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Note

4-Deoxy-(1→6)-β-L-*ribo*-hexopyranan*

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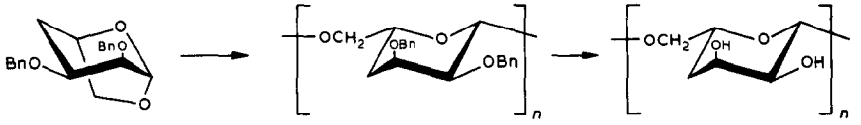
During studies on the chemical synthesis of DL polysaccharides starting from non-carbohydrate sources[1–7], we have recently synthesized a new polysaccharide, identified as 4-deoxy-(1→6)-β-DL-*ribo*-hexopyranan, by the ring-opening polymerization of 1,6-anhydro-2,3-di-*O*-benzyl-4-deoxy-β-DL-*ribo*-hexopyranose followed by removal of the protecting groups[8]. The ^{13}C-n.m.r. spectra of the free polysaccharide and its benzylated precursor suggested that the arrangement of the D and L enantiomeric monomeric units along the polymer chain varied markedly according to the solvents used for the ring-opening polymerization. In order to evaluate the tacticity of the DL polysaccharide, it was necessary to synthesize the corresponding optically active polysaccharide consisting exclusively of either the D or L enantiomeric monomeric units, and to compare its ^{13}C-n.m.r. chemical shifts with those of the DL polysaccharide. We decided to prepare 4-deoxy-(1→6)-β-L-*ribo*-hexopyranan (**3**) by the cationic ring-opening polymerization of 1,6-anhydro-2,3-di-*O*-benzyl-4-deoxy-β-L-*ribo*-hexopyranose (**1**) and subsequent debenzylation of the resulting polymer (**2**). The L polysaccharide was chosen, in view of the fact that a number of biologically important carbohydrate derivatives containing so-called "rare sugars" have been found[9], and the L polysaccharide might be useful as a model compound for elucidating the functions of these naturally occurring carbohydrates.

Previously we synthesized 2,3,4-trideoxy-(1→6)-α-L-*glycero*-hexopyranan



1 **2** **3**

Bn, $-CH_2C_6H_5$

*Chemical Synthesis of Polysaccharides Part 5.

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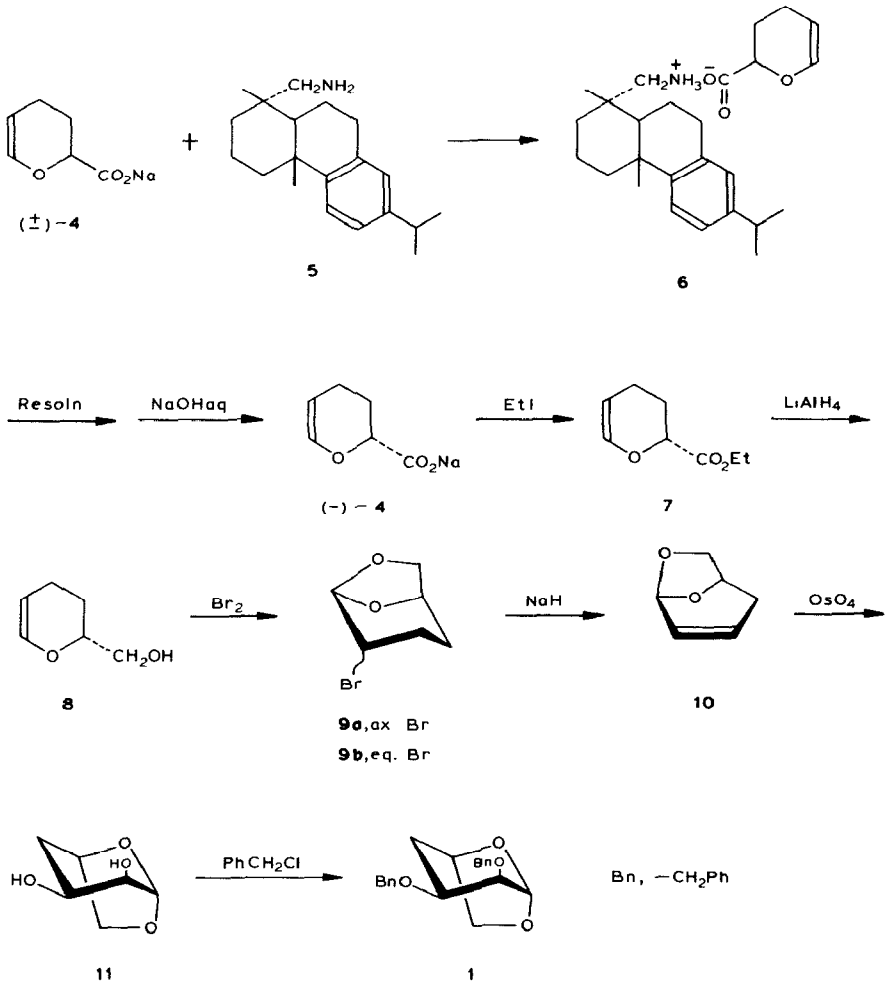
and 2-bromo-2,3,4-trideoxy-(1→6)-α-L-*erythro*-hexopyranan by the ring-opening polymerization of the corresponding (1→6)-anhydro sugars, which were derived from sodium 3,4-dihydro-2*H*-pyran-2-carboxylate through optical resolution with dehydroabietylamine as a resolving reagent[10,11]. Therefore, this procedure was applied to the preparation of **1**. The synthetic route is illustrated in Scheme I.



