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<td>著者</td>
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<tr>
<td>引用</td>
<td>Bulletin of the Chemical Society of Japan, 46(5): 1515-1519</td>
</tr>
<tr>
<td>日付</td>
<td>1973-05</td>
</tr>
<tr>
<td>種類</td>
<td>学術論文</td>
</tr>
<tr>
<td>権利</td>
<td>出版社</td>
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Branched-Chain Sugars. II. On the Configuration of Branched-Chain Sugars from Methyl 2-O-Benzoyl-4,6-O-benzylidene-\(\alpha\)-d-ribo-hexopyranosid-3-ulose

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(Received November 30, 1972)

Stereoselectivities in diazomethane and nitromethane reaction of methyl 2-O-benzoyl-4,6-O-benzylidene-\(\alpha\)-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, methanolic 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, we reported that the nitromethane and the Reformatsky reaction of 1,2:5,6-di-O-isopropylidene-\(\alpha\)-d-ribo-hexofuranos-3-ulose gave \(\alpha\)-allo-type branched-chain sugars, while the diazomethane reaction afforded \(\alpha\)-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-\(\alpha\)-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 allo-type, 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 (\(\delta \) 1.95) and 8 (\(\delta \) 2.05) indicated an equatorial and axial one, respectively. Thus, the configuration of 2 was confirmed to be of \(\alpha\)-gluco-type.

The epoxide-ring of 2 resisted, to some extent, to alkaline opening than the corresponding furanose derivative, and alkali treatment of 2 at room temperature gave de-O-benzylated 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). Acetation 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-\(\alpha\)-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 \(\alpha\)-benzoyl derivative (18), its di-O-acetate (19), and \(\alpha\),\(\beta\)-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-benzamidomethyl 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 a 3-C-aminomethyl derivative (26), an orthoester-type product (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 [350°] of 22 in cuprammonium solution) and negative change ([M]_D [350°] of 18 indicated n-allo and n-gluco-configuration, respectively. Thus, the configuration of 21 was proved to be of d-allo-type.

Compound 25, having still two phenyl groups in the structure of 25, was proved to be of n-allo-type. On the other hand, partial hydrogenation of 21 in the presence of palladium-charcoal or hydrolysis with 0.1 n-sulfuric acid gave methyl 2-O-benzoyl-3-C-nitromethyl-α-D-allo-pyranoside (28), which was then converted into the tri-O-acetate (29) by acid-catalyzed acetylation. Acetonation of 28 gave an isopropylidene derivative (30), which was then converted to mono-O-acetate (31). The structure of 30 was deduced to be 3,4,6-isopropylidene derivative from the chemical shift of C-CH₃ protons (δ 1.47 and 1.49).

Discussion

On the stereoselectivities in nucleophilic addition to methyl 4,6-O-benzylidene-α-D-ribo-hexopyranosid-3-uloses, following facts are known. Reduction of 2-O-tosyl derivative; reduction,8) the Grignard9) and dimethylsulfoxonium methyldide10) reaction of the corresponding 2-acetamido-2-deoxy derivative; and the Grignard11) and the oxosulfonium ylide12) reaction of 2-deoxy derivative gave d-allo-type products, while the reaction of acetonitrile with the 2-deoxy derivative in liquid ammonia gave n-glucopyranose type product.13) These results indicate that nucleophiles in the former reactions attacked the carbonyl group from the less hindered site, and in the latter from the hindered site (Fig. 1). Thus, nitromethane condensation mentioned here is classified into the former type, though it generally gives various mixture of diastereomers,


depending on the condition used.\textsuperscript{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.\textsuperscript{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-O-benzylidene-2-deoxy-\(\alpha\)-d-erythro-hexopyranosid-3-ulose. However, 1,2-O-isopropylidene-\(\alpha\)-d-furanos-3-uloses gave the normal epoxi-epoxides which are resulted by attacking the reagent from the inside of the \(V\)-shaped five-membered ring.\textsuperscript{11,18)} Reaction of methyl \(\alpha\)-D-pyranosid-2-uloses in ether-alcohol, having two oxygens at the both vicinal carbon, gave a mixture of diastereomers,\textsuperscript{13)} however, one which has the epoxide carbomer in the site of \(C_2\)-methoxy group was predominant. Inch et al.\textsuperscript{18)} examined the steric influence of \(C\)-alkyl group vicinal to the carbonyl group by the reaction with 4,6-O-benzylidene-3-deoxy-3-\(C\)-ethyl-\(\alpha\)-d-arabinopyranosid-2-uloses, and showed that \(C\)-ethyl group in reverse side to \(C_2\)-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 stereoselectivities of the Grignard and diazo-


