The Direct Synthesis of Methyl 2,4-Di-*O*-benzyl-α-D-xylopyranoside by the Regiospecific Benzylation of Methyl α-D-Xylopyranoside

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Synopsis. The regiospecific benzylation of methyl α-D-xylopyranoside with benzyl chloride and sodium hydride produces methyl 2,4-di-*O*-benzyl-α-D-xylopyranoside in a 70% yield, together with the by-products, methyl 2,3- and 3,4-di-*O*-benzyl-α-D-xylopyranosides. The structure of the 2,4-di-*O*-benzyl derivative was confirmed through the alternative synthesis of the 2,3- and 3,4-di-*O*-benzyl derivatives *via* the *O*-isopropylidene and *O*-cyclohexylidene derivatives of methyl α-D-xylopyranoside.

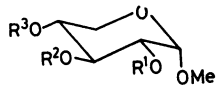
Partially benzylated monosaccharide derivatives are important synthetic intermediates, especially in the synthesis of oligosaccharides.[1] Usually, they are prepared *via* a multi-step sequence of reactions.[2] However, the regiospecific benzylation has often been useful for the ready preparation of the partially benzylated derivative of carbohydrates.[3] This report will present the direct synthesis of methyl 2,4-di-*O*-benzyl-α-D-xylopyranoside (**3**) through the regiospecific benzylation[3] of methyl α-D-xylopyranoside (**1**).

A brief heating of **1** with benzyl chloride containing the stoichiometric amount of sodium hydride, followed by chromatography, furnished crystalline **3** in a 70% yield. Small amounts of two other isomers, 2,3- and 3,4-di-*O*-benzyl derivatives (**2** and **4**), were also isolated through the chromatography. This shows that the reactivity of OH-2 and OH-4 is greater than that of OH-3 under such benzylation reactions.[4] The structure of the main product, **3**, was confirmed through the the alternative synthesis of **2** and **4** from **1**, as will be described below.

The reaction of 2,2-dimethoxypropane with **1** in *N,N*-dimethylformamide containing *p*-toluenesulfonic acid gave the 2,3- and 3,4-*O*-isopropyridene derivatives (**5** and **6**); the former predominated. The structure of the isopropylidene derivatives was confirmed by observing the ^{1}H NMR spectra of their acetates (**7** and **8**). The isopropylidene derivative, **5**, was transformed into **2** *via* allylation, deisopropylidenation, benzylation, and then deallylation, successively. Another isopropylidene compound, **6**, was similarly derived into **4**.

Compounds **2** and **4** were also synthesized *via* the cyclohexylidene derivatives (**9** and **10**) in essentially the same manner as above: 1,1-dimethoxycyclohexane, with *p*-toluenesulfonic acid as the catalyst, in *N,N*-dimethylformamide converted **1** into a mixture of **9** and **10**, which were then derived into **2** and **4** respec-

TABLE 1. PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS[a]



Compound	R¹	R²	R³	M_p θ_m/°C	$[\alpha]_D^{20}$/°(*c*)[b]	Mol. form.	Calcd (%) C	Calcd (%) H	Found (%) C	Found (%) H
2	Bn	Bn	H	—	+22(1.6)				69.55	7.01
3	Bn	H	Bn	77—77.5	+63(1.0)	$C_{20}H_{24}O_5$	69.75	7.02	69.75	7.08
4	H	Bn	Bn	89—91	+56(0.4)				69.53	7.08
5	Me, Me		H	—	+139(1.0)				52.71	8.15
6	H	Me, Me		—	+132(1.0)	$C_9H_{16}O_5$	52.93	7.90	52.86	7.85
7	Me, Me		Ac	—	+112(1.0)				53.46	7.52
8	Ac	Me, Me		60—61	+138(0.5)	$C_{11}H_{18}O_6$	53.65	7.37	53.22	7.53
9	H (cyclohexylidene)		H	—	+124(0.6)				59.01	8.44
10	H	H (cyclohexylidene)		65—67	+127(1.3)	$C_{12}H_{20}O_5$	59.00	8.25	58.92	8.40
11	Bn	Bn	All	—	+20(2.0)				71.57	7.31
12	All	Bn	Bn	—	+54(1.6)	$C_{23}H_{28}O_5$	71.85	7.34	71.56	7.30
13	Ac	Me	Ac	—	+109(0.2)	$C_{11}H_{18}O_7$	50.38	6.92	50.37	6.92

