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CHAIN ELONGATION OF SUGARS WITH ETHYL ISOCYANOACETATE

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ABSTRACT

Addition of ethyl isocyanoacetate to 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose in ethanolic sodium cyanide gave two oxazolines that were hydrolysed during chromatography to two isomeric ethyl 3-*O*-benzyl-6-deoxy-6-formamido-1,2-*O*-isopropylidene-heptofuranuronates. Similarly, 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose gave the 3-*O*-methyl-heptofuranuronates **7** and **11**. Reduction of **7** and **11** gave *N*-methylamino esters that exhibited Cotton effects from which the configurations at C-6 of **7** and **11** were deduced. The chiralities at C-5 of **7** and **11** were established by tetrahydropyranylation of **7** and **11**, followed by consecutive treatment with bis(2-methoxyethoxy)aluminium hydride, periodate, sodium borohydride, and dilute acid, to give 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose and its β-L-*ido* epimer, respectively. Attempts to methylate HO-5 of **7** and **11** resulted in elimination. On formylaminomethylenation (ethyl isocyanoacetate and potassium hydride in tetrahydrofuran), 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose and its 3-*O*-methyl-α-D-*xylo* epimer each gave (*E*)- and (*Z*)-mixtures of alkenes that were hydrogenated to give mixtures of 5,6-dideoxy-6-formamido-heptofuranuronates.

DISCUSSION

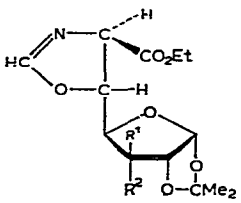
Many less-readily available sugars can be synthesized by the elongation[1] of the carbon chains of other, more-abundant sugar derivatives. We now report the use of ethyl isocyanoacetate to effect such chain elongations.

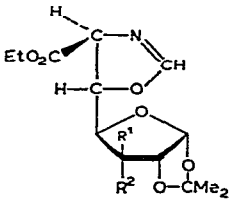
Ethyl isocyanoacetate reacts with aldehydes and ketones[2], in ethanol in the presence of sodium cyanide as base, to give ethyl 2-oxazoline-4-carboxylates which are very readily hydrolysed to the corresponding ethyl esters of *N*-formylamino-β-hydroxy-α-amino acids. In tetrahydrofuran with strong base, aldehydes and ketones[3–5], as well as suitably protected aldonolactones[6,7], react with the reagent to give ethyl α-(formylamino)acrylates (the formylaminomethylenation reaction[8]).

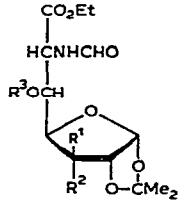
3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose, obtained by the oxidation[9] of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose[10] with sodium periodate, reacted with ethyl isocyanoacetate in ethanolic sodium cyanide to give two

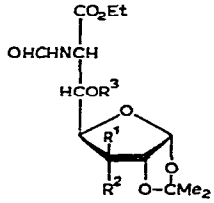
unstable oxazolines, **1** and **3**. Attempted purification of **1** and **3** by column chromatography simultaneously resulted in hydrolysis, and gave, in 71% yield, the ethyl 3-*O*-benzyl-6-deoxy-6-formamido-1,2-*O*-isopropylidene-α-D-heptofuranuronates **5** and **9**, from which the crystalline acetates **6** and **10**, respectively, were obtained. The crystal structures and the stereochemistry of **6** and **10** have been determined[11] by X-ray diffraction methods.

Similar treatment of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose[12] with ethyl isocyanoacetate also gave two heptofuranuronates, **7** and **11**, from which the acetates **8** and **12**, respectively, were obtained. Except for the chiralities at C-5 and C-6, the structures of these compounds were readily deducible from their spectral and analytical properties.









1 $R^1 = H, R^2 = OBzl$
2 $R^1 = OMe, R^2 = H$

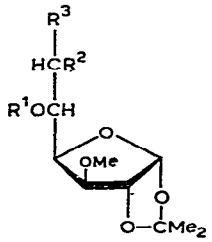
3 $R^1 = H, R^2 = OBzl$
4 $R^1 = OMe, R^2 = H$

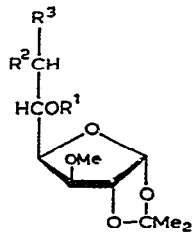
5 $R^1 = R^3 = H, R^2 = OBzl$
6 $R^1 = H, R^2 = OBzl, R^3 = Ac$
7 $R^1 = OMe, R^2 = R^3 = H$
8 $R^1 = OMe, R^2 = H, R^3 = Ac$

