Cyano-sugars. Part 3.[1] Synthesis of 2-*C*-Cyano-2-deoxy-sugars from 2-*C*-Cyano-galactals and Attempts to Prepare Pentofuranosyl Cyanides from Aldonic Acid Lactones with Tosylmethyl Isocyanide

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1,5-Anhydro-2-*C*-cyano-2-deoxy-D-*lyxo*-hex-1-enitol (2) reacted with sodium methoxide in methanol to give, after acetylation, methyl 3,4,6-tri-*O*-acetyl-2-*C*-cyano-2-deoxy-β-D-galactopyranoside (6) as the main product. Similar treatment of 1,5-anhydro-2-*C*-cyano-2-deoxy-1,2-*O*-isopropylidene-D-*lyxo*-hex-1-enitol (3) gave methyl 4,6-di-*O*-acetyl-2-*C*-cyano-2-deoxy-3-*O*-methyl-α-D- and -β-D-galactopyranoside (11) and (7), respectively, as the main products. Compounds (6), (7), and (11) were converted into their 2-*C*-acetamidomethyl analogues (8), (9), and (12), respectively, in high yield by catalytic hydrogenation in ethanol–acetic anhydride.

The formylaminomethylenation of 2,3 : 5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone with tosylmethyl isocyanide gave (*E*)- and (*Z*)-2,5-anhydro-1-deoxy-1-formylamino-3,4 : 6.7-di-*O*-isopropylidene-1-tosyl-D-*manno*-hept-1-enitol [(17) and (18)]. The reaction of the main isomer (17) with 2 equiv. of sodium ethoxide in ethanol, gave ethyl [(1*R*)-*O*-ethyl-1-formylamino-3,4 : 6,7-di-*O*-isoproyplidene-*aldehydo*-α-D-*manno*-heptafuranos]uloside and its (1*S*)-epimer [(21) and (22)], and not 2,3 : 5,6-di-*O*-isopropylidene-α,β-D-mannofuranosyl cyanide,as expected. 2,3 : 5,6-Di-*O*-isopropylidene-D-gulono-1,4-lactone behaved similarly.

DURING the last decade there has been a rapid development in the synthetic chemistry of branched-chain sugars [2,3] and *C*-glycosyl compounds.[4,5] Sugar derivatives bearing a cyano-group, particularly at C-1, C-2, and C-3, are not only of intrinsic interest but are useful precursors for the synthesis of other *C*-glycosyl compounds and branched-chain sugars, since the cyano-group can be transformed readily into a wide range of functional groups. The preparation and reactions of pento- and hexofuranosyl cyanides have been reviewed [4] and, recently, several methods have been developed for the preparation of 2-*C*-cyano-2-deoxy- and 3-*C*-cyano-3-deoxy-sugars; treatment of sugar oxirans with buffered aqueous sodium cyanide [6] or with hydrogen cyanide–triethylaluminium in ether [7] gave 3-*C*-cyano-3-deoxy-sugars; addition of hydrogen cyanide to nitro-olefinic sugars, in the presence of a number of catalysts, gave 2-*C*-cyano-2,3-dideoxy-3-nitro-derivatives; [8,9] and 2-deoxy-2-*C*-nitromethyl- and 3-deoxy-3-*C*-nitromethyl-furanosides have been converted [1,10] into their respective *C*-cyano-analogues. We report here the preparation of methyl 2-*C*-cyano-2-deoxy-D-hexopyranosides from 1,5-anhydro-2-*C*-cyano-2-deoxy-D-*lyxo*-hex-1-enitols (2-*C*-cyano-galactals) and unsuccessful attempts to convert aldonic acid 1,4-lactones into pentofuranosyl cyanides using tosylmethyl isocyanide (TMIC).

RESULTS AND DISCUSSION

Compound (1) has been prepared [11] in good yield from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol but difficulties were encountered on scaling up the reaction. However, with tetrahydrofuran as the solvent in place of diethyl ether, it was found that the initial reaction was complete after 2 h at 0 °C and that crystalline compound (1) could be prepared in 66% yield on a 0.1 mol scale. Deacetylation of compound (1) with ammonia in methanol gave crystalline compound (2) in 78% yield and acetalization of compound (2) with acetone, 2,2-dimethoxypropane, and a trace of perchloric acid gave crystalline compound (3) in 88% yield.

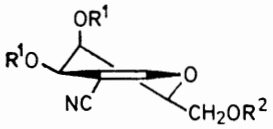
Attempts to duplicate known reactions [12] of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol with compound (1) showed that, as expected, the introduction of the cyano-group at C-2 had a marked effect on the chemical behaviour of the glycals. Compound (1) was recovered, in each case, on treatment with aqueous sulphuric acid (5%), bromine in carbon tetrachloride, nitrosyl chloride in ethyl acetate, osmium tetraoxide in pyridine, *m*-chloroperbenzoic acid in chloroform, and mercury(II) acetate in methanol. Further, attempts to hydrogenate compound (1) failed, as did attempts to prepare nucleosides by the acid-catalysed fusion method.

With hydrogen bromide in acetic acid compound (1) gave a single unsaturated product, compound (4) (54%), in contrast with the products [13] obtained with glycals bearing no substituent at C-2. The reaction of compound (2) with sodium methoxide in methanol gave, on acetylation of the products, compounds (6), (7), and (10) in 47, 3, and 4% yield, respectively, and similar treatment of compound (3) gave compounds (5), (11), (7), and (13) in 6, 55, 20, and 4% yield, respectively.

