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Note

Chemical synthesis of 4-deoxy-(1→6)-α-D-*xylo*-hexopyranan and 3,4-dideoxy-(1→6)-α-D-*erythro*-hexopyranan*

Masahiko Okada, Ayako Banno, and Hiroshi Sumitomo
Faculty of Agriculture, Nagoya University, Chikusa-ku, Nagoya 464-01 (Japan)

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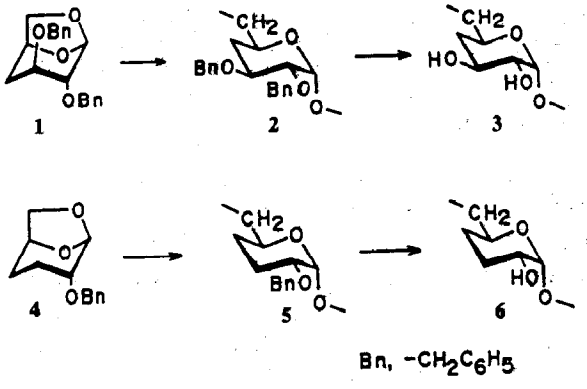
During a previous series of studies on the chemical synthesis of polysaccharides from non-carbohydrate sources, we synthesized 4-deoxy-(1→6)-α-DL-*xylo*-hexopyranan[1] and 3,4-dideoxy-(1→6)-α-DL-*erythro*-hexopyranan[2] via the ring-opening polymerization of the corresponding 1,6-anhydro sugar derivatives. ^{13}C-N.m.r. analysis of these DL-polysaccharides revealed that the arrangement of the D- and L-enantiomeric monomeric units along the polymer chains was not completely random, but was somewhat regular. By analogy with the ring-opening polymerization of bicyclic acetals, which are structurally related to 1,6-anhydro sugars[3,4] we speculated that an enantiomeric monomeric unit in these polymer chains was followed more frequently by a monomeric unit of the same chirality than by a monomeric unit of the opposite chirality, in other words, these polysaccharides were rich in isotactic sequences (in the terminology of polymer chemistry).

In order to clarify this point, it was necessary to synthesize the corresponding optically active polysaccharides consisting exclusively of either the D- or L-enantiomeric monomeric units, and to compare their ^{13}C-n.m.r. chemical shifts with those of the



*Part 9 of the series: Chemical Synthesis of Polysaccharides.

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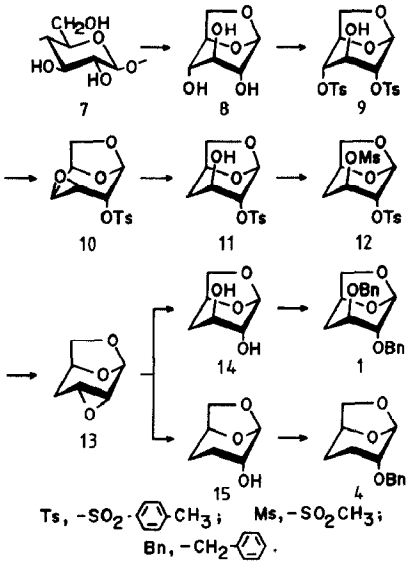

Scheme 1. Synthetic routes for 1,6-anhydro-2,3-di-*O*-benzyl-4-deoxy-β-D-*xylo*-hexopyranose (**1**) and 1,6-anhydro-2-*O*-benzyl-3,4-dideoxy-β-D-*erythro*-hexopyranose (**4**).

DL-polysaccharides. We therefore synthesized the corresponding D-polysaccharides starting from cellulose. This paper describes the chemical synthesis of 4-deoxy-(1→6)-α-D-*xylo*-hexopyranan (**3**) and 3,4-dideoxy-(1→6)-α-D-*erythro*-hexopyranan (**6**) by the ring-opening polymerization of 1,6-anhydro-2,3-di-*O*-benzyl-4-deoxy-β-D-*xylo*-hexopyranose (**1**) and 1,6-anhydro-2-*O*-benzyl-3,4-dideoxy-β-D-*erythro*-hexopyranose (**4**), respectively, followed by debenzylation of the resulting polymers (**2** and **5**).

