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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-xylopyranose

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At an earlier stage of our investigations on the synthesis of sugar analogs having a phosphorus atom in the hemiacetal ring, 5-*C*-(alkylphosphinyl)-D-xylopyranose derivatives (alkyl = ethyl or butyl)[1,2] were prepared, but conformational analysis of these compounds was not performed.

In order to study the conformational and steric effects of a bulky alkyl group situated on the ring-phosphorus atom, the title compounds were prepared, and three kinds of them were separated.

RESULTS AND DISCUSSION

The Michaelis–Arbuzov reaction of 3-*O*-acetyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose[2] (**1**) with diethyl isopropylphosphonite gave, in 41% yield, syrupy 3-*O*-acetyl-5-deoxy-5-*C*-(ethoxyisopropylphosphinyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (**2**) which was purified by column chromatography on silica gel. Reduction of **2** with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) in oxolane (tetrahydrofuran; THF) in the usual way[1–3] afforded 5-deoxy-1,2-*O*-isopropylidene-5-*C*-(isopropylphosphinyl)-α-D-xylofuranose (**3**) in almost quantitative yield; this showed an i.r. absorption band at 2310 cm^{-1} (P–H), and in the ^{1}H-n.m.r. spectrum, a characteristic J_{P-H} value of 459 Hz at δ 6.77 (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 in the usual way[1–3], afforded a crude syrup (**5**). The syrup was separated by column chromatography on silica gel, using ethyl acetate–methanol as the eluant, into two major fractions and one minor fraction, which will be refered to as A, B, and C (according to their decreasing R_F values).

Fractions A, B, and C respectively gave colorless needles, m.p. 203.5–204.5°; colorless needles, m.p. 239–240°; and a colorless syrup; each exhibited four acetoxyl groups in its ^{1}H-n.m.r. spectrum, and the molecular-ion peak at *m/z* 392,

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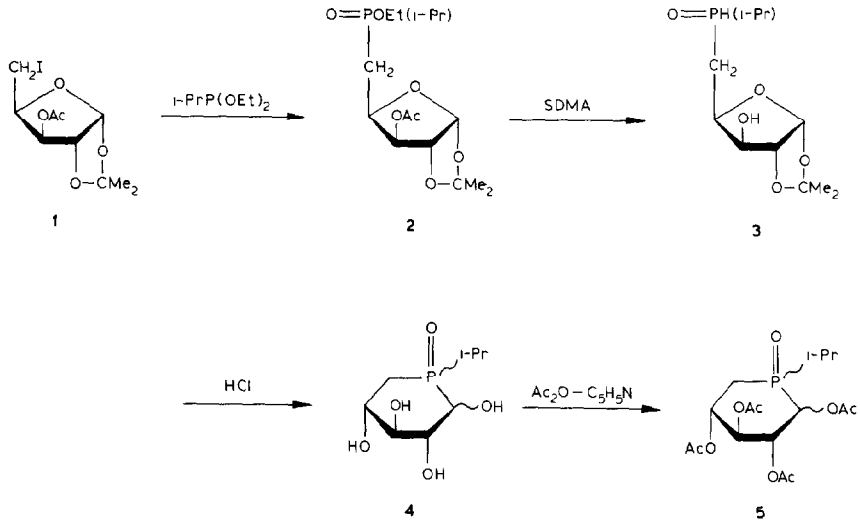
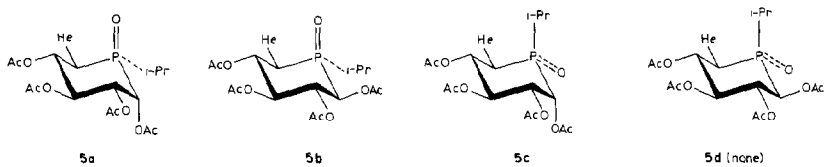


corresponding to $C_{16}H_{25}O_9P$, in its high-resolution, mass spectrum, and this formula was supported by the elemental analysis of fractions A and B.

The structural assignments of these compounds were determined by comparing the ^{1}H-n.m.r. spectra with those of structurally similar analogs: 5,6-dideoxy-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-α- and -β-L-idohexopyranose[4] (**6**), 5-deoxy-5-*C*-[(*R*)- and (*S*)-methoxyphosphinyl]-α- and -β-D-xylopyranose[5] (**7**), 5-deoxy-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-α- and -β-D-xylopyranose[6] (**8**), and 5-deoxy-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-β-D-ribopyranose[7] (**9**).

