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CARBOHYDRATE RESEARCH

Note

Synthesis of 3-acetamido-1,2,4-tri-*O*-acetyl-3,5-dideoxy-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-α- and -β-D-xylopyranoses

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Amino sugars in which a hydroxyl group of a monosaccharide is replaced by an amino group play a wide variety of important biological roles [1]. Sugar analogs having nitrogen, sulfur, or phosphorus as a ring heteroatom are known as biologically active compounds [2–5]. Therefore, amino sugars having phosphorus in the hemiacetal ring may possibly possess biological activities, such as anticarcinogenic, antibacterial, antiviral, insecticidal, fungicidal, or herbicidal activity. However, only a few hexopyranoses of this kind have been prepared [6,7]. In the present paper we report on the synthesis of the title pentopyranose analogs (Scheme 1).

3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**1**), obtained by hydrolysis and subsequent glycol cleavage of 3-acetamido-3-deoxy-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose [8], was used as the starting material for this synthesis. Compound **1** was treated with methyl phenylphosphinate and triethylamine at room temperature to give the 5-*C*-[methoxy(phenyl)phosphinyl] adduct (**2**) in 88% yield. Treatment of **2** with 1,1-(thiocarbonyl)diimidazole (TCDI) in 1,2-dichloroethane at room temperature [9] afforded the 5-*O*-(imidazol-1-ylthiocarbonyl) compound (**3**). A reductive deoxygenation of **3** by refluxing with tributyltin hydride produced syrupy 3-acetamido-

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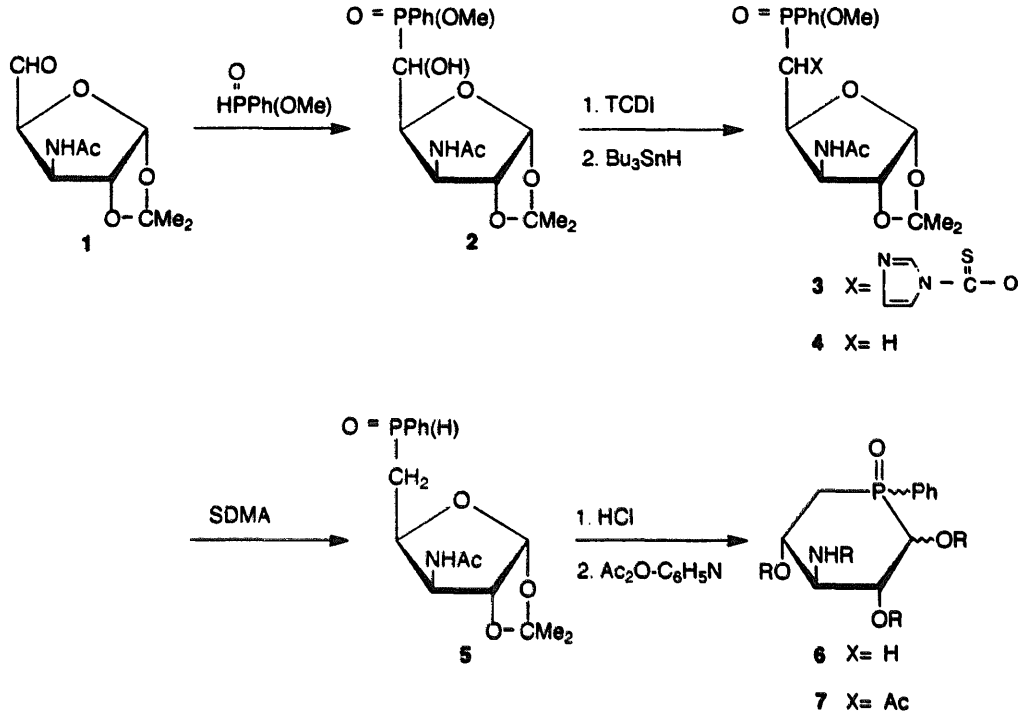

Scheme 1.

3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-[methoxy(phenyl)phosphinyl]-α-D-xylofuranose (**4**) in quantitative yield.

