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# SYNTHESIS OF 1,2,4-TRI-*O*-ACETYL-5-DEOXY-3-*O*-METHYL-5-*C*-[(*R*)- AND -(*S*)-PHENYLPHOSPHINYL]-β-D-RIBOPYRANOSE

KUNIAKI SEO
*Department of Industrial Chemistry, Numazu College of Technology, Numazu-shi 410 (Japan)*
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## ABSTRACT

5-Deoxy-1,2-*O*-isopropylidene-5-*C*-(methoxyphenylphosphinyl)-3-*O*-methyl-α-D-ribofuranose (**4**) was prepared from 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*ribo*-pentodialdo-1,4-furanose by an addition reaction with methyl phenylphosphinate, followed by deoxygenation of the terminal HO-CH-P group of the adduct by successive reaction with 1,1′-thiocarbonyldiimidazole and tributyltin hydride. Treatment of **4** with sodium dihydrobis(2-methoxyethoxy)aluminate, followed by deacetonation with mineral acid, and acetylation with acetic anhydride–pyridine, gave mainly the two title compounds, which were isolated by column chromatography on silica gel, and characterized by 90-MHz, $^1$H-n.m.r.-spectral analysis.

## INTRODUCTION

Sugar analogs having a phosphorus atom in the hemiacetal ring are interesting not only from the viewpoint of their physicochemical properties but also from that of the possible utility of their biological activities.

In earlier work[1–4], a few compounds of the pentopyranose type were prepared from 5-deoxy-5-*C*-phosphinyl-D-pentofuranose precursors afforded by the Michaelis–Arbuzov reaction of 5-deoxy-5-halo derivatives with phosphorus compounds. In a previous paper[5], a new method for C–P bond-formation, by deoxygenation of a HO-CH-P group at the terminal carbon atom of sugars by use of 1,1′-thiocarbonyldiimidazole (TCDI) followed by treatment with tributyltin hydride[6–8], and the synthesis of 1,2,4-tri-*O*-acetyl-5-deoxy-3-*O*-methyl-5-*C*-[(*R*) and (*S*)-phenylphosphinyl]-α- and -β-D-xylopyranose (**10**) were described.

Synthesis is now reported of 1,2,4-tri-*O*-acetyl-5-deoxy-3-*O*-methyl-5-*C*-[(*R*) and (*S*)-phenylphosphinyl]-β-D-ribopyranose (**7**), through 5-deoxy-1,2-*O*-isopropylidene-5-*C*-(methoxyphenylphosphinyl)-3-*O*-methyl-α-D-ribofuranose (**4**), which was achieved in the foregoing convenient way.

## RESULTS AND DISCUSSION

1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-*ribo*-pentodialdo-1,4-furanose[9]

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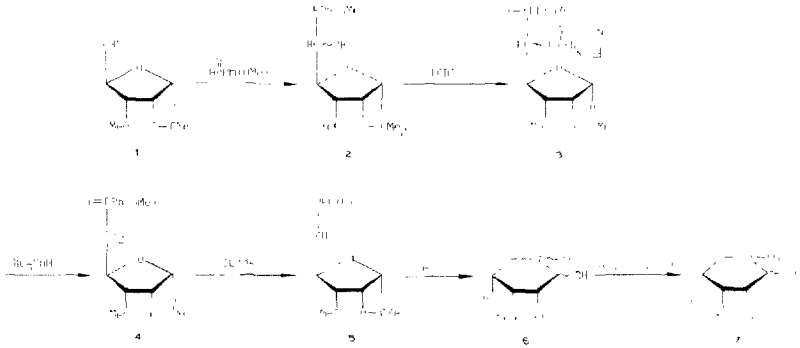
(**1**), obtained by glycol-cleavage oxidation of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-allofuranose with sodium metaperiodate, was used as the starting material for this synthesis.

Compound **1** was treated in a refrigerator with methyl phenylphosphinate and triethylamine, to give 1,2-*O*-isopropylidene-5-*C*-(methoxyphenylphosphinyl)-3-*O*-methyl-α-D-ribofuranose (**2**) in quantitative yield. Treatment of **2** with 1,1'-thiocarbonyldiimidazole (TCDI) in 1,2-dichloroethane at 90° (bath) afforded syrupy 1,2-*O*-isopropylidene-5-*C*-(methoxyphenylphosphinyl)-3-*O*-methyl-5-*O*-(imidazol-1-yl-thiocarbonyl)-α-D-ribofuranose (**3**) in 95% yield; compound **3** showed, in the $^1$H-n.m.r. spectrum, the characteristic signals at δ 6.25–8.8 of an imidazoyl group, which clearly indicated the presence of four diastereoisomers with respect to the terminal carbon atom and the phosphorus atom, namely, at δ 5.64, 5.74, 5.79, and 5.84 ($J_{1,2}$ 3.0 Hz, H-1), 4.49, 4.54, 4.65, and 4.70 ($J_{1,2}$ 3.0 Hz, H-2), and 3.76, 3.79, 3.84, and 3.86 ($J_P$ 10.0 Hz, P-OMe).