The 1,6-anhydro sugar derivatives **1** and **4** were synthesized as illustrated in Scheme 1. Microcrystalline cellulose (**7**) was pyrolyzed under vacuum to give 1,6-anhydro-β-D-glucopyranose[5] (**8**). Tosylation of **8** with two equivalents of tosyl chloride in pyridine yielded 1,6-anhydro-2,4-di-*O*-tosyl-β-D-glucopyranose (**9**), which on treatment with sodium methoxide was converted into 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose[6] (**10**). Catalytic hydrogenation of **10** with Raney nickel[7] in ethanol gave 1,6-anhydro-4-deoxy-2-*O*-tosyl-β-D-*xylo*-hexopyranose[8] (**11**). Reaction of **11** with methylsulfonyl chloride in pyridine afforded 1,6-anhydro-4-deoxy-3-*O*-methylsulfonyl-2-*O*-tosyl-β-D-*xylo*-hexopyranose (**12**), which was then treated with sodium methoxide in methanol to yield 1,6:2,3-dianhydro-β-D-*ribo*-hexopyranose[9] (**13**). Alkaline hydrolysis of **13** in ethanol[10], followed by benzylation of the resulting 4-deoxy-(1→6)-β-D-*xylo*-hexopyranose (**14**) with benzyl chloride in dimethyl sulfoxide, provided the monodeoxy anhydro sugar derivative **1**. The overall yield of **1** from **8** was ~ 24%.

Reduction of **13** with lithium aluminum hydride in tetrahydropyran gave 1,6-anhydro-3,4-dideoxy-β-D-*erythro*-hexopyranose (**15**). Benzylation of **15** with benzyl chloride in dimethyl sulfoxide yielded the dideoxy anhydro sugar derivative **4**. The overall yield of **4** from **8** was ~ 23%.

Ring-opening polymerizations of **1** and **4** were carried out in dichloromethane at −60° with phosphorus pentafluoride as the initiator by using a high-vacuum technique. The detailed procedures are described in the experimental section. The α-(1→6)-linked stereoregular polymers having number-average molecular weights of 7.8×10^4 (**2**) and 14×10^4 (**5**) were obtained in high yield.

Debenzylation of polymer **2** was readily achieved by conventional reduction with metallic sodium and liquid ammonia. In contrast, debenzylation of polymer **5** was sluggish, because of the limited solubility of **5** in a mixed solvent of toluene and 1,2-dimethoxyethane used for the reaction. It took 15 h to complete the reaction. Polysaccharide **3** was a white powder, soluble in water and dimethyl sulfoxide. It had a number-average molecular weight of 6.3×10^3 and $[\alpha]_D^{25} = +138°$ (H_2O). Polysaccharide **3** did not have a definite melting point and decomposed gradually above 190°, whereas the corresponding DL-polysaccharide had a melting point of 90–103°.

Polysaccharide **6** was also a white powder, soluble in methanol, ethanol, *N,N*-dimethylformamide, and dimethyl sulfoxide. It was, however, insoluble in water. Polysaccharide **6** had a number-average molecular weight of 1.3×10^4 and $[\alpha]_D^{25} = +165°$ (MeOH). Its melting point, determined by differential-scanning calorimetry, was 130–140°, somewhat higher than the melting point of the corresponding DL-polysaccharide.

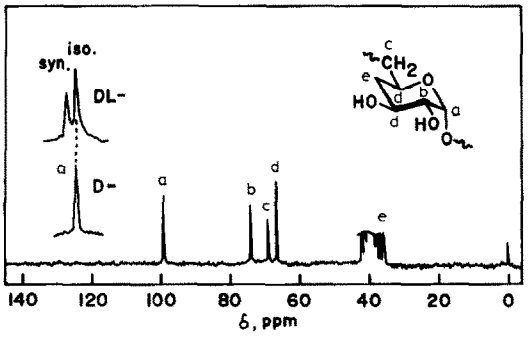

Fig. 1. ^{13}C-N.m.r. spectrum of 4-deoxy-(1→6)-α-D-*xylo*-hexopyranan (**3**) (solvent, Me_2SO-d_6; temperature, 50°; 25 MHz; internal reference, Me_4Si).

