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Preliminary communication

A stereochemically defined route to branched-chain amino sugars, *via* spiro-oxiranes, and related studies

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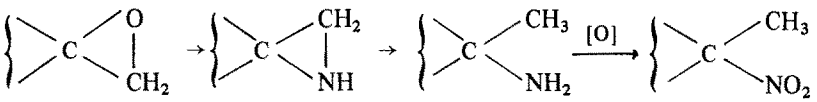
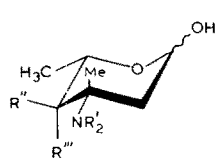
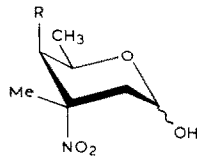
Despite recent success in the synthesis of the antibiotic sugars L-evernitrose[1] (**1**), L-vancosamine[2] (**2**), D-rubranitrose[3]** (**3**), D-kijanose[4] (or D-tetronitrose) (**4**), and 3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*xylo*-hexose[5] (**5**) and their derivatives, there is still a need for efficient methods for the introduction of CH_3-C-NR_2 (R = O or H) branching into sugars in a stereo-controlled manner, particularly in those instances where the C–N bond is axial. Difficulties encountered in our recent synthesis[5] of derivatives of **5**, *via* the cyanohydrin route[6], prompted a search for alternative routes to sugars related to **3** and **4**. Since spiro-oxiranes are readily prepared[7] and the stereochemistry of their ring-opening reactions is firmly established[7–9], the route given below in broad outline warranted investigation. The first and crucial stage involves the conversion of a spiro-oxirane into a spiro-aziridine, with inversion of the configuration at the tertiary centre. We describe an example



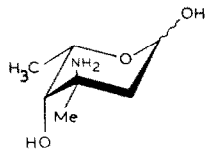
of this approach, which, doubtless, could be extended to other cases.



1 R' = O, R'' = OMe, R''' = H
2 R' = R'' = H, R''' = OH



3 R = OMe
4 R = $NHCO_2Me$



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Methyl 3,3[1]-anhydro-4,6-*O*-benzylidene-2-deoxy-3-*C*-hydroxymethyl-α-D-*arabino*-hexopyranoside[9] (**6**) reacted with sodium azide in *N*,*N*-dimethylformamide at 100° to give

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**The L enantiomer has been prepared[3].

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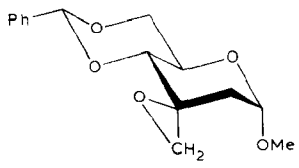
methyl 3-*C*-azidomethyl-4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside (**7**, 61%), m.p. 129–130°, $[\alpha]_D$ +108° (*c* 1, chloroform), which afforded the 3-mesylate **8** (76%), $[\alpha]_D$ +32° (*c* 1, chloroform), accompanied by methyl 3-*C*-azidomethylene-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**9**, 16%), m.p. 122–123°, $[\alpha]_D$ +154° (*c* 1, chloroform), on treatment with methanesulphonyl chloride in pyridine at ~4°. Hydrogenation of a methanolic solution of **8** over Adams' catalyst with a slight overpressure of hydrogen at room temperature (taking care to avoid hydrogenation of the aromatic ring), followed by *N*-acetylation of the products and chromatography, gave methyl 3-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**13**), m.p. 124–125°, $[\alpha]_D$ +107° (*c* 1, chloroform) {lit.[10] (oil), $[\alpha]_D$ +104° (chloroform)}, in 54% overall yield. The reaction sequence **8** → **10** → **11** → **12** → **13** is clearly implicated in this one-pot conversion, with the catalyst participating in the first and penultimate steps. Literature precedents were then followed in effecting the transformations **13** → **14** → **15** → methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**16**), m.p. 138–139°, $[\alpha]_D$ +31° (*c* 1, chloroform) {lit.[10] m.p. 134–135°, $[\alpha]_D$ +41° (chloroform)}, and **16** → methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-D-*erythro*-hexopyranosid-4-ulose (**17**) → methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-D-*xylo*-hexopyranoside (**18**), m.p. 149–150°, $[\alpha]_D$ +85° (*c* 0.5, chloroform) {lit.[5] (L enantiomer) m.p. 151–153°, $[\alpha]_D$ −85° (*c* 1, chloroform)}. Methylation[11] of **18** gave methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-D-*xylo*-hexopyranoside (**19**, 81%), m.p. 84–85°, $[\alpha]_D$ +129° (*c* 0.7, chloroform), which can be derived formally from D-rubranitrose[12] (**3**).