The ^{1}H-n.m.r. spectra of fractions A and B showed relatively low values of δ for the H-2 and H-4 signals (compared with those of fraction C). The downfield shifts of the H-2 and H-4 signals can be explained in terms of the deshielding effect of the oxygen atom linked axially to the ring-P atom. The H-1 signal of the α-acetate **5a** consisted of a double triplet at δ 5.73, with a large $J_{1,P}$ (9.3 Hz) and a small $J_{1,2}$ (1.9 Hz) value, and, probably, $J_{1,5}$ (1.9 Hz), due to 1.5 W coupling, whereas that of the β anomer **5b** showed a double doublet at δ 5.42 with $J_{1,2}$ 9.0 Hz and $J_{1,P}$ 2.8 Hz. These splitting patterns of fractions A and B resembled those of **6** (*S*-α,β), **7** (*R*-α,β), **8** (*R*-α,β), and **9** (*R*-β). The optical rotation of fraction A was larger than that of fraction B. Therefore, fractions A and B were respectively identified as 5-deoxy-5-*C*-[(*R*)-isopropylphosphinyl]-α-D-xylopyranose (**5a**) and 5-deoxy-5-*C*-[(*R*)-isopropylphosphinyl]-β-D-xylopyranose (**5b**), both in the $^4C_1$(D) conformation.



In the ^{1}H-n.m.r. spectrum of fraction C, a double triplet at δ 5.79, with $J_{1,2}$ 2.3, $J_{1,5}$ (probably) 2.3, and $J_{1,P}$ 9.0 Hz, indicated that H-1 and H-2 are gauche, as observed in the ^{1}H-n.m.r. spectra of **6** (*R*-α), **7** (*S*-α), and **8** (*S*-α). Therefore, fraction C was identified as 5-deoxy-5-*C*-[(*S*)-isopropylphosphinyl]-α-D-xylopyranose (**5c**), in the $^4C_1$(D) conformation.

Compound **5c** was obtained in low yield, compared with compounds **5a** and **5b**, and 5-deoxy-5-*C*-[(*S*)-isopropylphosphinyl]-β-D-xylopyranose (**5d**) was not detected. These results were explained in terms of steric interaction between the axial H-2 and H-4, the equatorial OH at the anomeric carbon atom, and the bulky isopropyl group linked axially to the ring-P atom of the precursor **4**.

EXPERIMENTAL

General methods. — Melting points were measured with a micro melting-point apparatus (Yanagimoto Seisakusho, Japan) and are uncorrected. Column chromatography was performed by using Merck Lobar silica gel. T.l.c. was conducted on layers of silica G-10 (Nakarai Chemicals, Ltd., Japan). All reactions were monitored by t.l.c., and the products were detected with sulfuric acid–ethanol, or cobalt(II) chloride–ethanol. Optical rotations were determined with an Atago–Polax polarimeter (Atago, Ltd., Japan). I.r. spectra were recorded with an A-3 spectrophotometer (Japan Spectroscopic Co., Ltd.). ^{1}H-N.m.r. spectra were recorded, for solutions in $CDCl_3$, with a Hitachi–Perkin–Elmer R-20 (60 MHz) instrument. Chemical shifts are reported as δ values, relative to tetramethylsilane (δ 0.0) as the internal standard. Mass spectra were recorded with a Hitachi RMU7MGGS-MS spectrometer.

3-O-Acetyl-5-deoxy-5-C-(ethoxyisopropylphosphinyl)-1,2-O-isopropylidene-α-D-xylofuranose (**2**). — A solution of **1** (10 g) in diethyl isopropylphosphonite (20 mL) was heated at 130–140° (bath), while the phosphonite (5 mL) was added in several portions. The excess of phosphonite was evaporated *in vacuo*. The residue was dissolved in chloroform, and the solution was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*; the residue was purified by chromatography on silica gel, using 20:1 EtOAc–methanol as the eluant, to give **2** as a colorless syrup (4.2 g, 41%); $[\alpha]_D^{23}$ −0.40° (*c* 2.48, $CHCl_3$); ^{1}H-n.m.r. data: δ 0.9–1.65 (m, 15 H, CMe_2, P–OCMe, P–CMe_2), 1.65–2.35 (m, 3 H, H-5,5′, P–CH–), 2.05 (s, 3 H, OAc), 3.75–4.35 (m, 2 H, P–OCH_2–), 4.47 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-2, overlapping with H-4), 5.10 (d, 1 H, $J_{3,4}$ 2.6 Hz), and 5.8 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1); *m/z* 350 (M^+).