9 $R^1 = R^3 = H, R^2 = OBzl$
10 $R^1 = H, R^2 = OBzl, R^3 = Ac$
11 $R^1 = OMe, R^2 = R^3 = H$
12 $R^1 = OMe, R^2 = H, R^3 = Ac$

Bzl = Benzyl

The configurations at C-6 of **7** and **11** followed from the observation that all α-D-amino acids, except the cyclic amino acid proline, give negative Cotton-effect curves[13]. Diborane in tetrahydrofuran[3,5,6] reduced **7** in low yield to the *N*-methylamino ester **13**, which exhibited a negative Cotton effect at 213 nm. Compounds **13** and **7** were therefore α-D-amino acids, *i.e.*, C-6 has the *R* configuration. Similar reduction of **11** gave **20**, which exhibited a positive Cotton effect at 210 nm, thus establishing the *S* configuration for C-6.





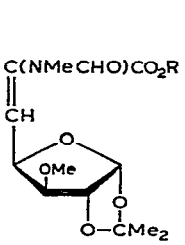
13 $R^1 = H, R^2 = NHMe, R^3 = CO_2Et$
14 $R^1 = THP, R^2 = NHCHO, R^3 = CO_2Et$
15 $R^1 = THP, R^2 = NHMe, R^3 = CH_2OH$
16 $R^1 = THP, R^2, R^3 = O$
17 $R^1 = THP, R^2 = H, R^3 = OH$
18 $R^1 = H, R^2 = H, R^3 = OH$
19 $R^1 = Ac, R^2 = H, R^3 = OAc$

20 $R^1 = H, R^2 = NHMe, R^3 = CO_2Et$
21 $R^1 = THP, R^2 = NHCHO, R^3 = CO_2Et$
22 $R^1 = THP, R^2 = NHMe, R^3 = CH_2OH$
23 $R^1 = THP, R^2, R^3 = O$
24 $R^1 = THP, R^2 = H, R^3 = OH$
25 $R^1 = H, R^2 = H, R^3 = OH$
26 $R^1 = Ac, R^2 = H, R^3 = OAc$

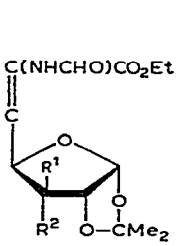
THP = Tetrahydropyranyl

To determine the chirality at C-5 of **7**, the free hydroxyl group was tetrahydropyranylated to give **14**, which behaved as a single compound on t.l.c., but was shown by n.m.r. spectroscopy to be the expected mixture of diastereoisomers. Reduction of **14** with an excess of bis(2-methoxyethoxy)aluminium hydride gave the amino-alcohols **15** which, on treatment in sequence with periodate, sodium borohydride, and dilute acid, gave known[12] 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose[12] (**18**); **18** was converted into the known[14] diacetate **19**. The formation of **18** thus established the *R* configuration at C-5 of **7**. In a similar sequence of reactions, **11** was converted into the L-*ido* derivative **25** and its diacetate **26**, and hence had the *S* configuration at C-5. The structures of **25** and **26** were confirmed by unambiguous synthesis. Treatment of 1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-trityl-α-D-xylohexofuranos-5-ulose[15] with sodium borohydride, dilute acid, and acetic anhydride–pyridine, in sequence, gave a mixture that was fractionated to give the D-*gluco*- and L-*ido*-diacetates, **19** and **26**, respectively. The X-ray data[11] and the results described above show that hydrolysis of the initially formed oxazolines on silica gel leads only to the formation of compounds in which HO-5 and the formamido group at C-6 are *threo*. These results are in agreement with previous findings[2] that aldehydes and ethyl isocyanoacetate give mainly the *trans*-C-4,C-5-substituted oxazolines, which are hydrolysed to *N*-formyl-β-hydroxy-α-amino acid esters without inversion of configuration at C-4 or C-5. Thus, **5** and **9** were formed by hydrolysis of the *trans*-oxazolines **1** and **3**, respectively, and **6** and **10** by hydrolysis of the *trans*-oxazolines **2** and **4**, respectively.

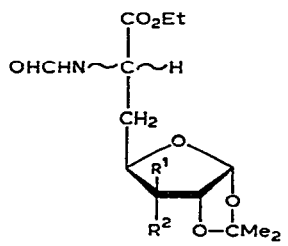
Attempts to methylate HO-5 of **7** and **11** with methyl iodide and silver oxide in *N*,*N*-dimethylformamide resulted in elimination[16] to give an inseparable mixture of (*E*)- and (*Z*)-isomers **27**, and products (**28**) of transesterification. An inseparable mixture of (*E*)- and (*Z*)-acrylic esters **29** was also obtained when 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose was formylaminomethylenated with ethyl isocyanoacetate. Similarly, 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose gave an inseparable mixture of (*E*)- and (*Z*)-isomers **30** under the same conditions. Hydrogenation of the mixtures **29** and **30** gave the respective product mixtures **31** and **32**, each of which behaved as one compound in t.l.c.



