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Note

Synthesis of the 4-, 6-deoxy, and 4,6-dideoxy derivatives of D-mannose

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Dale et al. discussed the role of the hydroxyl groups in the interaction of sugars with the β-glucosidase by investigating the inhibitory effects of some monosaccharides and their derivatives against the enzyme [1]. We planned to investigate the role of glycon hydroxyl groups via a kinetic study on the hydrolysis of deoxymonosaccharide-containing substrates by glycosidases. In our program, simple and efficient syntheses of various deoxymonosaccharides was required. In this report, a convenient synthesis of deoxy derivatives of D-mannose, namely D-rhamnose (6-deoxy-D-mannose, **7**), 4-deoxy-D-*lyxo*-hexose ("4-deoxy-D-mannose", **8**), and 4,6-dideoxy-D-*lyxo*-hexose ("4,6-dideoxy-D-mannose", **9**), is described. Several reports have been published on the synthesis of D-rhamnose [2–5] and 4-deoxy-D-*lyxo*-hexose [6–10]; however, there is no report on the synthesis of 4,6-dideoxy-D-*lyxo*-hexose.

Methyl 2,3-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-D-mannopyranoside (**1**), available in two steps from methyl α-D-mannopyranoside [11,12], was the common intermediate for the synthesis of these three deoxy monosaccharides. The *p*-tolylsulfonyl group is useful for the protection and the deoxgenation of the C-6 hydroxyl group of **1**; thus treatment with sodium borohydride in hot dimethyl sulfoxide gave a deoxygenated product, methyl 2,3-*O*-isopropylidene-α-D-rhamnopyranoside **2**. Similarly, Fang et al. produced **2** from **1** using lithium aluminum hydride as a reducing agent [12].

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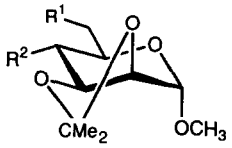

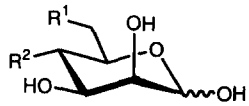

1 R^1 = OTs, R^2 = OH
2 R^1 = H, R^2 = OH
3 R^1 = OTs, R^2 = OItc
4 R^1 = OTs, R^2 = H
5 R^1 = OH, R^2 = H
6 R^1 = H, R^2 = H

Ts = *p*-tolylsulfonyl
Itc = imidazol-1-ylthiocarbonyl

7 R^1 = H, R^2 = OH
8 R^1 = OH, R^2 = H
9 R^1 = H, R^2 = H

Reaction of **1** with 1,1′-thiocarbonyldiimidazole (TCDI), in refluxing toluene, gave methyl 4-*O*-(imidazol-1-ylthiocarbonyl)-2,3-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-D-mannopyranoside (**3**) as light-yellow crystals. Compound **3** was reduced with tributyltin hydride in refluxing toluene to afford methyl 4-deoxy-2,3-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-D-*lyxo*-hexopyranoside (**4**), which was isolated in 84% yield after chromatography on silica gel. The deoxygenation of free hydroxyl groups of sugar derivatives using TCDI and tributyltin hydride was developed by Rasmussen et al. [13]. The ^{1}H-NMR spectrum of **4** confirmed the presence of two C-4 protons (H_a, δ 1.48, ddd, *J* 13.5, 8.52, 9.55 Hz; H_e, δ 1.88, ddd, *J* 13.5, 6.03, 3.40 Hz). Reductive desulfonylation of **4** with 5% sodium amalgam in 80% methanol, a procedure developed by Tipson [14], gave methyl 4-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranoside (**5**) in 92% yield. Rasmussen obtained **5** from methyl 6-*O*-benzoyl-4-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranoside, by treatment with base, in the process of synthesizing 4-deoxy-D-*lyxo*-hexose (**8**) [7].

When **4** was reduced with sodium borohydride in hot Me_2SO, methyl 4,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranoside (**6**) was obtained as a syrup. The signal for a C-6 methyl proton (δ 1.22, d, *J* 6.33 Hz) was confirmed in the ^{1}H-NMR spectrum of **6** (see Tables 1 and 2).