Reductive elimination of the imidazol-1-yl-thiocarbonyloxy group of **3** by refluxing with tributyltin hydride in toluene afforded syrupy 5-deoxy-1,2-*O*-isopropylidene-5-*C*-(methoxyphenylphosphinyl)-3-*O*-methyl-α-D-ribofuranose (**4**) in quantitative yield; this showed the signals of H-5,5' at δ 2.0–2.5 in its $^1$H-n.m.r. spectrum.

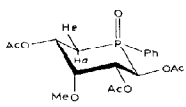


Reduction of **4** with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) in oxolane (tetrahydrofuran; THF) in the usual way[4,5], and separation by column chromatography on silica gel, afforded 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-5-*C*-(phenylphosphinyl)-α-D-ribofuranose (**5**) in 55% yield. Compound **5** showed i.r. absorption at 2330 cm$^{-1}$ (P–H), and a half P–H signal at δ 11.68 (disappearing on deuteration) in its $^1$H-n.m.r. spectrum.

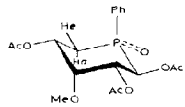
Hydrolysis of **5** with 0.1M hydrochloric acid under argon for 2 h at 100°

(bath), and acetylation of the product (**6**) with acetic anhydride–pyridine in the usual way[1–5] afforded crude, syrupy **7** (75% from **5**). Compound **7** was separated by column chromatography on silica gel, using ethyl acetate–methanol as the eluant, into two major fraction (A and B). Fraction A (the first eluate) and fraction B respectively gave colorless needles, m.p. 228–229°, and colorless prisms, m.p. 181–181.5°, which exhibited three acetoxyl groups in each $^1$H-n.m.r. spectrum, and a molecular-ion peak at *m/z* 398 corresponding to $C_{18}H_{23}O_8P$ in each high-resolution mass spectrum, supporting the results of elemental analysis.

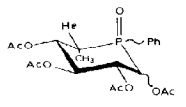
The structure assignments of these compounds were determined by comparing their $^1$H-n.m.r. spectra with those of similar analogs whose structures had already been determined, namely, 1,2,3,4-tetra-*O*-acetyl-5,6-dideoxy-5-*C*-[(*R*) and (*S*)-phenylphosphinyl]-α- and -β-L-idopyranose[10] (**8**), 1,2,4-tri-*O*-acetyl-5-deoxy-5-*C*-[(*R*) and (*S*)-methoxyphosphinyl]-3-*O*-methyl-α- and -β-D-xylopyranose[4] (**9**), and 1,2,4-tri-*O*-acetyl-5-deoxy-3-*O*-methyl-5-*C*-[(*R*) and (*S*)-phenylphosphinyl]-α- and -β-D-xylopyranose[5] (**10**).



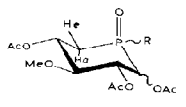

**7a**




**7b**




**8**




**9** R = OMe
**10** R = Ph

The 90-MHz, $^1$H-n.m.r. spectrum of fraction B showed relatively high δ values for the H-2, H-3, and H-4 signals, and a relatively low δ value for the H-1 signal compared with those of fraction A, whereas the remaining signals were essentially the same. Significantly upfield shifts of the H-2 and H-4 signals, and a slightly upfield shift of that for H-3 are explicable in terms of the shielding effect of the axial phenyl group linked to the ring P atom (H-2,4: axial; H-3: equatorial), and the slightly downfield shift of the H-1 signal is considered to indicate that H-1 and the phosphoryl oxygen atom are gauche-disposed. The large $J_{1,2}$ (11.7 Hz) and $J_{1,p}$ (11.7 Hz) values of H-1 of fraction B, and the lack of a $J_{1,5}$ value due to the 1,5-W coupling indicate that H-1 and H-2 are *trans*-disposed, as observed in $^1$H-n.m.r. spectra of **8** [(*R*), β; ref. 10] and **10** [(*S*), β; ref. 5]. Therefore, fraction B was identified as 5-deoxy-5-*C*-[(*S*)-phenylphosphinyl]-β-D-ribopyranose (structure **7b**) in the $^4C_1$(D) conformation.