Scheme I. Synthetic route for 1,6-anhydro-2,3-di-*O*-benzyl-4-deoxy-β-L-*ribo*-hexopyranose (**1**).

Sodium 3,4-dihydro-2*H*-pyran-2-carboxylate [(±)-**4**] was converted by hydrochloric acid into its free acid, which was then treated with dehydroabietylamine (**5**) to yield dehydroabietylammonium 3,4-dihydro-2*H*-pyran-2-carboxylate (**6**). Repeated recrystallization of **6** from methanol and finally from ethanol gave white crystals having a constant specific rotation of $[\alpha]_D^{25}$ +11.6° (ethanol). The ammonium salt was transformed into its sodium salt [(−)-**4**], which was then esterified with ethyl iodide to afford (−)-ethyl 3,4-dihydro-2*H*-pyran-2-carboxylate

(**7**). Subsequent reduction of **7** by lithium aluminum hydride gave (−)-2-hydroxymethyl-3,4-dihydro-2*H*-pyran (**8**). Bromination of **8** accompanied by cyclization produced (+)-4-bromo-6,8-dioxabicyclo[3.2.1]octane as a mixture of stereoisomers (**9a**:**9b** = ~50:~50). Dehydrobromination of the stereoisomeric mixture with sodium hydride in 1,2-dimethoxyethane converted only **9a** into (−)-6,8-dioxabicyclo[3.2.1]oct-3-ene (**10**). The unreacted **9b** showed $[\alpha]_D^{25}$ +111.7° (ethanol). As it had been previously confirmed that **9b** having $[\alpha]_D^{25}$ +111° (ethanol) was 99% optically pure[11], the observed $[\alpha]_D^{25}$ value of **9b** indicates that the foregoing optical resolution was almost perfectly achieved. The absolute configurations of the bicyclic acetals **9b** and **10** have been determined to be (1*R*,4*R*,5*S*) and (1*R*,5*S*), respectively, that is, they belong to the category of L sugars[10,11]. Stereoselective oxidation of **10** by osmium tetraoxide and hydrogen peroxide[12] afforded 1,6-anhydro-4-deoxy-β-L-*ribo*-hexopyranose [(1*R*,3*S*,4*S*,5*S*)-3,4-dihydroxy-6,8-dioxabicyclo[3.2.1]octane, **11**]. It was benzylated with benzyl chloride and sodium hydride in *N*,*N*-dimethylformamide to give 1,6-anhydro-2,3-di-*O*-benzyl-4-deoxy-β-L-*ribo*-hexopyranose (**1**). As this compound was reluctant to crystallize, it was purified by column chromatography [column, silica gel; eluent, 1:1 (v/v) ethyl acetate–hexane]. The structure of this compound was confirmed by elemental analysis and by ^{1}H- and ^{13}C-n.m.r. spectroscopy.

