Branched-chain Sugars. II. Synthesis of Methyl 5-Deoxy-3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-DL-*lyxo*-furanoside (Dihydrostreptose) and Ribofuranoside Derivatives

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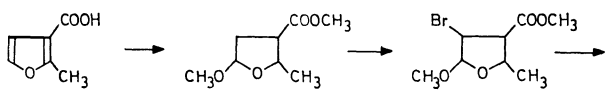
The title compounds, methyl 5-deoxy-3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-DL-*lyxo*-furanoside, and ribofuranoside derivatives were conveniently synthesized *via* the Birch reduction of 2-methyl-3-furoic acid, and the latter was identified with the sample prepared from D-xylose.

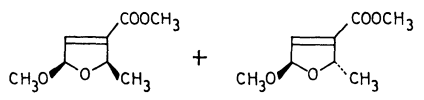
In a previous paper,[1] we reported the synthesis of DL-apiose from 2-methoxy-4-(methoxycarbonyl)tetrahydrofuran which had been prepared *via* the Birch reduction of 3-furoic acid.[2] This paper will describe the synthesis of 5-deoxy-3-*C*-branched-DL-*lyxo*- and ribofuranoses of Type A[3] as an application of the method to the total synthesis of 3-*C*-branched-chain sugars from substituted 3-furoic acids.

Results and Discussion

The Birch reduction of 2-methyl-3-furoic acid (**1**) gave 2-methyl-2,3-dihydro-3-furoic acid, which, after esterification with diazomethane, followed by the acid-catalyzed addition of methanol, was isolated as a methoxy methyl ester (**2**) in a 95% yield. This compound was shown by gas chromatography (GLC) to be a mixture of four diastereoisomers with respect to each functional group, but the constituents could not be separated. The bromination of **2** by pyridinium tribromide in tetrahydrofuran at room temperature afforded a bromo compound (**3**) in a 75% yield. On the treatment of the isomeric mixture **3** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in benzene at room temperature for one minute, 5-methyl-2-methoxy-4-(methoxycarbonyl)-2,5-dihydrofuran (**4**), a mixture of (**4a**) and (**4b**) with the expected spectroscopic data, was obtained in a 75% yield. The oxidation of **4** with osmium tetraoxide–sodium chlorate[4] in aqueous tetrahydrofuran yielded diol in a 95% yield; it was subsequently isolated as an isomeric mixture of isopropylidene compounds, (**5a**), (**5b**), and (**5c**). These were separated by GLC in a ratio of 1.0: 1.5 : 1.7.