a) All=allyl, Bn=benzyl. b) In $CHCl_3$.

tively *via* allylation, decyclohexylidenation, benzylation, and deallylation.

Experimental

The melting points were determined on an MP-1 melting-point apparatus (Yanagimoto); they are uncorrected. The optical rotations were measured in a jacketed 1-dm cell at 20 °C, with a DIP-180 automatic polarimeter (Japan Spectroscopic). The ^{1}H NMR spectra were recorded with a Varian EM-390 spectrometer in $CDCl_3$, using Me_4Si as the internal standard. Column chromatography was carried out on silica gel (Kanto Kagaku); each fraction was examined by TLC on silica gel (Merck, 7731).

Methyl 2,4-Di-O-benzyl-α-D-xylopyranoside (3). A mixture of **1** (Pfanstiehl, 2.0 g, 12 mmol), NaH (Wako, ≈50% disp., 1.2 g, 24 mmol), and benzyl chloride (Tokyo Kasei, 40 ml) was stirred for 1.5 h at 100 °C. After acetic acid (0.1 ml) had then been added, the mixture was evaporated at 95 °C to give an oily residue. This was chromatographed (benzene–butanone, gradient, 100 : 1→3 : 1) to afford three fractions (Fraction A, R_f=0.55; B, 0.30; and C, 0.23 and 0.21; benzene–butanone (10 : 1)). Fraction A (0.05 g, 1%) was crystallized from hexane and identified with methyl 2,3,4-tri-*O*-benzyl-α-D-xylopyranoside.[5] Fraction B (2.88 g, 70%) was crystallized from diisopropyl ether to yield **3** (2.10 g). Fraction C (0.32 g) was rechromatographed to afford **2** (0.15 g, 8%) and then **4** (0.04 g, 1%).

Methyl 2,3- and 3,4-O-Isopropylidene-α-D-xylopyranosides (5 and 6). A solution of **1** (656 mg, 4 mmol), 2,2-dimethoxypropane (Tokyo Kasei, 4.9 ml), and *p*-toluenesulfonic acid monohydrate (Wako, 38 mg) in distilled *N,N*-dimethylformamide (Tokyo Kasei, 13 ml) was heated for 2 h at 70 °C.[6] After a few drops of triethylamine had then been added, the mixture was evaporated and chromatographed (diisopropyl ether–ethylacetate (20 : 1)) to afford **5** (380 mg, 39%) and **6** (123 mg, 13%).

A small portion of **5** was acetylated with acetic anhydride and pyridine to afford the 4-*O*-acetyl derivative (**7**); ^{1}H NMR: δ 1.42 and 1.46 (2s, Me_2C), 2.06 (s, Ac), 3.28 (t, $J_{4,5ax}$=10 Hz, $J_{5ax,5eq}$=10.5 Hz, H-5ax), 3.42 (s, MeO), 3.50 (q, $J_{1,2}$=3 Hz, $J_{2,3}$=10 Hz, H-2), 3.89 (q, $J_{4,5eq}$=5.5 Hz, H-5eq), 4.07 (t, $J_{3,4}$=10 Hz, H-3), 4.99 (d, H-1), and 5.01 (sext, H-4). Compound **6** was similarly converted into the 2-*O*-acetyl derivative (**8**); ^{1}H NMR: δ 1.44 (s, Me_2C), 2.12 (s, Ac), 3.36 (s, MeO), 3.47 (sext, $J_{3,4}$=9 Hz, $J_{4,5eq}$=4.5 Hz, $J_{4,5ax}$=9 Hz, H-4), 3.70 (t, $J_{5ax,5eq}$=9 Hz, H-5ax), 3.87 (q, $J_{2,3}$=10.5 Hz, H-3), 3.94 (q, H-5eq), 4.83 (q, $J_{1,2}$=4 Hz, H-2), and 5.02 (d, H-1).