Treatment of **2**, **5**, and **6** with Amberlite IR-120 (H^+ form) in refluxing water gave D-rhamnose (**7**) 4-deoxy-D-*lyxo*-hexose (**8**), and 4,6-dideoxy-D-*lyxo*-hexose (**9**), respectively, in good yields. The specific rotation of **9** is $[\alpha]_D^{20}$ +2.1° (*c* 1, H_2O, equil.), while that of 4,6-dideoxy-L-*lyxo*-hexose [15] was reported to be $[\alpha]_D^{20}$ −2.8° (*c* 0.5, H_2O, equil.).

1. Experimental

General methods.—New compounds were characterized by elemental analysis, infrared spectra, and ^{1}H- and ^{13}C-NMR spectra. Melting points were determined with a

Yamato Model MP-21 capillary apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. Infrared spectra were recorded with a Shimazu IR-440 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian Gemini-300 spectrometer and with a Jeol α-500 spectrometer, respectively. Chemical shifts are expressed in ppm downfield from Me_4Si. Mass spectra were obtained with a Jeol JMS SX-102A spectrometer. Positive-ion FABMS were measured, after each sample was dispersed in a glycerol or *m*-nitrobenzyl alcohol matrix. Column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). The progress of all reactions was monitored by thin-layer chromatography (TLC) on Silica Gel 60 F_{254} (0.25 mm, Merck).

*Methyl 2,3-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-*D*-mannopyranoside* (**1**).—Compound **1** was prepared according to the procedure described by Fang et al. [12]. Although this compound was reported to be a syrup, a crystalline material (mp 85 °C) was obtained by recrystallization from hexane–EtOAc: $[\alpha]_D^{19}$ +22.3° (*c* 1, MeOH); FABMS: *m/z* 389 (MH^+). Anal. Calcd for $C_{17}H_{24}O_8S$: C, 52.56; H, 6.23; S, 8.26. Found: C, 52.40; H, 6.24; S, 8.26.

*Methyl 2,3-*O*-isopropylidene-α-*D*-rhamnopyranoside* (**2**).—Sodium borohydride (4.30 g, 114 mmol) was added by parts to a stirred solution of **1** (8.80 g, 22.7 mmol) in Me_2SO (80 mL). The mixture was heated at 80 °C for 2 h with stirring and poured into ice-water (400 mL). The product was extracted with diethyl ether (4 × 200 mL) and washed with water (300 mL). The extract dried (Na_2SO_4) and evaporated to a syrup. The product was purified by column chromatography on silica gel (5:1 CH_2Cl_2–EtOAc) to afford 3.29 g (66.5%) of **2** as a colorless syrup: $[\alpha]_D^{19}$ +14.5° (*c* 1, MeOH) [lit. [16] $[\alpha]_D^{20}$ +10° (*c* 1, $CHCl_3$)]; FABMS: *m/z* 219 (MH^+). The ^{1}H-NMR spectrum of **2** confirmed the presence of a C-6 methyl group (δ 1.31, d, *J* 6.27 Hz). Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.51; H, 8.40.

*Methyl 4-*O*-(imidazol-1-ylthiocarbonyl)-2,3-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-*D*-mannopyranoside* (**3**).—A mixture of compound **1** (9.01 g, 23.2 mmol) and 1,1′-thiocarbonyldiimidazole (6.20 g, 34.8 mmol) in dry toluene (300 mL) was boiled under reflux for 3 h with stirring. The solution was decanted to remove insoluble viscous dark brown by-products and evaporated to a brown oil. The product was purified by column chromatography on silica gel (1:2 hexane–EtOAc) to afford 8.01 g (69.2%) of **3** as light-yellow crystals, that were recrystallized from hexane–EtOAc: mp 111–112 °C; $[\alpha]_D^{19}$ +24.4° (*c* 1, MeOH); IR (KBr) 1190, 1195, 1360, 1450 and 1600 cm^{-1} (tosyloxy group), 1210 cm^{-1} (thiocarbonyl ester); FABMS: *m/z* 499 (MH^+). Anal. Calcd for $C_{21}H_{26}N_2O_8S_2$: C, 50.59; H, 5.26; N, 5.62; S, 12.86. Found: C, 50.58; H, 5.25; N, 5.55; S, 12.71.

