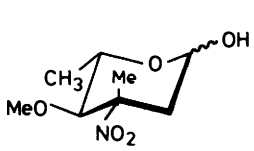
Branched-chain Sugars. Part 17.[1] A Synthesis of L-Rubranitrose (2,3,6-Trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-L-*xylo*-hexopyranose)[2]

John S. Brimacombe* and Khandker M. M. Rahman
Chemistry Department, The University, Dundee DD1 4HN

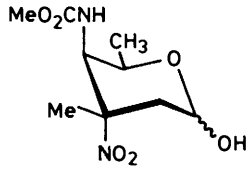
L-Rubranitrose (2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-L-*xylo*-hexopyranose) (**4**) has been elaborated from methyl 3-acetamido-2,3,6-trideoxy-3-C-methyl-α-L-*xylo*-hexopyranoside (**27**). *N*-Deacetylation of the corresponding 4-*O*-methyl derivative (**26**), with calcium in liquid ammonia, afforded the amino sugar (**25**), which was then oxidised to methyl 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-α-L-*xylo*-hexopyranoside (**28**). Acidic hydrolysis of the latter compound gave L-rubranitrose (**4**), which proved to be enantiomeric with the novel methyl-branched nitro sugar found in the antibiotic rubradirin.

In another approach to L-rubranitrose (**4**), methyl 2,6-dideoxy-4-*O*-methyl-α-L-*threo*-hexopyranosid-3-ulose (**11**) was shown to react with cyanide ion under equilibrating conditions to give methyl 3-*C*-cyano-2,6-dideoxy-4-*O*-methyl-α-L-*xylo*-hexopyranoside (**12**), whereas the corresponding L-*lyxo* cyanohydrin (**22**) is the kinetically favoured product.

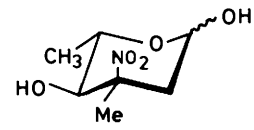
Rubranitrose,[3] a constituent of rubradirin,[4,5] is a member of a novel group of methyl-branched nitro sugars found as antibiotic components. Other members of this group are L-evernitrose[6] (**1**) (from the everninomicins[7]), D-kijanose[8] (or D-tetronitrose[9]) (**2**) (from kijanimicin[8] and tetrocarcins A and B[10]), and L-decilonitrose[11] (**3**) (from arugomycin[12] and decilorubicin[13]). At the inception of this work, rubranitrose had been identified[3,5] as 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-L-*xylo*-hexopyranose (**4**), but later it was pointed out,[8] chiefly from a comparison of c.d. and rotational data, that rubranitrose and D-kijanose (**2**) should possess the same relative and absolute configurations. Since the relative stereochemistry of rubranitrose was firmly established[3,5] by a crystal-structure determination on its β-acetate, only its absolute configuration was disputed. Although persuaded by the arguments[8] assigning rubranitrose to the D-series, we decided to persevere with a synthesis of L-rubranitrose (**4**) in hand, knowing that it would settle the question of the absolute configuration of the antibiotic sugar.



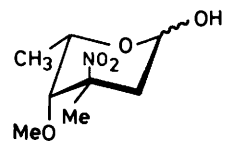
(1)



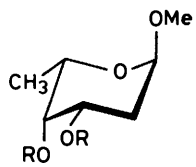
(2)



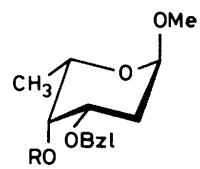
(3)



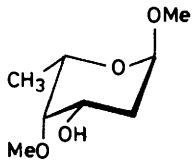
(4)



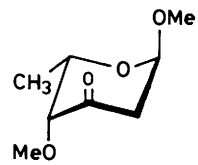
(5) R = H
(6) R,R = $SnBu_2$



(7) R = H
(8) R = Ac
(9) R = Me



(10)



(11)

Bzl = benzyl

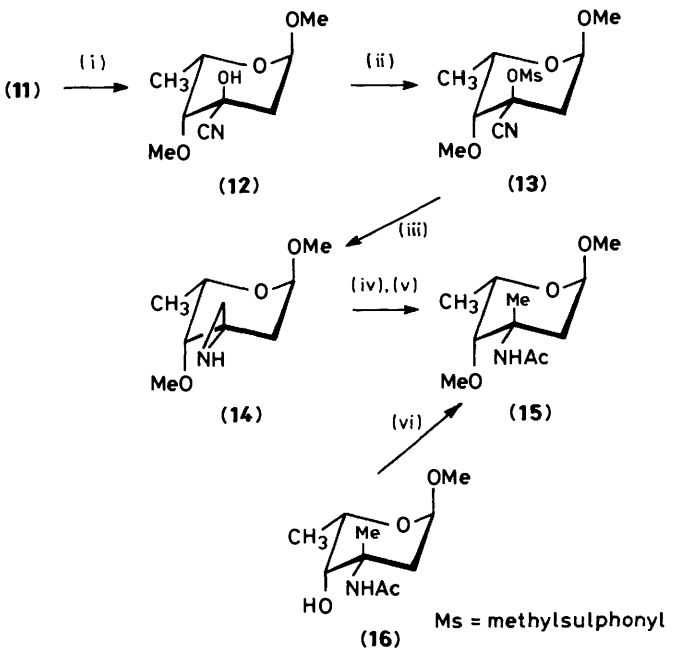
Results and Discussion

Our first approach was founded on the cyano mesylate (**23**) (Scheme 2), which we planned to convert into methyl 3-amino-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*xylo*-hexopyranoside (**25**), and thence into L-rubranitrose (**4**), by well precedented steps.[14,15] This approach was appealing in the light of contemporary work which had not only indicated a route to the keto sugar (**11**), but had also provided the means of distinguishing between the cyanohydrins (**12**) and (**22**) at a crucial stage of the synthesis.

