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Preliminary communication

Some approaches to the synthesis of evernitrose and its enantiomer

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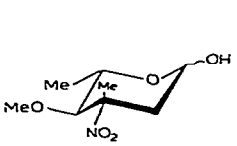
Evernitrose (**1**) is an unusual, branched-chain nitro sugar that occurs[1] as a component of the oligosaccharide antibiotics everninomicins B, C, and D. Although originally assigned[2] the L-*ribo* configuration, evernitrose is now known[3] to be 2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-3-nitro-L-*arabino*-hexopyranose (**1**). This revision of the structure of evernitrose revived our interest in the synthesis of branched-chain amino sugars from the glycal **2**[4], which possesses the same stereochemistry as evernitrose at the asymmetric centres. The glycal **2** is readily prepared[4] from methyl α-L-rhamnopyranoside.

Addition of methanol to **2** in the presence of boron trifluoride gave, after chromatography on silica gel, methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranoside (**3**), m.p. 123–125°, $[\alpha]_D$ −133° (*c* 1.7, chloroform), and the corresponding β-glycoside **4**, m.p. 167–169°, $[\alpha]_D$ +8° (*c* 0.95, chloroform), in the ratio of ~3:1. Catalytic *O*-deacetylation of **3** gave the alcohol **5** (89%), $[\alpha]_D$ −104° (*c* 0.7, chloroform), which on methylation (methyl iodide and sodium hydride in tetrahydrofuran[5]) gave methyl 3-acetamido-2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-α-L-*arabino*-hexopyranoside (**6**, 95%), m.p. 136–138°, $[\alpha]_D$ −71° (*c* 0.85, chloroform). Since the D enantiomer {m.p. 136–138°, $[\alpha]_D$ +73° (*c* 1, chloroform)} of **6** has recently been transformed into D-evernitrose by Yoshimura *et al.*[6,7], the foregoing route formally constitutes a synthesis of L-evernitrose (**1**), which has also been synthesized[6,7] by way of the cyanohydrin route originally developed by Bourgeois[8]. A sequence of reactions analogous to that described above was used to transform the β-glycoside **4** into methyl 3-acetamido-2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-β-L-*arabino*-hexopyranoside (**7**), m.p. 151–152°, $[\alpha]_D$ +57° (*c* 1, chloroform); lit.[7] (D enantiomer), m.p. 159–160°, $[\alpha]_D$ −57° (*c* 1, chloroform).

The evernitrose precursor **6** was also obtained by another, though less efficient, route that relied on deoxygenation of the readily available methyl 3-acetamido-3,6-



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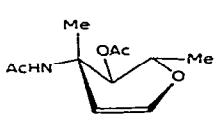

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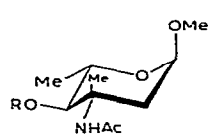
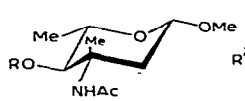
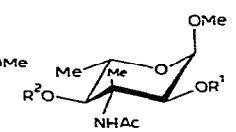