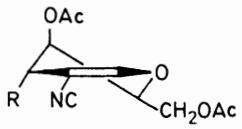
Absorptions at $\nu_{max.}$ 2 220 (conjugated CN) and *ca.* 1 625 cm^{-1} (conjugated C=C) in the i.r. spectra of compounds (4) and (5) showed that they were 2-*C*-cyano-glycals, and accurate mass analyses of their molecular ions and their n.m.r. spectra established that they were a 4,6-di-*O*-acetyl-1,5-anhydro-3-bromo-2-*C*-cyano-2,3-dideoxy-D-hex-1-enitol and a 4,6-di-*O*-acetyl-1,5-anhydro-2-*C*-cyano-2-deoxy-3-*O*-methyl-D-hex-1-enitol, respectively. Also, their n.m.r. spectra with $J_{1,3}$ and $J_{3,4}$ couplings of 0 and 2.5 Hz, respectively, showed [14] that they were the D-*xylo*-compounds (4) and (5) and not the epimeric D-*lyxo*-compounds. [The D-*lyxo*-derivatives (1) and (2) have $J_{1,3}$ and $J_{3,4}$ couplings of *ca.* 1 and 4 Hz, respectively].

Compounds (6), (7), (10), and (11) were readily identified from their analytical and spectral data and their n.m.r. spectra established the configurations at C-1, C-2, and C-3 for each compound. Assuming that epimerization at C-3 and C-4 has not occurred, the $J_{1,2}$, $J_{2,3}$,

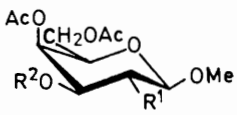
$J_{3,4}$, and $J_{4,5}$ vicinal couplings (*ca.* 8, 12, 3, and 1 Hz, respectively) of compounds (6) and (7) established [15] the *trans*, *trans*, *cis*, *cis* relationships between H-1, H-2, H-3, H-4, and H-5 and that the molecules exist in the $^4C_1$ conformation in $CDCl_3$, *i.e.* that they were the β-D-galactopyranoside derivatives (6) and (7). Similar analyses showed that compounds (10) and (11) were a β-D-talopyranoside and a α-D-galactopyranoside derivative, respectively.



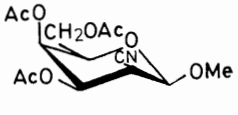
(1) $R^1 = R^2 = Ac$
(2) $R^1 = R^2 = H$
(3) $R^1R^1 = CMe_2, R^2 = H$



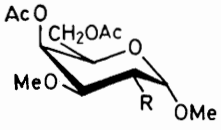
(4) R = Br
(5) R = OMe



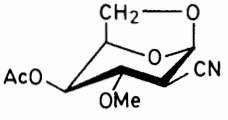
(6) $R^1 = CN, R^2 = Ac$
(7) $R^1 = CN, R^2 = Me$
(8) $R^1 = CH_2NHAc, R^2 = Ac$
(9) $R^1 = CH_2NHAc, R^2 = Me$



(10)



(11) R = CN
(12) R = CH_2NHAc



(13)

(14) $R^1 = OMe, R^2 = H$
(15) $R^1 = H, R^2 = OMe$

Compound (13) was also readily identified from its analytical and spectral data, as a 4-*O*-acetyl-1,6-anhydro-2-*C*-cyano-2-deoxy-3-*O*-methyl-β-D-pyranose. The large $J_{2,3}$ and $J_{3,4}$ vicinal couplings (7 and 9 Hz, respectively) established [15] the all-*trans* relationship between H-2, H-3, and H-4 and, since 1,6-anhydro-β-D-pyranoses must exist in the $_4C^1$ conformation, it followed that the compound was the β-D-idopyranose (13).

Compounds (6) and (10) were formed by addition of methanol across the olefinic bond of compound (1), followed by acetylation. The isolation of only β-isomers suggests that attack by the methoxy-group took place exclusively from the β-face of compound (1) and, as expected,[5,6] the thermodynamically more stable *galacto*-isomer was formed preferentially. The minor product, compound (7), is presumed to have arisen by an allylic displacement to give the cyano-olefinic derivative (14). Attack of compound (14) from its β-face at C-3 by methoxide gave a product which, on acetylation, gave compound (7).

The anomers (7) and (11), the major products of the reaction of compound (3) with methoxide, were produced by an allylic rearrangement, involving the loss of acetone, which gave, on protonation by methanol, the anomers (14) and (15). Again, attack by methoxide at C-3 of anomers (14) and (15) from their β-faces gave products which, on acetylation, gave anomers (7) and (11). The ratio of the anomers (*ca.* 3 : 1 in favour of the α-anomer) indicates that the presence of the 3,4-*O*-isopropylidene group in compound (3) hinders the approach of methoxide to C-1 from the β-face.

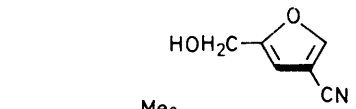
Compound (5) was probably produced by a double allylic rearrangement [16] involving attack of the intermediate (14) or (15) at C-3 by methoxide from the α-face. However, direct nucleophilic attack by methoxide at the allylic centre, with displacement of acetone, cannot be ruled out. Again, the preparation of compound (4) from compound (1) can also be explained by either a double allylic rearrangement with bromide ions or by direct nucleophilic displacement of the allylic acetoxy-group by bromide. It is not clear whether compound (13) was formed *via* anhydration of an unsaturated intermediate such as (14) or (15) and then addition of methanol, or whether C-3 methoxylation of such an intermediate preceded anhydration.

Hydrogenation of compounds (6), (7), and (11) over platinum in a mixture of ethanol and acetic anhydride gave the acetamidomethyl analogues (8), (9), and (12), respectively, in good yield.

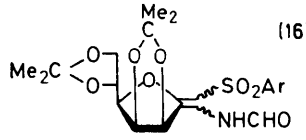
Our second approach to the preparation of cyano-sugars was prompted by recent reports [17-21] describing the conversion of carbonyl compounds into their homologous nitriles, either directly [17-19] or *via* their homologous *N*-(1-tosyl-1-alkenyl)-1-formamides,[18,20,21] using TMIC. However, an attempt to convert 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose directly into its 3-*C*-cyano-3-deoxy-analogue gave only an unidentified crystalline compound of high molecular weight (*m/e* 511). Further, a similar attempt with methyl 3,5-*O*-isopropylidene-α-D-*threo*-pentofuranosuloside [22] gave 3-cyano-1-hydroxymethylfuran (16) (42%) as the only identifiable product. Clearly, the desired 2-*C*-cyano-2-deoxy-sugar does form but, under the basic conditions of the reaction, the C-2 proton was readily abstracted to give an intermediate which eliminated first acetone and then methanol to give compound (16).