The keto sugar (**11**) was synthesised uneventfully in the following way. Methyl 2,6-dideoxy-α-L-*lyxo*-hexopyranoside[16] (**5**) was converted into its 3,4-*O*-dibutylstannylene derivative (**6**), which then reacted regioselectively with benzyl bromide in boiling benzene in the presence of tetrabutylammonium iodide[17] to give methyl 3-*O*-benzyl-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (**7**) in 48% yield, after removal of the organotin by-products by chromatography. For the purpose of characterisation, compound (**7**) was converted into the crystalline 4-acetate (**8**), whose ^{1}H n.m.r. spectrum revealed 4-H as a doublet ($J_{3,4} \approx 3$,$J_{4,5} \approx 0$ Hz) at δ_H 5.34, in accord with the structure assigned. Methylation of compound (**7**) furnished the product (**9**), hydrogenolysis of which gave methyl 2,6-dideoxy-4-*O*-methyl-α-L-*lyxo*-hexopyranoside (**10**). Oxidation of compound (**10**) with pyridinium chlorochromate[18] in the presence of 3 Å molecular sieves[19] produced the keto sugar (**11**), whose ^{1}H n.m.r. spectrum (see Experimental section) signified that no

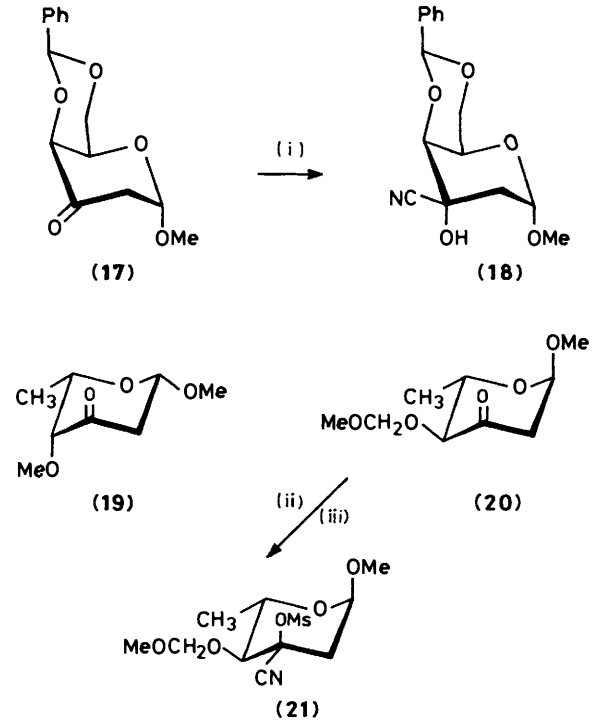
epimerisation of the axial 4-*O*-methyl group had taken place during its preparation.

In order to progress along the synthetic route, the keto sugar (**11**) must be converted into the L-*lyxo* cyano mesylate (**23**), so that the nitro group subsequently introduced at the branch-point has the required axial orientation. Since there was no way of predicting the stereochemical outcome of the reaction between compound (**11**) and cyanide ion, they were allowed to react first under equilibrating conditions.[14] This gave a crystalline cyanohydrin, which was identified as the L-*xylo* isomer (**12**) by its conversion into methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-α-L-*lyxo*-hexopyranoside (**15**) by the well precedented reactions[14] outlined in Scheme 1. An authentic sample of the acetamide (**15**) was obtained by careful methylation of methyl *N*-acetyl-α-L-vancosaminide[20] (**16**). In parallel studies, That Thang and co-workers[21] demonstrated that the keto sugar (**17**) behaves in exactly the same way, yielding the D-*xylo* cyanohydrin (**18**) as the thermodynamically favoured product. It is noteworthy that the thermodynamically favoured cyanohydrins obtained from the 4-epimers of both keto sugars (**11**) and (**17**) have the cyano group axially disposed,[14,22] so that the configuration at C-4 has a pronounced effect on the stability of the products.



Scheme 1. *Reagents*: (i) KCN–$NaHCO_3$–CH_2Cl_2–water; (ii) MsCl–C_5H_5N; (iii) $LiAlH_4$–Et_2O; (iv) Ni–H_2–MeOH; (v) Ac_2O–C_5H_5N; (vi) MeI–NaH–DMF

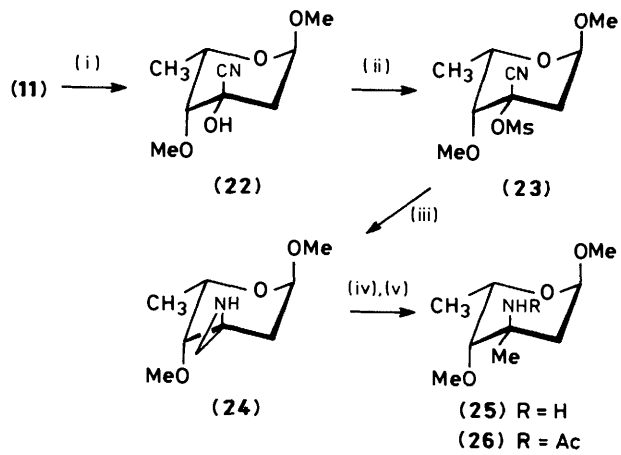
The reaction between the keto sugar (**11**) and hydrogen cyanide in pyridine was expected[21] to favour the formation of the kinetic cyanohydrin (**22**), but, after mesylation *in situ*, we were unable to isolate any of the cyano mesylate (**23**). The keto sugar (**20**) was readily transformed[23] into the cyano mesylate (**21**) under identical experimental conditions, and other workers have been equally successful in preparing cyano mesylates from precursors (**17**)[21] and (**19**)[24] *via* the kinetically favoured cyanohydrins. The problem was traced to a sluggish reaction between hydrogen cyanide and the keto sugar (**11**) in pyridine, which yielded the cyanohydrin (**22**) in only 13% yield when conducted for 67 h at room temperature with a moderate excess of the reagent. Workable quantities of the cyanohydrin (**22**)



