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Technical note

Preparation of a Thioglycoside, Useful as a Galactosamine Synthon: *p*-Methylphenyl 2-Azido-3,4,6-tri-*O*-*p*-chlorobenzyl-2-deoxy-1-thio-β-D-galactopyranoside.

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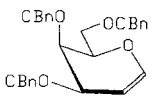
Galactosamine and its derivatives are difficult to isolate from natural sources, therefore several synthetic routes [1-8] to such derivatives have been reported. The most useful of these is the azidonitration procedure which, as reported by Lemieux *et al.* [8], gives easy access to 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-*galacto* derivatives from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol.

We now report the preparation of crystalline 1,5-anhydro-3,4,6-tri-*O*-*p*-chlorobenzyl-2-deoxy-D-*lyxo*-hex-1-enitol **1** in 84% yield from 1,5-anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-D-*lyxo*-hex-1-enitol and its azidonitration with sodium azide and ceric ammonium nitrate to give an α/β mixture of 2-azido-2-deoxy-1-nitrates **2** with predominantly *galacto* configurations. Treatment of the mixture of 1-nitrates *in situ* with tetraethylammonium chloride gave the α-chloride **3**. If the crude chloride was reacted directly with sodium thiocresolate in ethanol/chloroform the crystalline thioglycoside **4** was formed (31.5% yield from **1**).

The thioglycoside function of **4** can be activated for glycosidation [9] and **4** is therefore a relatively easily accessible and crystalline synthon for use in synthesis of oligosaccharides containing terminal galactosamine. The advantage of **4** as compared to *O*-acylated galactosamine derivatives is that it can be used in a synthetic sequence where *O*-benzyl or *O*-*p*-chlorobenzyl groups are used for persistent blocking and *O*-acyl groups are used for temporary blocking. The use of **4** in oligosaccharide synthesis will be reported elsewhere.

Abbreviations: CBn, 4-chlorobenzyl; Ph, phenyl; Ar, aryl.



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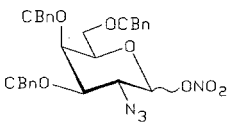

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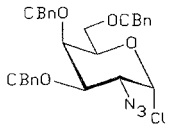

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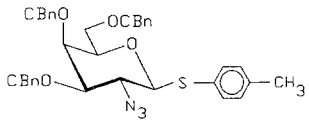

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Experimental

General Methods

Melting points were determined with a Büchi 512 melting-point apparatus and are uncorrected. Concentrations were performed at 1-2 kPa at < 40°C (bath). Optical rotations were recorded in 0.5% solutions in chloroform using a Perkin-Elmer 241 polarimeter. NMR spectra were recorded at 25°C for solutions in C^2HCl_3 using a Bruker AM 500 instrument. The following reference signals were used: C^2HCl_3 δ 77.00 (^{13}C in C^2HCl_3); internal Me_4Si δ 0.00 (^1H in C^2HCl_3). Only selected NMR data are reported. TLC was performed on Silica Gel F_{254} (Merck, Darmstadt, W.Germany) with detection by charring with sulphuric acid or by u.v. light if applicable. Column chromatography was performed on silica gel (0.035-0.070 mm, Matrex LC 60 A, Grace, Worms W. Germany) and elution with toluene/ethyl acetate mixtures unless otherwise stated. Organic solutions were dried over $MgSO_4$. Molecular sieves (4Å, Union Carbide, powder, obtained from Fluka, Buchs, Switzerland) were used directly without further drying.

*1,5-Anhydro-3,4,6-tri-O-p-chlorobenzyl-2-deoxy-D-lyxo-hex-1-enitol (**1**)*

Syrupy 1,5-anhydro-3,4,6-tri-O-acetyl-2-deoxy-D-*lyxo*-hex-1-enitol [10] (14.3 g) was dissolved in methanol (140 ml) and a 0.5 M solution of sodium methoxide in methanol (30 ml) was added. The mixture was stirred for 3 h at room temperature, then concentrated to dryness. The residue was suspended in dry *N,N*-dimethyl formamide (160 ml) and 4-chlorobenzyl chloride (27 g) was added. The mixture was cooled to 0°C. Sodium hydride (5.4 g of a 80% suspension in mineral oil, washed with light petroleum immediately before use), suspended in dry *N,N*-dimethyl formamide (20 ml), was added slowly in portions. The mixture was allowed to attain room temperature and then stirred overnight. Methanol (25 ml) was added and the mixture was stirred for 15 min. The mixture was diluted with toluene (800 ml) and water (500 ml). The organic layer was washed twice with water, dried and concentrated. The residue was purified on silica gel

to yield **1** as a solid (22.1 g, 84%). Recrystallisation from diethyl ether and light petroleum gave material with m.p. 60-62°C, $[\alpha]_D$ -49°. NMR data: ^{13}C, δ 68.1, 70.0, 72.4, 72.5 (C-6, Ar**C**H_2O), 70.7, 71.5, 75.3 (C-3, C-4, C-5), 99.5 (C-2), 144.1 (C-1); ^1H, δ 3.63 (dd, H-6), 3.74 (t, H-6'), 3.90 (broad s, H-4), 4.15 (broad s, H-3), 4.18 (broad s, H-5), 4.84 (q, $J_{2,3}$ 3.0 Hz, H-2), 6.35 (d, $J_{1,2}$ 6.7 Hz, H-1).