and then dried, and evaporated to give a crystals which was recrystallized from ethanol-water. Yield, 91% (105 mg); mp 156–157°C; [α]D +15.4° (c 0.95; CHCl3); IR: 1740 (Ph); NMR: ca. 7.37 (Ph; m), 5.89 (H2; d, J= 4.2), 5.35 (PhCH=), 4.87 (H; d), 4.85 (H; d; J= 7.5), 4.30 (H3; s, J= 7.5; m), 3.97–3.65 (Hα and Hβ; m), 3.40 (OMe), 2.14 (sec-OAc), 1.95 (tert-OAc), 1.62 (CH3).

Found: C, 60.18; H, 6.45%. Calecd for C19H16O5: 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-glucopyranoside (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 +69.8° (c 1.2, CHCl3); IR: 3475 (OH), 1730 (OAc); NMR: 2.16 (OAc), 1.28 (CH3). Caled for C19H16O5: C, 57.67; H, 6.10%.

Found: C, 61.35; H, 7.00%. Caled for C19H16O5: C, 61.35; H, 6.86%.

Acetylation of 6 by the usual method gave the sirupy 2-O-acetate (14) in a good yield. [α]D +49.8° (c 1.31, CHCl3); IR: 1750 (OAc), 1730 and 1380 (C-CH3); NMR: ca. 7.40 (Ph; m), 5.60 (PhCH=), 5.03 (H3; d; J= 7.5), 4.89 (H2; d), 4.40 and 4.25 (C5H2; ABq, J= 9.7), 4.45–4.25 (H3; m), 3.90–3.60 (Hα and Hβ; m), 3.38 (OMe), 2.16 (OAc), 1.49 and 1.36 (2×CH3).

Found: C, 60.85; H, 7.09%. Caled for C19H16O5: C, 60.90; H, 6.64%.

Methyl 3-C-Acetoxymethyl-3,4,6-tri-O-acetyl-2-0-benzoyl-IX-D-glucopyranoside (19). A solution of 6 (300 mg, 0.753 mmol) in acetic acid (80%, 60 ml) was refluxed for 18 hr., and evaporated to give a sirupy. n-Butanol solution (150 ml) of the sirupy was washed with saturated sodium bicarbonate and then a small amount of water, decolorized, and evaporated to give a sirupy (15) in 73% (180 mg) yield. [α]D +112° (c 1.10, CHCl3).

Found: C, 54.34; H, 6.11%. Caled for C19H16O5: C, 54.67; H, 6.14%.

Acid-catalyzed acetylation of 15 (120 mg) gave 16 in a quantitative yield, which was recrystallized from ether–hexane. Mp 84–86°C; [α]D +109° (c 1.01, CHCl3); IR: ca. 8.13 and 7.55 (Ph; m), 6.24 (H5; d; J= 7.5), 5.92 (H4; d; J= 10.0), 5.03 (H5; d), 5.02 and 4.85 (C5H2; ABq, J= 10.5), 4.48–4.02 (H3, Hα and Hβ; m), 3.42 (OMe), 2.10, 2.00, and 1.92 (4×OAc).

Found: C, 55.63; H, 5.72%. Caled for C19H16O12: C, 55.62; H, 5.69%.

Methyl 4,6-O-Benzylidene-3-C-aminomethyl-a-D-glucopyranoside (17). A solution of 9 (1.0 g, 3.3 mmol) in saturated ethanolic ammonia (25 ml) was heated for 3 hr in a sealed tube at 80–90°C, and evaporated to give needles, which was recrystallized from ethanol. Yield, 78% (0.5 g); mp 158–159°C; [α]D +92.0° (c 1.07, CHCl3); IR: 3390 and 3350 (OH), 3300 (NH3).

