

Bromine Oxidation of Methyl 2-Acetamido-2-deoxy- α -D-glucopyranoside

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On oxidation of glycopyranosides with bromine water at pH 7,¹ the secondary alcohol groups are preferentially oxidized. When the (C)-H of the secondary alcohol group and a bulky substituent (the aglycon or a hydroxyl group) are in *syn*-diaxial relationship, the reaction is considerably hindered. For certain glycosides, the reaction therefore shows high regioselectivity; thus, methyl α -D-galactopyranoside reacts mainly in the 4-position. The reaction offers a convenient synthesis of unprotected glycosiduloses, a class of substances not easily available by other methods. A limitation is that the uloses are further oxidized and the yields, even under optimal conditions, are only moderate.

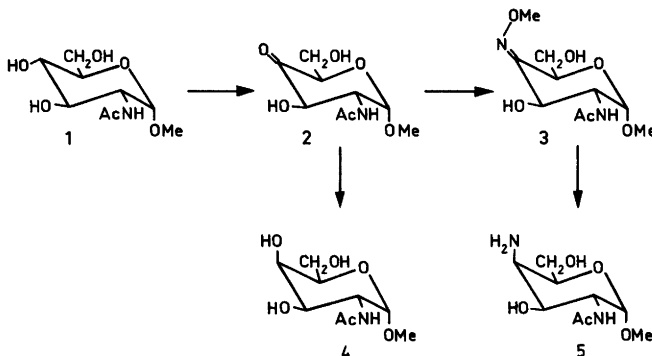
Acetamido groups should become *N*-brominated during the reaction but this reaction is reversible and the acetamido groups should be regenerated during the work-up. The oxidation of acetamido-deoxyglycosides should therefore be more regio-specific than for ordinary glycosides. We now report the oxidation of methyl 2-acetamido-2-deoxy- α -D-glucopyranoside and the transformation of the resulting 4-ulose into the corresponding 2-acetamido-2-deoxy-D-galacto and 2-acetamido-4-amino-2,4-dideoxy-D-galacto derivatives.

Methyl 2-acetamido-2-deoxy- α -D-glucopyranoside (1) was treated with bromine (3.7 mol) in water at pH 7 and room temperature. The resulting methyl 2-acetamido-2-deoxy- α -D-xylo-hexopyranosid-4-ulose (2) was not isolated but converted into the more stable *O*-methyloxime (3). The chromatographically homogeneous oxime was isolated by chromatography on silica gel. The compound resisted all attempts at crystallization. NMR spectra and GLC of its TMS derivative indicated that only one of the two possible isomers had been formed. The same observation was made by Schnarr and Szarek on preparing *O*-methyloximes of methyl pentosid-4-uloses.² These authors deduced the configurations of their *O*-methyloximes from the differences in chemical shifts in the ¹³C NMR spectra of the C-3 and C-5 signals when going from the ulose to the *O*-methyloxime. The free 4-ulose (2) was prepared by treating 3 with an acidic cation exchange resin. The same upfield shift (1.6 ppm) was, however, observed for the C-3 and C-5 signals on going from 2 to 3 and no conclusion regarding the configuration of 3 could be drawn from this experiment. In the ¹H NMR spectrum of 3, the shift of H-5 (δ 5.03), was 0.8 ppm downfield of that of H-3 (δ ~4.26), indicating that the *O*-methyloxime 3 has the *Z* configuration.^{3,4} The same shift difference was observed in dimethylsulfoxide-*d*₆.

The 4-ulose (2) was recovered by treating the oxime (3) with acidic cation exchange resin and then hydrogenated over palladium on charcoal to give methyl 2-acetamido-2-deoxy- α -D-galacto-pyranoside (4) in 59 % yield. Only traces of the corresponding D-gluco derivative were found, when the trimethylsilylated product was examined by GLC.

Catalytic hydrogenation of the oxime (3) yielded methyl 2-acetamido-4-amino-2,4-dideoxy- α -D-galactopyranoside (5, 75 %), identified by its ¹H and ¹³C NMR spectra. No signals for the D-gluco-isomer were observed in these spectra. The compound resisted all attempts at crystallization.

The ¹H and ¹³C NMR spectra of 2, 3 and 5 (see



the experimental part) were in agreement with the postulated structures. Signals in the ^1H NMR spectrum were assigned by homonuclear decoupling experiments and those in the ^{13}C NMR spectra by comparison with related substances and by using the deuterium-induced differential isotope shift technique.⁵

The transformation of the D -glucosamine derivative (1) into the considerably more expensive D -galactosamine derivative (4), by the route described above, would be of practical value if the yields could be improved.

The route to aminodeoxyglycosides *via* glycosiduloses, as exemplified above, is short and should, despite the moderate yields, be a useful alternative to other methods. One such synthesis has been previously described.⁶

Experimental. Melting points are uncorrected. Concentrations were carried out under reduced pressure at bath temperatures not exceeding 40°C . NMR spectra were recorded in D_2O or dimethylsulfoxide- d_6 at 30°C , using a JEOL FX 90Q instrument. Differential ^{13}C spectra were measured using a coaxial, dual cell from Wilmad Glass Co. As references, external TMS (^{13}C) and internal sodium 1,1,2,2,3,3-hexadeuterio-4,4-dimethyl-4-silapentane-1-sulfonate (^1H) were used. TLC and column chromatography were performed on Silica Gel F₂₅₄ (Merck) and Silica Gel 60 (Merck), respectively. Optical rotations were determined with a Perkin Elmer 141 polarimeter. For GLC a Packard 427 instrument and glass capillary columns ($25\text{ m} \times 0.3\text{ mm}$), coated with OV-101, were used.