27 R = Et
28 R = Me



29 R^1 = H, R^2 = OBzl
30 R^1 = OMe, R^2 = H



31 R^1 = H, R^2 = OBzl
32 R^1 = OMe, R^2 = H

The preparation of other derivatives of **29** and **30** is being investigated with the view of preparing analogues of the carbohydrate moiety of the polyoxins[17].

EXPERIMENTAL

General methods. — All solvent extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* below 50°. T.l.c. and column chromatography were performed on silica gel (Merck GF_{254}; 100 g per g of residue for column separations). Melting points were determined on a hot-stage apparatus. Unless stated otherwise, i.r. spectra and optical rotations were measured for solutions in chloroform with a Perkin–Elmer 237 spectrophotometer and 241 automatic polarimeter (*c* 1.0 ±0.3), respectively. C.d. spectra were recorded on a Jasco J-20 automatic recording spectropolarimeter. Mass spectra (70 eV) were determined with an A.E.I. MS-9 spectrometer by direct insertion. N.m.r. spectra were recorded on a Varian HA-100 instrument for solutions in $CDCl_3$ (internal Me_4Si) unless otherwise stated. For syrups, microanalytical figures are given only for distilled products. Otherwise, accurate mass measurements were made on the detectable ions of highest mass.

*Ethyl 3-O-benzyl-6-deoxy-6-formamido-1,2-O-isopropylidene-*L*-glycero-α-*D*-allo-heptofuranuronate* (**5**) *and its* D-glycero-β-L-talo *isomer* (**9**). — 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-allofuranose[7] (5.25 g, 16.9 mmol) was oxidized with sodium periodate, as described[9] for its *gluco* epimer, to give syrupy 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose (~5.1 g); ν_{max}^{liquid} 1730 cm^{-1}; M^+ 278. A solution of the syrup and ethyl isocyanoacetate (1.9 g, 16.9 mmol) in ethanol (50 ml) was added dropwise to a stirred suspension of sodium cyanide (2 g) in ethanol (100 ml) at 0°. The mixture was left at 25° for 4 h and then concentrated, chloroform (50 ml) was added to the residue, and the solution was filtered, dried, and concentrated to give a syrupy mixture of the oxazolines **1** and **3** and their products of hydrolysis **5** and **9** (t.l.c. and i.r.). On chromatography of this mixture, **1** and **3** were hydrolyzed and only **5** and **9** were obtained. Elution with ethyl acetate–chloroform (4:1) and rechromatography gave a solid which was recrystallized from ethyl acetate–hexane to give **5** (2.31 g, 33%), m.p. 121–123°, $[\alpha]_D^{21}$ +55°; ν_{max} 3500 (OH), 3420 (NH), and 1740 and 1690 cm^{-1} (CO). Mass spectrum: *m/e* 394 ($M^+ - Me$). N.m.r. data: τ 1.79 and 2.01 (bs and d, 1 H, $J_{CHO,NH}$ 12 Hz, simplifies on addition of D_2O, CHO), 2.66 (s, 5 H, Ph), 3.51 (bd, 1 H, $J_{NH,6}$ 9 Hz, disappears on addition of D_2O, NH), 4.31 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.16 (dd, 1 H, $J_{6,NH}$ 9, $J_{6,5}$ 1.5 Hz, simplifies on addition of D_2O, H-6), 5.34 (q, 2 H, OCH_2Ph), 5.43 (t, 1 H, $J_{2,1}$ 3.5 Hz, H-2), 5.70–6.10 (m, 4 H, simplifies with D_2O, H-4,5, OCH_2Me), 6.22 (dd, 1 H, $J_{3,4}$ 8, $J_{3,2}$ 4 Hz, H-3), 6.88 and 7.08 (2 d, 1 H, $J_{OH,5}$ 4 Hz, disappears on addition of D_2O, OH), 8.46 and 8.67 (2 s, 6 H, 2 Me), and 8.75 (t, 3 H, OCH_2Me).

Anal. Calc. for $C_{20}H_{27}NO_8$: C, 58.7; H, 6.7; N, 3.4. Found: C, 58.8; H, 6.7; N, 3.5.

The acetate (**6**) of **5** had m.p. 88–90° (from ethyl acetate–hexane), $[\alpha]_D^{21}$ +20°.

Anal. Calc. for $C_{22}H_{29}NO_9$: C, 58.5; H, 6.5; N, 3.1. Found: C, 58.5; H, 6.7; N, 3.0.