Polymerization of **1** was performed in dichloromethane at −60° with phosphorus pentafluoride as the initiator. A high-vacuum technique was employed for the polymerization. A polymer (**2**) having a number-average molecular weight of 2.0×10^4 (gel-permeation chromatography, polystyrene standard) was obtained in 90% yield.

Debenzylation of the polymer **2** was achieved by conventional reduction with liquid ammonia and metallic sodium. The resulting polysaccharide (**3**) was a white powder, soluble only in dimethyl sulfoxide. It showed no melting point up to 327° (differential scanning calorimetry). The elemental analytical data were in good agreement with the theoretical values. The ^{1}H-n.m.r. signal of the anomeric proton of **3** appeared at δ 4.54 as a doublet having a coupling constant of 7.8 Hz, indicating that the anomeric proton and the vicinal proton on C-2 were in antiparallel disposition. The ^{13}C-n.m.r. chemical shift of the anomeric carbon atom (δ 101.88) of **3** (Fig. 1) corresponded to those for methyl β-D-glucopyranoside[13] (δ 102.6) and methyl β-D-allopyranoside[14] (δ 101.9). These n.m.r. data suggest that **3** consists of (1→6)-β-linked glycosidic units. This was further confirmed by the measurement of the specific rotation and the coupling constant between the anomeric carbon and hydrogen atoms.

Generally speaking, 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-hexopyranoses having negative specific rotations undergo cationic polymerization with inversion of configuration at C-1 to yield, after debenzylation, (1→6)-α-D-glycans having large positive specific rotations[15,16]. By comparison, the polysaccharide **3** prepared from the monomer **1** possessing a specific rotation of $[\alpha]_D^{25}$ +8.96° (ethanol) showed a specific rotation of $[\alpha]_D^{25}$ +115.5° (dimethyl sulfoxide). The large positive value

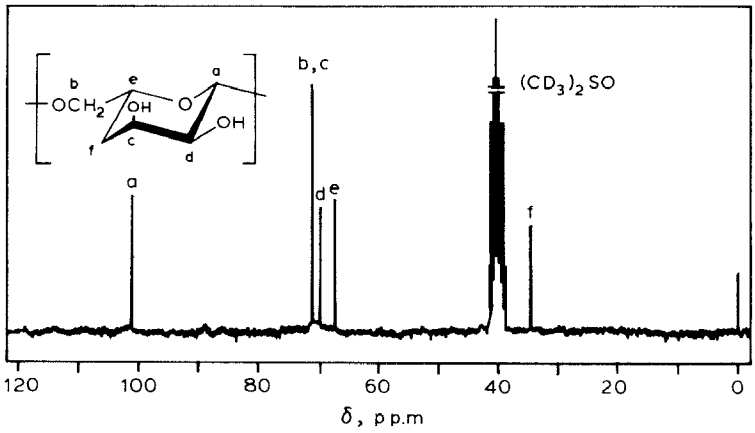


Fig. 1. ^{13}C-N.m.r. spectrum of 4-deoxy-(1→6)-β-L-*ribo*-hexopyranan (**3**). Solvent, dimethyl sulfoxide-d_6; temp., 70°; 50 MHz; internal reference, tetramethylsilane.

for the polysaccharide **3** clearly indicates that the configuration of the anomeric carbon atom was not altered during polymerization.

Additional evidence for the β-glycosidic structure of the polymer **3** was provided by the one-bond coupling-constant between the anomeric carbon and hydrogen atoms, $J_{C\text{-}1,H\text{-}1}$. It is generally accepted that β-glycosides give a $J_{C\text{-}1,H\text{-}1}$ value of ~160 Hz, whereas α-glycosides give a $J_{C\text{-}1,H\text{-}1}$ value[14,17] of ~170 Hz. This empirical rule is valid not only for monosaccharides but also for oligo- and polysaccharides[18,19]. The synthetic polysaccharide **3** showed a $J_{C\text{-}1,H\text{-}1}$ value of 156.3 Hz in dimethyl sulfoxide-d_6, substantiating that **3** was composed of β-glycosidic units.