Methyl 2,3- and 3,4-O-Cyclohexylidene-α-D-xylopyranosides (9 and 10). A solution of **1** (500 mg, 3.05 mmol), 1,1-dimethoxycyclohexane (0.8 ml), and *p*-toluenesulfonic acid monohydrate (5.7 mg) in *N,N*-dimethylformamide (4.0 ml) was heated for 15 h at 140 °C.[7] After triethylamine had then been added, the mixture was evaporated and chromatographed (toluene–butanone, gradient, 100 : 1→3 : 1) to elute **10** (94 mg, 13%) and **9** (467 mg, 63%).

Alternative Synthesis of 2. Compound **5** (180 mg, 0.88 mmol) was stirred in allyl bromide (1.8 ml) containing NaH (≈60% disp., 50 mg) for 1.5 h at 65 °C. The mixture was then filtered and evaporated to give the sirupy 4-*O*-allyl derivative (180 mg). This was treated with a mixture of 0.25 M H_2SO_4, acetone, and 1,4-dioxane (1 : 1 : 1) for 0.5 h at 25 °C. After methanol and $Ba(OH)_2 \cdot 8H_2O$ had been added, the mixture was evaporated to dryness. The residue was stirred in benzyl chloride (3.0 ml) containing KOH (0.8 g) for 5 h at 110 °C, followed by chromatography, to give methyl 4-*O*-allyl-2,3-di-*O*-benzyl-α-D-xylopyranoside (**11**) (150 mg, 44%). Compound **9** was also converted into **11** in a similar way.

Compound **11** (42.5 mg, 0.11 mmol) was heated in dimethyl sulfoxide (0.34 ml) containing potassium *t*-butoxide (Aldrich, 119 mg) for 2.5 h at 110 °C under N_2.[8] The mixture was then diluted with benzene and processed as usual. The organic layer was evaporated, and the residue was heated in a mixture of 2.6 M H_2SO_4† (0.09 ml) and 1,4-dioxane (0.9 ml) for 1 h at 85 °C. After neutralization with $Ba(OH)_2 \cdot 8H_2O$, evaporation and chromatography gave **2** (24.6 mg, 65%).

Alternative Synthesis of 4. Compound **6** was similarly converted into methyl 2-*O*-allyl-3,4-di-*O*-benzyl-α-D-xylopyranoside (**12**), which was, in turn, derived into **4**.

Methyl 2,4-Di-O-acetyl-3-O-methyl-α-D-xylopyranoside (13). Compound **3** (50 mg, 0.15 mmol) was heated in *N,N*-dimethylformamide (0.25 ml) containing methyl iodide (70 μl) and BaO (95 mg) for 1.5 h at 90 °C under stirring.[9] Chromatography gave a homogeneous oil (49.2 mg), which was subsequently hydrogenated over Pd in acetic acid at 340 KPa. The hydrogenolyzate, which was not oxidized with aq $NaIO_4$, was acetylated as usual to give **13** (32.6 mg, 83%); ^{1}H NMR: δ 2.06 (s, Ac), 2.12 (s, Ac), 3.37 (s, MeO), and 3.47 (s, MeO); ^{13}C NMR: δ 20.9, 55.3 (Me-1), 58.5 (C-5), 60.4 (Me-3), 71.1 (C-4), 72.7 (C-2), 77.9 (C-3), 97.1 (C-1), 169.8, and 170.1.

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† 1 M=1 mol dm^{-3}.