Further elution gave isomer **9** as a glass (2.63 g, 38%), $[\alpha]_D^{21}$ +80°; ν_{max} 3500 (OH), 3420 (NH), and 1740 and 1690 cm^{-1} (CO). Mass spectrum: *m/e* 394

($M^+ - Me$). N.m.r. data: τ 1.82 and 2.12 (bs and d, 1 H, $J_{CHO,NH}$ 12 Hz, simplifies on addition of D_2O, CHO), 2.66 (s, 5 H, Ph), 3.40 (bd, 1 H, $J_{NH,6}$ 10 Hz, disappears on addition of D_2O, NH), 4.31 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.22 (dd, 1 H, $J_{6,NH}$ 10, $J_{6,5}$ 3.5 Hz, simplifies on addition of D_2O, H-6), 5.36 (q, 2 H, OCH_2Ph), 5.51 (t, 1 H, $J_{2,3}$ 4, $J_{2,1}$ 3.5 Hz, H-2), 5.69–6.00 (m, 4 H, simplifies on addition of D_2O, H-4,5, OCH_2Me), 6.11 (dd, 1 H, $J_{3,4}$ 8.5, $J_{3,2}$ 4 Hz, H-3), ~6.98 (bs, 1 H, disappears on addition of D_2O, OH), 8.45 and 8.67 (2 s, 6 H, 2 Me), and 6.74 (t, 3 H, OCH_2Me).

Anal. Calc. for $C_{20}H_{27}NO_8$ ($M^+ - 15$): 394.150. Found: 394.150.

The acetate (**10**) of **9** had m.p. 164–166° (from ethyl acetate–hexane), $[\alpha]_D^{21}$ +98°.

Anal. Calc. for $C_{22}H_{29}NO_9$: C, 58.5; H, 6.5; N, 3.1. Found: C, 58.5; H, 6.6; N, 3.1.

*Ethyl 6-deoxy-6-formamido-1,2-O-isopropylidene-3-O-methyl-*D-glycero-*β*-L-ido-*heptofuranuronate* (**11**) *and its* L-glycero-*α*-D-gluco *isomer* (**7**). — 1,2-*O*-Isopropylidene-3-*O*-methyl-*α*-D-*xylo*-pentodialdo-1,4-furanose[12] (20 g, 0.1 mmol) was treated with ethyl isocyanoacetate in ethanol, in the presence of sodium cyanide as described above, to give a mixture of oxazolines **2** and **4** and their products of hydrolysis **7** and **11** (t.l.c. and i.r. evidence). Chromatography and rechromatography gave only **7** and **11**. Eluted first, with ethyl acetate–ethanol (9:1), was a solid which, on recrystallisation from ethyl acetate–hexane, gave **11** (7.4 g, 22%), m.p. 122–123°, $[\alpha]_D^{20}$ −16°; ν_{max} 3420 (OH and NH), and 1740 and 1690 cm^{-1} (CO). Mass spectrum: *m/e* 318 ($M^+ - Me$). N.m.r. data: τ 1.72 (bs, 1 H, sharpens on addition of D_2O, CHO), 3.18 (b, 1 H, $J_{NH,6}$ 10 Hz, disappears on addition of D_2O, NH), 4.10 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.13 (bd, 1 H, $J_{6,NH}$ 10, $J_{6,5}$ ~1 Hz, simplifies on addition of D_2O, H-6), 5.43 (d, 1 H, $J_{2,1}$ 3.5 Hz, H-2), 5.52 (m, 1 H, $J_{5,4}$ 7, $J_{5,OH}$ ~2, $J_{5,6}$ ~1 Hz, simplifies on addition of D_2O, H-5), 5.78 (q, 2 H, OCH_2Me), 5.92 (dd, 1 H, $J_{4,5}$ 7, $J_{4,3}$ 3 Hz, H-4), 6.13 (d, 1 H, $J_{3,4}$ 3 Hz, H-3), 6.54 (s, 3 H, OMe), 6.87 (bs, 1 H, disappears on addition of D_2O, OH), 8.55 and 8.70 (2 s, 6 H, 2 OAc), and 8.72 (t, 3 H, OCH_2Me).

Anal. Calc. for $C_{14}H_{23}NO_8$: C, 50.5; H, 7.0; N, 4.2. Found: C, 50.7; H, 7.2; N, 4.3.

The acetate (**12**) of **11** had m.p. 134.5–135.5° (from ethyl acetate–hexane), $[\alpha]_D^{20}$ +31°.

Anal. Calc. for $C_{16}H_{25}NO_9$: C, 51.2; H, 6.7; N, 3.7. Found: C, 51.3; H, 6.5; N, 3.6.

