Branched-chain Sugars V. Stereoselective Synthesis of 3-*C*- and 5-*C*-Methyl-D-glucoses, and 5-*C*-Methyl-L-idose Derivatives[1)]

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The title compounds were prepared stereoselectively from 1,2: 5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose (**1**) and 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-methylene-6-*O*-trityl-α-D-*xylo*-hexofuranose (**5b**) by the successive epoxidation and reduction, and from 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-trityl-α-D-*xylo*-hexofuranos-5-ulose (**5a**) by the Grignard reaction, respectively.

The high stereoselectivity of nucleophilic reaction to 2-,[2)] 3-,[3)] 4-,[4)] and 5-[5)] keto-sugars has generally been recognized in the synthesis of branched-chain sugars, and as a matter of fact, most of such stereoselectivities (sometimes stereospecificities) have been interpreted in terms of the intrinsic conformational and configurational characters of each keto-sugars.

If this is the case applicable to addition reactions to 2-, 3-, 4-, and 5-*C*-methylene-sugars, which could be obtained from the corresponding uloses by the Wittig reaction, the reversal of the configuration by the similar stereochemical process would be possible to give the desired diastereomeric *C*-substituted sugars not accessible in the conventional manner.

The present paper, therefore, describes the model system applying the above idea to a couple of compounds such as 1,2: 5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose (**1**)[6)] and 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-methylene-6-*O*-trityl-α-D-*xylo*-hexofuranose (**5b**) in order to obtain 3-*C*-methyl-D-glucose and 5-*C*-methyl-L-idose derivatives. A part of which was reported in the preliminary communication.[7)]

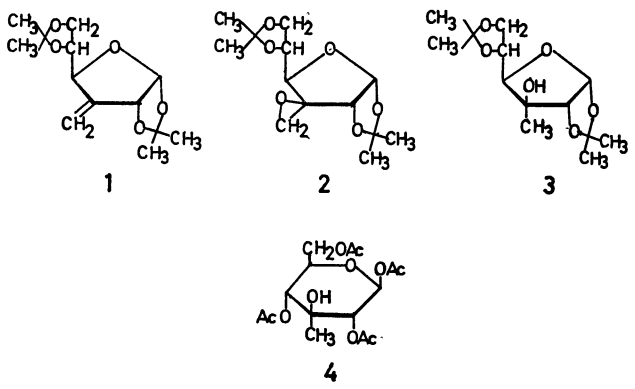
Results and Discussions

The principle of this experiment is to apply epoxidation followed by reduction to compounds **1** and **5b** to get 3-*C*-methyl-D-glucose and 5-*C*-methyl-L-idose derivatives stereoselectively, and we selected as references 1,2: 5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose[8)] and newly prepared 3-*O*-benzyl-1,2-isopropylidene-5-*C*-methyl-6-*O*-trityl-α-D-glucofuranose (**7b**) in order to confirm the reversal of the configuration at the branched carbon.

The preparation of 1,2: 5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-gluco-furanose (**3**) was done in a following way. 3-*C*-Methylene derivative (**1**) obtained from 1,2: 5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[9)] by a modified procedure using butyllithium in tetrahydrofuran in place of sodium amide–liquid ammonia[6a)] or sodium hydride–dimethyl sulfoxide[6b)] was oxidized with *m*-chloroperbenzoic acid in 1,2-dichloroethane at room temperature to D-*gluco*-epoxide (**2**) in an excellent yield. Compound **2** was also isolated from reaction between **1** and diazomethane in *ca.* 20% yield.[3c)] NMR spectrum showed the typical terminal epoxide-methylene protons at δ 3.08 as AB quartet (J=5.0 Hz). The epoxide was then reduced with lithium aluminum hydride in ether to yield a crystalline 1,2; 5,6-*di*-*O*-isopropylidene-3-*C*-methyl-α-D-glucofuranose (**3**) in 85% yield.

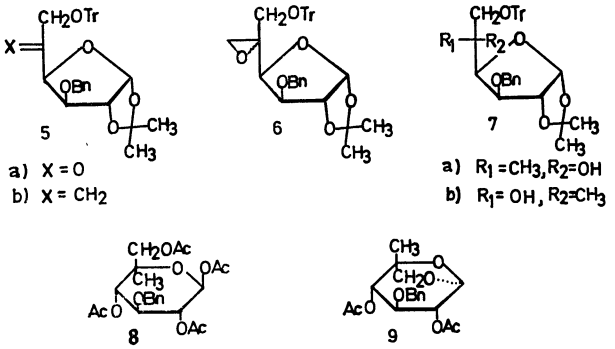
Compound **3** was completely differentiated from the corresponding D-allose isomer.