On reacting 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone with potassio-TMIC in tetrahydrofuran the expected [23] formylaminomethylenation products (17) and (18) were obtained in 53% combined yield. Similarly, the isomeric-D-gulono-1,4-lactone [24] gave isomers (19) and (20) in 44% combined yield. However, treatment of the major isomers (17) and (19) with 2

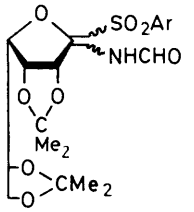
equiv. of sodium ethoxide in ethanol gave the C-1 epimers (21) and (22), and (23) and (24), respectively, and not the expected D-pentofuranosyl cyanides.



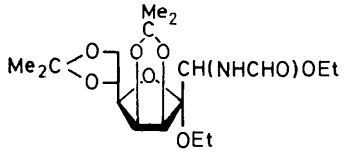
(16)



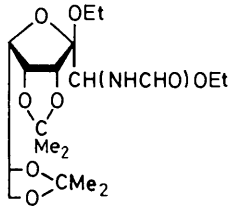
(17), (18)



(19), (20)



(21), (22)



(23), (24)

The facile attack of the ethoxide at C-2 of the R^1-(R^2O)C=C(NHCHO)SO_2Ar system, presumably from the less hindered side, must determine the course of the reaction which then proceeds as shown in the Scheme. The overall reaction is a chain-extension by one carbon unit.

We conclude that the potential of TMIC in branched-chain sugar and *C*-glycosyl synthesis seems to be limited.

EXPERIMENTAL

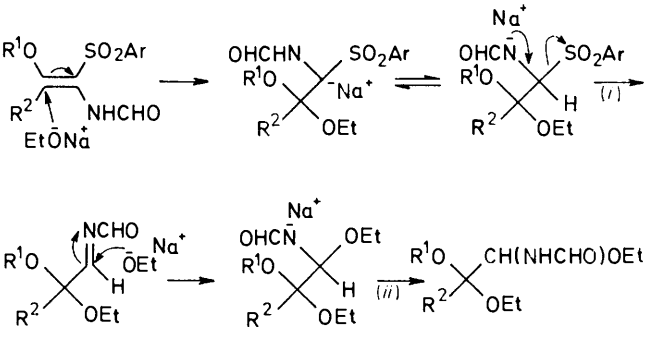
For general experimental procedure see ref. 23.

3,4,6-*Tri*-O-*acetyl*-1,5-*anhydro*-2-C-*cyano*-2-*deoxy*-D-lyxo-*hex*-1-*enitol* (1).—A solution of chlorosulphonyl isocyanide (14.15 g, 0.1 mol) in dry tetrahydrofuran (50 ml) was added dropwise to a solution of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (27.22 g, 0.1 mol) in dry tetrahydrofuran (150 ml) at 0 °C and the solution was stirred at 0 °C for 2 h. A solution of triethylamine (10.12 g, 0.1 mol) in dichloromethane (50 ml) was added dropwise, and the solution was warmed to 25 °C. After 30 min the solvents were removed *in vacuo* (<40 °C) and a saturated, aqueous solution of sodium hydrogen carbonate (300 ml) was added to the residue. After evolution of carbon dioxide had ceased the solvents were evaporated off (<50 °C) and the residue was co-evaporated twice with dry acetone. The residue was extracted with warm ethyl acetate and filtered. The solution was dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo* to give a syrup which solidified. Chromatography, using a short thick column with chloroform–ethyl acetate (4 : 1) as eluant, gave a solid which, on recrystallization from ethyl acetate–hexane gave the compound (1) (19.62 g, 66%), $[\alpha]_D^{20}$ +99°, identical with material prepared previously.[9]

The above altered procedure was adopted to prevent the formation of emulsions which complicate extraction.

1,5-*Anhydro*-2-C-*cyano*-2-*deoxy*-D-lyxo-*hex*-1-*enitol* (2).—Dry ammonia was passed through a solution of compound (1) (5.94 g, 20 mmol) in dry methanol (100 ml) at −20 °C for 1 h. The solution was kept at 25 °C for 6 h and the solvent was then removed *in vacuo* (<30 °C) to give a solid which was recrystallized from ethyl acetate containing a trace of ethanol to give *compound* (2) (2.68 g, 78%), m.p. 145—147 °C; $[\alpha]_D^{20}$ (MeOH) + 143°; $\nu_{max.}$ (KBr) *ca.* 3 440—3 180 (OH), 2 220 (CN), and 1 620 cm^{-1} (C=C); M^+ 171; τ[$(CD_3)_2CO$–D_2O] 2.77(br, 1 H, s, $J_{1.3}$ <1 Hz, H-1), 5.53(br, 1 H, d, $J_{3.4}$ 4, $J_{3.1}$ <1 Hz, H-3), and 5.78—5.97 and 6.16—6.20 (4 H, m, H-4, H-5, and H_2-6) (Found: C, 49.1; H, 5.4; N, 8.3. $C_7H_9NO_4$ requires C, 49.1, H, 5.3; N, 8.2%).

