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Note

Synthesis of methyl α-L-decilonitroside

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The branched-chain, nitro sugar L-decilonitrose occurs in the trisaccharide moiety of the new anthracycline antibiotics decilorubicin[1] and arugomycin[2]. Other nitro sugars obtained from antibiotics are L-evernitrose[3], D-rubranitrose[4], and D-kijanose[5]. Stereocontrol at the geminally substituted C-3 atom is the most critical part of the synthetic strategy for this class of compounds. Existing routes have relied on spiroaziridines as precursors to the geminal methyl and nitro functionalities[6], and this approach has been most successful in cases where the C-3–nitrogen bond is equatorial rather than axial. Spiroaziridine-based syntheses of methyl β-L-decilonitroside[7] (11 steps) and of the corresponding α-glycoside[8] **1** (12 steps) have been reported. In both, the introduction of the required axial nitrogen atom at C-3 was attended by formation of the (undesired) epimer, or other side products.

In the course of our studies of the synthesis of branched-chain carbohydrates, we have discovered that dimethylcyanamide is a useful reagent for the conversion of allylic alcohols into *cis*-1,2-amino alcohols[9]. Because the amino group can readily be oxidized to a nitro group when it is attached to a tertiary carbon atom, this sequence offers an alternative route to the branched-chain, nitro sugars. Herein, we describe the application of this strategy to the synthesis of methyl α-L-decilonitroside.

Methyl 2,3,6-trideoxy-3-*C*-methylene-α-L-*erythro*-hexopyranoside (**2**) was prepared from di-*O*-acetyl-L-rhamnal (**1**) as described previously[10]. Allylic imidate **3** was obtained in 89% yield by the reaction of **2** with sodium hydride and dimethylcyanamide. Consistent with our earlier results, higher yields of imidate were obtained if solvent was omitted from the reaction mixture. Cyclization of **3** occurred satisfactorily in the presence of mercuric trifluoroacetate in tetrahydrofuran, to give, after reductive demercuration with sodium borohydride, oxazoline **4** in 85% yield. Cyclization takes place exclusively from the β-face, with the imidate nitrogen atom attacking the more-substituted C-3 position.

Hydrolysis of **4** with barium hydroxide gave methyl 3-amino-2,3,6-trideoxy-3-

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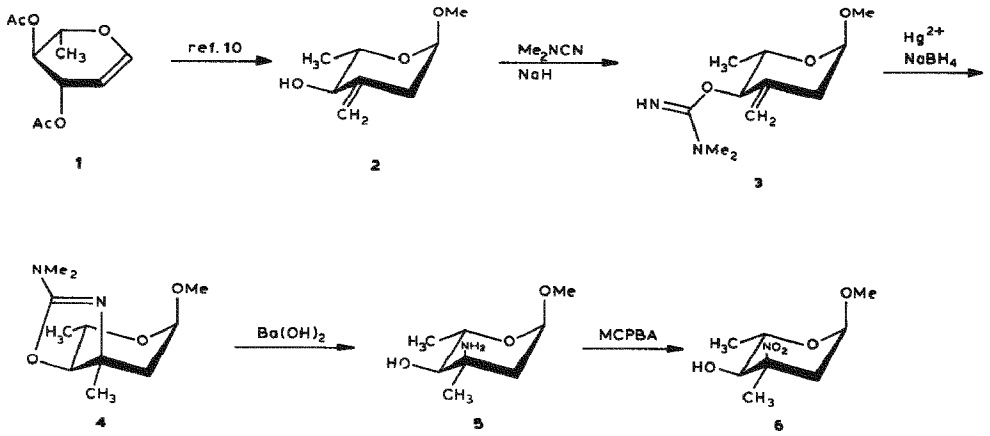
C-methyl-α-L-*ribo*-hexopyranoside (**5**) in 58% yield. This three-flask sequence converts allylic alcohol **2** into amino alcohol **5** in 44% overall yield. We consider that, as a reagent for converting allylic alcohols into *cis*-1,2 amino alcohols, dimethylcyanamide is a useful alternative to the more commonly used trichloroacetonitrile[11]. We have observed that allylic imidates derived from dimethylcyanamide are more stable than those obtained from trichloroacetonitrile. Furthermore, the dimethylamino group is insensitive to reduction with sodium borohydride, whereas the trichloromethyl group suffers partial reduction, to give a complex mixture of products.

Oxidation of **5** with *m*-chloroperoxybenzoic acid in refluxing dichloromethane gave methyl α-L-decilonitroside **6**. This convenient synthesis of **6** requires a total of nine steps and is completely stereoselective.



EXPERIMENTAL

General procedures. — Melting points were determined on a Thomas–Hoover melting-point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Thin-layer chromatography was performed on aluminum-supported plates of silica gel 60 (0.2 mm, F-254, E. Merck). Flash chromatography was conducted on silica gel 60 (230–400 mesh, Merck 9385). Dichloromethane was dried by passing it through a column of basic alumina (Woelm, activity 1). Oxolane (tetrahydrofuran, THF) was distilled from calcium hydride before use. Infrared spectra were recorded with an Analect 6160 FT-IR instrument, and ^{1}H-n.m.r. spectra with a Varian XL-200 spectrometer. Chemical shifts for proton resonances are given relative to tetramethylsilane (δ 0.0). High-resolution mass spectra were obtained on a VG 7070H spectrometer by John Dykins at the Chemistry Department of the University of Pennsylvania.