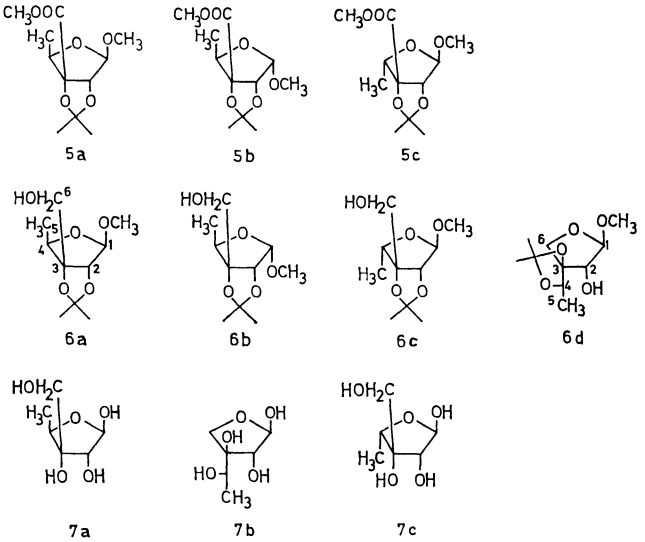


1 **2** **3**



4a **4b**

The structures of the compounds were assigned on the basis of the PMR spectrum. No coupling was observed between H-1 and H-2 in **5a** and **5c**, indicating that the methoxyl group is *trans*-disposed[5] to the 2,3-*O*-isopropylidene group. On the other hand, the doublets ($J_{1,2}$=4.6 Hz) for H-1 and H-2 in **5b** indicate these protons to be *cis* on the furanoid ring.[1] Although the exact orientation of the methyl group on carbon-4 was assigned by independent synthesis (see below), the signals of the methyl group in **5c** and that of the anomeric methoxyl group in **5b** appeared at the lowest field as a result of deshielding by the dioxolan ring. At this point, some comments may be added regarding the hydroxylation of **4**. In the oxidation of **4** with osmium tetraoxide, *cis*-**4a** gave exclusively **5a**, while *trans*-**4b** gave **5b** and **5c** in approximately equal quantities; this means that the steric bulkiness towards hydroxylation is almost the same in the methyl and methoxyl group.



5a **5b** **5c**

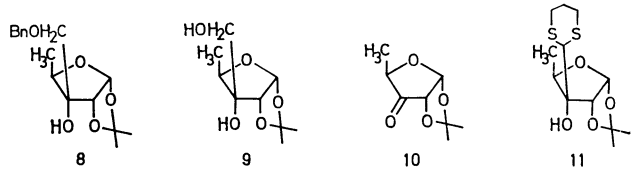
6a **6b** **6c** **6d**

7a **7b** **7c**

The acid-catalyzed hydrolysis of **5a**, followed by reglycosidation in methanol and acetonation , yielded **5a** and **5b** in a ratio of 2 : 7 (by GLC). This fact shows that **5b**, being an α-anomer, is more stable than **5a**. The methyl esters, **5a**—**c**, were reduced quantitatively to the corresponding alcohols (**6a**—**c**). The assignment of the configuration of (**6**) was based on its PMR spectral data and on the individual conversion of **5** to **6**. The chemical shifts and coupling constants were assigned as is shown in the Table. The fact that the methyl signal in **6a** appeared at the lowest may be explained by the deshielding effect being by the hydroxymethyl group rather than by the dioxolan ring.

A mixture of **6a** and **6b** was converted to a 1,2-*O*-isopropylidene derivative (**8**) *via* the following sequence of reactions: benzylation[6] in DMSO (37%), acid-catalyzed hydrolysis (85%), and acetonation (15%).[7]

Hydrogenation on Pd–charcoal of **8** gave a crystalline 5-deoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-DL-ribofuranose (**9**) (mp 128—129 °C[8]) in a 90% yield. Compound **9** was synthesized in three steps from 5-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (**10**),[9] which had been prepared from D-xylose. The reaction of **10** with 2-lithio-1,3-dithiane gave the branched-chain sugar, 5-deoxy-3-*C*-formyl-1,2-*O*-isopropylidene-α-D-ribofuranose trimethylene dithioacetal (**11**). Mercury(II) oxide and boron trifluoride etherate hydrolyzed **11** to 5-deoxy-3-*C*-formyl-1,2-*O*-isopropylidene-α-D-ribofuranose, which was then reduced with sodium borohydride to give **9**. The resulting compound was identified by comparing its PMR and mass spectra with those of the sample derived from 2-methyl-3-furoic acid.



8 9 10 11

The acid-catalyzed hydrolysis of the alcohol **6c** with hydrochloric acid gave dihydrostreptose (**7c**), while that of **6a** or **6b** gave (**7a**). The hydrolysis of **6b**, followed by reglycosidation in methanol and acetonation, gave (**6d**) and **6a** in a ratio of 1 : 5. These substances were separated by GLC. **6a** was identified by comparing its GLC, MS, and PMR. The structure of **6d** was established by spin-decoupling studies. In the PMR spectrum of **6d**, the irradiation of C-5 methyl protons (δ, 1.28) collapsed the H-4 methin proton (δ, 4.20, quartet) to a singlet. The irradiation of H-2 (δ; 3.76) changed the H-1 (δ, 4.78, doublet) and the hydroxyl signals (δ, 2.60, doublet) both into singlets. A small H-1, H-2 coupling constant (1.2 Hz) could be taken as an indication of the *trans* arrangement of the protons. From the above data, **6d** was concluded to be a methyl 3-*C*-(1-hydroxyethyl)-3,3′-*O*-isopropylidene-β-DL-*threo*-furanoside.