Methyl 2-acetamido-2-deoxy- α -D-xylo-hexopyranosid-4-ulose O-methylxime (3). A solution of methyl 2-acetamido-2-deoxy- α -D-glucopyranoside (1, 1 g) in 0.13 M bromine water was kept at room temperature and the pH maintained at 7.0 by titration with 1 M sodium hydroxide. After 4 h, when all bromine was consumed, the pH was adjusted to 5.0, the solution concentrated to 50 ml and methoxylamine hydrochloride (2.5 g) added. The mixture was kept at 50°C and the pH maintained at 4.0 by titration with M sodium hydroxide. After 2.5 h, the pH was raised to 7.0 and the solution concentrated to dryness. Extraction of the residue with chloroform ($4 \times 25\text{ ml}$), concentration and chromatography on a silica gel column ($50 \times 1.5\text{ cm}$), irrigated with chloroform-ethanol, 9:1, and monitored by TLC, yielded 3 (0.34 g), $[\alpha]_{\text{D}}^{25} + 103^\circ$ (c 0.6, chloroform). ^1H NMR (D_2O) δ , Hz: 5.08, $J_{1,2}$ 2.3, (H-1); 4.28–4.24 (H-2, H-3); 5.03, $J_{5,6}$ 3.4, $J_{5,6}$ 7.0 (H-5); 3.78, $J_{6,6}$ 12.0, (H-6); 4.01 (H-6'); 2.04 ($\text{CH}_3\text{C}=\text{O}$); 3.47 ($\text{CH}_3-\text{O}-\text{C}$); 3.91 ($\text{CH}_3-\text{O}-\text{N}$). ^{13}C NMR (differential isotope shifts in parentheses), δ : 96.6 (0.00, C-1); 55.1 (0.14, C-2); 69.7 (0.11, C-3); 154.8 (0.06, C-4); 71.3 (0.06, C-5); 61.5 (0.12, C-6); 175.4 (0.09, $\text{CH}_3\text{C}=\text{O}$); 23.0

($\text{CH}_3\text{C}=\text{O}$); 57.6 (0.06, $\text{CH}_3-\text{O}-\text{C}$); 63.3 (0.05, $\text{CH}_3-\text{O}-\text{N}$).

Methyl 2-acetamido-2-deoxy- α -D-xylo-hexopyranosid-4-ulose (2). A solution of 3 (224 mg) in water (25 ml) was stirred with Dowex 50 (H^+ , 1 g) at room temperature for 3 h and filtered. Evaporation with toluene and drying overnight in a desiccator (phosphorus II oxide) yielded 2 (180 mg). ^1H NMR (dimethylsulfoxide- d_6), δ , Hz: 4.77, $J_{1,2}$ 2.8 (H-1); 3.96–4.30 (H-2, H-3, H-5); 3.54–3.82 (H-6, H-6'), 8.17, $J_{2,\text{NH}}$ 7.7 (NH); 3.37 (CH_3O); 1.85 ($\text{CH}_3\text{C}=\text{O}$). ^{13}C NMR (differential isotope shifts in parentheses), δ : 97.8 (0.00, C-1); 56.3 (0.14, C-2); 72.3 (0.11, C-3); 204.0 (0.03, C-4); 73.9 (0.00, C-5); 59.0 (0.11, C-6); 55.2 ($\text{CH}_3-\text{O}-\text{C}$); 22.4 ($\text{CH}_3\text{C}=\text{O}$), and 169.2 ($\text{CH}_3\text{C}=\text{O}$).

Methyl 2-acetamido-2-deoxy- α -D-galactopyranoside (4). The 4-ulose, 2 (200 mg), in methanol (25 ml) containing triethylamine (3 ml), was hydrogenated at atmospheric pressure and room temperature overnight, using 10% palladium on charcoal (200 mg) as catalyst. The mixture was filtered and the solution concentrated. The residue was crystallized from ethanol-light petroleum (1:1), yielding the title compound (105 mg), m.p. $212-213^\circ\text{C}$ (decomp.), $[\alpha]_{\text{D}}^{25} + 172^\circ$ (c 1.06, methanol). It was indistinguishable from an authentic sample (NMR).

Methyl 2-acetamido-4-amino-2,4-dideoxy- α -D-galactopyranoside (5). The oxime 3 (70 mg) was hydrogenated as above and the product fractionated on a Dowex 50 (H^+) column ($15 \times 1\text{ cm}$) which was irrigated first with water (300 ml) and then with 2% aqueous ammonia (300 ml). The fractionation was monitored by TLC and the title compound was obtained as a syrup (46 mg), $[\alpha]_{\text{D}}^{25} + 170^\circ$ (c 1.8, methanol). ^1H NMR, δ , Hz: 4.81, $J_{1,2}$ 2.3 (H-1); 4.14, $J_{2,3}$ 11.1 (H-2); 3.95, $J_{3,4}$ 3.6 (H-3); 3.29, $J_{4,5}$ 1.4 (H-4); 3.94, $J_{5,6}$ 4.9, $J_{5,6}$ 6.7 (H-5); 3.76 (H-6, H-6'); 2.05 ($\text{CH}_3\text{C}=\text{O}$); 3.40 ($\text{CH}_3-\text{O}-\text{C}$). ^{13}C NMR, δ : 99.5 (0.00, C-1); 50.9 (0.14, C-2); 69.7 (0.12, C-3); 53.0 (0.25, C-4); 71.3 (0.02, C-5); 63.1 (0.13, C-6); 176.0 (0.09, $\text{CH}_3\text{C}=\text{O}$); 23.3 (0.13, $\text{CH}_3\text{C}=\text{O}$); 56.5 (0.07, $\text{CH}_3-\text{O}-\text{C}$).

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Received February 17, 1982.