Reduction of **4** with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) in oxolane (tetrahydrofuran; THF) at 0 °C afforded 3-acetamido-3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-(phenylphosphinyl)-α-D-xylofuranose (**5**) in 62% yield; compound **5** gave an IR absorption band at 2340 cm^{-1} (P–H), and a characteristic P–H signal at δ 7.57 in its ^1H NMR spectrum ($J_{P,H}$ 481 Hz, disappearing on deuteration).

Hydrolysis of **5** with 0.1 M hydrochloric acid under N_2 for 4 h at 110 °C (bath), and acetylation of the product (**6**) with acetic anhydride–pyridine, afforded a crude mixture of isomers **7** (85% from **5**), which was separated by column chromatography on silica gel to give 5-acetamido-1,2,4-tri-*O*-acetyl-3,5-dideoxy-5-*C*-[(*R*)-phenylphosphinyl]-α-D-xylopyranose (**7a**, 7% overall yield from **1**), its β anomer (**7b**, 4%), 5-acetamido-1,2,4-tri-*O*-acetyl-3,5-dideoxy-5-*C*-[(*S*)-phenylphosphinyl]-α-D-xylopyranose (**7c**, 4%), and its β anomer (**7d**, 4%). Compound **7** can be deacetylated with sodium methoxide in methanol [10].

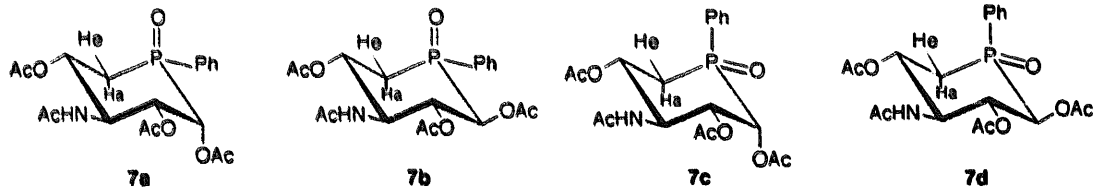

Table 1
^{1}H (400 MHz) and ^{31}P (36.10 MHz) NMR data for compounds **7a–d**

Compounds	Chemical shifts (δ)												
	H-1	H-2	H-3	H-4	H-5a	H-5e	NH	OAc-1,2,4, and NAc-3 [a]				C_6H_5–P	^{31}P
7a	5.89	5.72	4.70	5.66	2.47	2.66	6.55	2.07	2.03	1.96	1.92	7.5–7.9	25.83
7b	5.82	5.75	4.71	5.69	2.05	2.67	7.10	2.06	2.01	1.99	1.94	7.5–7.8	28.89
7c	5.61	5.01	4.53	4.97	2.52	2.77	5.96	2.10	2.09	2.02	1.86	7.6–8.0	24.14
7d	5.49	4.68	4.71	4.83	2.67	3.01	6.14	2.31	2.10	1.98	1.84	7.6–7.9	23.40

	Coupling constants (Hz)												
	$J_{1,2}$	$J_{1,P}$	$J_{1,5e}$	$J_{2,3}$	$J_{2,P}$	$J_{3,4}$	$J_{3,NH}$	$J_{4,5a}$	$J_{4,5e}$	$J_{4,NH}$	$J_{4,P}$	$J_{5a,5e}$	$J_{5a,P}$	$J_{5e,P}$
7a	2.4	11.2	0	10.4	2.0	10.0	8.8	12.3	4.0	0	2.0	12.8	12.8	23.4
7b	12.4	1.5	0	10.4	0.5	10.4	8.6	11.5	4.5	0	2.8	14.5	14.2	19.5
7c	3.7	9.2	2.0	10.4	3.2	10.0	10.8	9.6	3.6	11.2	4.0	15.6	15.6	16.8
7d	8.4	1.5	0	10.8	1.5	10.4	10.4	12.0	4.0	2.0	2.0	14.4	18.4	17.2

[a] The assignments of the acetyl signals may be interchanged.