Accordingly, in the production of **6d** it may be assumed that **7a** comprised an isomer (**7b**). In the PMR spectrum of **7c**, the methyl signals (doublet, J=6.5) appeared at δ 1.24 (75%, β-anomer) and δ 1.29 (25%, α-anomer), as had been reported by Dyer.[10] The predominance of the β-anomer, contrasted with methyl glycoside, is apparently due to the hydrogen bonding with the 3-*C*-hydroxymethyl group. Although the PMR spectrum of **7a** could not be assigned because of the concomitance of isomeric **7b**, the same situation was observed with the 4-epimer **7a**, which showed the methyl signals at δ 1.20 (25%, α-anomer) and δ 1.24 (75%, β-anomer) in a lower field than those of **7c**.

Experimental

Melting points were determined on a micro hot stage and are uncorrected. GLC was performed on a Varian Aerograph Model 90-P instrument equipped with a 4 mm × 1 mm column of Poly(ethylene glycol) (20% on Chromosorb W-AW, DMCS). The column temperature was 180 °C, and the flow rate was 60 ml of helium/min. IR spectra were taken on a JASCO Model IR-E. PMR spectra were recorded in chloroform-*d* solution at 100 MHz with a JEOLCO PS-100 spectrometer. Mass spectra were recorded with a HITACHI M-52 mass spectrometer at 70 eV. Elemental analyses were carried out on a Perkin Elmer Model 240 elemental analyzer.

*2-Methyl-3-furoic Acid (**1**)* (mp 102 °C) was prepared from ethyl 2-methyl-3-furoate; bp 87—95 °C/25 mmHg (lit,[11] bp 81—84 °C/18 mmHg).

The Birch Reduction of 2-Methyl-3-furoic Acid. To a mixture of 2-methyl-3-furoic acid (5.68 g) and anhydrous methanol (20 ml) in liquid ammonia (150 ml) was added sodium metal (5.2 g) little by little with constant stirring under reflux. The mixture was then stirred for an additional hour and ammonium chloride (11 g) was added. After evaporation of the liquid ammonia at room temperature, the residue was dissolved in water (100 ml). The aqueous solution was acidified with hydrochloric acid to pH 2 and extracted continuously with ether for 15 h. The ether extract was esterified with diazomethane, and, after the evaporation of the solvent, the residue was distilled to give **2**; 7.38 g (95%); bp 99—101 °C/20 mmHg; IR cm^{-1} 2830 (OCH_3), 1735 (C=O) Found: C, 55.09; H, 8.22%. Calcd for **2** ($C_8H_{14}O_4$): C, 55.16; H, 8.10%.

Bromination of 2. To a stirred solution of **2** (1.74 g)

Table 1. PMR-spectra of 5-deoxy sugars (in $CDCl_3$). Chemical shifts (δ values) and coupling constants (Hz)

	5a	**5b**	**5c**	**6a**	**6b**	**6c**	**6d**
H_1	5.00, s	5.03, d	4.84, s	4.93, s	4.86, d	4.85, s	4.78, d
H_2	4.93, s	4.97, d	4.78, s	4.40, s	4.62, d	4.36, s	3.76, bs
H_4	4.42, q	4.30, q	4.35, q	4.38, q	4.20, q	3.98, q	4.20, q
H_6				3.80, s	3.77, q	3.71, s	4.04, q
$COOCH_3$	3.83	3.84	3.80				
OCH_3	3.38	3.48	3.37	3.37	3.50	3.37	3.37
OH				2.05	1.90	1.90	2.60, d
$(CH_3)_2$	1.53	1.60	1.52	1.53	1.60	1.53	1.55
	1.28	1.33	1.37	1.45	1.45	1.45	1.43
CH_3-	1.23, d	1.20, d	1.30, d	1.30, d	1.22, d	1.29, d	1.28, d
		$J_{1,2}$=4.6			$J_{1,2}$=4.5		$J_{1,2}$=1.2
	$J_{4,5}$=7	$J_{4,5}$=7	$J_{4,5}$=7	$J_{4,5}$=7	$J_{4,5}$=7	$J_{4,5}$=7	$J_{4,5}$=6.8
					$J_{6,6'}$=13		$J_{6,6'}$=9.5
							$J_{2,OH}$=2.0