Removal of isopropylidene group of **3**, followed by acetylation gave 1,3,4,6-tetra-*O*-acetyl-3-*C*-methyl-β-D-glucopyranose (**4**) as a major product.



Scheme 1.

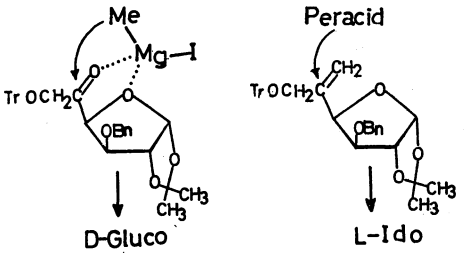
The same techniques were also applied to the compound **5b**, which was newly prepared from 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-trityl-α-D-*xylo*-hexofuranos-5-ulose (**5a**) and methylenetriphenylphosphorane in tetrahydrofuran in 80% yield. **5b** was then oxidized in the same way as in the case of the compound **1** in 1,2-dichloroethane to a mixture of epoxide (**6**: L-*ido* and D-*gluco*), quantitatively. Reduction of **6** with lithium aluminum hydride in ether gave 5-*C*-methyl-hexofuranose derivatives (**7a** and **7b**). The ratio of **7a** to **7b** was estimated to be *ca.* 2: 1 by comparing the intensity of



Scheme 2.

H-6 and H-6′ protons of both compounds in NMR spectrum.

On the other hand, the reference compound, 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-methyl-6-*O*-trityl-α-D-glucofuranose (**7b**) was exclucively prepared by reacting **5a** with an excess amount of methylmagnesium iodide in ether. This stereospecificity must be explained if such a cyclic intermediate (scheme 3) could be possible; the attack of methyl group should take place from the less-hindered site opposite to benzyl group at C-3 to give only D-gluco configuration as was suggested in the case of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-xylohexofuranos-5-ulose with phenylmagnesium bromide.[5] The situation would be almost same in the epoxidation of **5b** since the attack by peracid could preferentially from the less-hindered site mentioned above to give L-*ido* configuration predominantly if bulkier trityloxymethyl group situated rather rigidly.



Scheme 3.

As a matter of fact, the configuration of both compounds (**7a** and **7b**) was unambiguously established in the following way. When the compounds **7a** and **7b** were hydrolyzed in hot acetic acid (70%) and followed by acetylation with acetic anhydride in pyridine, 2,4-di-*O*-acetyl-1,6-anhydro-3-*O*-benzyl-5-*C*-methyl-β-L-idopyranose (**9**) from **7a** and 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-5-*C*-methyl-β-D-glucopyranose (**8**) from **7b** were isolated respectively in good yields.

The structure of both compounds (**8** and **9**) was easily established by NMR (see experimental section), comparing the intensity between acetoxy methyl and methyl signals, $J_{1,2}$ (**8**; 7.5 Hz, **9**; 1.5 Hz) and by elemental analysis. It may be noted that similar intramolecular condensation occurrs in a solvolytic process of 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose[10] to yield 1,6-anhydro-3-*O*-benzyl-β-L-idopyranose.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and uncorrected. NMR spectra were measured with JNM-4H-100 spectrometer in chloroform-*d* using tetramethylsilane as the internal reference. Specific rotations were measured in a 0.5-dm tube with a Carl Zeis photoelectric polarimeter. IR spectra were taken with a Hitachi Model EPI-G2 spectrophotometer. Tlc and preparative tlc was effected on a silica-gel (Merk type 60) plate using solvent systems such as (A) benzene/methanol (25/3), (B) benzene/ether (10/1), (C) benzene/ethyl acetate (8/1), and (D) benzene/ethyl acetate (1/1) respectively by detecting compounds with iodine vapor or with 5% methanolic sulfuric acid spray followed by heating on a hot plate.