Further elution gave a solid which, on recrystallisation from ethyl acetate–hexane, gave **7** (15.2 g, 46%), m.p. 130–132°, $[\alpha]_D^{20}$ −61°; ν_{max} 3420 (NH and OH), and 1740 and 1690 cm^{-1} (CO). Mass spectrum: *m/e* 318 ($M^+ - Me$). N.m.r. data: τ 1.74 and 1.96 (bs and d, 1 H, $J_{CHO,NH}$ 12 Hz, simplifies on addition of D_2O, CHO), 3.12 (bd, 1 H, $J_{NH,6}$ 9 Hz, disappears on addition of D_2O, NH), 4.16 and 4.18 (2 d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.16 (dd, 1 H, $J_{6,NH}$ 9, $J_{6,5}$ 2 Hz, simplifies on addition of D_2O, H-6), 5.42 and 5.44 (2d, 1 H, $J_{2,1}$ 4 Hz, H-2), 5.61 (m, 1 H, simplifies on addition of D_2O, H-5), 5.79 (q, 2 H, OCH_2Me), 5.96 (dd, 1 H, $J_{4,5}$ 8, $J_{4,3}$ 3.5 Hz, H-4), 6.14

(d, 1 H, $J_{3,4}$ 3.5 Hz, H-3), 6.30 (bd, 1 H, $J_{OH,5}$ ~5 Hz, disappears on addition of D_2O, OH), 6.56 (s, 3 H, OMe), 8.56 and 8.70 (2s, 6 H, 2 OAc), and 8.52 (t, 3 H, OCH_2Me).

Anal. Calc. for $C_{14}H_{23}NO_8$: C, 50.5; H, 7.0; N, 4.2. Found: C, 50.5; H, 7.2; N, 4.3.

The acetate (**8**) of **7** had m.p. 127.5–129° (from ethyl acetate–hexane), $[\alpha]_D^{20}$ −84°.

Anal. Calc. for $C_{16}H_{25}NO_9$: C, 51.2; H, 6.7; N, 3.7. Found: C, 51.4; H, 6.7; N, 3.6.

*Ethyl 6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-6-methylamino-*D-glycero-*β*-L-ido-heptofuranuronate* (**20**) *and its* L-glycero-α-D-gluco *isomer* (**13**). — A M solution of diborane in tetrahydrofuran (5 ml) was added to a solution of **11** (330 mg, 1 mmol) in tetrahydrofuran (5 ml) at 0°. The solution was then stirred (25°) for 18 h, ethanol (5 drops) was added, and the solvents were removed. Ethanol (5 ml) was added to the residue and the solution was heated (~80°) for 30 sec. The solvent was again removed, and chloroform (5 ml) was added to the residue. The solution was washed with saturated, aqueous sodium hydrogen carbonate (5 ml) and water (5 ml), and concentrated to give an oil (~40 mg) which was eluted from silica gel with ethyl acetate to give **20** as an oil (15 mg, 5%), $[\alpha]_D^{20}$ −39°; ν_{max}^{liquid} ~3400 (NH and OH) and 1710 cm^{-1} (CO). Mass spectrum: *m/e* 304 (M^+−Me). C.d. data (*c* 1.4 × 10^{-3}, 20°, methanol): $\Delta\varepsilon$ (240) 0, (220) 1.36, (213) 1.73, and (200) 1.24.

Anal. Calc. for $C_{13}H_{22}NO_7$ (M^+ −15); 304.140. Found: 304.141.

Similar treatment of **7** (330 mg, 1 mmol) gave **13** as an oil (41 mg, 13%), $[\alpha]_D^{20}$ −53°; ν_{max}^{liquid} ~3400 (NH and OH) and 1705 cm^{-1} (CO). Mass spectrum: *m/e* 304 (M^+−Me). C.d. data (*c* 2.5 × 10^{-3}, 20°, methanol: $\Delta\varepsilon$ (245) 0, (220) −1.92, (210) −2.44, and (200) −1.64. N.m.r. data: τ 4.14 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.46 (d, 1 H, $J_{2,1}$ 4 Hz, H-2), 5.81 (q, 2 H, OCH_2Me), ~5.90–6.15 (m, 3 H, H-4,5,6), 6.58 (s, 3 H, OMe), ~6.66 (m, 1 H, H-3), 7.56 (s, 3 H, NMe), 7.62 (bs, 1 H, disappears on addition of D_2O, OH), 8.54 and 8.71 (2 s, 6 H, 2 Me), and 8.74 (t, 3 H, OCH_2Me).

Anal. Calc. for $C_{13}H_{22}NO_7$ (M^+ −15): 304.140. Found: 304.141.

