Branched-chain Sugars. XVII. Stereoselectivity in the Oxidation of Several Methyl 4,6-O-Benzylidene-2-C- or -3-C-methylene-α- and-β-D-hexopyranosides with m-Chloroperbenzoic Acid

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Stereoselectivity in the perox y acid oxidation of methyl 4,6-O-benzylidene-3-O-methyl-2-C-methylene-α-D-ribo-hexopyranoside (1b), its 3-epimer (2b), \( \beta \)-anomer of 1b and 2b, methyl 4,6-O-benzylidene-2-O-methyl-3-C-methylene-\( \alpha \)-D-arabino-hexopyranoside and its 2-epimer was examined. The results were compared with those of rigid methylenecyclohexane systems.

In previous papers reports were given on the stereoselectivity examined in the reaction of methyl 4,6-O-benzylidene-\( \alpha \)- and \( \beta \)-D-hexopyranosid-2-uloses and 3-uloses with nucleophiles. It was found that in the reaction of diazomethane stereoselectivity is mainly controlled by the electronic attractive interaction between neighboring axial oxygen s and diazomethyl cation in the zwitterionic intermediates. The interaction sometimes resulted in a complemental stereoselectivity of diazomethane reaction to that of usual nucleophiles such as hydride anions and carbanions, valuable for a stereospecific synthesis of a proper branched-chain sugar. However, the diazomethane reaction of uloses is sometimes accompanied by ring-expansion reaction, even when the stereoselectivity is the desired one. For such cases, it was found that the perox y acid oxidation of the corresponding methylene derivative provides a reliable pathway to obtain the spiro epoxide which is also afforded by the diazomethane reaction of the ulose.

We have examined the stereoselectivity in the perox y acid oxidation of several 2- or 3-methylene-\( \alpha \)- and \( \beta \)-d-hexopyranosides in comparison with that of the diazomethane reaction of the corresponding uloses.

Results and Discussion

As the substrates, methyl 4,6-O-benzylidene-3-O-methyl-2-C-methylene-\( \alpha \)-D-ribo-hexopyranoside (1b), its 3-epimer (2b), \( \beta \)-anomer of 1b (3b) and 2b, methyl 4,6-O-benzylidene-2-O-methyl-3-C-methylene-\( \alpha \)-D-arabino- (5b) -\( \beta \)-D-ribo-hexopyranosides (6b) were synthesized from the corresponding uloses and methyl-triphenylphosphonium bromide by the usual method. In the case of 3b, the corresponding ulose (3a) was synthesized by the dimethyl sulfoxide–trifluoroacetic anhydride oxidation of methyl 4,6-O-benzylidene-3-O-methyl-\( \beta \)-D-altropyranoside (7) obtained by the preferential ring-opening of the corresponding 2,3-epoxide of D-\( \alpha \)-manno configuration with methanol. The 2,3-epoxide was synthesized by an improved method.

\( m \)-Chloroperbenzoic acid oxidation of methylene derivatives was carried out in dry 1,2-dichloroethane at 60 °C, until the starting material disappeared on TLC.

Oxidation of 1b exclusively gave methyl 2,2'-anhydro-4,6-O-benzylidene-2-C-hydroxymethyl-3-O-methyl-\( \alpha \)-D-altropyranoside (8) in 82% yield, the product being identical with that obtained by the diazomethane reaction of the corresponding ulose (1a). Similarly, oxidation of 2b exclusively gave the corresponding spiro epoxide (9) of D-\( \alpha \)-manno configuration in 86% yield, the main product in the reaction of diazomethane with 2a. Oxidation of 3b gave an epimeric mixture of the corresponding spiro epoxides (10 and 11) in 79% yield. Separation of the mixture on preparative TLC gave pure 10 and 11 in the ratio 2:1. In order to determine the configuration of these epimers, they were reduced with lithium aluminum hydride to give the corresponding 2-C-methyl derivatives (12 and 13), subsequent acetylation afforded the corresponding tetra-O-acetates (14 and 15), respectively. By comparison of these \( \alpha \),\( \beta \)-acetates with those obtained from methyl 4,6-O-benzylidene-2-C-methyl-3-O-methyl-\( \alpha \)-D-altro- and -\( \alpha \)-allo-pyranoside, the configuration of the main products (10, 12, and 14) was determined to be D-altro (H1 protons of 14 appeared at \( \delta \) 6.41 and 6.22), and that of the minor product D-allo (15; \( \delta \) 6.37 and 5.86).