Methyl 2,3,6-trideoxy-3-C-methylene-4-O-(dimethylamidino)-α-L-erythro-hexopyranoside (**3**). — A mixture of methyl 2,3,6-trideoxy-3-*C*-methylene-α-L-

ribo-hexopyranoside (**2**; 1.62 g, 10.2 mmol), dimethylcyanamide (6.5 mL), and sodium hydride (0.272 g, 11 mmol) was stirred for 24 h at room temperature under nitrogen. Pentane (19 mL) containing a few drops of methanol was added with stirring, and the mixture was washed with water (8 mL), and extracted with chloroform (3 × 20 mL). The extracts were combined, dried (magnesium sulfate), and evaporated under diminished pressure at 30°, to give a residue which was dried further under vacuum. There was obtained 2.06 g (89%) of syrupy imidate **3**; $\nu_{max}^{thin\ film}$ 1629 cm^{-1} (C=N); $[\alpha]_D^{20}$ −168° (*c* 0.319, chloroform); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 7.34 (bs, 1 H, N–H), 5.05–4.90 (m, 3 H, vinyl, H-4), 4.74 (d, 1 H, H-1, $J_{1,2a}$ 3.6 Hz), 3.85 (dq, 1 H, H-5), 3.37 (s, 3 H, OCH_3), 2.92 [s, 6 H, $N(CH_3)_2$], 2.64 (dd, 1 H, H-2*a* $J_{2a,2e}$ 16 Hz), 2.50 (d, 1 H, H-2*e*), 1.27 (d, 3 H, H-6, $J_{5,6}$ 6.2 Hz); h.r.-m.s. Calc. for $C_{11}H_{20}N_2O_3$ 229.1552 (M + 1). Found 229.1498.

*Methyl 2,3,6-trideoxy-3-*C*-methyl-4,3-(2-*N*,*N*-dimethyl-1-oxa-3-azaprop-2-eno)-α-*L*-ribo-hex-2-enopyranoside* (**4**). — A solution of imidate **3** (1.5 g, 6.62 mmol) in dry THF (25 mL) and mercuric trifluoroacetate (3.0 g, 7.25 mmol) were stirred for 10 h at room temperature. The mixture was made basic with 2M sodium hydroxide, cooled to 0°, and a solution of 4M sodium borohydride in 2M sodium hydroxide was added until the reaction was no longer exothermic. The mixture was centrifuged and the supernatant liquor was decanted, and extracted with ether (2 × 20 mL). The extracts were combined, dried (sodium sulfate), and evaporated to give syrupy **4**; yield, 1.30 g (85%); $\nu_{max}^{thin\ film}$ 1656 cm^{-1} (C=N); $[\alpha]_D^{20}$ −120° (*c* 0.426, chloroform). The 200-MHz, ^{1}H-n.m.r. spectrum of **4** was identical with that of its enantiomer[9].

*Methyl 3-amino-2,3,6-trideoxy-3-*C*-methyl-α-*L*-ribo-hexopyranoside* (**5**). — A mixture of oxazoline **4** (1.30 g, 5.64 mmol) and M barium hydroxide (3 mL) was stirred under reflux for 24 h. Water (2.5 mL) was added, the mixture was extracted with chloroform (3 × 3 mL), and the extracts were combined, dried (sodium sulfate), and evaporated, to give **5** as a colorless syrup which crystallized under vacuum; yield, 0.57 g (58%); m.p. 92–94°, $[\alpha]_D^{20}$ −120° (*c* 0.131, chloroform); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 4.69 (d, 1 H, H-1), 3.44 (m, 1 H, H-5), 3.26 (s, 3 H, OCH_3), 2.83 (d, 1 H, H-4, $J_{4,5}$ 9 Hz), 2.27 (bs, 3 H, O*H*, NH_2), 1.92–1.52 (m, 2 H, H-2*a*, H-2*e*), 1.29 (d, 3 H, H-6, $J_{5,6}$ 6.5 Hz), 1.10 (s, 3 H, CH_3-3).

*Methyl 2,3,6-trideoxy-3-*C*-methyl-3-nitro-α-*L*-ribo-hexopyranoside* (**6**). — To a refluxing solution of MCPBA (2.72 g, 16 mmol) in dry dichloromethane (38 mL) was added, dropwise with stirring, a solution of amino alcohol **5** (0.38 g, 2.18 mmol) in dichloromethane (9.5 mL). The amino alcohol was added during 20 min, and the mixture was then refluxed for 20 min. Sodium sulfite (10% aqueous solution, 16 mL) was added with stirring, and the mixture was filtered. The organic phase was separated, washed with 2M sodium carbonate solution (2 × 16 mL) and brine (8 mL), dried (sodium sulfate), and evaporated, to give a clear syrup in a yield of 0.20 g (45%). The product was purified by flash chromatography[12] on silica gel, using 4:3 petroleum ether–ethyl acetate (R_F 0.58), to give white crystalline **6**; yield, 10 g (22%); m.p. 96–98° (lit.[8] m.p. 101.5–103°), $[\alpha]_D^{20}$ −185° (*c* 0.094, chloroform) {lit.[8]

$[\alpha]_D$ −172° (*c* 0.25, chloroform)}; ν_{max}^{KBr} 3516 (OH) and 1540 cm^{-1} (NO_2). The ^1H-n.m.r. spectrum of **6** recorded at 200 MHz matched that recorded[8] at 360 MHz.

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