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Note

Synthesis of 5(*R*)- or 5(*S*)- 5,6-anhydro-1,2-*O*-isopropylidene-5-*C*-phosphinyl-α-D-*xylo*-hexofuranose derivatives

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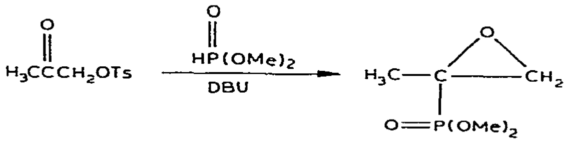
Ever since fosfomycin (1,2-epoxypropylphosphonic acid) was found to be an antibiotic, many α,β-epoxyphosphinyl compounds have been synthesized. We have found that dimethyl 1,2-epoxy-1-methylethanephosphonate (**2**) is readily obtained in good yield by reaction of 2-oxo-1-(*p*-tolylsulfonyloxy)propane (**1**) with dimethyl phosphite in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1 equiv.) at room temperature[1].



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By using this reaction, α,β-epoxyphosphinyl derivatives having sugar moieties were synthesized, and we now describe the synthesis of 5,6-anhydro-1,2-*O*-isopropylidene-5-*C*-phosphinyl-α-D-*xylo*-hexofuranose derivatives.

RESULTS AND DISCUSSION

The reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexofuranos-5-ulose[2] (**3**) with dimethyl phosphite (**5**) in methanol in the presence

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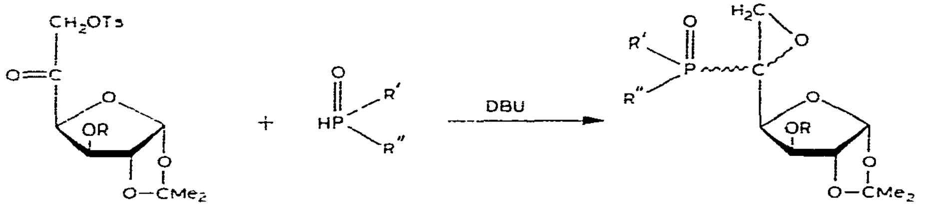
of one equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene for 20 h at room temperature gave a crystalline compound of (5*R* or 5*S*)-5,6-anhydro-3-*O*-benzyl-5-*C*-(dimethoxyphosphinyl)-1,2-*O*-isopropylidene-α-D-*xylo*-furanose (**8**) in 70% yield: m.p. 107–108°, $[\alpha]_D^{24}$ −6.0° (*c* 1.27, $CHCl_3$). The structure of **8** was determined by elemental analysis and by study of the ^1H-n.m.r. and i.r. spectra. The ^1H-n.m.r. spectrum of **8** in chloroform-*d* showed a signal, due to a methylene group of the terminal epoxide group, at δ 2.98, 3.05; the signals due to the tosyl group disappeared, and the i.r. spectrum (liq. film) showed an absorption due to the P=O group at 1225 cm^{-1}; the absorption at 1740 cm^{-1}, due to the C=O group, disappeared.

Similarly, **9**, $[\alpha]_D^{23}$ +2.7° (*c* 2.96, $CHCl_3$), was prepared in 69% yield from **3**, **5**, and DBU; **10**, $[\alpha]_D^{24}$ −35.4° (*c* 4.52, $CHCl_3$), in 69% yield from **4**, **5**, and DBU: and **11**, m.p. 120–121°, $[\alpha]_D^{24}$ −43.6° (*c* 0.99, ethanol), in 46% yield from **4**, **7**, and DBU. Each product mainly consisted of one stereoisomer (*R* or *S*) at C-5.



3 R = PhCH$_2$
4 R = Me

5 R' = R'' = OMe
6 R' = OEt , R'' = Ph
7 R' = OMe , R'' = Ph

8 R = PhCH$_2$, R' = R'' = OMe
9 R = PhCH$_2$, R' = OEt , R'' = Ph
10 R = Me , R' = R'' = OMe
11 R = Me , R' = OMe , R'' = Ph

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were determined with a Yanagimoto-OR-10 polarimeter. Silica gel B-5F (Wako Pure Chemical Industries Ltd., Japan) was used for t.l.c. Products were detected, in t.l.c., with sulfuric acid–ethanol or cobalt(II) chloride–acetone, or both, as indicator. All reactions were monitored by t.l.c. I.r. spectra were recorded with IR-S and IR-A-1 (Japan Optical Laboratory) spectrophotometers. ^1H-N.m.r. spectra were recorded with a Hitachi–Perkin–Elmer R-20A (60 MHz) spectrometer, with tetramethylsilane as the internal standard.

Materials. — 3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexofuranose[2] (**3**) and 1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexofuranos-5-ulose[3] (**4**) were prepared by Inouye's[2] and Zhdanov and Polenov's[3] methods. However, although the **3** and **4** obtained contained some of the 5-*O*-(methylthio)methyl derivative, they were used without further purification. Ethyl phenylphosphonite (**6**) and methyl phenylphosphonite (**7**) were prepared from phenylphosphonous dichloride[4].

