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Note

The synthesis of some derivatives of L-vancosamine (3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose)*

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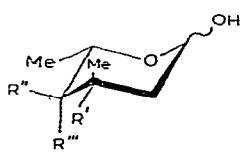
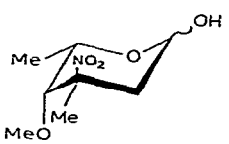
The presence of L-evernitrose[2] (**1**) in the everninomicins[3], of L-vancosamine[4,5] (**2**) in vancomycin[6], of *N*,*N*-dimethyl-L-vancosamine in kidamycin[7], pluramycin A[8], and hedamycin[9], and of L-rubranitrose[10] (**3**) in rubradirin[11] has fostered a lively interest in the synthesis of sugars containing a Me–C–N branch. Besides the cyclisation of sugar "dialdehydes" with nitroethane[12,13], such procedures as the addition of hydrogen cyanide to hexosulose derivatives[14] and of either mercury(II) azide[15] or iodine azide[16] to *C*-methylene sugars have been used in the synthesis of methyl-branched nitro and amino sugars, including derivatives of D-[16,17] and L-evernitrose[18,19] and L-vancosamine[20].



1 R' = NO_2, R" = OMe, R''' = H
2 R' = NH_2, R" = H, R''' = OH



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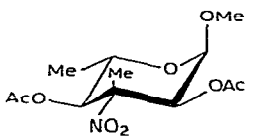

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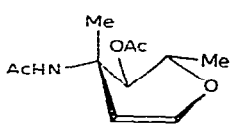

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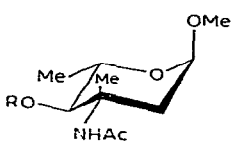
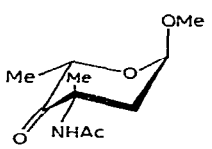


6 R = Ac
7 R = H



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*Branched-chain Sugars, Part XIII. For Part XII, see ref. 1.
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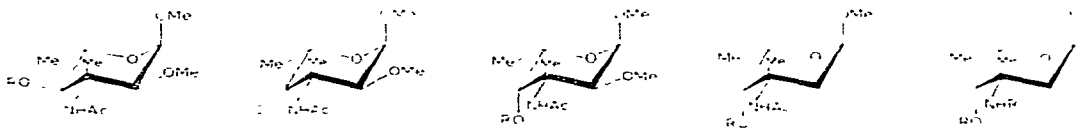
We have shown[13] that the methyl-branched nitro sugar **4*** can be transformed in a straightforward manner into the glycal **5**, which yields principally the α-glycoside **6** on the addition of methanol[18]. Oxidation of the corresponding alcohol **7** with ruthenium tetraoxide furnished **8**, which reverted to the equatorial alcohol **7** on reduction with sodium borohydride. Our rationale[18] for stereospecific, axial attack in this case led us to believe that a reducing agent much bulkier than sodium borohydride would be inclined to approach the carbonyl group of **8** from the equatorial direction, thereby yielding the axial alcohol **14**, namely methyl *N*-acetyl-α-L-vancosaminide**. Reports[22] that lithium tri-*sec*-butylborohydride (L-Selectride), among others, reduces alkyl-substituted cyclohexanones to give the axial alcohol stereoselectively were encouraging in this regard.

Initially, we examined the reduction of the more accessible hexosidulose **11**, which was obtained on oxidation of[18] **9** with ruthenium tetraoxide. Whereas reduction of **11** with sodium borohydride in methanol returned the equatorial alcohol **9**, reduction with L-Selectride in anhydrous tetrahydrofuran at −10° gave a mixture containing more of the axial alcohol **12** than **9**. The alcohols **12** and **9** were eventually isolated in the ratio of ~3:1 by preparative chromatography. The identity of **12** was confirmed by its conversion into the acetylated derivative **13** {m.p. 171–173°, $[\alpha]_D$ −178° (*c* 0.85, chloroform)}, whose physical properties and p.m.r. spectrum readily distinguished it from the epimeric acetate **10** {m.p. 147–149°, $[\alpha]_D$ −109° (*c* 0.7, chloroform)}. Significantly, H-4 was observed as a singlet at δ 5.63 in the p.m.r. spectrum of **13**, whereas it appeared as a doublet ($J_{4,5}$ 10 Hz) at δ 5.66 in the p.m.r. spectrum of **10**.