Our projected routes (*vide infra*) to D-rubranitrose (**3**) and D-kijanose (**4**) required the protection of an amino group at the branch-point by a substituent that could be



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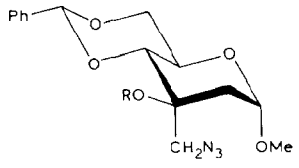
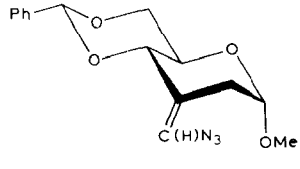


7 R = H
8 R = Ms



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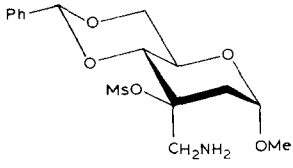

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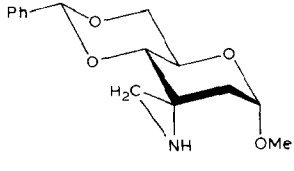

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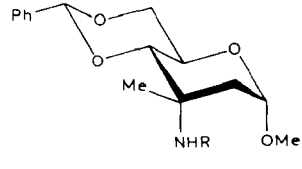
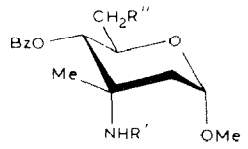
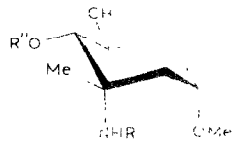


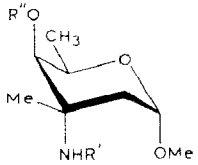
12 R = H
13 R = Ac
20 R = $COCF_3$



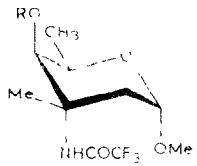
14 R′ = Ac, R″ = Br
21 R′ = $COCF_3$, R″ = Br
22 R′ = $COCF_3$, R″ = I



15 R = Ac, R = H
16 R = Ac R = H
23 R = COC R″ = Br
24 R′ = $COCF_3$ R = H



18 R′ = Ac, R″ = H
19 R = Ac R″ = Me
26 R′ = $COCF_3$, R″ = H



27 R = Me
28 R = Ms

29

removed efficiently under mild, basic conditions. Difficulties have been experienced in previous attempts[1] to remove *N*-acetyl substituents from branched-chain amino sugars. With this in mind, methyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**12**) was transformed into the *N*-trifluoroacetyl derivative **20** (52% from **8**), m.p. 122–123°, $[\alpha]_D$ +76° (*c* 0.6, chloroform). Treatment of **20** with *N*-bromosuccinimide in refluxing carbon tetrachloride for 4 h gave methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-*ribo*-hexopyranoside (**21**, 75%), m.p. 120–121°, $[\alpha]_D$ −16° (*c* 0.4, chloroform), which was converted in a straightforward manner into the corresponding iodide **22** (85%), m.p. 105–106°, $[\alpha]_D$ −34° (*c* 1, chloroform). Catalytic hydrogenolysis of a methanolic solution of **22** containing triethylamine over 5% Pd/C at room temperature gave methyl 4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-*ribo*-hexopyranoside (**23**, 89%), m.p. 120–121°, $[\alpha]_D$ +2° (*c* 1, chloroform), which yielded the debenzoylated compound **24** (78%), m.p. 79–80°, $[\alpha]_D$ +36° (*c* 1, chloroform), on stirring with an excess of sodamide in 1,2-dimethoxyethane at room temperature for 30 h. Oxidation of **24** to methyl 2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-*erythro*-hexopyranosid-4-ulose (**25**, 93%), $[\alpha]_D$ +181° (*c* 1, chloroform), was accomplished with pyridinium chlorochromate[13] in dichloromethane in the presence of 3 Å molecular sieves[14]. Preliminary experiments indicated that reduction of **25** with L-Selectride[15], although extremely sluggish, afforded the key intermediate methyl 2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-*xylo*-hexopyranoside (**26**).

Our original plan calls for the conversion of **26** into D-rubranitrose[12] (**3**), *via* the methylated derivative **27**, and into D-kijanose[16] (D-tetronitrose[4,17]) (**4**), *via* the aziridine **29**

prepared by base treatment of the mesylate **28**, and details of this and related work will be reported elsewhere. Compound **29**, prepared by a different route, was a key intermediate in a recent synthesis of methyl α-D-kijanoside (tetronitroside) reported by Yoshii and co-workers[4].

New compounds had elemental analyses and/or spectroscopic properties in agreement with the structures assigned.

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