<table>
<thead>
<tr>
<th>篇名</th>
<th>Branched-Chain Sugars. II. On the Configuration of Branched-Chain Sugars from Methyl 2-O-Benzoyl-4,6-O-benzylidene-α-D-ribo-hexopyranosid-3-ulose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>吉村, 寿次; YOSHIMURA, Juji; 佐藤, 憲一; SATO, Kenichi; KOBAYASHI, Kazuhiko; 辛, 重基; SHIN, Chung-gi</td>
</tr>
<tr>
<td>Citation</td>
<td>Bulletin of the Chemical Society of Japan, 46(5): 1515-1519</td>
</tr>
<tr>
<td>Date</td>
<td>1973-05</td>
</tr>
<tr>
<td>Type</td>
<td>Journal Article</td>
</tr>
<tr>
<td>Rights</td>
<td>publisher</td>
</tr>
</tbody>
</table>
Branched-Chain Sugars. II. On the Configuration of Branched-Chain Sugars from Methyl 2-O-Benzoyl-4,6-O-benzylidene-α-D-ribo-hexopyranosid-3-ulose

Juji Yoshimura, Ken-ichi Sato, Kazuhiko Kobayashi, and Chung-gi Shin*  
Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo  
*Laboratory of Organic Chemistry, Kanagawa University, Kanagawa-ku, Yokohama  
(Received November 30, 1972)

Stereoselectivities in diazomethane and nitromethane reaction of methyl 2-O-benzoyl-4,6-O-benzylidene-α-D-ribo-hexopyranosid-3-ulose were examined. Reduction of the epoxidation product (2) gave an epimeric 3-C-methyl derivative in contrast with that obtained by the Grignard reaction. Comparison of NMR spectra of the corresponding di-O-acetate of the both epimers proved that 2 has the gluco-configuration. Ring-opening of the epoxide with alkali, methane ammonia, and acid gave the corresponding 3-C-hydroxymethyl, 3-C-aminomethyl (17), and de-O-benzylidened product, respectively. Hydrogenation of the 3-C-nitromethyl derivative (21) obtained by nitromethane condensation, in the presence of Raney nickel, accompanied with benzoyl-migration to give 3-C-benzamidomethyl derivative (22). De-benzoylation of 22 with methanolic potassium hydroxide gave 3-C-aminomethyl derivative (26) and an orthoester-type compound. Comparison of 26 with 17 and their derivatives indicated that 21 has the allo-configuration. The both configurations were also supported by the optical rotation of 3-C-benzamidomethyl derivatives in cuprammonium solution.

In the previous paper,1) we reported that the nitromethane and the Reformatsky reaction of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose gave α-allo-type branched-chain sugars, while the diazomethane reaction afforded α-gluco-type product, indicating that the reagent attacked the carbonyl group from the more hindered site. The stereoselectivity of the latter stimulated us to examine with a pyranosid-3-ulose, and nitromethane and diazomethane reaction of methyl 2-O-benzoyl-4,6-O-benzylidene-α-D-ribo-hexopyranosid-3-ulose (IF) were examined in this report.

Results

Diazomethane Condensation. Diazomethane condensation of 1 in benzene-ethanol gave a sirupy spiro-epoxide (2) in 77% yield. In order to determine the configuration, 2 was hydrogenated with lithium aluminium hydride to the 3-C-methyl derivative (3), which was successively converted into the corresponding 2-O-acetate (4) and 2,3-di-O-acetate (5) by base- and acid-catalyzed acetylation, respectively. On the other hand, a 3-C-methyl derivative (6) obtained by the Grignard reaction, of which the configuration was assigned to be of αallo-type,2,3) was also converted into 2-O-acetate (7) and 2,3-di-O-acetate (8). Comparison of 3 with 6 and their derivatives showed that they are 3-epimers to each other, and the chemical shifts of tert-acetoxy protons in 5 (δ 1.95) and 8 (δ 2.05) indicated an equatorial and axial one, respectively.4) Thus, the configuration of 2 was confirmed to be of α-gluco-type.