1,5-*Anhydro*-2-C-*cyano*-2-*deoxy*-3,4-O-*isopropylidene*-D-lyxo-*hex*-1-*enitol* (3).—Perchloric acid (0.5 ml) was added



Scheme (i) $-NaSO_2Ar$; (ii) AcOH, $-NaOAc$ (Ar=C_6H_4Me-*p*)

dropwise to a solution of compound (2) (8.56 g, 50 mmol) in dry acetone (200 ml) and 2,2-dimethoxypropane (25 ml), and the solution was stirred at 25 °C for 16 h. The solution was concentrated *in vacuo* (<30 °C; *ca.* 100 ml), added to saturated aqueous sodium hydrogen carbonate solution (400 ml) and the resulting mixture was stirred (30 min). The mixture was extracted with chloroform (4 × 100 ml), the combined extracts were dried ($MgSO_4$), and the solvent was removed to give an oil. Chromatography on a short thick column with ethyl acetate–hexane (1 : 1) as eluant removed fast-running impurities and with ethyl acetate–chloroform (4 : 1) as eluant a solid was obtained. Recrystallization from ethyl acetate-hexane gave *compound* (3) (9.24 g, 88%), m.p. 121—122 °C, $[\alpha]_D^{20}$ +199°; $\nu_{max.}$ *ca.* 3 600—3 400 (OH), 2 220 (CN), 1 630 (C=C), and 1 380 and 1 370 cm^{-1} (CMe_2); M^+ 211; τ 2.86 (1 H, s, H-1), 5.25 (1 H, d, $J_{3.4}$ 6 Hz, H-3), 5.60(br, 1 H, d, $J_{4.3}$ 6, $J_{4.5}$ <1 Hz, H-4), 5.77—6.10 (3 H, m, simplifies on addition of D_2O, H-5 and H_2-6), 7.62 (br, 1 H, m, disappears on addition of D_2O, OH), and 8.52 and 8.60 (6 H, 2 s, 2 Me) (Found: C, 56.8; H, 6.3; N, 6.8. $C_{10}H_{13}NO_4$ requires C, 56.9; H, 6.2; N, 6.6%).

4,6-*Di*-O-*acetyl*-1,5-*anhydro*-3-*bromo*-2,3-*dideoxy*-D-xylo-*hex*-1-*enitol* (4).—Compound (1) (297 mg, 1 mmol) was stirred in HBr in acetic acid (40%; 2 ml) at 25 °C for 2 h. The solution was added to ice–water (30 ml) and stirred (30 min). The mixture was extracted with chloroform

(3 × 20 ml), the combined extracts were dried ($MgSO_4$), and the solvent was evaporated to give the unstable *glycal* (4) as a colourless oil (173 mg, 54%); $\nu_{max.}$ 2 220 (conjugated CN), 1 760 (CO), and 1 620 (conjugated C=C); M^+ 317 and 319; $\tau(C_6D_6)$ 3.64 (1 H, s, H-1), 4.86 (1 H, dd, $J_{4.3}$ 2.5, $J_{4.5}$ 1.5 Hz, H-4), 5.55 (br, 1 H, m, H-5), 5.85 (1 H, d, $J_{3.4}$ 2.5 Hz. H-3), *ca.* 6.10 (2 H, m, H_2-6), and 8.40 and 8.53 (6 H, 2 s, 2 OAc) (Found: M^+ 316.990 and 318.988. $C_{11}H_{12}BrNO_5$ requires M^+, 316.990 and 318.988).

Reaction of Compound (2) *with Sodium Methoxide in Methanol.*—Compound (2) (3 g, 17.5 mmol) was stirred in dry methanol (150 ml) containing sodium methoxide (1%) at 25 °C for 16 h. The solution was neutralized with acetic acid, the solvent was evaporated off, and after co-evaporation with ethyl acetate (2 × 100 ml), warm ethyl acetate was added, and the mixture was filtered. Removal of the solvent gave an oil which was acetylated with acetic anhydride in pyridine to give an oil. Chromatography with ethyl acetate–chloroform (1 : 1) as eluant gave *methyl* 3,4,6-*tri*-O-*acetyl*-2-C-*cyano*-2-*deoxy*-β-D-*galactopyranoside* (6), (2.7 g, 47%), m.p. 118—120 °C (ethyl acetate–hexane); $[\alpha]_D^{20}$ +9°; $\nu_{max.}$ 2 250 (CN) and 1 750 cm^{-1} (CO); *m/e* 328 ($M^+ - 1$); τ 4.67 (1 H, dd, $J_{4.3}$ 3, $J_{4.5}$ 1 Hz, H-4), 4.88 (1 H, dd, $J_{3.2}$ 12, $J_{3.4}$ 3 Hz, H-3), 5.44 (1 H, d, $J_{1.2}$ 8 Hz, H-1), *ca.* 5.87 (2 H, m, H_2-6), 6.13 (1 H, m, H-5), 6.43 (3 H, s, OMe), 6.96 (1 H, dd, $J_{2.3}$ 12, $J_{2,1}$ 8 Hz, H-2), and 7.90, 7.97, and 7.99 (9 H, 3 s, 3 OAc) (Found: C, 51.2; H, 5.8; N, 4.4. $C_{14}H_{19}NO_8$ requires C, 51.1; H, 5.8; N, 4.3%). Next eluted was *methyl* 4,6-*di*-O-*acetyl*-2-C-*cyano*-2-*deoxy*-3-O-*methyl*-β-D-*galactopyranoside* (7) (173 mg, 3%), m.p. 180—181 °C (ethyl acetate–hexane); $[\alpha]_D^{20}$ +2°; $\nu_{max.}$ 2 250 (CN) and 1 750 cm^{-1} (CO); *m/e* 300 ($M^+ - 1$); τ 3.58 (br, 1 H, dd, $J_{4.3}$ 3, $J_{4.5}$ *ca.* 1 Hz, H-4), 5.51 (1 H, d, $J_{1.2}$ 8.5 Hz, H-1), *ca.* 5.84 (2 H, m, H_2-6), 6.22 (1 H, m, H-5), 6.43 and 6.52 (6 H, 2 s 2 OMe), *ca.* 6.52 (1 H, obscured by OMe signals, H-3), 7.13 (1 H, dd, $J_{2.3}$ 11.5, $J_{2.1}$ 8.5 Hz, H-2), and 7.86 and 7.96 (6 H, 2 s, 2 OAc) (Found: C, 52.0; H, 6.4; N, 4.9. $C_{13}H_{19}NO_7$ requires C, 51.9; H, 6.4; N, 4.7%). Last eluted was *methyl* 3,4,6-*tri*-O-*acetyl*-2-C-*cyano*-2-*deoxy*-β-D-*talopyranoside* (10) (247 mg, 4%), m.p. 109—110 °C (ethyl acetate–hexane); $[\alpha]_D^{20}$ −96°; $\nu_{max.}$ 2 250 (CN) and 1 750 cm^{-1} (CO); *m/e* 328 ($M^+ - 1$), τ 4.71 (br, 1 H, dd, $J_{4.3}$ 3, $J_{4.5}$ *ca.* 1 Hz, H-4), 5.01 (1 H, dd, $J_{3,2}$ 6, $J_{3.4}$ 3 Hz, H-3), 5.49 (1 H, d, $J_{1.2}$ 2 Hz, H-2), *ca.* 5.79 (2 H, m, H_2-6), 6.13 (1 H, m, $J_{5.6a} = J_{5.6b} = 7$, $J_{5.4}$ 1 Hz, H-5), 6.42 (3 H, s, OMe), 6.68 (1 H, dd, $J_{2.3}$ 6, $J_{2,1}$ 2 Hz, H-2), and 7.82, 7.94, and 7.97 (9 H, 3 s, 3 OAc) (Found: C, 51.1; H, 5.8; N, 4.4. $C_{14}H_{19}NO_8$ requires C, 51.1; H, 5.8; N, 4.3%).