The structures of these compounds were determined by analysis of their 400 MHz ^{1}H NMR spectra (data in Table 1) and by comparing these data with those obtained on structural analogs [11–13]. The $^4C_1$(D) conformation of **7a–d** was derived from the large values of $^3J_{H2,H3}$ and $^3J_{H3,H4}$ (10.0–10.8 Hz), and small values of $^3J_{H2,P}$ and $^3J_{H4,P}$ (0.5–5.2 Hz). The ^{1}H NMR spectra of **7a** and **7b** showed relatively high values of δ for the H-2 and H-4 signals, compared with those of **7c** and **7d**. The downfield shifts of those signals indicate the axial orientation (*R*) of the ring P=O group [5]. The anomeric configuration at C-1 was readily assigned from the magnitudes of $^3J_{H1,H2}$, $^2J_{H1,P}$ and $^4J_{H1,H5e}$. The H-1 signal of the α-acetates **7a** and **7c** showed a small $^3J_{H1,H2}$ (2.4 and 3.7 Hz) and a large $^2J_{H1,P}$ (11.2 and 9.2 Hz) value, whereas that of the β anomers **7b** and **7d** showed a large $^3J_{H1,H2}$ (12.4 and 8.4 Hz) and a small $^2J_{H1,P}$ (1.5 and 1.5 Hz).

1. Experimental

General methods.—Melting points were measured with a micro melting point apparatus (Yanagimoto Co., Ltd., Japan) and are uncorrected. Column chromatography was performed with Merck Lobar silica gel. Preparative TLC was conducted on Merck Kieselgel 60 F_{254}. Optical rotations were determined with an Atago-Polax polarimeter. IR spectra were recorded with an A-3 spectrophotometer (Japan Spectroscopic Co., Ltd.). NMR spectra were recorded ($CDCl_3$ solution) with a JEOL EX90A (^{1}H: 90 MHz), an EX270 (^{13}C: 67.80 MHz for **7a–d**), or an EX400 (^{1}H: 400 MHz and ^{31}P: 36.10 MHz for **7a–d**) spectrometer. Chemical shifts are reported in δ values, relative to tetramethylsilane (δ 0.0) as the internal standard.

*3-Acetamido-3-deoxy-1,2-O-isopropylidene-5-C-[methoxy(phenyl)phosphinyl]-α-*D*-xylofuranose* (**2**).—A mixture of **1** (2.06 g), methyl phenylphosphinate (1.6 mL), and Et_3N (2 mL) was kept for one night at room temperature, diluted with $CHCl_3$, and washed with saturated $NaHCO_3$ (to decompose the excess of phosphinate). The aqueous

layer was extracted with EtOAc, and the filtrate and washings were combined, dried (Na_2SO_4), and evaporated in vacuo to give **2** as a syrup (3.00 g, 88%); $[\alpha]_D$ −24.8° (*c* 1.61, $CHCl_3$); ^1H NMR; δ 1.2–1.5 (m, 6 H, CMe_2), 1.9 (broad s, 1 H, disappearing on deuteration, OH), 1.96, 1.97, 2.05 (3 s, 3 H, N–Ac), 3.77, 3.78, 3.82 (3 d, 3 H, $J_{P,Me}$ 10.5 Hz, P–OMe), 4.0–4.4 (m, 4 H, H-3,4,5, NH), 4.5–4.7 (m, 1 H, H-2), 5.88, 5.89, 5.92 (3 d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 7.5–8.0 (m, 5 H, P–C_6H_5). Calcd for $C_{17}H_{25}NO_7P$: (M + H), *m/z* 386.1358. Found: 386.1376.