In Table I, the ^{13}C-n.m.r. chemical shifts of **3** are compared with those of the corresponding DL polysaccharide prepared by the ring-opening polymerization of 1,6-anhydro-2,3-di-*O*-benzyl-4-deoxy-β-DL-*ribo*-hexopyranose in toluene (DL-I) and in dichloromethane (DL-II), respectively, followed by debenzylation[8]. The remarkable difference in the ^{13}C-n.m.r. spectrum between the two DL poly-

TABLE I

^{13}C-N M R CHEMICAL SHIFTS OF 4-DEOXY-(1→6)-β-L-*ribo*-HEXOPYRANAN (**3**) AND 4-DEOXY-(1→6)-β-DL-*ribo*-HEXOPYRANAN[a]

Sample[b]	*C-1*	*C-3 and C-6*[c]	*C-2*	*C-5*	*C-4*
L	101.86	71.68	70 34	67.87	35.26
DL-I	101.90	71.72	70.36	67.87	35.32
DL-II	101.88	71.68	70.32(60)[d] 69.91(40)[d]	67.87	35.30

[a]Solvent, dimethyl sulfoxide-d_6; temp., 70°; 50 MHz; internal reference, tetramethylsilane. [b]L, L polysaccharide (**3**); DL-I, DL polysaccharide obtained via polymerization in toluene[8]; DL-II, DL polysaccharide obtained via polymerization in dichloromethane[8]. [c]The signals assignable to these carbon atoms are overlapped. [d]Figures in parentheses denote the relative peak intensities of the signals.

saccharides is that the signal assignable to C-2 appears as a pair of peaks of different intensities in the spectrum of DL-II, whereas it appears as a singlet for DL-I. The chemical shift of the latter DL polysaccharide (DL-I) is in agreement with the corresponding chemical shift of the L polysaccharide **3**. Therefore, in the spectrum of DL-II, the signal appearing at δ 70.32 is reasonably assigned to C-2 in the isotactic dyads (DD and LL consecutive units), and hence the signal appearing at δ 69.91 is assigned to that in the syndiotactic dyads (DL and LD crossover units). On the basis of the assignments, the DL polysaccharide (DL-I) obtained by the polymerization in toluene is highly isotactic, in other words, there are long sequences consisting of the enantiomeric monomeric units of the same chirality along a polymer chain. In contrast, the tacticity of the DL polysaccharide (DL-II) prepared by polymerization in dichloromethane followed by debenzylation is much lower, judging from the relative peak-intensities of the two peaks of the C-2 signal. The mechanism for the formation of the stereoregular polysaccharide consisting of (1→6)-β-linked glycosidic units will be discussed in detail elsewhere.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. (200 MHz) and ^{13}C-n.m.r. (50 MHz) spectra were recorded with a JEOL FX-200 spectrometer for solutions in chloroform-*d* and dimethyl sulfoxide-d_6, tetramethylsilane being used as the internal reference. Specific rotations were measured on solutions in ethanol (**1** and **4**), chloroform (**2**), dimethyl sulfoxide (**3**), and water (**11**) at 25° with a Jasco DIP-181 automatic polarimeter. The number-average molecular weight of **2** was estimated by gel-permeation chromatography (column, Shodex A80M, 1 m; eluent, chloroform; polystyrene standard). The thermal properties of **2** and **3** were determined by a Perkin–Elmer DSC 2 differential scanning calorimeter.