Synthesis of (5R *or* 5S)-*5,6-anhydro-3-*O*-benzyl-5-*C*-(dimethoxyphosphinyl)-*

*1,2-*O*-isopropylidene-α-*D-xylo-*hexofuranose* (**8**). — To a mixture of **3** (5.6 g) and dimethyl phosphite (1.5 g) in methanol (10 mL) was added DBU (2.1 g) during 1 h at 0°, and the solution was kept in a refrigerator for 48 h. The methanol and unreacted dimethyl phosphite were removed *in vacuo*, and then a solution of the residue in chloroform was successively washed with aqueous sodium hydrogencarbonate and water, dried (sodium sulfate), and evaporated, to afford a syrup which was chromatographed in a column of silica gel, using 1:2 (v/v) ethyl acetate–petroleum ether as the eluant. The fractions were suitably pooled, and evaporated *in vacuo*, to give a syrup (3.4 g, 70%) which crystallized after 2 days; m.p. 107–108° (ethyl acetate–hexane), $[\alpha]_D^{24}$ −6.1° (*c* 1.27, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.28, 1.47 (s, 6 H, CMe_2), 2.98, 3.05 (dd, 2 H, $J_{6,6'}$ 6.0, $J_{P,CCH}$ 12.0 Hz, H-6,6′), 3.73 [d, 6 H, $J_{P,OCH}$ 11.0 Hz, $P(OMe)_2$], 4.25–4.65 (m, 3 H, H-2,3,4), 4.65 (s, 2 H, CH_2Ph), 5.87 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), and 7.21–7.48 (m, 5 H, Ph).

Anal. Calc. for $C_{18}H_{25}O_8P$: C, 54.00; H, 6.29. Found: C, 53.90; H, 6.46.

Synthesis of (5R *or* 5S)*-5,6-anhydro-3-*O*-benzyl-5-*C*-(ethoxyphenylphosphinyl)-1,2-*O*-isopropylidene-α-*D-xylo-*hexofuranose* (**9**). — To a mixture of **3** (12.0 g) and ethyl phenylphosphonite (4.8 g) in ethanol (30 mL) was added DBU (4.4 g) during 2 h at 0°; the solution was kept in a refrigerator for 48 h, and processed as already described, to give syrupy **9** (8.2 g, 69%), $[\alpha]_D^{23}$ +2.7° (*c* 2.96, $CHCl_3$); ^{1}H-n.m.r. data (CCl_4): δ 1.10–1.42 (m, 9 H, POCMe, CMe_2), 2.50–3.15 (m, 2 H, H-6,6′), 3.78–4.77 (m, 7 H, H-2,3,4, CH_2Ph, $POCH_2C$), 5.65, 5.73 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), and 7.17–8.00 (m, 10H, CPh, PPh); *m/z* 460 (M^+).

Synthesis of (5R *or* 5S)*-5,6-anhydro-5-*C*-(dimethoxyphosphinyl)-1,2-*O*-isopropylidene-3-*O*-methyl-α-*D-xylo-*hexofuranose* (**10**). — To a mixture of **4** (4.0 g) and dimethyl phosphite (1.4 g) in methanol (15 mL) was added DBU (1.9 g) during 1 h at 0°, and the solution was kept in a refrigerator for 48 h. Processing as already described gave syrupy **10** (2.5 g, 75%); $[\alpha]_D^{24}$ −35.4° (*c* 4.52, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.31, 1.48 (s, 6 H, CMe_2), 2.98, 3.06 (dd, 2 H, $J_{6,6'}$ 6.2, $J_{P,CCH}$ 11.5 Hz, H-6,6′), 3.48 (s, 3 H, OMe), 3.83 [d, 6 H, $J_{P,OCH}$ 10.7 Hz, $P(OMe)_2$], 4.05 (d, 1 H, H-4), 4.50–4.69 (m, 2 H, H-2,3), and 5.87 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1).

Anal. Calc. for $C_{17}H_{23}O_7P$: C, 55.14; H, 6.26. Found: C, 54.57; H, 6.38.

Synthesis of (5R *or* 5S)*-5,6-anhydro-1,2-*O*-isopropylidene-5-*C*-(methoxyphenylphosphinyl)-3-*O*-methyl-α-*D-xylo-*hexofuranose* (**11**). — To a mixture of **4** (5.0 g) and methyl phenylphosphonite (2.5 g) in methanol (20 mL) was added DBU (2.5 g) during 1 h at 0°, and the solution was kept in a refrigerator for 48 h. Processing as already described gave crystalline compound **11** (2.6 g, 46%); m.p. 120–121°, $[\alpha]_D^{24}$ −43.6° (*c* 0.99, EtOH); ^{1}H-n.m.r. data ($CDCl_3$): δ 1.28, 1.45 (s, 6 H, CMe_2), 2.95–3.40 (m, 2 H, H-6,6′), 3.25 (s, 3 H, COMe), 3.75 (d, 3 H, $J_{P,OCH}$ 10.7 Hz, POMe), 4.0–4.8 (m, 3 H, H-2,3,4), 5.78 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), and 7.3–8.0 (m, 5 H, Ph).

Anal. Calc. for $C_{17}H_{23}O_7P$: C, 55.14; H, 6.26. Found: C, 54.57; H, 6.38.

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