Also, in the 90-MHz, $^1$H-n.m.r. spectrum of fraction A, a doublet of doublets at δ 5.96, having a large $J_{1,2}$ (11.6 Hz) and a small $J_{1,p}$ (2.5 Hz) value, and the lack of a $J_{1,5}$ value due to the 1,5-W coupling indicate that H-1 and H-2 are *trans*-disposed; the splitting patterns resembled those of **8** [(*S*), β; ref. 10], **9** [(*R*), β; ref. 4], and **10** [(*R*), β; ref. 5]. The downfield shifts of H-2, H-3, and H-4, and the slightly upfield shift of H-1 are considered to indicate that the phenyl group linked to the ring P atom is equatorial, and H-1 and the phenyl group are *gauche*-

disposed. Therefore, fraction A was identified as 5-deoxy-5-C-[(*R*)-phenylphosphinyl]-β-D-ribopyranose (structure **7a**) in the $^4C_1$(D) conformation.

The preponderance of β anomers on preparing these D-ribopyranose analogs, as compared with the D-xylopyranose analogs[5], may be rationalized in terms of the steric relationship between OMe-3 and OH-1 of the precursor **6**.

## EXPERIMENTAL

The general experimental methods have been reported[5]. $^1$H-N.m.r. spectra (90 MHz) were recorded with a JEOL FX-90Q spectrometer, with $CDCl_3$ as the solvent and $Me_4Si$ as the internal standard.

*1,2-O-Isopropylidene-5-C-(methoxyphenylphosphinyl)-3-O-methyl-α-D-ribofuranose* (**2**). — Compound[9] **1** (1.77 g) was treated with methyl phenylphosphinate (1.5 mL) and triethylamine (2 mL) as previously described[5], to give colorless, syrupy **2** in quantitative yield; $[\alpha]_D^{18}$ +46.9° (*c* 1.92, $CHCl_3$); $^1$H-n.m.r. data: δ 1.32, 1.46 (2 s, 6 H, $CMe_2$), 3.16, 3.73, 3.44 (3 s, 3 H, OMe-3), 4.65, 4.75, 4.77 (3 d, 3 H, $J_p$ 12.0 Hz, P-OMe), 3.5–4.5 (broad m, 4 H, 1 H disappearing on deuteration, H-3,4,5, and OH-5), 4.55, 4.56, 4.59 (3 d, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 5.60, 5.63, 5.66 (3 d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), and 7.15–8.10 (m, 5 H, P-$C_6H_5$); *m/z* 358 ($M^+$).

*1,2-O-Isopropylidene-5-C-(methoxyphenylphosphinyl)-3-O-methyl-5-O-(imidazol-1-yl-thiocarbonyl)-α-D-ribofuranose* (**3**). — Compound **2** (1.23 g) was treated with TCDI (1.0 g) as described[5], to give colorless syrupy **3** (1.53 g, 95%); $[\alpha]_D^{18}$ +15.2° (*c* 1.63, $CHCl_3$); $^1$H-n.m.r. data: δ 1.2–1.6 (m, 6 H, $CMe_2$), 3.38, 3.41 (2 s, 3 H, OMe-3), 3.76, 3.79, 3.84, 3.86 (4 d, 3 H, $J_p$ 10.0 Hz, P-OMe), 4.49, 4.54, 4.65, 4.70 (4 d, 1 H, $J_{1,2}$ 3.0 Hz, H-2), 3.0–4.5 (broad m, 3 H, H-3,4,5), 5.64, 5.74, 5.79, 5.84 (4 d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), and 6.25–8.8 (m, 8 H, P-$C_6H_5$ and imidazolyl 3 H); *m/z* 468 ($M^+$).

*5-Deoxy-1,2-O-isopropylidene-5-C-(methoxyphenylphosphinyl)-3-O-methyl-α-D-ribofuranose* (**4**). — Compound **3** (1.23 g) was treated with tributyltin hydride (2 mL) as described[5], to give colorless, syrupy **4** in quantitative yield; $[\alpha]_D^{18}$ +83.3° (*c* 2.10, $CHCl_3$); $^1$H-n.m.r. data: δ 1.1–1.6 (m, 6 H, $CMe_2$), 2.0–2.5 (m, 2 H, H-5,5'), 3.34, 3.40 (2 s, 3 H, OMe-3), 3.61, 3.65 (2 d, 3 H, $J_p$ 12.5 Hz, P-OMe), 3.6–4.4 (m, 2 H, H-3,4), 4.56, 4.60 (2 d, 1 H, $J_{1,2}$ 3.9 Hz, H-2), 5.65, 5.69 (2 d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), and 7.3–8.0 (m, 5 H, P-$C_6H_5$); *m/z* 342 ($M^+$).