*Ethyl 6-deoxy-6-formamido-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-(2-tetrahydropyranyl)-*L-glycero-α-D-gluco- (**14**) *and* -D-glycero-β-L-ido-*heptofuranuronate* (**21**). — A solution of **7** (680 mg) in dry 1,4-dioxane (15 ml) containing 2,3-dihydropyran (0.6 ml) and toluene-*p*-sulphonic acid (15 mg) was kept for 4 h at 20°. T.l.c. then showed that **7** had disappeared. Sodium hydrogen carbonate (100 mg) was added, and the mixture was stirred for 1 h and then concentrated. The residue was extracted with chloroform (100 ml), the extract was filtered and concentrated, and the oily residue was eluted from silica gel with acetone–hexane (1:1) to give **14** as a homogeneous (t.l.c.) oil (770 mg); ν_{max} 3430 (NH), 1745 (ester), and 1690 cm^{-1} (NHCHO). Mass spectrum: *m/e* 417 (M^+), 402 (M^+ −15), and 287 [M^+ −CH(NHCHO)CO_2Et].

Anal. Calc. for $C_{18}H_{28}NO_9$ (M^+ −15): 402.168. Found: 402.166.

Treatment of **11** (1.16 g), as described for **7**, gave **21** as a homogeneous (t.l.c.)

oil (1.37 g); ν_{max} 3430 (NH), 1730 (ester), and 1660 cm^{-1} (NHCHO). Mass spectrum *m/e* 402 ($M^+ - 15$) and 287 [$M^+ - CH(NHCHO)CO_2Et$].

Anal. Calc. for $C_{18}H_{28}NO_9$ ($M^+ - 15$): 402.168. Found: 402.168.

The n.m.r. spectra of **14** and **21** could not be readily analysed, but showed that each was an ~1:1 mixture of diastereoisomers.

1,2-O-Isopropylidene-3-O-methyl-α-D-glucofuranose (**18**) *and its 5,6-diacetate* (**19**). — A solution of **14** (645 mg) in dry benzene (100 ml) was mixed with sodium bis(2-methoxyethoxy)aluminium hydride (5 ml, 70% solution in benzene) and boiled under reflux for 18 h. Ethyl acetate (10 ml) and water (10 ml) were added, and the solvents were removed to leave a residue which was extracted with chloroform (2 × 250 ml). The filtered extracts were concentrated to leave **15** (507 mg) as an oil, *m/e* 346 ($M^+ - 15$) (Calc. for $C_{16}H_{28}NO_7$: M 361), ν_{max} 3400 cm^{-1} (NH and OH). A solution of the oil in ethanol–water (1:1, 40 ml) was treated with sodium metaperiodate (500 mg) for 3 h. Excess of oxidant was destroyed with ethylene glycol (0.2 ml), and the solvent was removed to leave a residue which was extracted with chloroform (2 × 250 ml). The extracts were washed with water (50 ml) and concentrated to leave **16** as an oil (Calc. for $C_{15}H_{26}NO_7 - Me$: 301.129. Found: 301.133). A solution of **16** in ethanol (20 ml) containing sodium borohydride (500 mg) was stirred for 1 h, acetone (10 ml) was then added, and the mixture was concentrated. The residue was extracted with chloroform (5 × 50 ml), and concentration of the extract left **17** (326 mg) as an oil, *m/e* 287 ($M^+ - CH_2OH$) (Calc. for $C_{15}H_{26}O_7$: M 318), ν_{max} 3420 cm^{-1} (OH). Treatment of **17** with 70% aqueous acetic acid (10 ml) at 60° for 45 min, followed by removal of solvents, gave a residue, a solution of which in chloroform (100 ml) was washed with saturated, aqueous sodium hydrogen carbonate and concentrated. The residue was eluted from silica gel with acetone–hexane (1:1) to give an oily product (130 mg) which was identical ($[\alpha]_D$, R_F) with 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose[12].

Conventional treatment of the oil (120 mg) with pyridine–acetic anhydride (1:1, 2 ml) and recrystallisation of the product (143 mg) from chloroform–hexane gave 5,6-di-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose[14] (**19**), m.p. and mixture m.p. 72°.

5,6-Di-O-acetyl-1,2-O-isopropylidene-3-O-methyl-β-L-idofuranose (**26**). — A solution of 1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-trityl-α-D-*ribo*-hexofuranos-5-ulose[15] (2 g) in methanol (50 ml) containing sodium borohydride (500 mg) was stirred for 2 h and then concentrated. A solution of the residue in 70% acetic acid (50 ml) was kept at 70° for 1 h and then concentrated, and the residue was conventionally treated with pyridine–acetic anhydride (1:1, 10 ml). Elution of the product mixture from silica gel with acetone–hexane (1:2) gave, first, **19** (705 mg), m.p. and mixture m.p. 72°.

