70 (ddd, 1 H, $J_{1,2}$ 2.8, $J_{1,P}$ 8.0, $J_{1,5}$ 1.1 Hz, H-1); *m/z* 392 (M^+).

Anal. Calc. for $C_{16}H_{26}O_9P$ (M + H): 393.1313. Found: 393.1323.

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