*1,2: 5,6-Di-*O*-isopropylidene-3-*C*-methylene-α-*D*-ribo-hexofuranose (**1b**).* To an ice-cooled suspension of methyltriphenylphosphonium bromide (25 g, 0.07 mol) in dry THF (150 ml) was added a solution of butyllithium in hexane (15%, w/v, 35 ml) with stirring under a nitrogen atmosphere. A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1a**) (10 g, 0.04 mol) in THF (50 ml) was then gradually added to the above yellow suspension with keeping cold in an ice-water bath. The stirring was continued for 10 min and the precipitate was filtered off. The filtrate and ether washings were concentrated *in vacuo* to a crude syrup, which was further chromatographed on silica gel column (Wakogel C-200, 150 g), and eluted with ether. Concentration of ether elutes gave a clear oil (6.5 g) pure enough for the next step. A part of which was further purified by preparative tlc, $[\alpha]_D^{22}$ 93° (*c* 2.0, $CHCl_3$) [lit,[5a]); $[\alpha]_D^{23}$ +104° (c, 2, $CHCl_3$), lit,[5b]); $[\alpha]_D^{23}$ +75° (*c* 1.0, $CHCl_3$)] NMR; 1.34, 1.40, 1.43 (6-H, 3-H, 3-H, s, isopropyl methyl), 4.0 (3-H, m, H_5, H_6, H_6'), 4.60 (1-H, m, H_4), 4.89 (1-H, m, H_2), 5.06 (2-H, m, exomethylene), 5.80 ppm. (1-H, d, H_1, $J_{1,2}$=3.8 Hz). (Found: C, 61.12; H, 7.65%)

*1,2: 5,6-Di-*O*-isopropylidene-3-*C*-hydroxymethyl-3,3′-anhydro-α-D-glucofuranose (**2**).* A solution of **1** (3.5 g, 0.014 mol) and *m*-chloroperbenzoic acid (3.5 g, 85% purity) in dry 1,2-dichloroethane (40 ml) was stirred at room temperature for 18 h. The precipitate was filtered off, and the filtrate was concentrated *in vacuo* to a syrup, which was redissolved in hexane or ether, washed with aqueous sodium hydrogen carbonate and water, dried over anhydrous magnesium sulfate, and concentrated to a clear syrup (3.2 g), $[\alpha]_D^{23}$ +55° (*c* 1.7, methanol). NMR; 1.31, 1.38, 1.54 (3-H, 6-H, 3-H, s, isopropyl methyl), 3.08 (1-H, q, J=5.0 Hz, epoxymethylene), 4.0 (3-H, m, H_5, H_6, H_6'), 4.25 (1-H, d, H_2, $J_{1,2}$=3.8 Hz), 4.3 (1-H, m, H_4), 5.92 ppm. (1-H, d, H_1).

Found: C, 57.26; H, 7.37%. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40%.

*1,2: 5,6-Di-*O*-isopropylidene-3-*C*-methyl-α-D-glucofuranose (**3**).* A mixture of **2** (0.17 g, 0.63 mmol) and lithium aluminium hydride (30 mg) in dry ether (5 ml) was allowed to stand at room temperature for 10 min and refluxed for 30 min. After usual work-up, the filtrate was extracted with ether (10 ml×3), washed with aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to a crystalline residue (0.14 g), which was recrystallized from hexane; mp 66—67 °C, $[\alpha]_D^{23}$ +23 °C (*c* 1.0, acetone). NMR; 1.30, 1.34, 1.42, 1.44, 1.50 (3-H×5, CH_3 at C-3 and isopropyl), 2.48 (1-H, broad, OH), 3.75—4.38 (5-H, m, H_2, H_4, H_5, H_6, H_6'), 5.86 ppm. (1-H, d, H_1, $J_{1,2}$=3.7 Hz). Found: C, 56.67; H, 7.99%. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%.