9 R = H
10 R = Ac

11

12 R = H
13 R = Ac

14 R = H
15 R = Ac

16 R = H
17 R = Ac

Although the oxidation of **7**→**8** was accomplished[18] previously in 45% yield using ruthenium tetraoxide, use of this reagent gave somewhat erratic and, invariably, low yields during the present work. Consistently good yields (≥66%) of **8** were obtained when **7** was oxidised with pyridinium chlorochromate[23] in dichloromethane in the presence of 3 Å molecular sieves[24] as a catalyst†. Reduction of **8** with L-Selectride in anhydrous tetrahydrofuran at −15° gave a mixture of **7** and **14** containing mainly the axial alcohol **14** (p.m.r. evidence). Preparative chromatography on silica

*This compound readily crystallises following acetylation of the products obtained on cyclisation of periodate-treated methyl α-L-rhamnopyranoside with nitroethane[13,21].

P.m.r.[4,5], chiroptical[5], and recent X-ray[6] studies have established that vancosamine is 3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose (2**).

†Oxidation of **7** was extremely slow in the absence of molecular sieves, requiring up to 96 h for completion.

gel gave **7** and **14** in isolated yields of 12 and 80%, respectively. Methyl *N*-acetyl-α-L-vancosaminide (**14**) was further characterised as the acetylated derivative **15**, whose p.m.r. spectrum, like those of related L-vancosaminide derivatives[5], revealed the signal for H-4 as a singlet, indicative of the equatorial–axial arrangement of H-4 and H-5. Alkaline hydrolysis of **14** provided the amino sugar **16**, benzoylation of which gave methyl *N*-benzoyl-*O*-benzoyl-α-L-vancosaminide (**17**). The physical properties and p.m.r. spectrum of synthetic **17** were in agreement with those reported[5] for methyl *N*-benzoyl-*O*-benzoyl-α-L-vancosaminide derived from vancomycin.

The foregoing route to L-vancosamine derivatives provides an alternative to the cyanohydrin-based route recently reported by That Thang *et al.*[20], and it has the added attraction that **7** can easily be diverted[18] to L-evernitrose (**1**). Finally, we note that *N*-dimethylation of **16** would provide access to *N*,*N*-dimethyl-L-vancosamine, which, as mentioned earlier, is a component of certain anticancer antibiotics.

EXPERIMENTAL

General methods. — Unless otherwise stated, the general experimental conditions were the same as those described previously[18]. Lithium tri-*sec*-butylborohydride (L-Selectride) was available as an ~M solution in anhydrous tetrahydrofuran from Aldrich Chemical Company, Inc.

Methyl 3-acetamido-4-O-acetyl-3,6-dideoxy-3-C-methyl-2-O-methyl-α-L-glucopyranoside (**10**). — A solution of **9**[18] (0.17 g) in anhydrous pyridine (3.5 ml) was treated with acetic anhydride (2.3 ml) for 24 h at room temperature, whereafter work-up in the usual way gave **10** (0.15 g, 76%), m.p. 147–149° [from ether–light petroleum (b.p. 40–60°)], $[\alpha]_D$ −109° (*c* 0.7, chloroform); ν_{max} 3320 (NH), 1720 (C=O), and 1675 and 1550 cm^{-1} (NHAc) (Found: C, 54.3; H, 8.2; N, 4.4. $C_{13}H_{23}NO_6$ calc.: C, 54.0; H, 8.0; N, 4.8%). P.m.r. data: δ 5.66 (d, 1 H, $J_{4,5}$ 10 Hz, H-4), 5.21 (broad s, 1 H, NH), 4.84 and 4.72 (2 d, 2 H, $J_{1,2}$ ~4 Hz, H-1,2), 3.76 (m, 1 H, H-5), 3.45 and 3.39 (2 s, 6 H, 2 OMe), 2.07 (s, 3 H, OAc), 1.89 (s, 3 H, NAc), 1.31 (s, 3 H, Me-3), and 1.14 (d, 3 H, $J_{5,6}$ 6 Hz, Me-5).

Methyl 3-acetamido-3,6-dideoxy-3-C-methyl-2-O-methyl-α-L-xylo-hexopyranosid-4-ulose (**11**). — Ruthenium dioxide dihydrate (1.1 g) was stirred briskly with a solution of sodium metaperiodate (1.9 g) in water (15 ml) until it was completely oxidised. Ruthenium tetraoxide was extracted from the aqueous solution with Analar carbon tetrachloride (2 × 30 ml), and the combined extracts were added to a stirred solution of[18] **9** (0.5 g) in carbon tetrachloride (25 ml); after 4 h, t.l.c. (light petroleum–acetone, 1:1) showed that no **9** remained. Propan-2-ol (2 ml) was added to reduce the excess of the oxidant, and the mixture was stirred for 30 min before solids were filtered off and washed thoroughly with dichloromethane. Concentration of the filtrate and washings gave **11** (0.35 g, 71%), m.p. 163–164° (from ether), $[\alpha]_D$ −67° (*c* 0.9, chloroform); ν_{max} 3270 (NH), 1730 (C=O), and 1635 and 1540 cm^{-1} (NHAc) (Found: C, 53.6; H, 7.5; N, 5.7. $C_{11}H_{19}NO_5$ calc.: C, 53.9; H, 7.8; N, 5.7%). P.m.r. data: δ 5.03 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.20 (d, overlying q, 2 H, H-2,5),