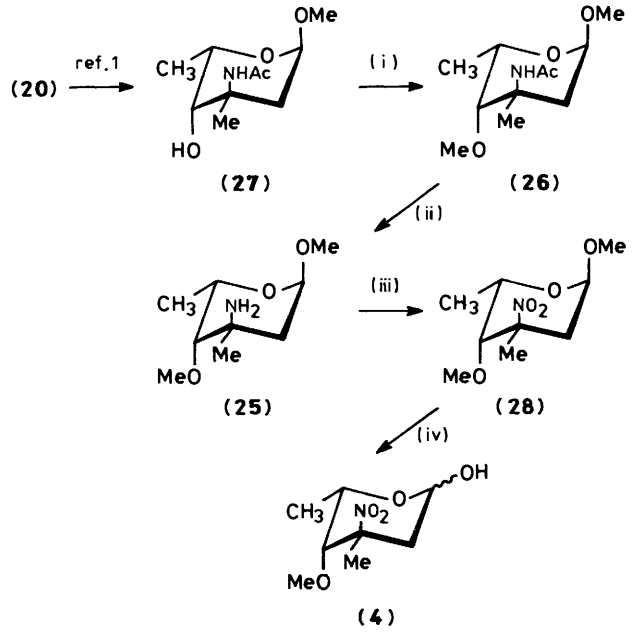
Reagents: (i) KCN–$NaHCO_3$–CH_2Cl_2–water; (ii) HCN–C_5H_5N; (iii) MsCl–C_5H_5N

were accumulated either by recycling of the recovered keto sugar or, more speedily, by quenching the equilibrating system at an early stage when the cyanohydrin (**22**) was present. Mesylation of the cyanohydrin (**22**) gave the crystalline cyano mesylate (**23**), but the remaining steps (Scheme 2) leading to the key intermediate (**25**) did not proceed cleanly, as judged from the isolation of the acetamido derivative (**26**) in only 7% yield after acetylation of the reaction products. From contiguous studies by Yoshimura *et al.*,[24] it emerged that the reactions summarised in Scheme 2 work much better with the corresponding β-anomers, enabling them to complete a synthesis of L-rubranitrose (**4**).

By this time, we had completed a synthesis of methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-L-*xylo*-hexopyranoside[1] (**27**), a derivative of the branched-chain amino sugar[25] from antibiotic A 35512B[26] and having the same



Scheme 2. *Reagents:* (i) see text; (ii)–(v) as in Scheme 1



Scheme 3. *Reagents:* (i) MeI–NaH–DMF; (ii) Ca–liq.NH_3; (iii) *m*-$ClC_6H_4CO_3H$–CH_2Cl_2; (iv) H_3O^+

configuration as L-rubranitrose (**4**), from the keto sugar (**20**). Although the synthesis of compound (**27**) was not without difficulties, they were surmounted to a greater or lesser degree, whereas the route (Scheme 2) leading to its *O*-methyl analogue (**26**), which we hoped would bypass these difficulties, had virtually petered out. Since our main concern was to establish the absolute configuration of rubranitrose, it was decided to effect the relatively minor changes (Scheme 3) to compound (**27**) that would transform it into L-rubranitrose (**4**). Careful methylation of compound (**27**) gave the methyl ether (**26**), which was identical with the compound obtained by the alternative route. Whereas standard methodologies, including hydrolysis with strong bases, were ineffective in cleaving the *N*-acetyl group from the product (**26**), smooth *N*-deacetylation was brought about by calcium in liquid ammonia[27] to give the methyl-branched amino sugar (**25**) in 83% yield. Although this procedure has not previously been used to remove *N*-acetyl groups from carbohydrate derivatives, we have adopted it as the method of choice in other cases (the following paper provides another example) and recommend its use.

Oxidation of the amine (**25**) with *m*-chloroperbenzoic acid in boiling methylene dichloride furnished methyl 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-α-L-*xylo*-hexopyranoside (**28**), which, on mild acidic hydrolysis, liberated L-rubranitrose (**4**), m.p. 152—154 °C; $[\alpha]_D$ −114.5° (7 min) → −83° (final; *c* 0.4 in EtOH). Since the naturally occurring sugar[3,5] has m.p. 150—153 °C; $[\alpha]_D$ +127° → +86° (final; *c* 0.285 in EtOH), it must be assigned to the D-series and the structure of rubradirin[5] amended accordingly. This conclusion was also reached by Yoshimura *et al.*[24] through another synthesis of L-rubranitrose (**4**) referred to earlier.

Experimental

T.l.c. was performed on Kieselgel G, and spots were detected with 1% aqueous sulphuric acid. I.r. spectra were recorded for films or Nujol mulls with a Perkin-Elmer Infracord spectrophotometer. ^1H N.m.r. spectra were recorded for solutions in deuteriochloroform (internal tetramethylsilane) with a Bruker Spectrospin (90 MHz) spectrometer. A Perkin-Elmer Model 141 polarimeter and 1 dm tubes were used for the measurement of specific optical rotations. M.p.s are uncorrected. Light petroleum refers to the fraction boiling in the range 80—100 °C.