Reaction of Compound (3) *with Sodium Methoxide in Methanol.*—Compound (3), (3 g, 14.2 mmol) was treated with sodium methoxide in methanol as described for compound (2) to give a semi-crystalline solid. Chromatography and rechromatography of mixed fractions with ethyl acetate–hexane (1 : 1) as eluant gave 4,6-*di*-O-*acetyl*-1,5-*anhydro*-2-C-*cyano*-2-*deoxy*-3-O-*methyl*-D-xylo-*hex*-1-*enitol* (5) (230 mg, 6%); $[\alpha]_D^{20}$ +140°; $\nu_{max.}$ 2 220 (conjugated CN), 1 750 (CO), and 1 630 cm^{-1} (C=C); M^+ 269; $\tau(C_6D_6)$ 3.44 (1 H, s, H-1), 5.04 (br, 1 H, d, $J_{4.3}$ 2.5, $J_{4.5}$ <1 Hz, H-4), *ca.* 5.97 (3 H, m, H-5 and H_2-6), 6.52 (1 H, d, $J_{3.4}$ 2.5 Hz, H-3), 6.82 (3 H, s, OMe), and 8.40 and 8.51 (6 H, 2 s, 2 OAc) (Found: M^+, 269.090. $C_{12}H_{15}NO_6$ requires M^+, 269.090). Next eluted was *methyl* 4,6-*di*-O-*acetyl*-2-C-*cyano*-2-*deoxy*-3-O-*methyl*-α-D-*galactopyranoside* (11) as an oil (2.36 g, 55%), $[\alpha]_D^{20}$ +98°; $\nu_{max.}$ 2 250 (CN) and 1 750 cm^{-1} (CO); M^+ 301; τ 4.53 (br, 1 H, d, $J_{4,3}$ 3, $J_{4.5}$ <1 Hz, H-4), 5.00 (1 H, d, $J_{1.2}$ 3.5 Hz, H-1), *ca.* 5.90 (3 H, m, H-5 and H_2-6), 6.20 (1 H, dd, $J_{3.2}$ 11, $J_{3.4}$ 3 Hz, H-3), 6.55 (3 H, s, OMe), 6.90 (1 H, dd, $J_{2.3}$ 11, $J_{2,1}$ 3.5 Hz, H-2), and 7.88 and 7.94 (6 H, 2 s, 2 OAc) (Found: *m/e* 270.098. $C_{13}H_{19}NO_7$ requires M^+ − OMe, 270.098). Eluted after compound (11) was its β-*anomer* (7) (845 mg, 20%), identical (m.p., i.r., n.m.r., and mass spectrum) with the material prepared from compound (2). Finally eluted was 4-O-*acetyl*-1,6-*anhydro*-2-C-*cyano*-2-*deoxy*-3-O-*methyl*-β-D-*idopyranose* (13) (120 mg, 4%), m.p. 155—156 °C (ethyl acetate–hexane), $[\alpha]_D^{20}$ +136°; $\nu_{max.}$ 2 250 (CN) and 1 750 cm^{-1} (CO); M^+ 227; τ 4.33 (1 H, d, $J_{1.2}$ 2 Hz, H-1), 4.89 (1 H, octet, $J_{4.3}$ 9, $J_{4.5}$ 4, $J_{4.6\text{-}exo}$ 1 Hz, H-4), 5.34 (br, 1 H, t, $J_{5.4} = J_{5.6\text{-}exo}$ 4, $J_{5.6\text{-}endo}$ <1 Hz, H-5), 5.95 (br, 1 H, d, $J_{6\text{-}endo,\ 6\text{-}exo}$ 8, $J_{6\text{-}endo.5}$ <1 Hz, H-6$_{endo}$). 6.29 (1 H, dd, $J_{3.4}$ 9, $J_{3.2}$ 7 Hz, H-3), *ca.* 6.28 (1 H, m, obscured by H-3 signal, H-6$_{exo}$), 6.51 (1 H, dd, $J_{2.3}$ 7, $J_{2.1}$ 2 Hz, H-2), 6.56 (3 H, s, OMe), and 7.91 (3 H, s, OAc) (Found: C, 53.1; H, 5.5; N, 6.3. $C_{10}H_{13}NO_5$ requires C, 52.9; H, 5.8; N, 6.2%).