*Methyl 4-deoxy-2,3-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-α-*D*-lyxo-hexopyranoside* (**4**).—A solution of compound **3** (5.0 g, 10.0 mmol) in dry toluene (50 mL) was added dropwise over 1 h to a stirred solution of refluxing toluene (150 mL) and Bu_3SnH (3.5 g, 12.0 mmol) under N_2. After the solution had been refluxed for an additional 3 h, the solvent was evaporated to give a light-yellow oil. The residue was dissolved in MeCN (150 mL) and washed with hexane (2 × 50 mL) to exclude the remaining Bu_3SnH. After evaporation, the product was purified by column chromatography on silica gel (2:1

Table 1
^{1}H-NMR data for compounds **3**, **4**, **6**, and **9**

Compound	δ, p.p.m., J, Hz									
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4e}$) ($J_{3,4a}$)	H-4e ($J_{4e,5}$) ($J_{4e,4a}$)	H-4a ($J_{4a,5}$)	H-5 ($J_{5,6}$) ($J_{5,6'}$)	H-6 ($J_{6,6'}$)	H-6′	$PhCH_3$	Aromatic
3 [a]	4.94	4.20 (5.56)	4.39 (7.14)	5.66 (8.94)		← 4.06–4.17 →			2.42	7.26–7.72(Ph) 7.05, 7.56, 8.26 (Imidazol)
4 [a]	4.81	3.92 (5.97)	4.32 (6.03) (8.52)	1.88 (3.40) (13.5)	1.48 (9.55)	3.93 (3.93) (8.76)	4.02 (10.3)	4.11	2.45	7.36–7.82
6 [a]	4.92	3.93 (5.53)	4.31 (6.81) (9.91)	1.86 (2.28) (13.2)	1.45 (11.1)	3.77 (6.33)	1.22			
9 [b]										
(α anomer)	5.16 (1.80)	3.76 (3.10)	4.07 (4.90) (12.3)	1.77 (2.40) (12.3)	1.59 (12.3)	4.12 (6.10)	1.21			
(β anomer)	4.73 (1.11)	3.80 (3.10)	3.86 (5.10) (11.9)	1.72 (2.10) (11.9)	1.48 (11.9)	3.66 (6.10)	1.24			

[a] Measured in $CDCl_3$. Anomeric proton gave a singlet (1 H). The OCH_3 gave a singlet (3 H) at δ 3.42 for **3**, at δ 3.35 for **4**, and at δ 3.38 for **6**. The $(CH_3)_2C$ gave two singlets (3 H each) at δ 1.31–1.34 and 1.43–1.55.
[b] Measured in D_2O.

Table 2
^{13}C-NMR data for compounds **3**, **4**, **6**, and **9**

Compound	δ (ppm)								
	C-1	C-2	C-3	C-4	C-5	C-6	$PhCH_3$	CS	C-aromatic
3 [a]	98.0	75.5	74.8	78.0	66.2	68.3	21.6	183.2	127.8, 129.8, 132.3, 145.1(Ph) 117.9, 131.1, 136.9 (Imidazol)
4 [a]	98.6	72.9	70.0	28.9	64.2	71.9	21.6		127.9, 129.8, 132.9, 144.8(Ph)
6 [a]	98.7	72.7	70.9	36.1	62.0	21.2			
9 [b]									
(α anomer)	95.3	69.2	65.6	35.5	65.8	21.0			
(β anomer)	94.5	70.4	68.8	34.8	69.4	20.8			

[a] Measured in $CDCl_3$. OCH_3 appeared at δ 54.8–55.4. $(CH_3)_2C$ appeared at δ 25.9–26.3, 27.3–28.2, and 108.7–110.6.
[b] Measured in D_2O.

hexane–EtOAc) to afford 3.14 g (84.3%) of **4** that was recrystallized from hexane–EtOAc: mp 72–73.5 °C; $[\alpha]_D^{19}$ +33.3° (*c* 1, MeOH); IR (KBr) 1170, 1190, 1350, 1460 and 1600 cm^{-1} (tosyloxy group); FABMS: *m/z* 373 (MH^+). Anal. Calcd for $C_{17}H_{24}O_7S$: C, 54.82; H, 6.50; S, 8.61. Found: C, 54.68; H, 6.45; S, 8.43.