Found: C, 57.87; H, 6.87; N, 4.45%. Caled for C19H16NO4: 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 resulting solution was refluxed for 5 hr, evaporated to give a sirupy which was crystallized from ether. Yield, 67.5% (260 mg); mp 154–155°C; [α]D +12.0° (c 1.05, CHCl3); IR: ca. 3400 (NH and OH), 1640 (amide).

Found: C, 63.60; H, 6.20; N, 3.67%. Caled for C19H16NO4: C, 63.60; H, 6.07; N, 3.37%.

b) 2,3-Di-O-acetyl-N-benzyl Derivative (19): Acid-catalyzed acetylation of 18 gave the corresponding sirupy di-O-acetate in a quantitative yield. [α]D +40.8° (c 1.48, CHCl3).

Found: C, 62.44; H, 5.96; N, 2.77%. Caled for C19H16O5: C, 57.57; H, 6.10%.
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H$_2$NNO$_2$: C, 62.51; H, 5.85; N, 2.80%.

c) N-O-Triacetate (20): Acid-catalyzed acetylation of 17 (100 mg, 0.329 mmol) gave the N-O-triacetate in 97% (136 mg) yield. Mp 180–181°C; [α]$_D^22$ -19.6° (c 1.36, CHCl$_3$). IR: 3300 (NH), 1750 and 1730 (OAc), 1640 and 1555 (amide); NMR: 7.42 (Ph; s), 6.45 (NH), 5.94 (H$_4$; d, J$_{1,2}$=4.7), 5.30 (PhCH$_3$), 5.10 (H$_3$; d, J$_{1,2}$=10.0), 4.84 (H$_4$; d), 4.42–3.80 (H$_5$, H$_6$, and H$_7$; m), 3.87 and 3.68 (C$_2$H$_5$; ABq, J=9.5), 3.39 (OMe), 2.13 (ac-OAc), 1.99 (ac-OAc).

Found: C, 56.72; H, 6.24; N, 3.30%. Calcd for C$_{32}$H$_{37}$NO$_{19}$: C, 66.72; H, 6.2%.

Methyl 2-O-Benzyl-4,6-O-benzylidene-3-C-nitromethyl-a-D-allopyranoside (21). To a solution of nitromethane (30 ml) in tetrahydrofuran (30 ml) were added successively sodium methoxide (Na; 0.4 g, 171 mmol) and 1 (6 g, 156 mmol) stirring, the resulted solution was stirred for 3 hr at room temperature, neutralized with acetic acid (60%), extracted with chloroform. The extract was washed with water, and evaporated to give needles which was recrystallized from acetone–ethanol. Yield, 80.5% (5.6 g); mp 169–170°C; [α]$_D^22$ +73.8° (c 1.0, acetone). IR: 3440 and 3360 (OH), 1720 (OBz), 1543 (N0$_2$); NMR: 7.72 (Ph; s), 7.00 (NH), 5.00 (H$_2$; d, J$_{1,2}$=10.0), 4.92 (H$_3$; q), 4.85 (H$_4$; d, J$_{1,2}$=4.5), 3.91 (H$_5$; t, J$_{3,4}$=6.0), 3.85 (H$_6$; ABq, J=12.0), 3.14 (H$_7$; d, J$_{5,6}$=2.5), 2.75 (NH$_2$; s). Found: C, 59.60; H, 5.40; N, 3.40%. Calcd for C$_{22}$H$_{23}$N$_2$O$_{16}$: C, 57.71; H, 5.40; N, 3.29%.

Acid-catalyzed acetylation of 22 gave the corresponding monoacetates (23) and 26. A suspended solution of 22 (4 g, 9 mmol) in methanol (60 ml) was hydrogenated in an autoclave in the presence of palladium-charcoal in 53% quantitative yield, which was recrystallized from ethanol–water. Yield, 2.4 g (65%); mp 234–235°C; [α]$_D^22$ +73.8° (c 0.92, CH$_2$Cl$_2$); IR: 3430 (OH), 3390 (NH), 1720 (OBz), 1530 (amide).