Analytical data, calculated for $C_{27}H_{25}Cl_3O_4$: C, 62.4; H, 4.8. Found: C, 62.3; H, 4.7.

*p-Methylphenyl 2-Azido-3,4,6-tri-O-p-chlorobenzyl-2-deoxy-1-thio-β-D-galactopyranoside (**4**)*

Compound **1** (6.0 g) in acetonitrile (60 ml) was added, in a nitrogen atmosphere, to a stirred and cooled (-10 to -20°C) mixture of sodium azide (1.58 g) and ceric ammonium nitrate (20.0 g). After 2 h, cold diethyl ether (300 ml) and ice-cold water (200 ml) were added. The organic layer was washed with ice-cold water, dried and concentrated to give a crude mixture of nitrates as a syrup (8.9 g). This mixture was used in the subsequent step. NMR data: α-nitrate: ^1H, δ 3.50 (dd, H-6), 3.58 (t, H-6'), 3.82 (dd, $J_{2,3}$ 11.0 Hz, $J_{3,4}$ 2.4 Hz, H-3), 4.03 (broad d, H-4), 4.06 (broad t, H-5), 4.24 (dd, H-2), 6.25 (d, $J_{1,2}$ 4.3 Hz, H-1); β-nitrate: ^1H, δ 5.43 (d, $J_{1,2}$ 8.5 Hz, H-1). The mixture of nitrates **2** (8.9 g) was stirred with powdered molecular sieves 4Å (60 g) in dichloromethane (200 ml) for 0.5 h. The mixture was then cooled to 0°C and tetraethyl ammonium chloride (20 g) was added. Stirring at room temperature was continued for 2 h, then the mixture was filtered and diluted with cold diethyl ether (350 ml) and ice-cold water (200 ml). The organic layer was washed with ice-cold water, dried and concentrated to yield the crude chloride **3** as a syrup (7.15 g). NMR data: ^{13}C, δ 60.8 (C-2), 67.5 (C-6), 71.7, 72.3, 72.8, 72.9, 74.2, 77.6 (C-3, C-4, C-5, Ar**C**H_2O), 94.1 (C-1); ^1H, δ 3.53 (dd, H-6), 3.60 (t, H-6'), 3.96 (dd, $J_{2,3}$ 10.4 Hz, $J_{3,4}$ 2.4 Hz, H-3), 4.02 (broad s, H-4), 4.20 (dd, H-2), 4.23 (t, H-5), 6.13 (d, $J_{1,2}$ 3.7 Hz, H-1). The crude chloride **3** (6.7 g) was dissolved in chloroform (30 ml) and added dropwise under 20 min to a solution of *p*-thiocresol (1.7 g) and potassium hydroxide (0.74 g) in ethanol (18 ml). The mixture was stirred for 15 min at room temperature, then diluted with chloroform, washed with saturated aqueous sodium hydrogen carbonate and water, dried and concentrated. The product was purified on a short column of silica gel and by crystallisation from diethyl ether/light petroleum to give **4** (5.8 g, 31.5% calculated from **1**), m.p 110-112°C, $[\alpha]_D$ -12°. NMR data: ^{13}C, δ 21.2 (SPh**C**H_3), 61.5 (C-2), 68.2 (C-6), 72.4 (C-4), 77.1 (C-5), 82.5 (C-3), 86.5 (C-1), 71.7, 72.8, 73.6 (Ar**C**H_2O); ^1H, δ 2.31 (s, SPh**C**H_3), 3.37 (dd, $J_{2,3}$ 9.8 Hz, $J_{3,4}$ 2.4 Hz, H-3), 3.55 (t, H-6), 3.61 (broad d, H-6', H-5), 3.72 (t, H-2), 3.87 (broad d, H-4), 4.32 (d, $J_{1,2}$ 10.5 Hz, H-1).

The FAB-MS of **4** showed an $(M+H)^+$ ion m/z = 684.

Analytical data, calculated for $C_{34}H_{32}Cl_3N_3O_4S$: C, 59.6; H, 4.7; N, 6.1. Found: C, 59.5; H, 4.6; N, 6.1.

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