*Methyl 4-deoxy-2,3-*O*-isopropylidene-α-*D-lyxo-*hexopyranoside* (**5**).—5% Sodium amalgam (9.23 g) was added to a stirred solution of **4** (2.67 g, 7.17 mmol) in 80% MeOH (75 mL). The mixture was stirred for 12 h at room temperature. Carbon dioxide gas was bubbled in until neutrality, and the solution was decanted to remove the mercury. The mercury was washed with water (3 × 10 mL), and the solutions were combined and concentrated to a gray solid. Absolute EtOH was added to the solid, insoluble salt was excluded by filtration, and the filtrate was evaporated to dryness. The product was extracted from the residue with diethyl ether (2 × 50 mL). The extract was dried (Na_2SO_4) and evaporated to afford 1.44 g (92.0%) of **5** as crystals: mp 58.5–59 °C [lit. [7] mp 59–60 °C]; $[\alpha]_D^{19}$ +53.9° (*c* 1, MeOH) [lit. [7] $[\alpha]_D^{18}$ +66.0° (*c* 1.5, $CHCl_3$)]; FABMS: *m/z* 219 (MH^+). Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.59; H, 8.13.

*Methyl 4,6-dideoxy-2,3-*O*-isopropylidene-α-*D-lyxo-*hexopyranoside* (**6**).—Sodium borohydride (2.32 g, 61.3 mmol) was added portionwise to a stirred solution of **4** (3.87 g, 10.4 mmol) in Me_2SO (40 mL). The mixture was heated for 2 h at 80 °C with stirring and poured into water (300 mL). The product was extracted with diethyl ether (2 × 150 mL) and washed with water (2 × 100 mL). The extract was dried (Na_2SO_4) and concentrated to afford 1.49 g (70.8%) of **6** as a colorless syrup: $[\alpha]_D^{16}$ +43.8° (*c* 1, MeOH); FABMS: *m/z* 203 (MH^+). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.70; H, 9.04.

D-Rhamnose (**7**).—Amberlite IR-120 (H^+ form, wet weight 5.0 g) was added to a suspension of compound **2** (1.36 g, 6.23 mmol) in water (50 mL). The mixture was boiled under reflux for 16 h with vigorous stirring and filtered to remove the resin. The filtrate was evaporated to afford 1.01 g (98.7%) of **7** as an amorphous solid: mp 74–88 °C [lit. [3] mp 75–93 °C; $[\alpha]_D^{25}$ −6.21° (*c* 2.1, H_2O, equil.) [lit. [3] $[\alpha]_D^{25}$ −6.13 ± 0.9° (*c* 1.4, H_2O, equil.)]. The ^{1}H-NMR spectrum of **7** was identical with that of L-rhamnose.

*4-Deoxy-*D*-lyxo-hexose* (**8**).—Amberlite IR-120 (H^+ form, wet weight 6.0 g) was added to a suspension of compound **5** (2.42 g, 11.1 mmol) in water (100 mL). The mixture was boiled under reflux for 16 h with vigorous stirring and filtered to remove the resin. The filtrate was evaporated to afford 1.59 g (87.2%) of **8** as crystals: mp 55–64 °C [lit. [7] mp 54–80 °C]; $[\alpha]_D^{20}$ +17.5° (*c* 1, H_2O, equil.) [lit. [9] $[\alpha]_D^{20}$ +17.7° (*c* 1.7, MeOH), lit. [10] $[\alpha]_D^{24}$ +13.2° (*c* 1.61, MeOH)]; FABMS: *m/z* 165 (MH^+). Anal. Calcd for $C_6H_{12}O_5 \cdot 1/2H_2O$: C, 41.62; H, 7.57. Found: C, 41.27; H, 7.43.

*4,6-Dideoxy-*D*-lyxo-hexose* (**9**).—Amberlite IR-120 (H^+ form, wet weight 1.5 g) was added to a suspension of compound **6** (0.58 g, 2.87 mmol) in water (25 mL). The mixture was boiled under reflux for 16 h with vigorous stirring and filtered to remove the resin. The filtrate was evaporated to syrup. The product was recrystallized from 2-propanol–petroleum ether to afford 0.25 g (58.8%) of **9** as crystals: mp 130–138 °C; $[\alpha]_D^{20}$ +2.1° (*c* 1, H_2O, equil.); FABMS: *m/z* 149 (MH^+). Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.56; H, 8.17.

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