Oxidation of 4b also gave an epimeric mixture of the corresponding spiro epoxides (16 and 17) in 84% yield in the ratio 1.2:1. The configuration of the main product was determined to be D-glucos by comparison with that obtained by the diazomethane reaction of 4a. Similarly the oxidation of 5b and 6b gave an epimeric mixture of the corresponding spiro epoxides (18 and 19, and 20 and 21), respectively. The configurations of these compounds were also determined by comparison with those obtained by the diazomethane reaction of 5a and 6a. The results are summarized...
September, 1979] Oxidation of Methyl 4,6-O-Benzylidene-2-α- or -3-C-methylene-α- and -β-o-hexopyranosides

The reaction of 3a and diazomethane in ethanol was carried out in order to confirm our hypothesis on stereoselectivity. Separation of the products (87% yield) on preparative TLC gave 4a and 5 in the ratio 3:1. Since 4a exclusively gave an axial attack product in the diazomethane reaction, the predominant equatorial attack also supports our hypothesis, in which the electrostatic attractive force of axial oxygen at C-3 position is stronger than that of lone pair electron of ring oxygen at β-position of the carbonyl group.

By considering both steric (non-bonded interactions) and electrostatic (attractive or repulsive) factors (Table 1), the stereoselectivity in the diazomethane reaction of uloses could be explained by the electrostatic attractive interaction between neighboring axial oxygen atom and diazomethyl cation in the transition state.

Peroxy acid oxidation is known to involve an electrophilic attack of the reagent from the less hindered side of the alkene to give the less hindered epoxide, through a highly ordered transition state.

In the m-chloroperbenzoic acid oxidation of rigid methylenecyclohexane systems, Carlson and Behn showed that the axial attack percentage is 59–69% due to stronger steric hindrance of axial hydrogen on α-carbon than that of β-carbon in the transition state. From the results obtained here, the axial attack percentage in the case of 4b (46%) and 6b (58%) can be considered as standards for 2-methylene and 3-methylene pyranosides, respectively, since they have no axial substituents. The lower percentage of axial attack in the case of 4b than that of cyclohexane systems suggests “the product development control” of C₂-O dipole bisecting C₁-O₁ and C₅-O₅ torsional angle in axial attack epoxide formation of β-annomers. The higher percentage in the case of 3b (68%) than that of 4b is estimated as the steric factor of the axial 3-methoxyl group. The predominant axial attack in the case of α-anomer of 2-methylene derivatives (1b and 2b) is attributed to the strong steric factor of the axial methoxyl group at C-1 position, as is known in the reduction of 2-uloses with hydride anions.

Lower percentage in the case of 5b (45%) than that of 6b should be attributed to the balance of steric factors between axial 1- and 2-methoxyl groups. However, the hindrance of the former seems to be larger than the latter, since the percentage of methyl 4,6-O-benzylidene-2-deoxy-3-methylene-α- and -β-o-hexopyranoside having no 2-methoxyl group is 25%.11)

**Experimental**

*General Methods.* All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Solvents were evaporated under reduced pressure at a bath temperature not exceeding 50°C. Optical rotations were measured in a 0.2 dm tube with a Carl Zeiss LEP-Al polarimeter in chloroform unless otherwise stated. IR spectra were recorded with a Hitachi Model EPI-G2 spectrometer, and NMR spectra with a JNM-FS-100 spectrometer in deuteriochloroform containing tetramethylsilane as an internal standard. Chemical shifts and coupling constants were recorded in δ and Hz units, and IR frequencies in cm⁻¹.

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**Table 1. Comparison of Stereochemistry in the Peroxy Acid Oxidation of Methyl 4,6-O-Benzylidene-2-α-or -3-C-Methylene-α- and -β-O-Hexopyranosides and in the Diazomethane Reaction of the Corresponding Uloses**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Yields (%) of Spire Epoxides in the Reaction of Uloses with Diazomethane (a) and that of Methylene Derivatives with M-Chloroperbenzoic Acid (b series)</th>
<th>Axial Attack Product</th>
<th>Equatorial Attack Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>83.5 (8)</td>
<td>63.7 (9)</td>
</tr>
<tr>
<td>1 a</td>
<td></td>
<td>82.0 (8)</td>
<td></td>
</tr>
<tr>
<td>2 a</td>
<td></td>
<td>31.1</td>
<td></td>
</tr>
<tr>
<td>2 b</td>
<td></td>
<td>86.0 (9)</td>
<td></td>
</tr>
<tr>
<td>3 a</td>
<td></td>
<td>21.8 (11)</td>
<td>65.3 (10)</td>
</tr>
<tr>
<td>3 b</td>
<td></td>
<td>52.7 (10)</td>
<td>26.3 (11)</td>
</tr>
<tr>
<td>4 a</td>
<td></td>
<td>92.5 (16)</td>
<td></td>
</tr>
<tr>
<td>4 b</td>
<td></td>
<td>38.2 (17)</td>
<td>45.2 (16)</td>
</tr>
<tr>
<td>5 a</td>
<td></td>
<td>39.5 (19)</td>
<td>41.0 (19)</td>
</tr>
<tr>
<td>6 a</td>
<td></td>
<td>17.6 (20)</td>
<td>76.5 (21)</td>
</tr>
<tr>
<td>6 b</td>
<td></td>
<td>42.0 (21)</td>
<td>30.0 (20)</td>
</tr>
</tbody>
</table>

a) The results are cited from Refs. 4 and 5, except those of 3a. b) The ring-expansion product of 19 was obtained in 36.9% yield.
Methyl-4,6-O-benzylidene-3-O-methyl-β-d-ribo-hexopyranosid-2-ule (3a).