*1,2,4,6-Tetra-*O*-acetyl-3-*C*-methyl-β-D-glucopyranose (**4a**).* A solution of **3a** (155 mg) in 70% acetic acid (6 ml) was heated at 95 °C for 2 h, and concentrated *in vacuo* to a dry syrup, which was then treated with acetic anhydride (2 ml) and pyridine (3 ml) for 3 h. The crude syrup (180 mg) obtained by the usual work-up was subjected to a preparative tlc (solvent D) to give an amorphous powder (120 mg), $[\alpha]_D^{22}$ −23 °C (*c* 2.34, $CHCl_3$). NMR; 1.29 (3-H, CH_3 at C_3), 2.05, 2.08, 2.09, 2.11 (3-H×4, acetyl), 3.01 (1-H, broad, OH), 3.80 (1-H, o, H_5, $J_{5,6}$=5.0, $J_{5,6'}$=2.5 Hz), 4.10 (1-H, H_6, q, $J_{6,6'}$=12.5 Hz), 4.30 (1-H, q, H_6), 5.03 (1-H, d, H_2, $J_{1,2}$=8.5 Hz), 5.05 (1-H, d, H_4), 5.68 ppm (1-H, d, H_1).

Found: C, 49.43; H, 6.09%. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12%.

*3-O-Benzyl-1,2-O-isopropylidene-5-C-methylene-6-O-trityl-α-D-xylohexofuranose (**5b**).* A solution of **5a** (0.5 g, 1.1 mmol) in dry THF (5 ml) was added to a yellow solution of methylenetriphenylphosphorane prepared from methyltriphenyl-

phosphonium bromide (0.7 g, 2.2 mmol) and butyllithium (15% w/v, 1 ml) in dry THF (10 ml). The stirring was continued at room temperature for 30 min. The precipitate was filtered off and filtrate and ether washings were concentrated *in vacuo* to a crude syrup, which was further subjected to preparative tlc (solvent B) to give a crystalline residue. Recrystallization from ethanol gave fine crystals having mp 113—114 °C, $[\alpha]_D^{23}$ −33 °C (*c* 1.0, $CHCl_3$). NMR: 1.28, 1.48 (3-H×2, isopropylidene), 3.48—3.81 (3-H, m, H_6 and $H_{6'}$), 4.25 (2-H, q, J_{AB}=12.0 Hz, benzyl methylene), 4.50 ppm (1-H, d, $J_{1,2}$=3.8 Hz).

Found: C, 78.91; H, 6.69%. Calcd for $C_{36}H_{36}O_5$; C, 78.80; H, 6.61%.

Oxidation of ***5b*** *with* m-*Chloroperbenzoic Acid.* A solution of **5b** (0.55 g, 1 mmol) and *m*-chloroperbenzoic acid (0.31 g, 1.8 mmol) in dry 1,2-dichloroethane (10 ml) was allowed to stand at room temperature for 24 h. After filtration of the precipitate, the filtrate was washed with dilute sodium hydroxide solution (0.7%, 10 ml) and water, dried over anhydrous magnessium sulfate and concentrated *in vacuo* to a crystalline residue, which was recrystallized from ethanol to give a mixture of 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-hydroxymethyl-5,6′-anhydro-6-*O*-trityl-α-D-gluco- and β-L-idofuranose, mp 179—180 °C, $[\alpha]_D^{23}$ −22.4 °C (*c* 1.0, $CHCl_3$).

Found: C, 76.32; H, 6.45%. Calcd for $C_{36}H_{36}O_6$: C, 76.57; H, 6.43%.

3-O-Benzyl-1,2-O-isopropylidene-5-C-methyl-6-O-trityl-β-L-idofuranose (7a). A mixture of **6** (0.41 g, 0.73 mmol) and lithium aluminum hydride (30 mg) was refluxed in dry THF (5 ml) for 2 h. After the usual work-up, the filtrate was extracted with ether, washed with aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated to a crystalline residue, which was subjected to a preparative tlc (solvent B) to give prismatic crystals (0.2 g) having mp 150—151 °C, $[\alpha]_D^{23}$ −54 °C (*c* 1.37, acetone). NMR: 1.20, 1.34, 1.50 (3-H×3, CH_3 at C-5 and isopropyl methyl), 2.75, 3.45 (1-H ×2, H_6, $H_{6'}$, $J_{6,6'}$=8.7 Hz), 3.64 (1-H, s, OH), 4.15 (1-H, d, H_3, $J_{3,4}$=3.0 Hz), 5.40, 4.60 (1-H×2, dd, benzyl methylene), 4.54 (1-H, d, H_4), 4.60 (1-H, d, H_2, $J_{1,2}$=3.8 Hz), 6.03 ppm (1-H, d, H_1).