5-Deoxy-1,2-O-isopropylidene-5-C-(isopropylphosphinyl)-D-xylofuranose (**3**). — To a solution of **2** (1.30 g) in THF (40 mL) was added a 70% solution of SDMA (5.0 g in benzene) plus THF (20 mL) at 0° under argon. After 30 min, a small amount of water containing conc. HCl (0.5 mL) was added at 0° (to decompose the excess of SDMA), the mixture filtered, and the filtrate evaporated *in vacuo*, to give **3** (0.97 g, 99%) as a syrup; $[\alpha]_D^{20}$ −17.3° (*c* 2.98, $CHCl_3$); ν_{max}^{KBr} 2310

cm^{-1} (P–H); ^{1}H-n.m.r. data: δ 0.95–1.65 (m, 12 H, CMe_2, P–CMe_2), 1.8–2.05 (m, 3 H, H-5,5′, P–CH–), 4.09 (d, 1 H, $J_{3,4}$ 2.6 Hz, H-3), 4.50 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-2, overlapping with H-4), 4.94 (broad, 1 H, disappearing on deuteration, OH), 5.85 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), and 6.77 (dm, 1 H, J_{P-H} 459 Hz, P-H); *m/z* 264 (M^+).

Hydrolysis of **3** *and 1,2,3,4-tetra-*O*-acetyl-5-deoxy-5-*C*-[(*R*)- and (*S*)-isopropylphosphinyl]-α- and -β-*D*-xylopyranose* (**5a–c**). — To a solution of **3** (429 mg) was added 0.1M HCl (20 mL). The mixture was heated under argon for 3 h at 110° (bath), cooled, diluted with water, and the acid neutralized with Amberlite IR-45 ion-exchange resin; this resin was then washed with water (3 × 20 mL) and ethanol (3 × 20 mL), and filtered, and the filtrate and washings were combined, and evaporated *in vacuo,* to give syrupy **4** (352 mg). This was treated with acetic anhydride (7 mL) in dry pyridine (20 mL) in the usual way[1–3], to give crude, syrupy **5** (488 mg, 77% from **3**). The syrup was separated by chromatography on a column of silica gel by elution with 10:1 EtOAc–hexane, which was gradually changed to 10:1 EtOAc–methanol, to give a mixture of **5a** and **5b** (371 mg, 58%), and **5c**. The mixture of **5a** and **5b** was separated by column chromatography, to give **5a** and **5b**.

5-C-[(R)-Isopropylphosphinyl]-α-D-xylopyranose derivative (**5a**): R_F 0.42 (EtOAc); colorless needles (149 mg, 23% from **3**); m.p. 203.5–204.5° (recrystallized from ethanol); $[\alpha]_D^{18}$ +22.2° (*c* 1.35, $CHCl_3$); ^{1}H-n.m.r. data: δ 0.85–1.55 (m, 6 H, P–CMe_2), 1.6–2.7 (m, 3 H, H-5,5′, P–CH–), 1.93, 1.99, 2.15 (3 s, 12 H, 4 OAc), 5.1–5.55 (m, 3 H, H-2,3,4), and 5.73 (dt, 1 H, $J_{1,2} = J_{1,5}$ = 1.9 Hz, $J_{1,P}$ 9.3 Hz, H-1); *m/z* 392 (M^+).

Anal. Calc. for $C_{16}H_{25}O_9P$: C, 48.98; H, 6.42. Found: C, 48.86; H, 6.40.

5-C-[(R)-Isopropylphosphinyl]-β-D-xylopyranose derivative (**5b**): R_F 0.32 (EtOAc); colorless needles (131 mg, 21% from **3**); m.p. 239–240° (recrystallized from ethanol); $[\alpha]_D^{18}$ −15.2° (*c* 0.66, $CHCl_3$); ^{1}H-n.m.r. data: δ 0.9–1.45 (m, 6 H, P–CMe_2), 1.45–2.60 (m, 3 H, H-5,5′, P–CH–), 1.93, 1.97, 2.06 (3 s, 12 H, 4 OAc), 5.1–5.7 (m, 3 H, H-2,3,4), and 5.42 (dd, 1 H, $J_{1,2}$ 9.0, $J_{1,P}$ 2.8 Hz); *m/z* 392 (M^+).

Anal. Calc. for $C_{16}H_{25}O_9P$: C, 48.98; H, 6.42. Found: C, 48.80; H, 6.30.

5-C-[(S)-Isopropylphosphinyl]-α-D-xylopyranose derivative (**5c**): R_F 0.19 (EtOAc); colorless syrup (73 mg, 11% from **3**); $[\alpha]_D^{18}$ +33.6° (*c* 1.19, $CHCl_3$); ^{1}H-n.m.r. data: δ 0.9–1.65 (m, 6 H, P–CMe_2), 1.65–2.9 (m, 3 H, H-5,5′, P–CH–), 1.99, 2.02, 2.19 (3 s, 12 H, 4 OAc), 4.93 (dd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 10.2 Hz, H-2, overlapping with H-4), 5.57 (t, 1 H, $J_{2,3} = J_{3,4}$ = 10.2 Hz, H-3) and 5.79 (dt, 1 H, $J_{1,2} = J_{1,5}$ = 3.5 Hz, $J_{1,P}$ 9.0 Hz, H-1); *m/z* 392 (M^+).

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