*3-Acetamido-3,5-dideoxy-1,2-*O*-isopropylidene-5-*C*-[methoxy(phenyl)phosphinyl]-α-*D*-xylofuranose* (**4**).—A solution of **2** (2.78 g) and TCDI (1.56 g) in 1,2-dichloroethane (100 mL) was kept for 1 h at room temperature, washed with cold dilute HCl, dilute $NaHCO_3$, and water, dried (Na_2SO_4), and evaporated in vacuo to give **3** as a syrup. A solution of **3** (3.73 g) and tributyltin hydride (3.8 mL) in toluene (150 mL) was heated for 2 h at 120 °C (bath), cooled, and evaporated in vacuo. The residue was dissolved in acetonitrile–hexane, and the layers were separated. The acetonitrile layer was washed with hexane (to extract the tin compound), and evaporated in vacuo to give **4** in quantitative yield from **2** as a syrup; $[\alpha]_D$ −17.3° (*c* 1.73, $CHCl_3$); ^1H NMR: δ 1.24, 1.30 1.31 (3 s, 6 H, CMe_2), 2.03 (s, 3 H, N–Ac), 2.2–2.6 (m, 2 H, H-5,5'), 3.64, 3.70 (2 d, 3 H, $J_{P,Me}$ 11.5 Hz, P–OMe), 4.3–4.5 (m, 3 H, H-2,3,4), 5.82 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 7.3–7.9 (m, 5 H, P–C_6H_5), 8.2 (m, 1 H, NH). Calcd for $C_{17}H_{25}NO_6P$: (M + H), *m/z* 370.1420. Found: 370.1416.

*3-Acetamido-3-deoxy-1,2-*O*-isopropylidene-5-*C*-(phenylphosphinyl)-α-*D*-xylofuranose* (**5**).—To a solution of **4** (1.49 g) in THF (150 mL) was added SDMA (3.2 g, a 70% solution in toluene) at 0 °C under nitrogen. After 1 h, a small amount of water containing coned HCl was added at 0 °C (to decompose the excess SDMA and neutralize the base), the mixture filtered, and the filtrate evaporated in vacuo. The residue was purified by chromatography on silica gel by elution with EtOAc–MeOH (10:1), giving **5** (825 mg, 62%) as a syrup; $[\alpha]_D$ −17.1° (*c* 1.46, $CHCl_3$); IR (KBr): 2340 cm^{-1} (P–H); ^1H NMR; δ 1.26, 1.38, 1.40, 1.46 (4 s, 6 H, CMe_2), 2.02, 2.04, 2.07 (3 s, 3 H, N–Ac), 2.2–2.5 (m, 2 H, H-5,5'), 4.3–4.8 (m, 3 H, H-2,3,4), 5.88, 5.95 (2 d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 7.5–8.0 (m, 5 H, P–C_6H_5), 7.57 (d m, 1 H, $J_{P,H}$ 481 Hz, P–H), 8.58 (broad d, 1 H, NH). Calcd for $C_{16}H_{23}NO_5P$: (M + H), *m/z* 340.1314. Found: 340.1309.

Hydrolysis of **5** *and 3-acetamido-1,2,4-tri-*O*-acetyl-5-*C*-[(*R*)- and (*S*)-phenylphosphinyl]-α- and -β-*D*-xylopyranose* (**7a–d**).—To a solution of **5** (237 mg) in a small amount of THF was added 0.1 M HCl (10 mL). The mixture was heated under nitrogen for 4 h at 110 °C (bath), the THF being allowed to evaporate gradually. The mixture was cooled, diluted with water, and the acid neutralized with Amberlite IR-45A ion-exchange resin; this was then washed with water and ethanol, and filtered, and the filtrate and washings were combined, and evaporated in vacuo to give syrupy **6** (247 mg). The syrup was treated with Ac_2O (2 mL) in dry pyridine (15 mL) in the usual way to give a crude mixture **7** as a solid in a syrup (253 mg, 85% from **5**). This product mixture was separated by chromatography on a column of silica gel by elution with EtOAc–MeOH (10:1) to give **7a–d**.