Base-catalyzed acetylation of 25 and 26 gave the corresponding 3-C-acetamidomethyl-2-O-acetyl derivative (27) in a quantitative yield. Mp 160°C; [α]$_D^22$ +92.5° (c 0.10, ethanol). IR: 3410 and 3510 (OH), 1720 (OBz), 1540 (NO$_2$).

Found: C, 51.85; H, 6.27; N, 3.80%. Calcd for C$_{21}$H$_{23}$N$_2$O$_{10}$: C, 61.86; H, 7.25; N, 4.03%.

Methyl 2-O-Benzyl-3-C-nitromethyl-a-D-allopyranoside (28). To a solution of 21 (3.0 g) in acetone (20 ml) was added portionwise 0.2 N sulfuric acid (15 ml) at 40°C, maintained at the temperature for 4 hr, neutralized with sodium bicarbonate, and concentrated. The residue was extracted with ethanol, and the ethanol solution was evaporated to give a sirup which was recrystallized from methanol–water. Yield, 87% (2.1 g); mp 152–154°C; [α]$_D^22$ +92.5° (c 0.10, ethanol). IR: 3410 and 3510 (OH), 1720 (OBz), 1540 (NO$_2$).

Acid-catalyzed acetylation of 22 in the presence of Raney nickel and paraformaldehyde in 53% yield, and it was converted into sirupy tri-O-acetate (29) by evolution of formaldehyde. IR: 3410 and 3450 (OH), 1720 (OBz), 1540 (NO$_2$). Yield, 50.63; H, 5.03; N, 4.04%. Calcd for C$_{22}$H$_{23}$N$_2$O$_{10}$: C, 50.42; H, 5.40; N, 3.80%.

This compound was also prepared by partial hydrolysis of 22 in the presence of palladium-charcoal in 53% yield, and it was converted into sirupy tri-O-acetate (29) by acid-catalyzed acetylation in 90% yield. [α]$_D^22$ +91.5° (c 1.25, CH$_2$Cl$_2$); IR: 1720 and 1760 (ester), 1550 (NO$_2$).

Found: C, 52.97; H, 5.55; N, 2.67%. Calcd for C$_{22}$H$_{23}$N$_2$O$_{10}$: C, 52.17; H, 5.21; N, 2.90%.

Methyl 2-O-Benzyl-3-C-nitromethyl-a-D-allopyranoside (30). A suspended solution of 28 (1 g), and anhydrous cupric sulfate (2 g) in acetonitrile (50 ml) containing one drop of sulfuric acid was stirred for 3 days at room temperature, neutralized with barium carbonate, filtered, and the filtrate was evaporated to give a sirupy product. The sirup was fractionated through a Kiesel gel 60 (Merck) column with benzene–methanol eluent (15:1) to give 28 (0.25 g) and 30 (0.67 g, 58%) which was crystallized from ethanol–n-hexane. Mp 138–139°C.

Found: C, 54.18; G, 5.57; N, 3.83%. Calcd for C$_{22}$H$_{23}$N$_2$O$_{10}$: G, 54.40; H, 5.83; N, 3.53%.

Acid-catalyzed acetylation of 30 gave 6-O-acetate (31) in a quantitative yield, which was recrystallized from ethanol–n-hexane. Mp 163–163.5°C; IR: 1720 (ester), 1560 (NO$_2$), 1730 (C=O) (CH$_3$); NMR: 8.07–4.51 (Ph; m), 5.87 (H$_3$; d, J$_{1,2}$=5.1), 4.99 (H$_4$; d), 4.64 (C$_2$H$_5$; s), 4.58–5.10 (H$_5$; H$_6$, and H$_7$; m), 3.40 (OMe), 2.10 (OAc), 1.40 and 1.29 (2 x CH$_2$).

Found: C, 54.44; H, 5.77; N, 3.11%. Calcd for C$_{22}$H$_{23}$N$_2$O$_{10}$: C, 54.66; H, 5.74; N, 3.19%.

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