Hydrogenation of Compounds (6), (7), *and* (11).—Each compound (1 mmol) was hydrogenated (25 °C; 4 h; 50 lb in^{-2}) over Adams catalyst (*ca.* 50 mg) in a mixture of ethanol (20 ml) and acetic anhydride (5 ml). After 3 h each of the mixtures was filtered and the solvent was removed to leave the reduced product.

Hydrogenation of compound (6) gave *methyl* 3,4,6-*tri*-O-*acetyl*-2-C-*acetamidomethyl*-2-*deoxy*-β-D-*galactopyranoside* (8) (83%), m.p. 150—151 °C (ethyl acetate–hexane); $[\alpha]_D^{20}$ +28°; $\nu_{max.}$ 3 430 (NH), 1 740 (ester), and 1 660 cm^{-1} (amide); *m/e* 360 (M^+ − Me), 343 (M^+ − MeOH), and 332 ($M^+ - CH_2CO - H$); τ *ca.* 3.90 (br, 1 H, disappears on addition of D_2O, NH), 4.72 (br, 1 H, d, $J_{4.3}$ 3, $J_{4.5}$ <1 Hz, H-4), 5.18 (1 H, dd, $J_{3.2}$ 12, $J_{3.4}$ 3 Hz, H-3), 5.73 (1 H, d, $J_{1,2}$ 9 Hz, H-1), *ca.* 5.84 (2 H, m, H_2-6), 6.00—6.14 (3 H, m, simplifies on addition of D_2O, H-2, H-5, and 2-CH_a), 6.43 (3 H, s, OMe), 7.08 (1 H, octet, $J_{2\text{-}CH_b,2\text{-}CH_a}$ 14, $J_{2\text{-}CH_b,2}$ 7, $J_{2\text{-}CH_b,NH}$ 4 Hz, simplifies on addition of D_2O, 2-CH_b) and 7.88, 7.97, and 8.06 (12 H, 3 s, 3 OAc and *N*-Ac) (Found: C, 51.2; H, 6.6; N, 3.9. $C_{16}H_{25}NO_9$ requires C, 51.2; H, 6.7; N, 3.7%).

Hydrogenation of compound (7) gave compound (9) (79%), m.p. 115—116 °C (ethyl acetate–hexane); $[\alpha]_D^{20}$ −3°; $\nu_{max.}$ 3 430 (NH), 1 750 (ester), and 1 670 cm^{-1} (amide); *m/e* 347(M^+), 332(M^+ − Me), and 315(M^+ − MeOH); τ *ca.* 3.80 (br, 1 H, disappears on addition of D_2O, NH), 4.62 (br, 1 H, d, $J_{4.3}$ 3, $J_{4.5}$ <1 Hz, H-4), 5.81 (1 H, d, $J_{1,2}$ 9 Hz, H-1), *ca.* 5.83 (2 H, m, H_2-6), 6.20—6.74 (4 H, m, simplifies on addition of D_2O, H-2, H-5, and 2-CH_2), 6.46 and 6.62 (6 H, 2 s, 2 OMe), 6.88 (1 H, dd, $J_{3,2}$ 11, $J_{3.4}$ 3 Hz, H-3), and 7.88, 7.94, and 8.05 (9 H, 3 s, 2 OAc and *N*-Ac) (Found: C, 51.8; H, 7.3; N, 4.2. $C_{15}H_{25}NO_8$ requires C, 51.9; H, 7.3; N, 4.0%).

Hydrogenation of compound (11) gave compound (12) (86%) as an oil, $[\alpha]_D^{20}$ +41°; $\nu_{max.}$ 3 430 (NH), 1 740 (ester), and 1 650 cm^{-1} (amide); *m/e* 347(M^+), 332(M^+ − Me), and 315(M^+ − MeOH); τ *ca.* 3.83 (br, 1 H, disappears on addition of D_2O, NH), 4.59 (br, 1 H, d, $J_{4.3}$ 3, $J_{4.5}$ <1 Hz, H-4), 5.80—*ca.* 6.65 (7 H, m, simplifies on addition of D_2O, H-2, H-3, H-5, and H_2-6 and 2-CH_2), 6.65 (6 H, s, 2 OMe), and 7.88, 7.94, and 8.04 (9 H, 3 s, 2 OAc and *N*-Ac) (Found: *m/e* 315.132. $C_{14}H_{21}NO_7$ requires M^+ − MeOH, 315.132).

3-*Cyano*-1-*hydroxymethylfuran* (16).—Methyl 3,5-*O*-isopropylidene-α-D-*threo*-pentofuranosuloside [21] (4.04 g, 20 mmol), and TMIC (4.5 g, 20 mmol), in dry tetrahydrofuran

(50 ml) were added dropwise to a stirred suspension of potassium hydride (1.00 g, 25 mmol; 50% suspension in oil; washed with hexane) in dry tetrahydrofuran at −70 °C. The temperature of the mixture was allowed to rise to *ca.* −20 °C when evolution of hydrogen started and then maintained at −20 °C until evolution of hydrogen had ceased before being allowed to rise to 0 °C. After 1 h, a solution of potassium t-butoxide in t-butanol (20 ml; 1M) was added and the mixture was stirred at 25 °C for 2 h. Solvent was removed, water (100 ml) was added, and the mixture was neutralized with hydrochloric acid (1N) and extracted with chloroform (4 × 100 ml). The combined extracts were washed with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and the solvent was removed to give an oil. Chromatography with chloroform–methanol (19 : 1) as eluant gave *compound* (16) (826 mg, 42%), m.p. 82—83 °C (ethyl acetate–hexane); $\nu_{max.}$ 3 400 (OH), 2 240 (CN), and 1 600 cm^{-1} (C=C); M^+ 123; τ 2.12 (1 H, s, H-1), 3.52 (1 H, s, H-3), 5.43 (2 H, s, 1-CH_2), and 7.47 (br, 1 H, disappears on addition of D_2O, OH) (Found: C, 58.2; H, 4.0; N, 11.0. $C_6H_5NO_2$ requires C, 58.5; H, 4.1; N, 11.3%).