Found: C, 76.25; H, 6.88%. Calcd for $C_{36}H_{38}O_6$: C, 76.30; H, 6.76%.

3-O-Benzyl-1,2-O-isopropylidene-5-C-methyl-6-O-trityl-α-D-glucofuranose (7b). A solution of **5a** (0.5 g, 0.9 mmol) in dry tetrahydrofuran (5 ml) was gradually added to a solution of methylmagnessium iodide prepared from magnesium (0.245 g, 10 mmol) and methyl iodide (2 ml, 17 mmol) in dry ether (10 ml). The reaction mixture was then refluxed for 30 min, poured into ice-water containing ammonium chloride (0.535 g, 10 mmol), extracted with ether (20 ml×2), washed with aqueous sodium chloride, dried over anhydrous magnesium sulfate, evaporated to a crystalline residue, which was recrystallized from ethanol, mp 182—183 °C, $[\alpha]_D^{23}$ −5.7 °C (*c* 1.0, $CHCl_3$). NMR: 1.28, 1.52, 1.55 (3-H×3, s, CH_3 at C-5 and isopropyl methyl), 2.93, 3.32 (1-H×2, d, H_6, $H_{6'}$, $J_{6,6'}$=8.5 Hz), 3.05 (1-H, d, H_3, $J_{3,4}$=3.3 Hz), 3.65, 4.20 (1-H×2, d, $C\underline{H}_2Ph$), 4.38 (1-H, d, H_4), 4.43 (1-H, d, H_2, $J_{1,2}$=4.0 Hz), 5.99 ppm (1-H, d, H_1).

Found: C, 76.49; H, 6.65%. Calcd for $C_{36}H_{38}O_6$: C, 76.30; H, 6.76%.

1,2,4,6-Tetra-O-acetyl-3-O-benzyl-5-C-methyl-β-D-gluco-pyranose (8). A suspension of **7b** (300 mg) in 70% acetic acid (10 ml) was refluxed for 2 h, and concentrated *in vacuo* to a syrup, which was then allowed to stand at room temperature in a mixture of acetic anhydride (2 ml) and pyridine (5 ml) for 8 h. The reaction solution was then treated with ice-water containing sodium hydrogen carbonate, extracted with chloroform, washed with aqueous sodium chloride and water, and dried over anhydrous magnesium sulfate. Concentration of the solvent gave fine needles, which was recrystalized from hexane; mp 128—129 °C (100 mg), $[\alpha]_D^{23}$ −18 °C (*c* 1.08, acetone). NMR: 1.34 (3-H, s, CH_3 at C-5), 1.85, 1.97, 2.08 (3-H×2, 3-H×2, s, acetyl methyl), 3.85 (1-H×2, d, H_6, $H_{6'}$, $J_{6,6'}$=12.0 Hz), 4.61 (2-H, s, $C\underline{H}_2Ph$), 5.14 (1-H, q, H_2, $J_{1,2}$=7.5 Hz), 5.33 (1-H, d, H_4), 5.89 ppm (1-H, d, H_1).

Found: C, 58.48; H, 6.26%. Calcd for $C_{22}H_{28}O_{10}$: C, 58.40; H, 6.24%.

1,6-Anhydro-2,4-di-O-acetyl-3-O-benzyl-5-C-methyl-β-L-idopyranose (9). A suspension of **7a** (200 mg) was treated as described above. Fine needles from hexane; mp 118—119 °C, $[\alpha]_D^{23}$ +67 °C (*c* 1.0, acetone). NMR: 1.30 (3-H, s, CH_3 at C-5), 1.98, 2.02 (3-H×2, s, acetyl methyl), 3.35 (1-H, q, $H_{6'}$, $J_{6,6'}$=8.7, $J_{1,6'}$=1.5 Hz), 3.83 (1-H, q, H_3, $J_{2,3}$=7.5, $J_{3,4}$=8.7 Hz), 4.08 (1-H, d, H_6), 4.60 (2-H, s, $C\underline{H}_2Ph$), 4.86 (1-H, q, H_2, $J_{1,2}$=1.5 Hz), 5.13 (1-H, q, H_4, $J_{4,6'}$=1.0 Hz), 5.42 ppm (1-H, H_1).

Found: C, 61.63; H, 6.24%. Calcd for $C_{18}H_{22}O_7$: C, 61.70; H, 6.33%.

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