in dry THF (20 ml) was added pyridinium tribromide (3.1 g). The reddish solution was stirred at room temperature. After 12 h, a white precipitate appeared and the color disappeared. The precipitate was filtered off and the filtrate was concentrated to a light-brown oil, which was then purified by chromatography on silica gel (80 g) with benzene to give a colorless liquid (**3**) (1.92 g, 75%); IR cm^{-1} 2830 (OCH_3), 1735(C=O). MS *m/e* (%) 254 (1) (M^+), 252(1) (M^+), 223 (50), 221(49), 191(25), 189 (22), 141 (78), 130 (75), 113(100), 83 (70).

*Dehydrobromination of **3** with DBU.* To a vigorously stirred solution of **3** (1.2 g) in dry benzene (25 ml) was added DBU (1.52 g) at room temperature. There immediately appeared a white precipitate of DBU-hydrobromide. Water (20 ml) was added to the reaction mixture and the organic layer was separated, washed with water, dried over sodium sulfate, and evaporated to give a 2,5-dihydrofuran derivative (**4**) as a colorless liquid (650 mg, 75%); IR cm^{-1} 3080, 2830, 1723, 1645; PMR δ1.47 (3H, d, J=6, CH_3), 3.40 (3H, s, OCH_3), 3.75 (3H, s, $COOCH_3$), 5.10—4.85 (1H, m, H-5), 5.70 (1H, s, H-2), 6.58 (1H, s, H-3).

*Methyl 5-Deoxy-3-*C*-methoxycarbonyl-2,3-*O*-isopropylidene-β- and α-*DL*-Ribofuranoside, **5a** and **5b**,* and *Methyl 5-Deoxy-3-*C*-methoxycarbonyl-2,3-*O*-isopropylidene-β-*DL*-lyxo-furanoside, **5c**.* To a stirred solution of the dihydro compound **4** (4.71 g) and osmium tetraoxide (80 mg) in THF (25 ml) was added a solution of sodium chlorate (3.82 g) in water (25 ml) at room temperature. After stirring for 24 h, the light-yellow solution was decomposed by passing hydrogen sulfide gas through it. Black precipitates were removed by filtration through Celite, and the colorless solution was concentrated to a volume of about 20 ml. The aqueous solution was extracted continuously with ether for 15 h to give a diol as a syrup; crude yield, 4.86 g (91%). IR cm^{-1} 3450, 2830, 1730.

The diol (2.06 g) was acetonated by treatment with dry acetone (150 ml), anhydrous copper(II) sulfate (15 g), and a catalytic amount of sulfuric acid at room temperature for 24 h to afford an oil, a mixture of **5a**, **5b**, and **5c**, after purification by column chromatography on silica gel; yield, 2.24 g (91%). The mixture was separated by GLC in a ratio of 1.0 : 1.5 : 1.7. The retention times: **5a**, 9.5 min; **5b**, 12.0 min; **5c**, 7.2 min. Found for **5a**: C, 53.51; H, 7.33%. Found for **5b**: C, 53.53; H, 7.44%. Found for **5c**: C, 53.50; H, 7.34%. Calcd for ($C_{11}H_{18}O_6$): C, 53.65; H, 7.37%.

*Chemical Conversion of **5a** to **5b**.* Compound **5a** (50 mg) in water–methanol (5 ml; 4 : 1) was hydrolyzed in the presence of a catalytic amount of *p*-toluenesulfonic acid at reflux for 2 h. After the disappearance of the anomeric methoxyl and isopropylidene groups has been ascertained by an estimation of the PMR spectrum in deuterium oxide, the syrup was boiled in dry methanol–dry acetone (20 ml; 10 ml) in the presence of *p*-toluenesulfornic acid for 6 h. The resulting compound (35 mg) was identified by comparing its GLC (**5a** : **5b**=2 : 7) with those of the sample.