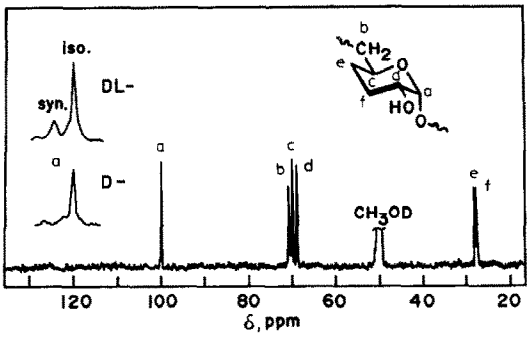

Fig. 2. ^{13}C-N.m.r. spectrum of 3,4-dideoxy-(1→6)-α-D-*erythro*-hexopyranan (**6**) (solvent, MeoH-d_4; room temperature; 50 MHz; internal reference, Me_4Si).

TABLE I

^{13}C-N.m.r. data for (1→6)-α-linked polysaccharides

Compound[a]	*Solvent*	*Chemical shift, p.p.m.*										*Ref.*
		C-1		C-2		C-3	C-4		C-5	C-6		
3 (DL)	Me_2SO-d_6	99.29	98.98	73.91		66.74	36.14	35.71	66.74	69.15		1
3 (D)	Me_2SO-d_6		99.01	73.92		66.71		35.81	66.71	69.04		
6 (DL)	CH_3OD	99.91	99.32	68.89	68.38	27.60	28.05		69.41	70.68	70.38	2
6 (D)	CH_3OD		99.27		68.35	27.58	27.99		69.37		70.29	

[a] **3** (DL), 4-deoxy-(1→6)-α-DL-*xylo*-hexopyranan; **3** (D), 4-deoxy-(1→6)-α-D-*xylo*-hexopyranan; **6** (DL), 3,4-dideoxy-(1→6)-α-DL-*erythro*-hexopyranan; **6** (D), 3,4-dideoxy-(1→6)-α-D-*erythro*-hexopyranan.

The ^{13}C-n.m.r. spectra of **3** and **6** are presented in Fig. 1 and 2, respectively. The chemical-shift data are presented in Table I, along with those for the corresponding DL-polysaccahrides.

The appearance of the ^{13}C-n.m.r. signals of the anomeric carbons at 99.01 (**3**) and 99.27 (**6**), respectively, along with their large specific rotations of positive sign, clearly indicates that these polysaccharides consist of α-(1→6)-linked glycosidic units. In Fig. 1 and 2, the expanded spectra of the anomeric carbon regions of the D- and DL-polysaccharides are also given for comparison. The anomeric-carbon signal of each DL-polysaccharide appears as a pair of peaks of different intensities. In each spectrum, the chemical shift of the higher-field peak of the signal pair is in agreement with that of the anomeric carbon of the corresponding D-polysaccharides (**3** or **6**). In addition to the anomeric carbon signals, the C-4 signal for 4-deoxy-(1→6)-α-DL-*xylo*-hexopyranan and the C-2 and C-6 signals of 3,4-dideoxy-(1→6)-α-DL-*erythro*-hexopyranan also appear as a pair of peaks, respectively, and the chemical shift of the higher-field signal of each peak pair is in agreement with the chemical shift of the respective carbons for the corresponding D-polysaccharides (See Table I).