*1,6-Anhydro-4-deoxy-β-*L-ribo-*hexopyranose* (**11**). — Detailed procedures for the optical resolution of sodium 3,4-dihydro-2*H*-pyran-2-carboxylate [(±)-**4**] using dehydroabietylamine as a resolving reagent and the subsequent reactions leading to (−)-(1*R*,5*S*)-6,8-dioxabicyclo[3.2.1]oct-3-ene (**10**) have been reported previously[10,11]. Osmium tetraoxide (100 mg, 0.39 mmol) was added to a solution of **10** (1.9 g, 0.017 mol) in 1,4-dioxane (30 mL) cooled to 15°. The mixture became black without generation of heat. A 30% aqueous solution of hydrogen peroxide (10 mL, 0.088 mol) was cautiously added to the mixture, keeping the temperature between 33 and 38° with external ice-cooling. After the mixture had been stirred for 1.5 h at room temperature, it was cooled in an ice–water bath, and potassium hydroxide (1.9 g, 0.034 mol) was added in small pieces. The rate of addition was carefully controlled to keep the temperature below 40°. The mixture was stirred for 1.5 h at room temperature and then extracted with six 100-mL portions of dichloromethane. The combined dichloromethane extracts were dried (anhydrous sodium sulfate) and the solvent was removed by a rotary evaporator, and the residue was recrystallized from ethanol to give white crystals; yield, 1.2 g (47%);

m.p. 99–101°, $[\alpha]_D^{25}$ +22.8° (*c* 0.55, water); ^{1}H-n.m.r. ($CDCl_3$): δ 5.47 (d, 1 H, H-1), 4.51 (t, 1 H, H-5), 3.85–4.10 (m, 1 H, H-3), 3.60–3.85 (m, 3 H, H-2 and 2 H-6), 2.59 (t, 2 H, 2 OH), and 1.74–2.00 (m, 2 H, 2 H-4); ^{13}C-n.m.r. ($CDCl_3$): δ 101.34 (C-1), 71.82 (C-5), 69.45 (C-2), 66.94 (C-6), 63.10 (C-3), and 34.96 (C-4).

*1,6-Anhydro-2,3-di-*O*-benzyl-4-deoxy-β-*L*-ribo-hexopyranose* (**1**). — Sodium hydride (50% oil dispersion, 1.2 g, 25 mmol) was washed with dry hexane to remove oil, and added to a solution of **11** (1.4 g, 9.7 mmol) in dry dimethyl sulfoxide (40 mL). After the mixture had been stirred for 0.5 h at room temperature, benzyl chloride (3.3 mL, 29 mmol) was added dropwise. The mixture was then heated for 2 h at 55–70° with vigorous stirring. It was cooled and poured into ice–water (250 mL). The mixture was extracted with five 100-mL portions of chloroform. The combined extracts were washed with two 200-mL portions of water and dried (anhydrous sodium sulfate). The solvent was removed by a rotary evaporator to afford an amber oil that was purified by column chromatography [column, silica gel; eluent, 1:1 (v/v) ethyl acetate–hexane] three times; yield, 1.8 g (56%); $[\alpha]_D^{25}$ +8.96 (*c* 4.79, ethanol); ^{1}H-n.m.r. ($CDCl_3$): δ 7.32 (m, 10 H, 2 Ph), 5.39 (d, 1 H, *J* 2.4 Hz, H-1), 4.76 (q, 2 H, CH_2Ph), 4.53 (d, 3 H, H-5 and CH_2Ph), 3.7–3.8 (m, 1 H, H-3), 3.6–3.7 (m, 1 H, H-2), 2.15 (t, 1 H, *J* 12.9 Hz, H-4), and 1.8–1.9 (m, 1 H, H-4); ^{13}C-n.m.r. ($CDCl_3$): δ 138.34 and 138.17 (phenyl, *ipso*), 128.13 (phenyl, *meta*), 127.74 (phenyl, *para*), 127.39 and 127.19 (phenyl, *ortho*), 100.51 (C-1), 73.74 (C-5), 72.91 (benzyl), 71.94 (C-2), 71.10 (C-3), 70.31 (benzyl), 66.81 (C-6), and 32.47 (C-4).

Anal. Calc. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.64; H, 6.83.

