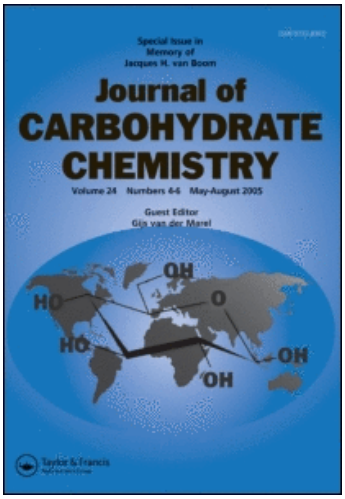

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An Improved Synthesis of 3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-d-galactopyranosyl Bromide: A Key Component for Synthesis of Glycopeptides and Glycolipids

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COMMUNICATION

AN IMPROVED SYNTHESIS OF 3,4,6-TRI-*O*-ACETYL-2-AZIDO-2-DEOXY-α-D-GALACTOPYRANOSYL BROMIDE: A KEY COMPONENT FOR SYNTHESIS OF GLYCOPEPTIDES AND GLYCOLIPIDS

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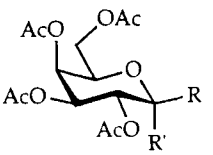
RESULTS AND DISCUSSION

The α-glycosidic bond between *N*-acetylgalactosamine and serine or threonine is one of the most important linkages between the carbohydrate and peptide parts of *O*-glycoproteins.[1] This linkage is found in mucous glycoproteins and is also a characteristic of many serum and membrane bound glycoproteins, including proteins containing the tumour associated T_N and T antigens. α-*O*-Glycosidically linked *N*-acetylgalactosamine also occurs in the blood group A determinant[2] and in glycolipids such as the Forssman antigen.[3]

Formation of α-*O*-glycosidic linkages to *N*-acetylgalactosamine has predominantly come to rely on 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl bromide[4] (**7**), the corresponding β-chloride[4] or trichloroacetimidates,[5] as key glycosyl donors.[6] These glycosyl halides are available from β-D-galactose pentaacetate[7] (**1**) with azidonitration of 3,4,6-tri-*O*-acetyl-D-galactal[8] (**3**), according to Lemieux and co-workers,[4] as the key step.

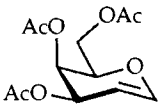
In our laboratory, syntheses of the azidobromide **7** on a 10 g scale, by treatment of the pentaacetate **1** with hydrogen bromide[7] (→ **2**), then reduction[8] (→ **3**), azidonitration[4] (→ **4** and **5**) and final substitution with bromide ion[4] gave only low overall yields (< 10%). In our hands, reduction[8] of the bromide **2** with zinc dust in acetic acid-aqueous sodium acetate to give the galactal **3** was often

irreproducible with yields, ranging from 25 to 70%. Chromatography was therefore required for purification of both **3** and the mixture of **4** and **5** obtained on azidonitration, as well as of the azidobromide **7**. In order to facilitate the preparation of **7** we have developed an improved procedure which results in an increase of the overall yield and eliminates the need for purification of synthetic intermediates by chromatography.

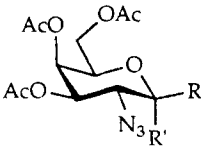


1 R = OAc, R' = H

2 R = H, R' = Br



3



4 R = H, R' = ONO_2

5 R = ONO_2, R' = H

6 R = H, R' = NHAc

7 R = H, R' = Br

Standard treatment[7] of β-D-galactose pentaacetate (**1**) with hydrogen bromide in acetic acid gave the bromide **2** in quantitative yield. We found that crude **2** could be reduced to the galactal **3** with zinc dust and *N*-methylimidazole in refluxing ethyl acetate, as recently reported[9] for preparation of 3,4,6-tri-O-acetyl-D-glucal. Reduction by this method was reproducible and gave quantitative yields of **3** (TLC, ^{1}H NMR) provided that the reaction mixture was stirred vigorously. Crude **3** could therefore be used directly for azidonitration[4] without further purification. Strict control of the temperature at -25 °C and vigorous stirring during the azidonitration were essential to maximize the yield of the mixture of azidonitrates, **4** and **5**. Under these conditions we did not detect the formation of the 1-acetamido derivative **6**, previously reported[4] as a significant by-product in this step. Finally, treatment[4] of the mixture of azidonitrates **4** and **5** with lithium bromide for at least 4 h gave the azidobromide **7**. Column chromatography of the product on silica gel gave material containing the *talo* isomer of **7** as the only impurity, and crystallization then gave pure **7** in 25% total yield over the four steps. This procedure therefore significantly improves the overall yield in the preparation of the key glycosyl donor **7** and minimizes time-consuming purifications by column chromatography. Furthermore, the procedure conveniently allows preparation of **7** on a 10-20 g scale.