The epoxide-ring of 2 resisted, to some extent, to alkaline opening than the corresponding furanosid derivative,1) and alkali treatment of 2 at room temperature gave de-O-benzoylated epoxide (9), which was further converted to the 2-O-acetate (10). Treatment of 9 with refluxing aqueous potassium hydroxide for 10 hr gave a water-soluble 3-C-hydroxymethyl derivative (11), which was then acetylated to 2,3-di-O-acetate (12). Acetonation of 11 gave 3,3′-O-isopropylidene derivative (13), of which the position of the isopropylidene group was determined from the fact that 13 gave the mono-O-acetate (14) by base-catalyzed acetylation. The epoxide-ring opening was also performed by refluxing 2 with 80% acetic acid, accompanying with hydrolysis of the benzylidene group, to give methyl 2-O-benzoyl-3-C-hydroxymethyl-α-D-glucopyranoside (15), which was confirmed by conversion into the corresponding tetra-O-acetate (16). Moreover, treatment of 9 with ethanolic ammonia in a sealed tube at 90°C for 3 hr gave 3-C-aminomethyl derivative (17), which was then converted into the corresponding N-benzoyl derivative (18), its di-O-acetate (19), and N,O-triacetate (20), respectively.

Nitromethane Condensation. Reaction of 1 with nitromethane in tetrahydrofuran in the presence of sodium methoxide gave a 3-C-nitromethyl derivative (21) in 80% yield. Hydrogenation of 21 in the presence of Raney nickel accompanied with the migration of 2-O-benzoyl group to give 3-C-benzamido derivative (22). Base- and acid-catalyzed acetylation of 22 gave the corresponding 2-O-acetate (23) and 2,3-di-O-acetate (24), respectively. Debenzylation of 22 with methanolic potassium hydroxide gave 3-C-aminomethyl derivative (25), and 22. Comparison of 22 with 18, 24 with 19, and 26 with 17 indicated them to be 3-epimers to each other. Furthermore, the positive rotational change ([M]$_{D}$ +1670°) of 22 in cuprammonium solution and negative change ([M]$_{D}$ -635°) of 18 indicated d-allyl and d-glucour configuration, respectively. Thus, the configuration of 21 was proved to be of d-allyl-type.

Compound 25, having still two phenyl groups in addition to methyl 4,6-O-benzylidene-α-D-ribo-hexopyranosid-3-ulose, following facts are known. Reduction of 25 into 27 might occur through hydrolysis of 23. The structure of 25 was deduced to be 3,4,6-isopropylidene derivative from the chemical shift of C-CH$_3$ protons (δ 1.47 and 1.49).7

Discussion

On the stereoselectivities in nucleophilic addition to methyl 4,6-O-benzylidene-α-D-ribo-hexopyranosid-3-ulose, various mixtures of diastereomers, generally gives various mixture of diastereomers, though it generally gives various mixture of diastereomers, though it generally gives various mixture of diastereomers.5

depending on the condition used.\(^\text{14}\)

On the other hand, stereoselectivity of diazomethane addition is usually complicated by the formation of ring-expanded product depending on the solvent used. For an example, Flaherty et al.\(^\text{15}\) obtained 30% of the ring-expanded product and a small amount of normal epoxide of \(\beta\)-gluco-type by the reaction with methyl 4,6-\(\beta\)-benzylidene-2-deoxy-\(\alpha\)-d-erythro-hexopyranosid-3-ulose in methanol. However, 1,2-0- isopropylidene-\(\beta\)-furano-3-uloses gave the normal spiro-epoxides which are resulted by attacking the reagent from the outside of the V-shaped five-membered ring.\(^\text{16}\) Reaction of methyl \(\alpha\)-d-pyranosid-2-uloses in ether-alcohol, having two oxygens at the both vicinal carbon, gave a mixture of diastereomers,\(^\text{17}\) however, one which has the epoxide carbon in the site of \(\alpha\)-C-ether group was predominant. Inch et al.\(^\text{18}\) examined the steric influence of C-alkyl group vicinal to the carbonyl group by the reaction with 4,6-\(\beta\)-benzylidene-3-deoxy-3-C-ethyl-\(\alpha\)-d-arabino- and -\(\beta\)-hexo-pyranosid-2-ulose, and showed that C-ethyl group in reverse side to \(\alpha\)-C-methoxy group enhanced the formation of the predominant product mentioned above, and that in the same side hindered it to afford another epimer predominantly. They discussed on the conformation of zwitterionic intermediates for explanation of the configuration of ring-expanded products.