Eluted second was **26**, as an oil, $[\alpha]_D^{19}$ −35°, ν_{max} 1735 cm^{-1} (ester). Mass spectrum: *m/e* 303 ($M^+ - 15$). N.m.r. data: τ 4.13 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.65 (o, 1 H, $J_{5,4}$ 8, $J_{5,6}$ 3, $J_{5,6'}$ 5 Hz, H-5), 5.45 (d, 1 H, $J_{2,1}$ 4 Hz, H-2), 5.65 (q, 1 H, $J_{6,5}$ 3, $J_{6,6'}$ 12 Hz, H-6), 5.72 (q, 1 H, $J_{4,3}$ 4, $J_{4,5}$ 8 Hz, H-4), 5.90 (q, 1 H, $J_{6',5}$ 5,

$J_{6',6}$ 12 Hz, H-6'), 6.33 (d, 1 H, $J_{3,4}$ 4 Hz, H-3), 6.65 (s, 3 H, OMe), 7.96 (s, 3 H, OAc), 7.98 (s, 3 H, OAc), 8.54 (s, 3 H, Me), and 8.72 (s, 3 H, Me).

Anal. Calc. for $C_{13}H_{19}O_8$ (M^+-15): 303.108. Found: 303.108.

1,2-O-Isopropylidene-3-O-methyl-β-L-idofuranose (**25**) *and its 5,6-diacetate* (**26**). — Following the procedures described above for **14**, **21** was converted *via* **22**–**24** into **25**, isolated as an oil, $[\alpha]_D^{19}$ −56°, ν_{max} 3480 cm^{-1} (OH). Mass spectrum: *m/e* 219 (M^+-Me). N.m.r. data: τ 4.04 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.42 (d, 1 H, $J_{2,1}$ 4 Hz, H-2), 5.82 (q, 1 H, $J_{4,3}$ 4, $J_{4,5}$ 6 Hz, H-4), 5.98 (m, 1 H, H-5), 6.23 (d, 1 H, $J_{3,4}$ 4 Hz, H-3), 6.34 (m, 2 H, H-6,6'), 6.62 (s, 3 H, OMe), 6.90 (s, 2 H, 2 OH, exchanges with D_2O), 8.65 (s, 3 H, Me), and 8.70 (s, 3 H, Me).

Anal. Calc. for $C_{10}H_{18}O_6$: C, 51.3; H, 7.8. Found: C, 51.3; H, 7.9.

Treatment of **25** (170 mg) with pyridine–acetic anhydride (1:1, 4 ml), followed by elution of the product from silica gel with acetone–hexane (1:2), gave **26** (180 mg) as an oil which was identical (n.m.r., $[\alpha]_D$, and R_F) with authentic 5,6-di-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-idofuranose described above.

Ethyl 5,6-dideoxy-1,2-O-isopropylidene-3-O-methyl-6-(N-methylformamido)-α-D-xylo-hept-5-enofuranuronate (**27**) *and its methyl analogue* (**28**). — A mixture of **7** (330 mg, 1 mmol), methyl iodide (2 ml), silver oxide (500 mg), and *N,N*-dimethylformamide (2 ml) was shaken at 5° for 2 days. Chloroform (10 ml) was added, the mixture was filtered and concentrated, and benzene (10 ml) was added to the residue. The solution was filtered, washed with saturated, aqueous sodium thiosulphate (2 × 5 ml) and water (10 ml), and concentrated, and the residue (~350 mg) was eluted from silica gel with ethyl acetate–hexane (3:1) to give **27** as an oil (197 mg, 60%); ν_{max}^{liquid} 1730 and 1690 (CO), and 1660 cm^{-1} (C=C). N.m.r. data: τ 1.84 and 2.02 (2 s, 1 H, CHO), 2.97 and 3.05 (2 d, 1 H, $J_{5,4}$ 8 Hz, H-5), 4.09 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.25 (dd, 1 H, $J_{4,5}$ 8, $J_{4,3}$ 3 Hz, H-4), 5.73 and 5.77 (2q, 2 H, OCH_2Me), 6.18 and 6.29 (2 d, 1 H, $J_{3,4}$ 3 Hz, H-3), 6.59 and 6.61 (2 s, 3 H, OMe), 6.86 and 6.98 (2 s, 3 H, NMe), and 8.54–8.76 (m, 9 H, 2 Me, OCH_2Me). The n.m.r. spectrum indicated that the oil was an ~1:4 mixture of the isomers **27**.

Anal. Calc. for $C_{14}H_{20}NO_7$ (M^+-15): 314.124. Found: 314.123.