EXPERIMENTAL

General Methods. TLC was performed on Silica Gel 60 F_{254} (Merck) with detection by UV light and charring with sulfuric acid. Column chromatography was performed on Silica Gel 60 (Grace Amicon, 35-70 μm) or on a Lichroprep Si 60 column (40-63 μm, 3.7 x 44 cm) with distilled solvents. Ethyl acetate and acetonitrile were dried over molecular sieve (4 Å and 3 Å, respectively). Organic solutions were dried over sodium sulfate. Before being used zinc dust was activated by washing with 10% aqueous hydrogen chloride, water, acetone, and diethyl ether, and then dried under vacuum. The optical rotation was measured with a Perkin-Elmer 141 polarimeter. The melting point is uncorrected.

3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl Bromide (7). Hydrogen bromide in acetic acid (33 %, 112 mL, 0.459 mol) was added to a suspension of 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose[7] (**1**, 30.0 g, 76.9 mmol) in 2:1 acetic acid-acetic anhydride (67 mL) at 0 °C during 30 min. After a further 30 min the mixture was allowed to attain room temperature and dichloromethane (600 mL) was added after 2 h at this temperature. The organic phase was washed with ice cold water (400 mL) and ice cold saturated aqueous sodium hydrogencarbonate (3 x 400 mL), then dried and concentrated to give crude 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**2**, 34.1 g).

N-Methyl imidazole (9.80 mL, 0.123 mol) was added to a refluxing mixture of the crude **2** and activated zinc dust (65.4 g, 1.00 mol) in dry ethyl acetate (500 mL) under vigorous stirring. After 25 min the mixture was cooled, filtered through Celite and washed with 0.1 M aqueous potassium hydrogensulfate (2 x 400 mL) and saturated aqueous sodium hydrogencarbonate (400 mL). The organic phase was dried and concentrated to give crude 3,4,6-tri-*O*-acetyl-D-galactal (**3**, 21.2 g).

The crude **3** in dry acetonitrile (500 mL) was added to sodium azide (7.49 g, 115 mmol) and ceric ammonium nitrate (126 g, 0.231 mol) at -25 °C during 20 min. The reaction was performed under nitrogen behind a safety shield with vigorous stirring and strict control of the temperature at -25 °C. After 20 h the mixture was diluted with cold diethyl ether (500 mL) and washed with cold water (3 x 500 mL). The organic phase was dried and concentrated to give a crude mixture of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α- and β-D-galactopyranosyl-nitrate (**4** and **5**, 20.1 g).

A mixture of the crude **4** and **5** and lithium bromide (23.2 g, 0.267 mol) in dry acetonitrile (200 mL) was stirred for at least 4 h at room temperature and

then filtered and concentrated. The residue was dissolved in 1:1 dichloromethane-water (1 L) and the organic phase was further washed with water (2 x 500 mL), dried and concentrated. Flash column chromatography of the residue (19.6 g) on silica gel (600 g) with 3:1 → 2:1 heptane-ethyl acetate gave material (10.3 g) which crystallized from diethyl ether-heptane to give **7** (7.28 g, 24.0%). Concentration of the mother liquor, chromatography of the residue on a Lichroprep column and crystallization gave a further crop of **7** (0.41 g, 1.4%; total overall yield: 25.4%). Compound **7** had mp 101-102 °C, $[\alpha]_D^{25}$ +188.3° (*c* 1.95, chloroform) [lit.[4a] mp 97-98 °C, $[\alpha]_D^{25}$ +188.6° (*c* 1.95, chloroform)] and ^{1}H NMR data as reported.[4a]

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