*Methyl 5-Deoxy-3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β- and α-*DL*-Ribofuranoside, **6a** and **6b**, and Methyl 5-Deoxy-3-*C*-hydroxymethyl-2,3-*O*-isopropylidene-β-*DL*-lyxo-furanoside, **6c**.* Those substances were obtained quantitatively by the lithium aluminium hydride reduction in boiling ether for 3 h of **5a**, **5b**, and **5c** respectively. MS *m/e* (%) for **6a**: M^+ (absent), 203(12), 187(16), 171(9), 143(52), 119(20), 100(48), 85(96), 82(88), 73(100), 71(60). **6b**: M^+(absent), 203(4), 187(12), 171(9), 143(32), 119(16), 100(20). 85(35), 82(55), 73(100), 71(80). **6c**: M^+(absent), 203(3), 187(10), 171(5), 143(25), 119(15), 100(25), 85(40), 82(55), 73(100), 71(75). *p*-Nitrobenzoate of **6a**: syrup; **6b**, mp 109—110 °C; **6c**, mp 130—130.5 °C. Found for **6b**: C, 55.86; H, 5.80; N, 3.87%. Found for **6c**: C, 55.54; H, 5.80; N, 3.77%. Calcd for *p*-nitrobenzoate ($C_{17}H_{21}O_8N$): C, 55.58; H, 5.76; N, 3.81%.

*Chemical Conversion of **6b** to **6a** and **6d**.* Compound (**6b**) (70 mg) in water (5 ml) was hydrolyzed in the presence of two drops of concentrated hydrochloric acid at reflux for 10 min. After the evaporation of the solvent, the syrup was boiled in dry methanol–dry acetone (20 ml; 10 ml) in the presence of ion-exchange resin (Dowex 50X8, 500 mg) for 20 h to afford an oil (crude; 85 mg) as a mixture of the two compounds. The mixture was separated by GLC (at 200 °C) in the ratio of 1 : 5. The retention times: 6.2 min (**6d**); 7.5 min (**6a**).

*α,β-DL-Dihydrostreptose, **7c**, and Its 4-Epimer, **7a**.* Compound (**6c**) (300 mg) in water (5 ml) was hydrolyzed in the presence of a catalytic amount of concentrated hydrochloric acid at room temperature for 15 h. The evaporation of the solvent under diminished pressure below 40 °C gave a syrup of **7c** (220 mg, 95%). The PMR spectrum in deuterium oxide showed the absorptions of two isomers. The β-anomer comprised 75% of the mixture and showed absorptions at δ1.24 (3H, d, J=6.5, CH_3–), 3.60 (2H, s, H-6), 4.09 (1H, d, J=4.0, H-2), 4.35 (1H, q, J=6.5, H-4), 5.26 (1H, d, J=4.0, H-1). The α-anomer: δ1.29 (3H, d, J=6.5), 3.60 (2H, s), 4.10 (1H, q, J=6.5), 4.17 (1H, d, J=5.0), 5.23 (1H, d, J=5.0).

By the same procedure, **7a** was also obtained from **6a** or **6b**. δ1.20 (3H, d, J=6.5); α-anomer, 25%. δ1.24 (3H, d, J=6.5); β-anomer, 75%.

*5-Deoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-*DL*-ribofuranose, **9**.* The benzylation of a mixture of **6a** and **6b** (1.0 g) was performed in accordance with Iwashige's method[6] to afford the benzyl ether in a 37% yield. The ether (200 mg) dissolved in dioxane–water (10 ml) was hydrolyzed at reflux for 2 h in the presence of concentrated hydrochloric acid to give a syrup (140 mg), which was then acetonated by the procedure described above to give 1,2-*O*-isopropylidene benzyl ether, **8**; 25 mg (15%); PMR δ5.60 (1H, d, $J_{1,2}$=4, H-1), 4.48 (1H, d, H-2), 3.91 (1H, q, $J_{4,5}$=6, H-4), 3.42(2H, q, $J_{6,6'}$=10, H-6), 2.66 (OH), 1.55 (3H, s), 1.35 (3H, s), 1.17 (3H, d, H-5), 4.52 (2H, q, J=12, benzyl), 7.27 (5H, s, arom.).