However, accumulated data mentioned here indicate that the stereoselectivity might be controlled at first by attractive interactions between vicinal or neighboring hydroxyl oxygens and diazomethylen cation of zwitterionic intermediates, and therefore, the polarity of solvents play an important role. The complementary steric selectivities of the Grignard and diazomethane reaction mentioned by us and by Horwitz et al.\(^\text{19}\) support this deduction. Thus, the steric position of \(\alpha\)-C-methoxy oxygen for the carbonyl group might control the configuration of the product in this experiment.

**Experimental**

All melting points are uncorrected. The solutions were evaporated under diminished pressure at a bath temperature not exceeding 45 °C. Specific rotations were measured in a 0.5-dm tube, with a Carl Zeiss LEP-Al Polarimeter. The IR spectra were recorded with a Hitachi Model EPI-G2 grating IR spectrophotometer. The NMR spectra were taken in deuteriochloroform, with a JNM-4H-100 MHz Spectrometer using tetramethylsilane as an internal standard. Chemical shifts and coupling constants were recorded in \(\delta\) and Hz units, and frequencies in cm\(^{-1}\).

Methyl 3,3'-Anhydro-2,4-O-benzylidene-3-C-4,6-O-benzylidene-3-C-glucopyranoside (2) To a suspending of 1 (4 g, 10.4 mmol) in benzene (150 ml)–ethanol (50 ml) was added dropwise a solution of diazomethane (20 mmol) in ether (50 ml) at 0 °C. With proceeding the reaction, the mixture turned to homogeneous. After standing at 0 °C for 3 hr and at room temperature for 28 hr, the solution was evaporated, and the resulted sirup was fractionated through Kiesel-gel (90–235 mesh, Merck Co.), by eluting with benzene-methanol (15: 1). From the first fraction, the spiro-epoxide was obtain as a sirup in 77.5% (3.2 g) yield. \([\alpha]_D^225 +119^\circ (c 1.06, \text{CHCl}_3); IR: 1720\) (ester), 1590 and 710 (Ph); NMR: ca. 7.30 and 7.95 (2× Ph, m), 5.51 (PhCH=), 5.41 (H; d, \(J_{6,3} = 3.7\)), 5.10 (H; d, 4.35 (H; s, \(J_{6,3} = 13.5\)), 3.97 (H; t, \(J_{6,2} = 10\)), 3.91 (H; d, 3.90 (H; s, \(J_{6,4} = 10\)), 3.40 (OME), 3.20 (epoxy-CH=) s. Found: C, 65.77; H, 6.10%. Calcd for \(\text{C}_{32}\text{H}_{34}\text{O}_{10}\); C, 66.32; H, 5.57%.

Methyl 4,6-O-benzylidene-3-C-methyl-4,6-O-benzylidene-3-C-glucopyranoside (3) To a solution of 9 (800 mg, 2.64 mmol) in ether (30 ml) was added lithium aluminium hydride (0.2 g, 53 mmol), and the mixture was refluxed for 7 hr. The excess LiAlH\(_4\) was carefully decomposed with water, and the water layer was extracted with ether. The combined ether extract was washed with water, dried with anhydrous magnesium sulphate, and evaporated to give a colorless sirup. The sirup was crystallized and recrystallized from chloroform–n-hexane. Yield, 86% (690 mg). A similar treatment of 2 gave the same compound in 79% yield. Mp 80–82 °C; \([\alpha]_D^2 +91^\circ (c 1.25, \text{CHCl}_3); IR: 3523 and 3250 (OH); NMR: 1.40 (G-\text{CH}_{2}, s).

Found: C, 60.84; H, 7.16%. Calcd for \(\text{C}_{32}\text{H}_{34}\text{O}_{10}\); C, 60.80; H, 6.80%.