*5-C-[(R)-Phenylphosphinyl]-α-*D*-xylopyranose derivative* (**7a**).—R_f 0.48 (10:1 EtOAc–MeOH); crystals (42 mg, 7% from **1**); mp 309–310 °C (from EtOH); $[\alpha]_D$

Table 2
^{13}C (67.80 MHz) NMR data for compounds **7a–d**

Compounds	Chemical shifts (δ) and coupling constants [a] $J_{C,P}$ (Hz)								
	C-1	C-2	C-3	C-4	C-5	P–Ph		–*C*(=O)Me	–C(=O)*Me*
7a	69.36	67.79	55.36	70.76	32.14	126.93 (103.6)	-x	169.09 (3.7)	20.11
	(74.0)	(3.6)		(10.7)	(60.7)	129.04 (11.8)	-m	170.10	20.41
						130.84 (11.2)	-o	170.22	20.71
						133.34 (2.7)	-p	170.38	23.05
7b	67.76	68.36	51.72	69.98	28.46	127.02 (103.6)	-x	168.36	20.52
	(89.0)	(14.6)		(11.0)	(62.2)	128.93 (12.2)	-m	168.43	20.67
						130.93 (8.5)	-o	169.79	20.88
						133.48 (2.4)	-p	170.58	23.15
7c	71.23	70.09	54.78	67.40	30.80	128.78 (101.2)	-x	168.44 (2.4)	20.39
	(67.8)	(15.9)		(7.3)	(59.7)	129.46 (12.1)	-m	169.82	20.48
						130.92 (9.7)	-o	170.65	20.81
						133.51 (2.4)	-p	170.69	22.96
7d	67.17	67.68	50.48	68.67	28.13	128.15 (99.9)	-x	169.64 (3.8)	20.48
	(69.7)	(14.8)		(15.4)	(63.5)	129.83 (11.8)	-m	170.20	20.65
						130.00 (9.9)	-o	170.40	20.76
						133.87 (2.4)	-p	170.52	23.02

[a] Values in parentheses.

+25.9° (*c* 0.44, $CHCl_3$); for ^1H, ^{31}P, and ^{13}C NMR data, see Tables 1 and 2. Calcd for $C_{19}H_{25}NO_8P$: (M + H), *m/z* 426.1317. Found: 426.1306. Anal. Calcd for $C_{19}H_{24}NO_8P$: C, 53.65; H, 5.69; N, 3.29; P, 7.28. Found: C, 53.53; H, 5.33; N, 3.17; P, 7.60.

*5-C-[(R)-Phenylphosphinyl]-β-*D*-xylopyranose derivative* (**7b**).—R_f 0.40 (10:1 EtOAc–MeOH); colorless syrup (27 mg, 4% from **1**); $[\alpha]_D$ +52.9° (*c* 0.44, $CHCl_3$); for ^1H, ^{31}P, and ^{13}C NMR data, see Tables 1 and 2. Calcd for $C_{19}H_{25}NO_8P$: (M + H), *m/z* 426.1317. Found: 426.1318.

*5-C-[(S)-Phenylphosphinyl]-α-*D*-xylopyranose derivative* (**7c**).—R_f 0.36 (10:1 EtOAc–MeOH); crystals (24 mg, 4% from **1**); mp 234–235 °C (from EtOAc); $[\alpha]_D$ −40.0° (*c* 0.55, $CHCl_3$); for ^1H, ^{31}P, and ^{13}C NMR data, see Tables 1 and 2. Calcd for $C_{19}H_{25}NO_8P$: (M + H), *m/z* 426.1317. Found: 426.1311. Anal. Calcd for $C_{19}H_{24}NO_8P$: C, 53.65; H, 5.69; N, 3.29; P, 7.28. Found: C, 53.36; H, 5.28; N, 3.15; P, 7.99.

*5-C-[(S)-Phenylphosphinyl]-β-*D*-xylopyranose derivative* (**7d**).—R_f 0.29 (10:1 EtOAc–MeOH); colorless syrup (23 mg, 4% from **1**); $[\alpha]_D$ −22.8° (*c* 0.68, $CHCl_3$); for ^1H, ^{31}P, and ^{13}C NMR data, see Tables 1 and 2. Calcd for $C_{19}H_{25}NO_8P$: (M + H), *m/z* 426.1317. Found: 426.1315.

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