Therefore, the higher-field peak of each signal pair is reasonably assigned to the respective carbon in the isotactic dyads (D-D and L-L consecutive units), and hence the lower-field peak is assigned to the same carbon in the syndiotactic dyads (D-L and L-D crossover units). On the basis of the assignments, it is concluded from the relative peak areas of the anomeric-carbon signals that both of the DL-polysaccharides are slightly or somewhat enriched in isotactic sequences (isotactic dyad content: 55% for 4-deoxy-(1→6)-α-DL-*xylo*-hexopyranan and 81% for 3,4-dideoxy-(1→6)-α-DL-*erythro*-hexopyranan). The preference of the isotactic placement in these DL-polysaccharides is consistent with previous observations for such synthetic polysaccharides as (1→6)-α-DL-glucan[11] and 4-deoxy-(1→6)-β-DL-*ribo*-hexopyranan[12] derived from the corresponding anhydro sugar derivatives via cationic ring-opening polymerization. However, we cannot say whether the difference in tacticity between the two DL-polysaccharides described here is intrinsic or not, because these polysaccharides were prepared under different polymerization conditions [4-deoxy-(1→6)-α-DL-*xylo*-hexopyranan: initiator, antimony pentachloride; solvent, dichloromethane; temperature, −60°. 3,4-dideoxy-(1→6)-α-DL-*erythro*-hexopyranan: initiator, phosphorus pentafluoride; solvent, toluene; temperature, −60°]. In this connection, it may be noted that the isotactic dyads of (1→6)-α-DL-glucans prepared by the ring-opening polymerization method varied from 55–72% depending on the polymerization conditions[11]. The stereospecific ring-opening polymerizations of anhydro sugar derivatives and their related compounds will be discussed in detail elsewhere[13].

EXPERIMENTAL

General methods. — ^{13}C-N.m.r. spectra were recorded with Jeol FX-200 (50 MHz) and FX-100 (25-MHz) spectrometers on solutions in $CDCl_3$, MeOH-d_4, and Me_2SO-d_6 with Me_4Si as the internal reference. Specific rotations were measured on solutions in $CHCl_3$, MeOH, and water at 25° with a Jasco DIP-181 automatic polarimeter. The

number-average molecular weights of the polymers were estimated by gel-permeation chromatography. (For **2** and **5**: column, Toyo Soda MHDXK7001C 30 cm plus MHDXK7002C 30 cm; eluent, $CHCl_3$; plystyrene standard. For **3** and **6**: column, Shodex KF803 30 cm plus KF804 30 cm; eluent, Me_2SO; dextran standard.) The thermal properties of the polymers were measured by a Perkin–Elmer DSC 2 differential-scanning calorimeter.

*1,6-Anhydro-2,3-di-*O*-benzyl-4-deoxy-β-*D*-*xylo*-hexopyranose* (**1**). — 1,6:2,3-Dianhydro-4-deoxy-β-D-*ribo*-hexopyranose (**13**) was synthesized according to the procedures described in the literature with some modifications[5–9]. A solution of **13** (1.3 g, 10 mmol) in 5% aq. KOH (20 mL) was refluxed for 5 h, cooled to room temperature, and neutralized with 2M HCl followed by treatment with activated charcoal. After filtration, the solvent was removed by rotary evaporation. The residue was extracted with hot 1,4-dioxane, and the extract was dried ($MgSO_4$). Rotary evaporation of the solvent afforded 1,6-anhydro-4-deoxy-β-D-*xylo*-hexopyranose (**14**) as a hygroscopic solid; yield, 1.2 g (85%).

Sodium hydride (0.6 g, in 60% oil dispersion) was washed with *n*-hexane three times and dissolved in anhydrous Me_2SO (10 mL). The solution was added to a solution of **14** (0.87 g, 5.9 mmol) in Me_2SO (25 mL). The mixture was stirred for 0.5 h at room temperature. Subsequently, benzyl chloride (1.7 mL, 15 mmol) was slowly dropped into the mixture. After an initial foam had disappeared, the mixture was heated for 2 h at 60°, cooled to room temperature, and poured into ice–water (100 mL). The mixture was extracted with three 50-mL portions of $CHCl_3$, and the combined extracts were dried ($MgSO_4$). Rotary evaporation of the solvent gave a light-brown oil that was purified by column chromatography on silica gel [eluent, 13:7 (v/v) *n*-hexane-EtOAc] followed by recrystallization from EtOH three times and finally from 97:3 (v/v) *n*-hexane–CH_2Cl_2. The monodeoxy anhydro sugar derivative **1** was obtained as needles; yield, 1.6 g (84%); m.p., 48.5–50°, $[\alpha]_D^{25}$ −53.3° (*c* 0.5, $CHCl_3$); ^{13}C-n.m.r. [$CDCl_3$]: δ 138.20 and 137.77 (phenyl, *ipso*), 128.40 (phenyl, *ortho*), 127.81, 127.58 and 127.38 (phenyl, *meta* and *para*), 100.24 (C-1), 74.51 (C-2), 72.41 (C-3), 71.93 (benzyl), 71.19 (C-5), 70.90 (benzyl), 67.05 (C-6), and 31.14 (C-4).