2-O-Acetyl and 2,3-di-O-acetyl derivatives of 3 was prepared as follows.

a) 2-O-Acetate (4): Acetylation of 3 with acetic anhydride in pyridine gave sirupy acetate in a quantitative yield. \([\alpha]_D^2 +72.5^\circ (c 1.44, \text{CHCl}_3); IR: 3450 (OH), 1740 (ester); NMR: 2.50 (OH, s), 2.10 (OAc) (G-CH=)

Found: C, 59.94; H, 6.60%. Calcd for \(\text{C}_{34}\text{H}_{36}\text{O}_{10}\); C, 60.34; H, 6.55%.

b) 2,3-Di-O-acetate (5): A solution of 3 (100 mg) and p-toluenesulfonic acid (20 mg) in acetic anhydride (3 ml) was stirred at room temperature for 1.5 hr, poured into ice-water, and the resulted solution was extracted with chloroform. The extracts were washed with sodium bicarbonate
and then dried, and evaporated to give a sirup which was recrystallized from ethanol-s-hexane. Yield, 91% (105 mg); mp 156–157°C; [α]_D^20 +15.4° (c 0.95; CHCl_3); IR: 1740 (ester); NMR: ca. 7.37 (Ph; m), 5.89 (H_d; J_1,2 = 4.2), 3.55 (PhCH=), 4.87 (H_d), 4.85 (H_d; J_3,4 = 7.5), 4.30 (H_2; sex, J_1,2 = 7.5), 3.97–3.65 (H_6a and H_6e; m), 3.40 (OMe), 2.14 (sec-OAc), 1.95 (tert-OAc), 1.62 (CH_3) (C-CH_3).

Found: C, 60.18; H, 6.45%. Caled for C_{13}H_{12}O_5: C, 59.99; H, 6.36%.

2-O-Acetyl and 2,3-Di-O-acetyl Derivatives of Methyl 4,6-O-benzylidene-3-C-methyl-a-D-allopyranoside (6). a) 2-O-Acetate (7): This compound was obtained from 6 by the usual method in a quantitative yield. Mp 95–96°C; [α]_D^20 +69.8° (c 1.10, CHCl_3); IR: 3450 (OH), 1735 (OAc); NMR: 7.32 (Ph; m), 5.41 (PhCH=), 5.10 and 4.27 (C_6H_5; ABq, J = 12.5), 4.96 (H_d; J_1,2 = 3.7), 4.83 (H_d; d, J = 4.27 (H_d; H_6a and H_6e; m), 3.40 (OMe), 2.12 (sec-OAc), 1.95 (tert-OAc), 1.62 (CH_3) (C-CH_3).

Found: C, 60.41; H, 6.52%. Caled for C_{13}H_{12}O_5: C, 59.99; H, 6.36%.

b) 2,3-Di-O-acetate (8): Acid-catalyzed acetylation of 6 gave 8 in a quantitative yield, which was recrystallized from ethanol-n-pentane. Mp 97–98°C; [α]_D^20 +69.8° (c 1.2, CHCl_3); IR: 1740 (ester); NMR: 7.32 (Ph; m), 5.11 (PhCH=), 4.90 (H_d; d, J_1,2 = 4.2), 4.71 (H_d; d), 4.40–3.55 (H_6a, H_6e, and H_6e; m), 3.40 (OMe), 2.16 (sec-OAc), 1.78 (CH_3) (C-CH_3).

Found: C, 60.14; H, 6.52%. Caled for C_{13}H_{12}O_5: C, 59.99; H, 6.36%.

Methyl 3,5'-Anhydro-4,6-O-benzylidene-3-C-(hydroxymethyl) -a-D-glucopyranoside (9). A solution of 2 (1.0 g, 2.51 mmol) and potassium hydroxide (0.5 g) in acetonitrile (20 ml) was stirred for 1.5 hr, then 2 has disappeared on TLC. Evaporation of acetonitrile caused deposition of needles, which was gathered after addition of water (15 ml). These crystals (0.67 g) contain crystalline water detectable in IR (3200, 3450, 3530 cm⁻¹) and NMR spectra. Recrystallization from ethanol-acetone gave needles in 81.5% yield. Mp 179–180°C; [α]_D^20 +112° (c 1.10, CHCl_3).

Found: C, 59.51; H, 5.99%. Caled for C_{13}H_{12}O_5: C, 59.99; H, 6.36%.

Usual acetylation of 9 gave the sirupy 2-O-acetate (10) in a quantitative yield. [α]_D^20 +96.0° (c 1.04, CHCl_3); IR: 1750 (OAc); NMR: ca. 7.35 (Ph; m), 5.11 (PhCH=), 4.90 (H_d; d, J_1,2 = 4.2), 4.71 (H_d; d), 4.40–3.55 (H_6a, H_6e, and H_6e; m), 3.38 (OMe), 2.16 (sec-OAc), 2.05 (tert-OAc), 1.78 (CH_3) (C-CH_3).