The hydrogenation of the benzyl ether **8** (25 mg) over 10% Pd–C in methanol for 5 h afforded a crystalline **9** (15 mg, 90%): mp 128—129 °C; PMR δ5.75 (1H, d, $J_{1,2}$=4, H-1), 4.55 (1H, d, H-2), 3.92 (1H, q, $J_{4,5}$=6.2, H-4), 3.75 (2H, d, $J_{6,6'}$=12, H-6), 2.73 (OH), 3.36 (OH), 1.56 (3H, s), 1.37 (3H, s), 1.18 (3H, d, CH_3–). MS *m/e* (%) M^+ (absent), 189 (14), 129(40), 99(36), 88(25), 71(89), 59(100). Found: C, 52.60; H, 7.86%. Calcd for **9** ($C_9H_{16}O_5$): C, 52.93; H, 7.92%.

*5-Deoxy-3-*C*-formyl-1,2-*O*-isopropylidene-α-*D*-ribofuranose Trimethylene Dithioacetal, **11**.* To a stirred solution of 1,3-dithiane (200 mg) in dry THF (4 ml) was added butyllithium (1.5 ml, 1.2 M in hexane) at −78 °C under a nitrogen atmosphere. After stirring at that temperature for 2 h, the ulose, **10** (170 mg) in dry THF (2 ml) was added and the reaction mixture was stirred for 3 h at room temperature. Water (10 ml) was then added and subsequently extracted with dichloromethane (20 ml×3). After an usual work-up and preparative thin-layer chromatography (0.75 mm silica gel on plate) (benzene–ether, 8 : 2), dithioacetal, **11** (270 mg, 92%), was obtained; mp 123—124 °C; $[\alpha]_D^{26}$ +5° (c=1, in acetone). PMR δ5.86 (1H, d, $J_{1,2}$=4, H-1), 4.74 (1H, d, H-2), 4.43 (1H, s, S–CH–S), 4.02 (1H, q, $J_{4,5}$=7, H-4), 3.00 (1H, s, OH), 2.80—3.00 (4H, m, $-CH_2$–S–), 2.05 (2H, bs, $-CH_2$–), 1.57 (3H, s,), 1.39 (3H, s), 1.45 (3H, d, H-5). MS *m/e* (%) 292 (6) (M^+), 277(1), 217(2), 190(1), 175(5), 146(3), 127(2), 119(100). Found C, 49.31; H, 6.89%. Calcd for

$C_{12}H_{20}O_4S_2$: C, 49.31; H, 6.90%.

*5-Deoxy-3-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-*D*-ribofuranose* **9**. To a suspension of red mercury(II) oxide (650 mg) and boron trifluoride etherate (365 mg) in 5 ml of 80% aqueous acetone was added, drop by drop, dithioacetal **11** (250 mg) in THF (2 ml) under a nitrogen atmosphere. After the mixture had been stirred overnight, the color disappeared. Water (2 ml) and acetone (6 ml) were then added, and the mixture was neutralized with a sodium hydroxide solution. The precipitate was filtered off, and the filtrate was concentrated to dryness under diminished pressure below 40 °C, extracted with chloroform, washed with water, and dried over sodium sulfate. The resulting syrup was reduced with sodium borohydride in 70% aqueous methanol (15 ml) to give an oil (120 mg). The residue was chromatographed on silica gel (5 g) (CH_2Cl_2–ether, 10 : 1); fractions were collected every 15 ml. Fraction 4—6 (30 mg) **9**, mp 112—113 °C. The PMR and mass spectra were identified with DL-**9**.

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