Methyl 3-O-*Benzyl*-2,6-*dideoxy*-α-L-lyxo-*hexopyranoside* (**7**).—A solution of methyl 2,6-dideoxy-α-L-*lyxo*-hexopyranoside[16] (**5**) (6.68 g, 41 mmol) in benzene (1 l) containing dibutyltin oxide (11.2 g, 45 mmol) was heated under reflux for 18 h with azeotropic removal of water by means of a Dean–Stark head. The solution, containing the 3,4-*O*-dibutylstannylene derivative (**6**), was then concentrated to *ca.* 750 ml. Tetrabutylammonium iodide (15.26 g, 41 mmol) and benzyl bromide (10.3 ml, 87 mmol) were added, and the solution was boiled under reflux for 6 h and then concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (10:1) as eluant] gave the benzyl derivative (**7**) (4.95 g, 48%), $[\alpha]_D$ −127° (*c* 1 in $CHCl_3$); δ_H 7.35 (5 H, m, Ph), 4.80 (1 H, t, $J_{1,2} \approx J_{1,2'} \approx 2$ Hz, 1-H), 4.57 (2 H, s, OCH_2Ph), 3.98—3.62 (3 H, m, 3-, 4-, and 5-H), 3.29 (3 H, s, OMe), 2.43 (1 H, s, OH), 1.93 (2 H, m, 2-H_2), and 1.28 (3 H, d, $J_{5,6}$ 6.5 Hz, 5-Me).

For the purpose of characterisation, compound (**7**) (0.39 g, 1.55 mmol) was acetylated with acetic anhydride (0.4 ml, 4.2 mmol) in anhydrous pyridine (2 ml) in the usual way, to give *methyl* 4-O-*acetyl*-3-O-*benzyl*-2,6-*dideoxy*-α-L-lyxo-*hexopyranoside* (**8**) (0.352 g, 77%), m.p. 93—95 °C (from light petroleum); $[\alpha]_D$ −177.5° (*c* 1.1 in $CHCl_3$) (Found: C, 65.0; H, 7.7. $C_{16}H_{22}O_5$ requires C, 65.3; H, 7.5%); δ_H 7.31 (5 H, m, Ph), 5.34 (1 H, d, $J_{3,4} \approx 3$ Hz, 4-H), 4.84 (1 H, t, $J_{1,2} \approx J_{1,2'} \approx 2$ Hz, 1-H), 4.57 (2 H, ABq, J_{AB} 12 Hz, OCH_2Ph), 4.09—3.75 (2 H, m, 3- and 5-H), 3.32 (3 H, s, OMe), 2.16 (3 H, s, OAc), 1.93 (2 H, m, 2-H_2), and 1.18 (3 H, d, $J_{5,6}$ 6.5 Hz, 5-Me) {lit. (D-enantiomer),[28] m.p. 87—92 °C; $[\alpha]_D$ +178° (*c* 1 in $CHCl_3$)}.

Methyl 3-O-*Benzyl*-2,6-*dideoxy*-4-O-*methyl*-α-L-lyxo-*hexopyranoside* (**9**).—To a stirred solution of compound (**7**) (5.42 g, 21.5 mmol) in *NN*-dimethylformamide (DMF) (117 ml) was added sodium hydride (50% dispersion in mineral oil; 2.33 g, 48.5 mmol) followed, after 30 min, by freshly distilled methyl iodide (4.7 ml, 75.5 mmol). The reaction mixture was stirred at room temperature overnight, the excess of the reagents was then destroyed by the careful addition of methanol, and the solvents were removed under reduced pressure. The residue was partitioned between chloroform and water, the aqueous layer was separated and further extracted with chloroform, and the chloroform extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (15:1) as eluant] gave the *methylated derivative* (**9**) (4.66 g, 81.5%), b.p. *ca.* 105 °C (bath) at 0.2 mmHg; $[\alpha]_D$ −124° (*c* 1 in $CHCl_3$) (Found: C, 67.9; H, 8.6. $C_{15}H_{22}O_4$ requires C, 67.6; H, 8.3%); δ_H 7.33 (5 H, m, Ph), 4.81 (1 H, t, $J_{1,2} \approx J_{1,2'} \approx 2$ Hz, 1-H), 4.58 (2 H, s, OCH_2Ph), 3.97—3.67 (2 H, m, 3- and 5-H), 3.62 and 3.28 (total 6 H, 2 × s, 2 × OMe), 3.31 [1 H, d(?), 4-H], 2.04 (2 H, m, 2-H_2), and 1.24 (3 H, d, $J_{5,6}$ 6.5 Hz, 5-Me) {lit. (D-enantiomer),[29] $[\alpha]_D$ + 134° (*c* 1.9 in $CHCl_3$)}.

Methyl 2,6-*Dideoxy*-4-O-*methyl*-α-L-lyxo-*hexopyranoside* (**10**).—A solution of compound (**9**) (4.15 g, 15.6 mmol) in anhydrous methanol (250 ml) containing 10% palladium–charcoal (3 g) was shaken for 22 h at room temperature under a slight overpressure of hydrogen and, after filtration, was concentrated under reduced pressure. The residue was taken up in chloroform, and the chloroform solution was filtered, dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallisation of the residue from hexane gave the *alcohol* (**10**) (2.07 g, 75%), m.p. 98.5—100.5 °C; $[\alpha]_D$ −173° (*c* 0.4 in EtOH) (Found:

C, 54.2; H, 9.4. $C_8H_{16}O_4$ requires C, 54.5; H, 9.15%); δ_H (*inter alia*) 4.78 (1 H, t, $J_{1,2} \approx J_{1,2'} \approx 2$ Hz, 1-H), 3.62 and 3.31 (total 6 H, 2 × s, 2 × OMe), and 1.31 (3 H, d, $J_{5,6}$ 6.5 Hz, 5-Me) {lit. (D-enantiomer),[29] m.p. 96—97 °C; $[\alpha]_D$ +174° (*c* 1.2 in EtOH)}.