(E)- *and* (Z)-2,5-*Anhydro*-1-*deoxy*-1-*formylamino*-3,4 : 6,7-di-O-*isopropylidene*-1-*tosyl*-D-manno-*hept*-1-*enitol*[(17) *and* (18)].—2,3 : 5,6-Di-*O*-isopropylidene-D-mannono-1,4-lactone (4.12 g, 16 mmol) was treated with TMIC (3.12 g, 16 mmol) and potassium hydride (1.28 g, 16 mmol; 50% suspension in oil) in dry tetrahydrofuran (80 ml) employing the conditions described for the reaction [23] of the lactone with ethyl isocyanoacetate. Similar work-up gave an oil which was chromatographed with ethyl acetate–chloroform (7 : 3) as eluant to give an oil (fraction A_1, *ca.* 750 mg). T.l.c. with ethyl acetate–hexane (1 : 1) showed that fraction A_1 was a mixture of at least two compounds. Further elution gave the *isomer* (17) as a pale yellow glass (3.5 g, 48%), $[\alpha]_D^{20}$ +28°; $\nu_{max.}$ 3 400 (NH), 1 700 (CO), and 1 650 cm^{-1} (C=C); M^+ 453; τ 1.80 and 2.15 (br, 1 H, s and d, $J_{CHO,NH}$ 12 Hz, simplifies on addition of D_2O, CHO), 2.14—2.30 and 2.60—2.79 (4 H, m, C_6H_4), 3.04 (br, 1 H, d, $J_{NH,CHO}$ 12 Hz, disappears on addition of D_2O, NH), 4.68 and 4.74 (1 H, 2 d, $J_{3,4}$ 5 Hz, H-3), 5.17—5.34 (1 H, m, H-4), 5.55—6.09 (4 H, m, H-5, H-6, and H_2-7), 7.59 (3 H, s, C_6H_4Me), and 8.51—8.79 (12 H, m, 4 Me) (Found: M^+, 453.146. $C_{21}H_{27}NO_8S$ requires M^+, 453.146).

Fraction A_1 was rechromatographed with ethyl acetate–hexane (1 : 1) as eluant, to give an oil (250 mg) which was not investigated further. Next eluted was an oil which solidified. Recrystallization from ethyl acetate–hexane gave the *isomer* (18) (203 mg, 3%), m.p. 206—207 °C, $[\alpha]_D^{20}$ −30°; $\nu_{max.}$ 3 400 and 3 370 (NH), 1 700 (CO), and 1 650 cm^{-1} (C=C); M^+ 453; τ 1.99 and 2.36 (br, 1 H, s and d, $J_{CHO,NH}$ 11 Hz, simplifies on addition of D_2O, CHO), 2.07—2.18 and 2.64—2.84 (4 H, m, C_6H_4), 3.19 (br, 1 H, d, $J_{NH,CHO}$ 11 Hz, disappears on addition of D_2O, NH), 3.90 and 3.93 (1 H, 2 d, $J_{3,4}$ 6 Hz, H-3), 5.10 (1 H, m, H-4), 5.50—6.14 (4 H, m, H-5, H-6, and H_2-7), 7.59 and 7.61 (3 H, 2 s, C_6H_4Me), and 8.54—8.70 (12 H, m, 4 Me) (Found: C, 55.9; H, 6.1; N, 3.3. $C_{21}H_{27}NO_8S$ requires C, 55.6; H, 6.0; N, 3.1%).

(E)- *and* -(Z)-2,5-*Anhydro*-1-*deoxy*-1-*formylamino*-3,4 : 6,-7-*di*-O-*isopropylidene*-1-*tosyl*-D-gulo-*hept*-1-*enitol* [(19) *and* (20)].—2,3 : 5,6-Di-*O*-isopropylidene-D-gulono-1,4-lactone (4.12 g, 16 mmol) was treated with TMIC as described for the preparation of compounds (17) and (18). Work-up gave an oil which was chromatographed with ethyl acetate–hexane (7 : 3) as eluant to give an oil (fraction A_2, *ca.* 350 mg) which was a mixture of two compounds (t.l.c.). Further elution gave an oil which solidified. Recrystallization from ethyl acetate–hexane gave the *isomer* (19) (2.9 g, 40%), m.p. 181—182 °C; $[\alpha]_D^{20}$ −82°; $\nu_{max.}$ 3 400 (NH), 1 700 (CO), and 1 655 cm^{-1} (C=C); M^+ 453; τ 1.75(br) and *ca.* 2.05 (1 H, s and d, simplifies on addition of D_2O, CHO), 2.43 (br, 1 H, s, disappears on addition of D_2O, NH), 2.02—2.16 and 2.68—2.79 (4 H, m, C_6H_4), 4.62 and 4.70 (1 H, 2 d, $J_{3,4}$ 6 Hz, H-3), 5.26—6.37 (5 H, m, H-4, H-5, H-6, and H_2-7), 7.62 (3 H, s, C_6H_4Me), and 8.55—8.80 (12 H, m, 4 Me) (Found: C, 55.6; H, 6.0; N, 3.2. $C_{21}H_{27}NO_8S$ requires C, 55.6; H, 6.0; N, 3.1%).