Mesylation of methyl 4,6-O-benzylidene-3-O-benzyl-β-glucopyranoside in pyridine with methyl anisole and chloroform gave the corresponding 2-O-mesylate in 98% yield, which was recrystallized from ethanol–hexane. 

Methyl 4,6-O-benzylidene-3-O-methyl-β-glucopyranoside in pyridine with methanesulfonyl chloride gave the corresponding 2-O-mesylate in 87% yield, which was recrystallized from ethanol–hexane in 98% yield. 

A solution of the above mesylate (1 g, 2.2 mmol) and sodium (607 mg, 2.6 mmol) in absolute methanol (50 ml) was refluxed for 1 h until the starting material and its de-O-benzoylated product disappeared on TLC. The reaction mixture was poured into water, and then extracted with chloroform. The chloroform layer was evaporated, and the residue was placed on a silica-gel column (Wako-gel C-200: 30 g) followed by elution with benzene to give white crystals (437 mg, 44%), methyl 4,6-O-benzylidene-3-O-methyl-2-C-methylene-α-β-ribo-hexopyranoside (1b) which were recrystallized from ether–hexane. 

A similar reaction of methyl 4,6-O-benzylidene-3-O-methyl-α-d-arabinose-hexopyranosid-2-ule (2a) gave the corresponding 2-C-methylene derivative (2b) in 52% yield, which was recrystallized from ether–hexane. 

A similar reaction of methyl 4,6-O-benzylidene-3-O-methyl-β-d-ribo-hexopyranoside (3b) in 57% yield, which was recrystallized from ethanol–hexane in 95% yield. 

A similar reaction of methyl 4,6-O-benzylidene-2-O-methyl-β-glucopyranoside gave the corresponding 2-C-methylene derivative (4b) in 67% yield, which was recrystallized from ethanol–hexane in 95% yield.

A similar reaction of methyl 4,6-O-benzylidene-2-O-methyl-β-d-ribo-hexopyranoside (5b) in 72% yield, which was recrystallized from ethanol–hexane in 95% yield.

A similar reaction of methyl 4,6-O-benzylidene-2-O-methyl-α-d-arabinose-hexopyranosid-3-ule (4a) gave the corresponding 3-C-methylene derivative (5b) in 60% yield, which was recrystallized from ethanol–hexane in 95% yield.
Oxidation of exo-Methylene Compounds (1b–6b) with m-Chloroperbenzoic Acid. A solution of 1b (300 mg, 1.0 mmol) and m-chloroperbenzoic acid (85% purity, 406 mg, 2.0 mmol) dissolved in 1,2-dichloroethane (15 ml) was heated at 60 °C overnight. The mixture was washed with 0.1 M sodium hydroxide and water, and dried with magnesium sulfate. The organic layer was evaporated to give crystalline methyl 2,2'-anhydro-4,6-O-benzylidene-2-C,3-0-dimethyl-a-d-allopyranoside (8) in 82% yield which was recrystallized from ethanol–hexane. Mp 108–109 °C; [α]D +74.2° (c 0.7). NMR spectrum was identical with that of the authentic sample.8

A similar reaction of 2b gave methyl 2,2'-anhydro-4,6-O-benzylidene-2-C,3-O-dimethyl-a-d-manno-pyranoside (9) in 86% yield which was recrystallized from ethanol–hexane. Mp 108–109 °C; [α]D +75.3° (c 0.8). NMR and IR spectra of both 20 and 21 were identical with those of the authentic samples9 obtained by the diazomethane reaction of 6a.

Reduction of 10 and 11 with Lithium Aluminium Hydride. Lithium aluminium hydride (50 mg) was added to a solution of 10 (150 mg, 0.52 mmol) in tetrahydrofuran (5 ml) and then filtered. The filtrate was extracted with chloroform. The extract was washed with water, dried with anhydrous magnesium sulfate, and evaporated to give crystalline methyl 4,6-O-benzylidene-2-C-methyl-3-O-methyl-a-d-allopyranoside (12) in 91% yield which was recrystallized from ethanol–hexane. Mp 113–114 °C; [α]D +64.4° (c 1.0). IR: 3520 (OH); NMR: 7.60–7.20 (Ph: m), 5.47 (PhCH: s), 4.44 (H1: t), 4.34 (H2: q), JH2-2H2 = 4.0, 4.0, 4.0, 4.0 (H2: q), 4.14 (H4: q), JH4-2H4 = 10.0, 1.0. 3.37 (H6: t, JH6-6H6 = 9.0), 3.47 (H6: d), 3.56 and 3.47 (2 × OMe), 2.70 (OH: broad s), 1.27 (CMe).