Methyl 2,6-*Dideoxy*-4-O-*methyl*-α-L-threo-*hexopyranosid*-3-*ulose* (**11**).—A solution of compound (**10**) (2.86 g, 16.25 mmol) in anhydrous methylene dichloride (9 ml) was added to a stirred solution of pyridinium chlorochromate[18] (10.43 g, 48.4 mmol) in anhydrous methylene dichloride (81 ml) containing powdered 3Å molecular sieves[19] (8.09 g) at room temperature. The mixture was stirred for 90 min and then poured into anhydrous diethyl ether (600 ml). The supernatant solution was decanted from the spent oxidant, which was washed with more diethyl ether (2 × 100 ml). The ethereal solutions were combined and concentrated under reduced pressure. The residue was extracted with diethyl ether, and the ethereal extract was filtered and concentrated; this procedure was repeated (with charcoaling). Chromatography of the final residue on silica gel [methylene dichloride–acetone (1:1) as eluant] gave the *keto sugar* (**11**) (2.2 g, 78%), $[\alpha]_D$ −135° (*c* 1.3 in $CHCl_3$); $\nu_{max.}$ 1 725 cm^{-1} (C=O) (Found: C, 55.5; H, 8.1. $C_8H_{14}O_4$ requires C, 55.2; H, 8.1%); δ_H 5.04 (1 H, dd, $J_{1,2}$ 4, $J_{1,2'} \approx 1.5$ Hz, 1-H), 4.11 (1 H, dq, $J_{4,5} \approx 2$, $J_{5,6}$ 6 Hz, 5-H), 3.30 (6 H, s, 2 × OMe), 3.24 (1 H, d, 4-H), 3.04 (1 H, dd, J_{gem} 13 Hz, 2-H), 2.33 (1 H, d with additional fine splitting, 2-H′), and 1.30 (3 H, d, 5-Me).

Methyl 3-C-*Cyano*-2,6-*dideoxy*-4-O-*methyl*-α-L-xylo-*hexopyranoside* (**12**).—Potassium cyanide (0.468 g, 7.2 mmol) was added to a briskly stirred system containing the keto sugar (**11**) (0.626 g, 3.6 mmol) and sodium hydrogen carbonate (0.604 g, 7.2 mmol) dispersed between methylene dichloride (10 ml) and water (2 ml) in a 50 ml Erlenmeyer flask. The flask was stoppered and the mixture was stirred for 48 h at room temperature. Methylene dichloride (50 ml) and water (5 ml) were then added and the organic layer was separated. The aqueous layer was extracted with methylene dichloride, and the organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallisation of the residue from hexane gave the *cyanohydrin* (**12**) (0.48 g, 66%), m.p. 92.5—93.5 °C; $[\alpha]_D$ −115° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 300 (OH) and 2 230 cm^{-1} (C≡N) (Found: C, 53.8; H, 7.5; N, 7.05. $C_9H_{15}NO_4$ requires C, 53.7; H, 7.5; N, 7.0%); δ_H 4.82 (1 H, d, $J_{1,2}$ 3.5 Hz, 1-H), 4.66 (1 H, s, OH), 4.16 (1 H, q, 5-H), 3.67 and 3.36 (total 6 H, 2 × s, 2 × OMe), 3.13 (1 H, s, 4-H), 2.42 (1 H, dd, J_{gem} 14 Hz, 2-H), 2.04 (1 H, d with additional fine splitting, 2-H′), and 1.27 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me). Chromatography of the mother liquors on silica gel [methylene dichloride–acetone (5:1) as eluant] gave a further quantity (0.119 g, total yield 83%) of the cyanohydrin (**12**).

Methyl 3-C-*Cyano*-2,6-*dideoxy*-4-O-*methyl*-3-O-*methylsulphonyl*-α-L-xylo-*hexopyranoside* (**13**).—Methanesulphonyl chloride (2 ml, 25.8 mmol) was added gradually to a cooled (0 °C) and stirred solution of the cyanohydrin (**12**) (0.931 g, 4.6 mmol) in anhydrous pyridine (20 ml), whereafter the solution was stored in a refrigerator (*ca.* 4 °C) for 48 h. Conventional aqueous work-up and chromatography of the residue on silica gel [methylene dichloride–acetone (5:1) as eluant] gave the cyano mesylate (**13**) (1.22 g, 94%), $[\alpha]_D$ −94° (*c* 1.1 in $CHCl_3$), which could not be induced to crystallise; δ_H 4.76 (1 H, d, $J_{1,2'}$ 4 Hz, 1-H), 4.14 (1 H, q, 5-H), 3.72, 3.33, and 3.24 (total 9 H, 3 × s, 2 × OMe and OMs), 3.44 (1 H, s, 4-H), 2.69 (1 H, d with additional fine splitting, J_{gem} 15 Hz, 2-H), 2.33 (1 H, dd, 2-H′), and 1.29 (3 H, d, $J_{5,6}$ 6.5 Hz, 5-Me).

Methyl 3-*Acetamido*-2,3,6-*trideoxy*-3-C-*methyl*-4-O-*methyl*-α-L-lyxo-*hexopyranoside* (**15**).—(*a*) Lithium aluminium hydride (0.171 g, *ca.* 4.5 mmol) was added to a suspension of the cyano mesylate (**13**) (0.82 g, 2.9 mmol) in anhydrous diethyl ether (16.5 ml), the reaction mixture was boiled under reflux for 3 h, and the excess of reagent was then destroyed by the dropwise addition of wet ethyl acetate. Inorganic material was filtered off and washed thoroughly with ethyl acetate, and the filtrate and washings were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue [*ca.* 0.62 g, containing the spiro-aziridine (**14**)] was dissolved in methanol (50 ml) and hydrogenated over Raney nickel under 30 atm of hydrogen for 70 h at room temperature. The catalyst was then filtered off and washed with methanol, and the filtrate and washings were combined and concentrated under reduced pressure. The residue was extracted with chloroform, the resulting solution was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue in pyridine (20 ml) was treated overnight with acetic anhydride (5 ml) at room temperature. Conventional aqueous work-up and chromatography of the residue on silica gel [methylene dichloride–acetone (1:1) as eluant] gave the *acetamido derivative* (**15**) (0.143 g, 21%), $[\alpha]_D$ −172 ± 3° (*c* 0.8 in $CHCl_3$) (Found: C, 57.0; H, 9.4; N, 6.0. $C_{11}H_{21}NO_4$ requires C, 57.1; H, 9.15; N, 6.05%); δ_H 5.63 (1 H, br s, NH), 4.73 (1 H, q, $J_{1,2}$ 4.5, $J_{1,2'}$ 2 Hz, 1-H), 4.00 (1 H, q, 5-H), 3.53 and 3.30 (total 6 H, 2 × s, 2 × OMe), 3.43 (1 H, s, 4-H), 1.95 (1 H, dd, $J_{gem} \approx 13$ Hz, 2-H), 1.94 (3 H, s, NAc), 1.71 (1 H, dd, 2-H′), 1.69 (3 H, s, 3-Me), and 1.26 (3 H, d, $J_{5,6}$ 6.5 Hz, 5-Me).