*2,3-Di-*O*-benzyl-4-deoxy-(1→6)-β-*L*-ribo-hexopyranan* (**2**). — A solution of **1** (0.65 g, 2.0 mmol) in dichloromethane was stirred with small pieces of calcium hydride in a flask connected to a high-vacuum line. After freezing and thawing had been repeated several times, the solution was transferred through a sintered-glass filter to a reaction vessel. The solution was concentrated to the desired volume (~3.5 mL). Phosphorus pentafluoride, generated by the decomposition of benzene diazonium hexafluorophosphate (25 mg, 0.10 mmol), was introduced to the reaction vessel cooled in a liquid-nitrogen bath. After sealing off, the vessel was kept in a bath maintained at −60°. After 16 h, the mixture was poured into a large volume of methanol to precipitate a polymer. It was separated and purified by repeated reprecipitation, using dichloromethane and methanol as a solvent–precipitant pair, and finally freeze-dried from a benzene solution, yield, 0.59 g (90%); M_n, 2.0 × 10^4 (gel-permeation chromatography, polystyrene standard); $[\alpha]_D^{25}$ +60.9° (*c* 0.50, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.24 (m, 10 H, 2 Ph), 4.82 (m, 2 H, CH_2Ph), 4.57 (m, 3 H, H-1 and CH_2Ph), 4.02 (br, 1 H, H-5), 3.78 (br, 2 H, H-6), 3.49 (br, 1 H, H-2), 3.15 (br, 1 H, H-3), 1.72 (d, 1 H, exo-H-4), and 1.17 (t, 1 H, endo-H-4); ^{13}C-n.m.r. ($CDCl_3$): δ 138.82 and 138.72 (phenyl, *ipso*), 127.95 (phenyl, *meta*), 127.33 (phenyl, *ortho*), 127.01 (phenyl, *para*), 101.21 (C-1), 79.01 (C-4), 74.01 (C-2), 72.77 and 71.78 (benzyl), 71.26 (C-6), 69.57 (C-5), and 32.45 (C-4).

*4-Deoxy-(1→6)-β-*L-ribo-*hexopyranan* (**3**). — To liquid ammonia (50 mL) in a three-necked flask equipped with a cold-finger trap, there was added dropwise a solution of **2** (0.52 g, 1.2 mmol) in a mixed solvent of dimethoxyethane (5 mL), toluene (5 mL), and benzene (15 mL) with external cooling by a Dry Ice–methanol bath. The bath was removed, and a small piece of metallic sodium was occasionally added to the solution until a dark-blue color persisted. After stirring the mixture for 1 h, a small amount of ammonium chloride was cautiously added to the mixture, followed by the dropwise addition of water (25 mL). The cold-finger trap was removed and the mixture was kept overnight at room temperature to evaporate ammonia. Water (5 mL) was added, and the aqueous and organic layers were separated. The organic layer was extracted with 3 30-mL portions of water and the combined aqueous solution was dialyzed in a stream of water for 2 days. The aqueous solution was concentrated by a rotary evaporator and finally freeze-dried to yield a white, powdery product; yield, 0.22 g (95%); $[\alpha]_D^{25}$ +115.5° (*c* 0.52, dimethyl sulfoxide); ^{1}H-n.m.r. [$(CD_3)_2SO$]: δ 4.54 (d, 1 H, *J* 7.8 Hz, H-1), 4.38 (s, 1 H, OH), 4.30 (s, 1 H, OH), 3.93 (s, 2 H, H-2 and H-5), 3.58 (m, 2 H, 2H-6), 3.15 (br. s, 1 H, H-3), 1.72 (q, 1 H, *J* 12.5 Hz, exo-H-4), and 1.48 (dd, 1 H, *J* 12.5, *J* 12.0 Hz, endo-H-4); ^{13}C-n.m.r. [$(CD_3)_2SO$]: δ 101.86 (C-1), 71.68 (C-3 and C-6, superposed), 70.34 (C-2), 67.87 (C-5), and 35.26 (C-4), $J_{C\text{-}1,H\text{-}1}$ 156.3 Hz.

Anal. Calc. for $(C_6H_{10}O_4)_n$: C, 49.31; H, 6.90. Found: C, 49.33; H, 7.19.

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