Found: C, 60.81; H, 5.93%. Caled for C_{13}H_{12}O_5: C, 60.71; H, 5.99%.

Methyl 3-Acetoxyethyl-2-O-acetyl-4,6-0-benzylidene-IX-D-glucopyranoside (12). A suspended solution of 11 (2.0 g, 0.965 mmol) in methanol (20 ml) was added benzoic anhydride (225 mg, 1.0 mmol) and the resulted solution was refluxed for 5 hr, evaporated to give a sirup which was crystallized from ether. Yield, 67.5% (260 mg); mp 154–155°C; [α]_D^20 +12.0° (c 1.05, CHCl_3).

Found: C, 60.78; H, 6.80; N, 4.50%. Caled for C_{13}H_{12}N_2O_5: C, 57.86; H, 6.80; N, 4.50%.

Acetyl derivatives (18, 19, and 20) of 17 was obtained as follows.

a) N-Benzyl Derivatives (18): To a solution of 17 (300 mg, 0.965 mmol) in methanol (20 ml) was added benzoic anhydride (225 mg, 1.0 mmol) and the solution was refluxed for 5 hr, evaporated to give a sirup which was recrystallized from ether. Yield, 78% (0.5 g); mp 158–159°C; [α]_D^20 +92.0° (c 1.07, CHCl_3).

Found: C, 57.87; H, 6.87; N, 4.45%. Caled for C_{13}H_{12}N_2O_5: C, 57.86; H, 6.80; N, 4.50%.

Acetyl derivatives (18) was obtained as follows.

b) 2,3-Di-O-acetyl-N-benzoyl Derivatives (19): Acid-catalyzed acetylation of 18 gave the corresponding sirupy di-O-acetate in a quantitative yield. [α]_D^20 +40.8° (c 1.48, CHCl_3).

Found: C, 62.44; H, 5.96; N, 2.77%. Caled for C_{13}H_{12}N_2O_5.
H₂NCO₃; C, 62.51; H, 5.85; N, 2.80%.

3) N-O-Triacetate (20): Acid-catalyzed acetylation of 17 (100 mg, 0.32 mmol) gave the N,O-triacetate in 97% (136 mg) yield. Mp 180–181°C; [α]²⁰D = −19.6° (c 1.36, CHCl₃).

IR: 3300 (NH), 1750 and 1730 (OAc), 1640 and 1555 (amide); NMR: 7.42 (Ph; s), 6.45 (NH), 5.94 (H₃d; J₃,1=4.7), 5.30 (PhCH₃), 5.10 (H₅; d, J₅,₆a=10.0), 4.84 (H₁; d), 4.42–3.80 (H₆, H₈ and H₉; m), 3.87 and 3.68 (C₂H₅; ABq, J = 9.5), 3.39 (OMe), 2.13 (3α-OAc), 1.35 (3β-OAc), 1.09 (3γ-OAc), 0.92, CHCl₃). IR: 3490 (OH), 3430 (NH), 1720 (ester), 1650 and 1515 (amide). NMR: 8.07–4.51 (Ph; m), 5.87 (H₅; d, J₅,₆a=4.5), 4.10 and 3.35 (C₂H₅), 4.25 (OH), 3.55 (H⁻; q, J₅,−₆a=9.0), 3.24 (H₈; d), 2.38 (H⁻; t, J₅,−₆a=9.0), 1.97 (NAc), 1.77 and 1.35 (2 × OAc).

Found: C, 60.69; H, 6.28; N, 3.23%.

On the other hand, the water layer was extracted with n-butanol, after neutralization with 4N hydrochloric acid. Evaporation of n-butanol extracts gave de-O-benzoylated free amine 26 (24.0%, 0.6 g) by fractional crystallization from ethanol–water (1 : 1, dec.). [α]²⁰D = +64.2° (c 1.0, EtOH); IR: 1600 (Ph), 1525 (C–N), and 1380.

Found: C, 61.03; H, 6.35; N, 3.20%. Calcd for C₂₄H₂₇NO₉·2H₂O: C, 60.96; H, 6.28; N, 3.23%.

The authors are grateful to Mr. Hitoshi Matsumoto for NMR measurements, and members of the Laboratory of Organic Analysis for elemental analysis.