(*b*) To a stirred solution of methyl *N*-acetyl-α-L-vancosaminide[20] (**16**) (0.16 g, 0.74 mmol) in DMF (2 ml) was added sodium hydride (60% dispersion in mineral oil; 37.4 mg, 0.93 mmol) followed, after 30 min, by a solution of freshly distilled methyl iodide (0.114 g, 0.8 mmol) in DMF (1 ml). The reaction mixture was stirred at room temperature for 2.5 h and then poured into ice–water. The aqueous solution was extracted with methylene dichloride, and the organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel [methylene dichloride–acetone (1:1) as eluant] gave the acetamido derivative (**15**) (0.098 g, 57.5%), $[\alpha]_D$ −179 ± 4° (*c* 0.5 in $CHCl_3$), whose ^1H n.m.r. spectrum was indistinguishable from that of the material obtained in (*a*).

Methyl 3-C-*Cyano*-2,6-*dideoxy*-4-O-*methyl*-α-L-lyxo-*hexopyranoside* (**22**).—(*a*) Hydrogen cyanide (0.25 ml, 6.25 mmol) was added to a cooled (0 °C) solution of the keto sugar (**11**) (0.281 g, 1.6 mmol) in anhydrous pyridine (5 ml), and the reaction mixture was kept for 67 h at room temperature. The solvent was then removed under reduced pressure (oil pump), the residue was dissolved in methylene dichloride, and the organic solution was washed successively with dil. hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on silica gel [methylene dichloride–acetone (5:1) as eluant] gave the *cyanohydrin* (**22**) (0.043 g, 13%) as the less mobile component. On recrystallisation from diethyl ether–hexane, compound (**22**) had m.p. 146.5—149.5 °C, $[\alpha]_D$ −194° (*c* 0.8 in $CHCl_3$); $\nu_{max.}$ 3 400 (OH) and 2 200 cm^{-1} (C≡N) (Found: C, 54.0; H, 7.5; N, 6.9. $C_9H_{15}NO_4$ requires C, 53.7; H, 7.5; N, 7.0%); δ_H 4.80 (1 H, t, $J_{1,2} = J_{1,2'} \approx 3$ Hz, 1-H), 4.19 (1 H, q, 5-H), 3.65 (3 H, s, OMe), 3.33 (total 4 H, s, OMe and 4-H), *ca.* 2.11 (2 H, m, 2-H_2), and 1.31 (3 H, d, $J_{5,6}$ 6.5 Hz, 5-Me).

(*b*) Potassium cyanide (0.351 g, 5.4 mmol) was added to a briskly stirred system containing the keto sugar (**11**) (0.31 g, 1.8 mmol) and sodium hydrogen carbonate (0.472 g, 5.6 mmol) dispersed between methylene dichloride (5 ml) and water (1 ml) in a 25 ml Erlenmeyer flask. The flask was stoppered and the mixture was stirred for 3 h at room temperature before it was processed as described earlier. Chromatography of the residue on silica gel [methylene dichloride–acetone (5:1) as eluant] give

first a mixture (0.26 g) containing the keto sugar (**11**) and the thermodynamic cyanohydrin (**12**); crystallisation from hexane gave compound (**12**) (0.121 g, 34%), identified by comparison (i.r. spectrum and m.p.) with an authentic sample. Continued elution afforded the kinetic product (**22**) (0.064 g, 18%), which was identical (m.p., and i.r. and ^{1}H n.m.r. spectra) with the material obtained in (*a*).

Methyl 3-C-*Cyano*-2,6-*dideoxy*-4-O-*methyl*-3-O-*methylsulphonyl*-α-L-lyxo-*hexopyranoside* (**23**).—Methanesulphonyl chloride (0.83 ml, 10.7 mmol) was added gradually to a cooled (0 °C) and stirred solution of the cyanohydrin (**22**) (0.354 g, 1.76 mmol) in anhydrous pyridine (6.5 ml), whereafter the solution was stored in a refrigerator (*ca.* 4 °C) for 48 h and then processed as described for compound (**13**). Chromatography of the residue on silica gel [methylene dichloride–acetone (10:1) as eluant] gave the *cyano mesylate* (**23**) (0.355 g, 72%), m.p. 86—88 °C (from diethyl ether–hexane); $[\alpha]_D$ −166° (*c* 1.3 in $CHCl_3$) (Found: C, 43.5; H, 5.9; N, 4.5; S, 11.3. $C_{10}H_{17}NO_6S$ requires C, 43.0; H, 6.1; N, 5.0; S, 11.5%); δ_H 4.82 (1 H, t, $J_{1,2} = J_{1,2'} \approx 3$ Hz, 1-H), 4.19 (1 H, q, 5-H), 3.64 (total 4 H, s, OMe and 4-H), 3.33 and 3.24 (total 6 H, 2 × s, OMe and OMs), *ca.* 2.44 (2 H, m, 2-H_2), and 1.30 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