Anal. Calc. for $C_{20}H_{22}O_4$: C, 73.59; H, 6.80. Found: C, 73.59; H, 6.99.

*1,6-Anhydro-2-*O*-benzyl-3,4-dideoxy-β-*D*-*erythro*-hexopyranose* (**4**). — A solution of **13** (1.0 g, 8.0 mmol) in diethyl ether (20 mL) was added over a period of 40 min to a solution of $LiAlH_4$ (0.66 g, 17 mmol). After the addition was completed, the mixture was stirred for 3.5 h at room temperature. Diethyl ether (20 mL) saturated with water was added to the mixture. Subsequently, 20% aq. NaOH (1.9 mL, 9.5 mmol) and water (1.5 mL) were added in that order, and the mixture was stirred for 15 min. A white granular precipitate was formed, which was removed by filtration. The filtrate was dried ($MgSO_4$), and removal of the solvent gave 1,6-anhydro-3,4-dideoxy-β-D-*erythro*-hexopyranose (**15**) as colorless crystals that were recrystallized from diethyl ether; yield, 0.76 g (73%); m.p., 86–89°.

Sodium hydride (0.60 g, in 60% oil dispersion, 15 mmol) was washed with *n*-hexane three times and dissolved in dry Me_2SO (8 mL). The solution was added to a

solution of **15** (1.6 g; 12 mmol) in Me_2SO (45 mL), and the resulting mixture was stirred for 30 min at room temperature. Benzyl chloride (1.5 mL, 13 mmol) was added dropwise to the mixture, which was then stirred for 5 h at room temperature, and poured into ice–water (150 mL). The mixture was extracted with four 60-mL portions of $CHCl_3$ and the combined extracts were washed with three 80-mL portions of water, dried ($MgSO_4$), and evaporated to afford a yellow oil that was purified by column chromatography on silica gel [7:3 (v/v) *n*-hexane–EtOAc]. It was recrystallized from EtOH and subsequently from *n*-hexane to yield the dideoxy anhydro sugar derivative **4** as colorless prisms; yield, 2.5 g (93%); m.p. 39°, $[\alpha]_D^{25}$ − 53.3° (*c* 0.93, $CHCl_3$); ^{13}C-n.m.r. [$CDCl_3$]: δ 138.44 (phenyl, *ipso*), 128.50 (phenyl, *ortho*), 127.77 (phenyl, *meta* and *para*), 100.87 (C-1) 73.14 (C-5), 71-39 (benzyl), 66.81 (C-6), 25.34 (C-4), and 20.27 (C-3).

Anal. Calc. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.33. Found: C, 70.90; H, 7.36.

*2,3-Di-O-benzyl-4-deoxy-(1→6)-α-*D-xylo-*hexopyranan* (**2**). — A high-vacuum technique was employed for the polymerization of **1**. The monomer **1** (0.95 g, 2.9 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and the reaction vessel was then cooled in a bath of liquid N_2. Phosphorus pentafluoride, generated by the decomposition of *p*-chlorobenzenediazonium hexafluorophosphate (75 mg, 0.30 mmol), was introduced into the reaction vessel. The vessel was sealed off and kept for 40 min in a bath thermostated at − 60°. Polymerization was terminated by the addition of a small amount of pyridine, and the mixture was poured into a large volume of MeOH to precipitate the polymer. This was separated and purified by reprecipitation using $CHCl_3$ and MeOH as a solvent–precipitant pair, and finally freeze-dried from a solution in benzene; yield, 0.90 g (95%); $[\alpha]_D^{25}$ + 94° (*c* 1.0, $CHCl_3$); ^{13}C-n.m.r. [$CDCl_3$]: δ 139.07, 138.92 (phenyl, *ipso*), 128.26 (phenyl, *ortho*), 127.43 (phenyl, *meta* and *para*), 98.05 (C-1), 80.84 (C-2), 75.16 (C-3), 72.56, 72.17 (benzyl), 69.69 (C-6), 66.85 (C-5), and 33.92 (C-4).