3 R = Ac
5 R = H
6 R = Me



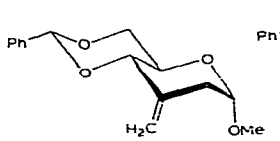
4 R = Ac
7 R = Me



8 $R^1 = R^2 = H$
9 R^1 = Ts; R^2 = Me
10 R^1 = H; R^2 = Me
11 R^1 = CSPn; R^2 =

dideoxy-3-*C*-methyl-α-L-glucopyranoside[4] (8) at C-2. Unimolar tosylation[9] of 8 and methylation (methyl iodide–silver oxide) of the resulting tosylate gave methyl 3-acetamido-3,6-dideoxy-3-*C*,4-*O*-dimethyl-2-*O*-toluene-*p*-sulphonyl-α-L-glucopyranoside (9), m.p. 173–174°, $[\alpha]_D$ −33° (*c* 0.9, chloroform), whose structure was readily established by ^{1}H-n.m.r. spectroscopy. Detosylation of 9 with sodium amalgam gave the alcohol **10** (63%), m.p. 186–187°, $[\alpha]_D$ −118° (*c* 0.8, chloroform), which afforded a crude 2-thiobenzoate **11** (27%) when treated, in sequence, with *N*,*N*-dimethyl-α-chlorobenzylideneammonium chloride and hydrogen sulphide[10]. Radical-induced cleavage of the 2-thiobenzoate **11** with tributyltin hydride[10] in refluxing toluene gave **6** (37%), which was identical (m.p., $[\alpha]_D$, and ^{1}H-n.m.r. spectrum) to the material obtained by way of the glycal 2, as well as a substantial amount (~50%) of an unidentified product. Although the deoxygenation procedure of Barton and McCombie[10] gave disappointingly low yields at both stages, other new deoxygenation procedures[11] may possibly be more efficient in converting **10** into **6**.

The synthesis of D-evernitrose (D-**1**) has been approached by a different route, which is based on addition of the pseudohalogen iodine azide[12] (generated *in situ* from sodium azide and iodine monochloride in acetonitrile) to the 3-*C*-methylene sugar derivative **12***. This reaction gave, *inter alia*, an adduct, m.p. 88–91°, $[\alpha]_D$ +45° (*c* 1, chloroform), that can reasonably be assigned the structure **13** by analogy** and its reduction (lithium aluminium hydride in ether at 0°) to the spiro-aziridine **14**, which was characterized as the *N*-acetyl derivative **15**, m.p. 114–115°, $[\alpha]_D$ +48° (*c* 1, chloroform).



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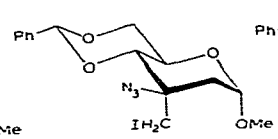

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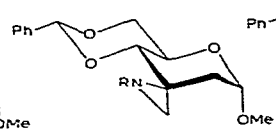
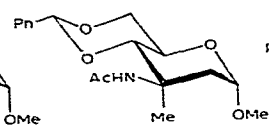


14 R = H
15 R = Ac



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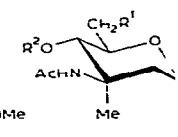

17 R^1 = Br, R^2
18 R^1 = R^2 =
19 R^1 = H, R^2

The configuration at the branch-point in **15** was established by single-crystal X-ray analysis[14]. High-pressure hydrogenolysis of **14** in methanol over Raney nickel at ambient temperature, followed by *N*-acetylation of the resulting amine, gave methyl 3-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-α-D-*arabino*-hexopyranoside (**16**, 40%), $[\alpha]_D$ +28° (*c* 1, chloroform). Cleavage of the 4,6-*O*-benzylidene ring of **16** with *N*-bromosuccinimide in refluxing carbon tetrachloride[15] furnished the 6-bromo 4-benzoate **17** (86%), $[\alpha]_D$ +78° (*c* 1, chloroform), which was transformed, with concomitant debenzoylation, into methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-D-*arabino*-hexopyranoside (**18**), $[\alpha]_D$ +96 ±3° (*c* 1, chloroform), on high-pressure hydrogenation in methanol over Raney nickel. The ^{1}H-n.m.r. spectrum of **18** was indistinguishable from that of its L enantiomer **5**. Methylation (as before) of **18** gave methyl 3-acetamido-2,3,6-trideoxy-3-*C*,4-*O*-dimethyl-α-D-*arabino*-

*Prepared essentially as described[13] for the L enantiomer.

**Methylenecyclohexane, for example, adds iodine azide regioselectively, to yield 1-azido-1-iodomethylcyclohexane[12].

hexopyranoside (**19**), m.p. 136–138°, $[\alpha]_D$ +72° (*c* 1, chloroform), which, as noted earlier, has been converted into D-evernitrose (D-**1**) by Yoshimura *et al.*[7].

New compounds had spectroscopic properties in agreement with the structures assigned and, when crystalline, gave satisfactory elemental analyses.

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