Methyl 3-*Acetamido*-2,3,6-*trideoxy*-3-C-*methyl*-4-O-*methyl*-α-L-xylo-*hexopyranoside* (**26**).—(*a*) To a stirred solution of methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-α-L-*xylo*-hexopyranoside[1] (**27**) (0.115 g, 0.53 mmol) in DMF (1.4 ml) was added sodium hydride (60% dispersion in mineral oil; 25.5 mg, 0.64 mmol), whereafter the mixture was stirred for 30 min before a solution of freshly distilled methyl iodide (0.078 g, 0.55 mmol) in DMF (0.7 ml) was added. The reaction mixture was stirred overnight, with additions of methyl iodide (3 drops) and sodium hydride (12 mg, 0.3 mmol) after 3.5 and 8 h, and then poured into ice–water. The aqueous solution was extracted with chloroform, and the extract was dried ($MgSO_4$) and concentrated under reduced pressure (oil pump). Chromatography of the residue on silica gel [methylene dichloride–acetone (1:1) as eluant] gave the *methylated compound* (**26**) (0.088 g, 72%), m.p. 84—85 °C (from hexane); $[\alpha]_D$ −125° (*c* 0.5 in $CHCl_3$); $\nu_{max.}$ 3 350 (NH) and 1 650 and 1 510 cm^{-1} (NHAc) (Found: C, 57.4; H, 9.1; N, 6.0. $C_{11}H_{21}NO_4$ requires C, 57.1; H, 9.15; N, 6.05%); δ_H 6.84 (1 H, br s, NH), 4.73 (1 H, d, $J_{1,2}$ 4 Hz, 1-H), 4.04 (1 H, q, 5-H), 3.62 (1 H, s, 4-H), 3.55 and 3.35 (total 6 H, 2 × s, 2 × OMe), 2.10—1.80 (2 H, m, 2-H_2), 1.88 (3 H, s, NAc), 1.53 (3 H, s, 3-Me), and 1.24 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

(*b*) Lithium aluminium hydride (55 mg, ~1.45 mmol) was added to a solution of the cyano mesylate (**23**) (0.26 g, 0.93 mmol) in anhydrous diethyl ether (5 ml), and the reaction mixture was boiled under reflux for 3 h and then processed as described for the preparation of intermediate (**14**) in the preparation of compound (**15**). Hydrogenolysis, *N*-acetylation, and chromatography, as described for compound (**15**), gave the acetamido derivative (**26**) (16 mg, 7%), which was identical (m.p. and ^{1}H n.m.r. spectroscopy) with the material obtained in (*a*).

Methyl 2,3,6-*Trideoxy*-3-C-*methyl*-4-O-*methyl*-3-*nitro*-α-L-xylo-*hexopyranoside* (**28**).—A solution of the acetamide (**26**) (0.116 g, 0.5 mmol) in 1,2-dimethoxyethane (5 ml) containing ethanol (0.1 ml) was added to refluxing liquid ammonia (40 ml), followed by calcium (0.146 g, 3.65 mg-atom). The resulting deep-blue solution was stirred for 4 h, the excess of the reagent was then destroyed by the dropwise addition of ethanol, and the ammonia was allowed to evaporate. The residue was partitioned between chloroform and water, and the stirred mixture was brought to pH 2 by the dropwise addition of 10% hydrochloric acid. After 30 s, the mixture was basified (to pH 9) with aqueous potassium carbonate and filtered. The filtrate was extracted thoroughly with chloroform, and the extract was dried ($MgSO_4$) and concentrated under reduced pressure to give the amine (**25**) (0.079 g, 83%) as a yellow oil, $[\alpha]_D$ *ca.* −165° (*c* 0.7 in $CHCl_3$); δ_H 4.75 (1 H, d, $J_{1,2}$ 4 Hz, 1-H), 4.18 (1 H, q, 5-H), 3.52 and 3.33 (total 6 H, 2 × s, 2 × OMe), 2.60 (1 H, s, 4-H), 2.07 (2 H, s, NH_2), 1.91 (1 H, dd, J_{gem} 14 Hz, 2-H), 1.44 (1 H, d, 2-H′), 1.27 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me), and 1.14 (3 H, s, 3-Me). This material was suitable for use in the next step.

A solution of the amine (**25**) (0.181 g, 0.95 mmol) in methylene dichloride (5 ml) was added during 20 min to a boiling solution of *m*-chloroperbenzoic acid (85%; 1.26 g, 6.2 mmol) in methylene dichloride (18 ml), whereafter the reaction mixture was boiled under reflux for a further 40 min. After having cooled, the solution was washed successively with 0.1M sodium hydroxide (3 × 50 ml) and water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue on silica gel [toluene–acetone (6:1) as eluant] furnished the *nitro sugar* (**28**) (0.144 g, 69%), m.p. 92—93 °C (from diethyl ether–hexane); $[\alpha]_D$ −171° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$ 1 540 and 1 340 cm^{-1} (NO_2) (Found: C, 49.6; H, 7.9; N, 6.3. $C_9H_{17}NO_5$ requires C, 49.3; H, 7.8; N, 6.4%); δ_H 4.69 (1 H, d, $J_{1,2'}$ 4 Hz, 1-H), 4.16 (1 H, q, 5-H), 3.70 (1 H, s, 4-H), 3.61 and 3.23 (total 6 H, 2 × s, 2 × OMe), 2.64 (1 H, d, J_{gem} 15 Hz, 2-H), 2.00 (1 H, dd, 2-H′), 1.62 (3 H, s, 3-Me), and 1.32 (3 H, d, $J_{5,6}$ 6 Hz, 5-Me).