*5-Deoxy-1,2-O-isopropylidene-5-C-(phenylphosphinyl)-3-O-methyl-α-D-ribofuranose* (**5**). — Compound **4** (896 mg) was treated with SDMA (1.6 g; 70% solution in benzene) as described[5], to give a crude mixture that afforded colorless, syrupy **5** (452 mg, 55%) by chromatography on a column of silica gel with 20:1 EtOAc–methanol as the eluant; $[\alpha]_D^{18}$ +49.7° (*c* 3.22, $CHCl_3$); $\nu_{max}^{KBr}$ 2330 cm$^{-1}$ (P-H); $^1$H-n.m.r. data: δ 1.36, 1.45, 1.51 (3 s, 6 H, $CMe_2$), 2.1–2.8 (m, 2 H, H-5,5'), 3.42 (s, 3 H, OMe-3), 3.55–4.4 (m, 2 H, H-3,4), 4.56, 4.63 (2 d, 1 H, $J_{1,2}$ 4.0 Hz, H-2), 5.62, 5.67 (2 d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 7.3–8.0 (m, 5 H, P-$C_6H_5$), and 11.68 (m, 0.5 H, P-H).

*Hydrolysis of* **5**, *and 1,2,4-tri-O-acetyl-5-deoxy-3-O-methyl-5-*C*-[(R) and (S)-phenylphosphinyl]-β-*D*-ribopyranose* (**7a,b**). — Compound **5** (381 mg) was treated with 0.1M HCl (15 mL) as described[5], to give syrupy **6** (287 mg), which was treated with acetic anhydride (6 mL) in dry pyridine (20 mL) in the usual way[1–5], to afford crude mixture **6** as a syrup (365 mg); this was separated by chromatography on a column of silica gel with EtOAc, gradually changed to 20:1 EtOAc–methanol, as the eluant, to give **7a** and **7b**, having the following properties.

*5-C-[(R)-Phenylphosphinyl]-β-D-ribopyranose* (**7a**); $R_F$ 0.59 (EtOAc); colorless needles (151 mg, 31% from **5**); m.p. 228–229° (recrystallized from ethanol), $[\alpha]_D^{18}$ +12.4° (*c* 1.61, $CHCl_3$); $^1$H-n.m.r. (90 MHz) data: δ 1.95, 2.10, 2.11 (3 s, 9 H, OAc-1,2,4), 2.25–2.80 (m, 2 H, H-5,5'), 3.66 (s, 3 H, OMe-3), 4.07 (d, 1 H, $J_{2,3} = J_{3,4} - 1.7$ Hz, H-3), 5.59 (4 d, 1 H, $J_{1,2}$ 11.6, $J_{2,3}$ 1.7, $J_{2,p}$ 3.1 Hz, H-2, overlapping with H-4), 5.96 (2 d, 1 H, $J_{1,2}$ 11.6, $J_{1,p}$ 2.5 Hz, H-1), and 7.40–7.95 (m, 5 H, P-$C_6H_5$); *m/z* 398 ($M^+$).

*Anal.* Calc. for $C_{18}H_{23}O_8P$: C, 54.27; H, 5.82. Found: C, 54.23; H, 5.82.

*5-C-[(S)-Phenylphosphinyl]-β-D-ribopyranose* (**7b**); $R_F$ 0.54 (EtOAc); colorless prisms (129 mg, 27% from **5**); m.p. 181–181.5° (recrystallized from ethanol–hexane), $[\alpha]_D^{18}$ −49.1° (*c* 1.73, $CHCl_3$); $^1$H-n.m.r. (90 MHz) data: 2.06, 2.12, 2.13 (3 s, 9 H, OAc-1,2,4), 2.65–3.0 (m, 2 H, H-5,5'), 3.65 (s, 3 H, OMe-3), 3.85 (d, 1 H, $J_{2,3} = J_{3,4} = 1.7$ Hz, H-3), 4.84 (4 d, 1 H, $J_{1,2}$ 11.7, $J_{2,3}$ 1.7, $J_{2,p}$ 3.9 Hz, H-2, overlapping with H-4), 6.26 (t, 1 H, $J_{1,2} = J_{1,p} = 11.7$ Hz, H-1), and 7.5–8.1 (m, 5 H, P-$C_6H_5$); *m/z* 398 ($M^+$).

*Anal.* Calc. for $C_{18}H_{23}O_8P$: C, 54.27; H, 5.82. Found: C, 53.92; H, 5.80.

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