Anal. Calc. for $(C_{20}H_{22}O_4)_n$: C, 73.59; H, 6.80. Found: C, 73.61, H, 7.02.

*2-O-Benzyl-3,4-dideoxy-(1→6)-α-*D-erythro-*hexopyranan* (**5**). — Polymerization of **4** was performed as described for the polymerization of **1**. The monomer **4** (1.12 g, 7.2 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and polymerizated by using *p*-chlorobenzenediazonium hexafluorophosphate (88 mg, 0.35 mmol) as precursor of the initiator. Yield, 0.95 g (85%); $[\alpha]_D^{25}$ + 112° (*c* 1.0, $CHCl_3$); ^{13}C-n.m.r. [$CDCl_3$]: δ 138.92 (phenyl, *ipso*), 128.31 (phenyl, *ortho*), 127.48 (phenyl, *meta and para*), 96.73 (C-1), 75.51 (C-2), 70.32 (benzyl), 69.43 (C-6), 67.44 (C-5), 27.13 (C-4), and 23.83 (C-3).

Anal. Calc. for $(C_{13}H_{16}O_3)_n$: C, 70.89, H, 7.33. Found: C, 70.90; H, 7.33.

*4-Deoxy-(1→6)-α-*D-xylo-*hexopyranan* (**3**). — Liquid NH_3 (100 mL) was introduced into a 3-necked flask equipped with a cold-finger trap. A solution of **2** (0.78 g, 2.4 base-mmol) in a mixed solvent of 1,2-dimethoxyethane (10 mL) and toluene (30 mL) was added dropwise to the liquid NH_3 cooled in a dry ice–MeOH bath. The bath was removed, and small pieces of metallic Na (total 1.3 g) were occasionally added to the solution until a dark-blue color persisted. The mixture was stirred for a further 40 min and a small amount of NH_4CL chloride was cautiously added to the mixture, followed by the dropwise addition of water. The cold-finger trap was removed, and the mixture was kept at room temperature overnight to evaporate the NH_3. The resulting organic

layer was separated from the aqueous layer, and extracted with two 20-mL portions of water. The combined aqueous layers were dialyzed for 2 days and subsequently washed with three 30-mL portions of CH_2Cl_2. The aqueous solution was concentrated by rotary evaporation and finally freeze-dried; yield, 0.32 g (89%); $[\alpha]_D^{25}$ + 138° (*c* 1.0, water); M_n 6.3 × 10^3 (by gel-permeation chromatography, dextran standard); ^{13}C-n.m.r. data are given in Table I.

*3,4-Dideoxy-(1→6)-α-*D-erythro-*hexopyranan* (**6**). — The debenzylation procedure just described was slightly modified for the conversion of **5** into **6**. A mixture of **5** (0.70 g, 3.2 base-mmol), 1,2-dimethoxyethane (10 mL), and toluene (30 mL) was stirred overnight at room temperature. Ammonia (100 mL) was introduced to this mixture, and small pieces of metallic Na (total 2.3 g) were added over 14.5 h. A small amount of NH_4Cl and water (15 mL) were added in this order, and the mixture was kept overnight at room temperature to remove NH_3. The resulting precipitate was separated by centrifugation, dried, and dissolved in MeOH. The solution was concentrated and poured into water (150 mL) to reprecipitate the polymer, which was dried under vacuum to constant weight; yield, 0.51 g (100%); $[\alpha]_D^{25}$ + 165° (*c* 1.0, MeOH); M_n 1.3 × 10^4 (by gel-permeation chromatography, dextran standard); ^{13}C-n.m.r. data are presented in Table I.

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