2,3,6-*Trideoxy*-3-C-*methyl*-4-O-*methyl*-3-*nitro*-L-xylo-*hexopyranose* (L-*Rubranitrose*) (**4**).—A solution of methyl α-L-rubranitroside (**28**) (0.129 g, 0.59 mmol) in 0.1M sulphuric acid–1,4-dioxane (1:1; 7.5 ml) was heated at 90—95 °C for 27 h and then neutralised with barium carbonate. After filtration, the solution was concentrated under reduced pressure. Chromatography of the residue on silica gel [toluene–acetone (2:1) as eluant] gave L-*rubranitrose* (**4**) (0.046 g, 38%), m.p. 152—154 °C (from benzene–hexane); $[\alpha]_D$ −114.5° (7 min) → −83° (final; *c* 0.4 in EtOH); $\nu_{max.}$(KBr) 3 380 (OH) and 1 540 and 1 340 cm^{-1} (NO_2) (Found: C, 46.5; H, 7.4; N, 6.5. $C_8H_{15}NO_5$ requires C, 46.8; H, 7.4; N, 6.8%). Since natural rubranitrose[3,5] has m.p. 150—153 °C; $[\alpha]_D$ +127° → +86° (final; *c* 0.285 in EtOH), it must belong to the D-series.

Acknowledgements

We thank the Commonwealth Scholarship Commission in the United Kingdom for financial support (to K. M. M. R.), Mr. J. A. Chudek for recording the n.m.r. spectra, and Mr. R. Hanna for advice on some experiments.

References

1 Part 16, J. S. Brimacombe, R. Hanna, and L. C. N. Tucker, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2277.
2 Preliminary communication, J. S. Brimacombe and K. M. M. Rahman, *Carbohydr. Res.*, 1983, **114**, C1.
3 S. A. Mizsak, H. Hoeksema, and L. M. Pschigoda, *J. Antibiot.*, 1979, **32**, 771.
4 H. Hoeksema, S. A. Mizsak, and L. Baczynskyj, *J. Antibiot.*, 1979, **32**, 773; H. Hoeksema, C. Chidester, S. A. Mizsak, and L. Baczynskyj, *ibid.*, 1978, **31**, 1067.
5 H. Hoeksema, S. A. Mizsak, L. Baczynskyj, and L. M. Pschigoda, *J. Am. Chem. Soc.*, 1982, **104**, 5173.
6 A. K. Ganguly, O. Z. Sarre, and H. Reimann, *J. Am. Chem. Soc.*, 1968, **90**, 7129; A. K. Ganguly, O. Z. Sarre, A. T. McPhail, and K. D. Onan, *J. Chem. Soc., Chem. Commun.*, 1977, 313.
7 D. E. Wright, *Tetrahedron*, 1979, **35**, 1207.
8 A. K. Mallams, M. S. Puar, and R. R. Rossman, *J. Am. Chem. Soc.*, 1981, **103**, 3938; A. K. Mallams, M. S. Puar, R. R. Rossman, A. T. McPhail, and R. D. Macfarlane, *ibid.*, p. 3940; A. K. Mallams, M. S. Puar, R. R. Rossman, A. T. McPhail, R. D. Macfarlane, and R. L. Stephens, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1497.

9 K. Funaki, K. Takeda, and E. Yoshii, *Tetrahedron Lett.*, 1982, **23**, 3069.
10 F. Tomita, T. Tamaoki, K. Shirahata, M. Kasai, M. Morimoto, S. Ohkubo, K. Mineura, and S. Ishii, *J. Antibiot.*, 1980, **33**, 668.
11 K. Ishii, Y. Nishimura, S. Kondo, and H. Umezawa, *J. Antibiot.*, 1983, **36**, 454.
12 H. Kawai, Y. Hayakawa, M. Nakagawa, K. Furihata, H. Seto, and N. Ōtaka, *Tetrahedron Lett.*, 1984, **25**, 1937, 1941.
13 K. Ishii, S. Kondo, Y. Nishimura, M. Hamada, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1983, **36**, 451.
14 T. That Thang, F. Winternitz, A. Olesker, A. Lagrange, and G. Lukacs, *J. Chem. Soc., Chem. Commun.*, 1979, 153; J. S. Brimacombe, A. S. Mengech, K. M. M. Rahman, and L. C. N. Tucker, *Carbohydr. Res.*, 1982, **110**, 207.
15 J. Yoshimura, M. Matsuzawa, and M. Funabashi, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2064.
16 P. J. Garegg and T. Norberg, *Acta Chem. Scand., Ser. B*, 1975, **29**, 507.
17 S. David, A. Thieffry, and A. Veyrières, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1796.
18 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.
19 J. Herscovici and K. Antonakis, *J. Chem. Soc., Chem. Commun.*, 1980, 561; J. Herscovici, M.-J. Egron, and K. Antonakis, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1967.
20 H. I. Ahmad, J. S. Brimacombe, A. S. Mengech, and L. C. N. Tucker, *Carbohydr. Res.*, 1981, **93**, 288.
21 T. That Thang, F. Winternitz, A. Lagrange, A. Olesker, and G. Lukacs, *Tetrahedron Lett.*, 1980, **21**, 4495.
22 J. Yoshimura, M. Matsuzawa, K. Sato, and Y. Nagasawa, *Carbohydr. Res.*, 1979, **76**, 67.
23 J. S. Brimacombe and R. Hanna, unpublished results.
24 J. Yoshimura, T. Yasumori, T. Kondo, and K. Sato, *Carbohydr. Res.*, 1982, **106**, C1.
25 M. Debono and R. M. Molloy, *J. Org. Chem.*, 1980, **45**, 4685.
26 K. Michel, R. M. Shah, and R. L. Hamill, *J. Antibiot.*, 1980, **33**, 1397; A. H. Hunt, *J. Am. Chem. Soc.*, 1983, **105**, 4463.
27 G. Stork, S. D. Darling, I. T. Harrison, and P. S. Wharton, *J. Am. Chem. Soc.*, 1962, **84**, 2018; A. J. Pearson and D. C. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2467.
28 J. S. Brimacombe and D. Portsmouth, *Carbohydr. Res.*, 1965, **1**, 128.
29 J. S. Brimacombe, D. Portsmouth, and M. Stacey, *J. Chem. Soc., Suppl. 1*, 1964, 5614.

Received 3rd *September* 1984; *Paper* 4/1512