Found: C, 61.90; H, 7.30%. Caled for C21H22O7: C, 61.92; H, 7.15%.

A similar reduction of 11 (150 mg) in THF (5 ml) afforded methyl 4,6-O-benzylidene-2-C-methyl-3-O-methyl-b-d-allopyranoside (13) in 89% yield which was recrystallized from ethanol–hexane. Mp 110–111 °C; [α]D -60.0° (c 1). NMR: 7.60–7.20 (Ph: m), 5.44 (PhCH: s), 4.43 (H1: t), 4.35 (H2: q), JH2-2H2 = 10.0, 4.0, 4.0–3.48 (H4: q), JH4-2H4 = 9.0, 9.0, 9.0 (H6: t, JH6-6H6 = 9.0), 3.47 (H6: d), 3.56 and 3.47 (2 × OMe), 3.30 (OH: broad s), 1.27 (CMe). Found: C, 61.82; H, 7.41%. Caled for C21H22O7: C, 61.92; H, 7.15%.

Determination of the Configuration of 12 and 13. A solution of 12 (100 mg) in acetic anhydride (3 ml) containing a drop of 60% perchloric acid was heated at 60 °C for 6 h. Since acetylation was incomplete, the reaction was repeated at room temperature for 18 h, using p-toluenesulfonic acid as a catalyst. The reaction mixture was then poured into cold sodium hydrogencarbonate solution and the resulting solution was extracted with chloroform.

The extracts were washed with water, dried, and evaporated to give a mixture of sirupy 1,2,4,6-tetra-O-acetyl-2,3-C,3-O-dimethyl-a- and -b-d-allopyranoses (14). The configuration was determined without isolation of anomers by direct comparison of the Rf value and NMR spectrum with those of the authentic sample prepared by acetylation of methyl 4,6-O-benzylidene-2-C,3-O-dimethyl-a-d-allopyranoside. 

Compounds 13 was also converted into a mixture of sirupy 1,2,4,6-tetra-O-acetyl-2,3-C,3-O-dimethyl-a- and -b-d-allopyranoses (15), which was identical with that obtained by the acetylation of methyl 4,6-O-benzylidene-2,3-C,3-O-dimethyl-a-d-allopyranoside.9

14: Rf values, 0.41 and 0.36 (on DC Fertigplatten Kiesgel 60, Merck AG; benzene–acetone 8:1). NMR: 6.37 and 5.86 (H4: each s), 3.37 (2 × OMe), 2.15–2.05 (8 × OAc), 1.60 and 1.34 (8 × GMe).
15: $R_f$ values, 0.36 and 0.31 (under the same conditions as above). NMR: 6.41 and 6.22 (H$_2$; each s), 3.50 and 3.40 (OMe), 2.15-2.05 (8 x OAc), 1.68 and 1.56 (CMe).

Reaction of 3a with Diazomethane.  To a solution of 3a (294 mg, 1.0 mmol) in ethanol (30 ml) was added dropwise a solution of diazomethane (2.0 mmol) in ether (10 ml) at 0°C. After the mixture had been left at room temperature for 12 h, the solution was evaporated to give a sirup. Separation of two products on preparative TLC (ether: hexane=1:1) gave 10 and 11 in 65.3% and 21.8% yields, respectively. Both were respectively identical with authentic samples obtained via the peroxy acid oxidation of (3b).

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References

5) K. Sato and J. Yoshimura, accepted by Carbohydr. Res.
13) 3a was also obtained by the same oxidation of methyl 4,6-O-benzylidene-3-O-methyl-β-D-allopyranoside which was obtained from 1,2,5,6-di-O-isopropylidene-3-O-methyl-α-D-allofuranose through a four step conversion. Private communication by Dr. Toshio Nakagawa, Yokohama City University.
14) The epoxide was prepared from methyl 4,6-O-benzylidene-2-O-mesyl-β-D-glucopyranoside obtained by the direct partial mesylation in 6—17 % yield by Guthrie et al. (J. Chem. Soc., C, 1970, 1961). To cover the poor stereoselectivity of the partial 2-O-mesylation, we carried out the partial 3-O-benzylation according to the method of Collins et al. (J. Chem. Soc., Perkin Trans. 1, 1972, 2596), followed by 2-O-mesylation.
17) The percentage refers to that of the axial attack product in both axial and equatorial attack products.