Fraction A_2 was rechromatographed with ethyl acetate–chloroform (2 : 3) as eluant to give a foam (44 mg) which was not investigated further. Further elution gave the *isomer* (20) as a colourless glass (270 mg, 4%); $[\alpha]_D^{20}$ +12°; $\nu_{max.}$ 3 400 and 3 370 (NH), 1 700 (CO), and 1 650 cm^{-1} (C=C); M^+ 453; τ 1.97(br) and 2.26 (1 H, s, and d, $J_{CHO,NH}$ 11.5 Hz, simplifies on addition of D_2O, CHO), 2.08—2.18 and 2.63—2.81 (4 H, m, C_6H_4), 3.02 and 3.33(br) (1 H, s, and d, $J_{NH,CHO}$ 11.5 Hz, simplifies on addition of D_2O, NH), 3.89 and 3.92 (1 H, 2 d, $J_{3,4}$ 6 Hz, H-3), *ca.* 5.20 (1 H, m, H-4), 5.54—6.32 (4 H, m, H-5, H-6, and H_2-7), 7.61 (3 H, s, C_6H_4Me), and 8.60—8.70 (12 H, m, 4 Me) (Found: M^+, 453.147. $C_{21}H_{27}NO_8S$ requires M^+, 453.146).

Ethyl [(1R)-O-*Ethyl*-1-*formylamino*-3,4 : 6,7-*di*-O-*isopropylidene*-aldehydo-α-D-manno-*heptofuranos*]*uloside and the* (1S)-*isomer* [(21) *and* (22)].—A solution of compound (19) (453 mg, 1 mmol) in ethanol (10 ml) was added to refluxing ethanol (10 ml) containing sodium ethoxide (168 mg, 2 mmol). After 30 min the solution was cooled and the solvent was removed *in vacuo* (<30 °C). Saturated, aqueous sodium hydrogencarbonate solution (10 ml) was added and the solution was extracted with chloroform (2 × 20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give an oil (*ca.* 500 mg). Chromatography with ethyl acetate–chloroform (7 : 3) as eluant gave *compound* (21) as an oil (248 mg, 72%), $[\alpha]_D^{21}$ +15°; $\nu_{max.}$ 3 400 (NH) and 1 690 cm^{-1} (CO); *m/e* 374 (M^+ − Me); τ 1.74 and 1.92 (1 H, 2 d, $J_{CHO,NH}$ <1 and 12 Hz, simplifies on addition of D_2O, CHO), 3.05 and 3.55(br) (1 H, d and t, $J_{NH.CHO}$ *ca.* 10, $J_{NH.H-1}$ 10 Hz, disappears on addition of D_2O, NH), 4.39 (1 H, d, $J_{H-1,NH}$ 10 Hz, simplifies on addition of D_2O, H-1), 5.15—6.84 (10 H, m, H-3—6, H_2-7, and 2 OCH_2CH_3), and 8.47—8.94 (18 H, m, 4 Me, 2 OCH_2CH_3) (Found: *m/e* 374.181. $C_{17}H_{28}NO_8$ requires M^+ − Me, 374.181).

Further elution gave compound (22) as an oil (30 mg, 8%); $[\alpha]_D^{21}$ +34°; $\nu_{max.}$ 3 410 (NH) and 1 690 cm^{-1} (CO); *m/e* 374 (M^+ − Me); τ 1.72 and 1.95 (1 H, 2 d, $J_{CHO,NH}$ <1 and 12 Hz, simplified on addition of D_2O, CHO), 3.64 and 3.91 (br) (1 H, d and t, $J_{NH.CHO}$ *ca.* 10, $J_{NH.H-1}$ 10 Hz, disappears on addition of D_2O, NH), 4.47 (1 H, d, $J_{H-1,NH}$ 10 Hz, simplifies on addition of D_2O, H-1), 5.14—6.65 (10 H, m, H-3—6, H_2-7, and 2 OCH_2CH_3), and 8.52—8.93 (18 H, m, 4 Me and 2 OCH_2CH_3) (Found: *m/e* 374.181. $C_{17}H_{28}NO_8$ requires M^+ − Me, 374.181).

Ethyl [(1*R*)-*O*-*Ethyl*-1-*formylamino*-3,4 : 6,7-*di*-O-*isopropylidene*-aldehydo-β-D-gulo-*heptofuranos*]*uloside and the* (1S)-*isomer* [(23) *and* (24)].—Compound (19) (1.11 g, 2.0 mmol) was treated as described above and work-up gave an oil (*ca.* 1 g). Chromatography with ethyl acetate–hexane (1 : 1) as eluant gave *compound* (23) as an oil (712 mg, 91%); $[\alpha]_D^{23}$ −30°; $\nu_{max.}$ 3 400 (NH) and 1 690 cm^{-1} (CO);

m/e 375 (M^+ − Me); τ 1.73 and 1.88 (1 H, 2 d, $J_{CHO,NH}$ <1 and 12 Hz, simplifies on addition of D_2O, CHO), 2.02 and 2.42(br) (1 H, d and t, $J_{NH,CHO}$ *ca.* 10, $J_{NH,H-1}$ 10 Hz, disappears on addition of D_2O, NH), 4.32 (1 H, d, $J_{H-1,NH}$ 10 Hz, simplifies on addition of D_2O, H-1), 5.28—6.54 (10 H, H-3—6, H_2-7, and 2 OCH_2CH_3), and 8.48—8.90 (18 H, m, 4 Me and 2 OCH_2CH_3) (Found: *m/e* 374.181. $C_{17}H_{28}NO_8$ requires M^+ − Me, 374.181).

Further elution gave *compound* (24) as an oil (44 mg, 6%); $[\alpha]_D^{20}$ −41°; $\nu_{max.}$ 3 400 (NH) and 1 690 cm^{-1} (CO); *m/e* 375 (M^+ − Me); τ 1.74 and 1.92 (1 H, 2 d, $J_{CHO.NH}$ <1 and 12 Hz, simplifies on addition of D_2O, CHO), *ca.* 3.5 (1 H, m, disappears on addition of D_2O, NH), 4.42 (1 H, d, $J_{H-1.NH}$ 9.5 Hz, simplifies on addition of D_2O, H-1), 5.22—6.52 (10 H, m, H-3—6, H_2-7, and 2 OCH_2CH_3), and 8.52—8.91 (18 H, m, 4 Me and 2 OCH_2CH_3) (Found: *m/e* 343.181. $C_{17}H_{28}NO_8$ requires M^+ − Me, 343.181).

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