3.49 (s, 6 H, 2 OMe), 1.98 (s, 3 H, NAc), and 1.42 (d overlying s, 6 H, $J_{5,6}$ ~6 Hz, Me-3,5).

Methyl 3-acetamido-3,6-dideoxy-3-C-methyl-2-O-methyl-α-L-galactopyranoside (**12**). — A 100-ml, three-necked flask equipped with a dropping funnel, a stirring bar, and a gas-inlet tube was flushed with nitrogen and charged with anhydrous tetrahydrofuran (10 ml) containing L-Selectride (4 mmol, 4 ml). The contents of the flask were cooled to −10° before **11** (0.49 g, 2 mmol) in anhydrous tetrahydrofuran (15 ml) was added dropwise to the stirred solution so that the temperature was maintained at ~−10°. Stirring was then continued at −10° for 1 h, whereafter aqueous 3M sodium hydroxide (1 ml) and 30% hydrogen peroxide (5 ml) were added. After the solution had attained room temperature, it was saturated with potassium carbonate and diluted with chloroform, and the chloroform layer was decanted and dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on silica gel (elution with light petroleum–acetone, 10:8) furnished, first, **9** (79 mg, 16%), which was identical (m.p., $[\alpha]_D$, and i.r. and p.m.r. spectra) with an authentic sample; and then **12** (222 mg, 45%), $[\alpha]_D$ −121° (*c* 1.2, chloroform); ν_{max} 3400 and 3280 (OH and NH), and 1645 and 1530 cm^{-1} (NHAc). P.m.r. data: δ 6.00 (broad s, 1 H, NH), 4.92 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.31–3.89 (m, 2 H, H-4,5), 3.67 (d, 1 H, H-2), 3.44 and 3.41 (2 s, 6 H, 2 OMe), 1.99 (s, 3 H, NAc), 1.47 (s, 3 H, Me-3), and 1.27 (d, 3 H, $J_{5,6}$ 6.4 Hz, Me-5).

Reduction of **11** with sodium borohydride in methanol (as previously described[18] for **8**) afforded the equatorial alcohol **9** (67%), m.p. 184–186° (from ether–light petroleum), $[\alpha]_D$ −86° (*c* 0.8, chloroform), which was indistinguishable from an authentic sample.

Methyl 3-acetamido-4-O-acetyl-3,6-dideoxy-3-C-methyl-2-O-methyl-α-L-galactopyranoside (**13**). — Acetylation of **12** with acetic anhydride in pyridine, in the usual way, gave **13** (71%), m.p. 171–173° (from ether–light petroleum), $[\alpha]_D$ −178° (*c* 0.85, chloroform) (Found: C, 53.7; H, 8.1; N, 4.85. $C_{13}H_{23}NO_6$ calc.: C, 54.0; H, 8.0; N, 4.8%). P.m.r. data: δ 5.63 (s, 1 H, H-4), 5.58 (broad s, 1 H, NH), 4.97 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-1), 4.18 (q, 1 H, H-5), 3.74 (d, 1 H, H-2), 3.47 and 3.43 (2 s, 6 H, 2 OMe), 2.11 (s, 3 H, OAc), 1.91 (s, 3 H, NAc), 1.63 (s, 3 H, Me-3), and 1.12 (d, 3 H, $J_{5,6}$ 6.5 Hz, Me-5).

Methyl 3-acetamido-2,3,6-trideoxy-3-C-methyl-α-L-threo-hexopyranosid-4-ulose (**8**). — A solution of[18] **7** (0.64 g) in anhydrous dichloromethane (4 ml) was added to a stirred suspension of pyridinium chlorochromate (1.9 g) and 3 Å molecular sieves[24] (1.5 g) in anhydrous dichloromethane (15 ml) at room temperature, whereafter stirring was continued for 3 h; t.l.c. (dichloromethane–acetone, 1:2) then revealed that no **7** remained. The mixture was diluted with ether, and the ethereal solution was decanted from the spent oxidant and concentrated. The resulting syrup was extracted with ether and the ethereal solution was filtered and concentrated; this process was repeated until no more inorganic material precipitated upon the addition of ether. Finally, concentration of the dried ($MgSO_4$) extract gave **8** (0.42 g, 66%), $[\alpha]_D$

−143° (*c* 0.6, chloroform), whose i.r. and p.m.r. spectra were indistinguishable from those of an authentic sample {lit.[18] $[\alpha]_D$ −137° (*c* 0.8, chloroform)}.

*Methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-*L*-lyxo-hexopyranoside* (**14**). — Reduction of **8** (0.61 g, 2.8 mmol) with L-Selectride (7.6 mmol) in anhydrous tetrahydrofuran (total volume, 39 ml) at −15°, essentially as described for **11**, gave, after chromatography (elution with 1:2 dichloromethane–acetone), **7** (75 mg, 12%), which was identified by its p.m.r. spectrum; and methyl *N*-acetyl-α-L-vancosaminide (**14**; 0.49 g, 80%). m.p. 131–132.5° (from ether–chloroform–light petroleum), $[\alpha]_D$ −117° (*c* 0.65, chloroform); ν_{max} 3325 and 3260 (OH and NH), and 1640 and 1540 cm^{-1} (NHAc) (Found: C, 55.5; H, 8.5; N, 6.5. $C_{10}H_{19}NO_4$ calc.: C, 55.3; H, 8.8; N, 6.4%). P.m.r. data: δ 4.71 (d, 1 H, $J_{1,2a}$ 4 Hz, H-1), 4.10 (q, 1 H, H-5), 3.30 (s, 3 H, OMe), 2.29 (d, 1 H, J_{gem} 14 Hz, H-2*e*), 1.93 (s, 3 H, NAc), 1.89 (q, 1 H, H-2*a*), 1.63 (s, 3 H, Me-3), and 1.24 (d, 3 H, $J_{5,6}$ 6 Hz, Me-5).

*Methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-α-*L*-lyxo-hexopyranoside* (**15**). — Acetylation of **14** with acetic anhydride in pyridine, in the usual way, gave methyl *N*-acetyl-*O*-acetyl-α-L-vancosaminide (**15**, 79%), m.p. 166–167.5° (from chloroform–light petroleum), $[\alpha]_D$ −121° (*c* 1, chloroform); ν_{max} 3295 (NH), 1730 (C=O), and 1650 and 1545 cm^{-1} (NHAc) (Found: C, 55.8; H, 8.5; N, 5.5. $C_{12}H_{21}NO_5$ calc.: C, 55.6; H, 8.2; N, 5.4%). P.m.r. data: δ 4.98 (s, 1 H, H-4), 4.78 (d, 1 H, $J_{1,2a}$ 4 Hz, H-1), 4.14 (q, 1 H, H-5), 3.33 (s, 3 H, OMe), 2.33 (d, 1 H, J_{gem} 14 Hz, H-2*e*), 2.18 (s, 3 H, OAc), 2.01 (q, 1 H, H-2*a*), 1.87 (s, 3 H, NAc), 1.73 (s, 3 H, Me-3), and 1.16 (d, 3 H, $J_{5,6}$ 6 Hz, Me-5).

*Methyl 3-benzamido-4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-α-*L*-lyxo-hexopyranoside* (**17**). — A solution of **14** (0.48 g) in water (20 ml) containing barium hydroxide octahydrate (2.3 g) was heated and stirred under reflux for 24 h, after which time it was diluted with water (150 ml), neutralised (carbon dioxide), and filtered. The filtrate was stirred briefly with Amberlite IRA-400 (HO^-) resin (15 ml), filtered, and concentrated. The residue was extracted with chloroform, and the extract was dried (Na_2SO_4) and concentrated to give **16** (0.24 g, 62%) as a clear syrup.

Conventional benzoylation of **16** with benzoyl chloride in pyridine gave, after work-up and chromatography on silica gel (elution with 1:2 dichloromethane–acetone), methyl *N*-benzoyl-*O*-benzoyl-α-L-vancosaminide (**17**, 79%), m.p. 168.5–169.5° (from ether–light petroleum), $[\alpha]_D$ −183° (*c* 0.3, methanol) (Found: C, 68.6; H, 6.2; N, 3.8. $C_{22}H_{25}NO_5$ calc.: C, 68.9; H, 6.5; N, 3.65%). The p.m.r. spectrum of the synthetic material was indistinguishable from that reported[5] for methyl *N*-benzoyl-*O*-benzoyl-α-L-vancosaminide {m.p. 168–169°, $[\alpha]_D$ −191° (*c* 0.1, methanol)} derived from vancomycin.

ACKNOWLEDGMENTS

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