Further elution gave **28** as an oil (82 mg, 26%); ν_{max}^{liquid} 1730 and 1690 (CO), and 1660 cm^{-1} (C=C). N.m.r. data: τ 1.85 and 2.04 (2 s, 1 H, CHO), 2.97 and 3.05 (2 d, 1 H, $J_{5,4}$ 8 Hz, H-5), 4.10 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.26 (dd, 1 H, $J_{4,5}$ 8, $J_{4,3}$ 3.5 Hz, H-4), 5.39 and 5.44 (2 d, 1 H, $J_{2,1}$ 3.5 Hz, H-2), 6.20 and 6.23 (2 s, 3 H, COOMe), ~6.22 and 6.31 (2 d, 1 H, $J_{3,4}$ 3.5 Hz, H-3), 6.60 and 6.62 (2 s, 3 H, OMe), 6.87 and 6.98 (2 s, 3 H, NMe), and 8.55 and 8.69 (2 s, 6 H, 2 Me). The n.m.r. spectrum indicated that the oil was an ~1:4 mixture of the isomers **28**.

Anal. Calc. for $C_{14}H_{21}NO_7$ (M^+): 315.132. Found: 315.131.

Compound **11** reacted similarly to give **27** and **28**.

Ethyl 3-O-benzyl-5,6-dideoxy-6-formamido-1,2-O-isopropylidene-α-D-ribo-hept-5-enofuranuronate (**29**), *and its hydrogenation to a mixture* (**31**) *of ethyl 3-O-benzyl-5,6-dideoxy-6-formamido-1,2-O-isopropylidene-α-D-allo-heptofuranuronate and its β-L-talo epimer.* — 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose

(2.78 g, 10 mmol), prepared as described previously, was treated[6] with ethyl isocyanoacetate and potassium hydride in tetrahydrofuran to give **29** as a brown syrup; ν_{max}^{liquid} 3380 (NH), 1720 and 1700 (CO), and 1640 cm^{-1} (C=C). Mass spectrum: *m/e* 391 (M^+). The impure **29** (attempts to purify the compound by chromatography led to decomposition) was hydrogenated[5] to give a pale-yellow oil, which was eluted from silica gel with ethyl acetate–chloroform (1:1) to give **31** as a colourless oil; ν_{max} 3400 (NH), and 1730 and 1690 cm^{-1} (CO). N.m.r. data: τ 1.88 and 1.94 (2 bs, 1 H, sharpens on addition of D_2O, CHO), 2.68 (s, 5 H, Ph), ~3.44 (m, 1 H, disappears on addition of D_2O, NH), 5.18–6.19 (m, 7 H, H-2,4,6, OCH_2Ph, OCH_2Me), 6.62 (m, 1 H, H-3), 7.63–8.37 (m, 2 H, H-5,5'), 8.48 and 8.68 (2 s, 6 H, 2 Me), and 8.77 (t, 3 H, OCH_2Me).

Anal. Calc. for $C_{20}H_{27}NO_7$ ($M^+ - 15$): 378.155. Found: 378.156.

*Ethyl 5,6-dideoxy-6-formamido-1,2-O-isopropylidene-3-O-methyl-α-*D*-xylo-hept-5-enofuranuronate* (**30**). — 1,2-*O*-Isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose (14.1 g, 70 mmol) was treated[6] with ethyl isocyanoacetate and potassium hydride in tetrahydrofuran to give a syrup which was eluted from silica gel with ethyl acetate–chloroform (1:1) to give **30** as a syrup (13.4 g, 61%); ν_{max} 3380 (NH), 1720 and 1700 (CO), and 1640 cm^{-1} (C=C). N.m.r. data: τ ~1.50–1.86 (m, 1 H, simplifies on addition of D_2O, CHO), 2.40 (bs, 1 H, disappears on addition of D_2O, NH), 3.35–3.58 (m, 1 H, H-5), 4.16 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.14 (dd, 1 H, $J_{4,5}$ 7, $J_{4,3}$ 3.5 Hz, H-4), 5.38 (d, 1 H, $J_{2,1}$ 4 Hz, H-2), 5.72 (q, 2 H, OCH_2Me), 5.97 and 6.24 (2 m, 1 H, H-3), 6.57 (s, 3 H, OMe), 8.50 and 8.67 (2 s, 6 H, 2Me), and 8.67 (t, 3 H, OCH_2Me).

Anal. Calc. for $C_{13}H_{18}NO_7$ ($M^+ - 15$): 300.108. Found: 300.107.

*Ethyl 5,6-dideoxy-6-formamido-1,2-O-isopropylidene-3-O-methyl-α-*D*-gluco-heptofuranuronate and its β-*L*-ido epimer.* — Compound **30** was hydrogenated[5] to give a pale-yellow oil, which was eluted from silica gel with ethyl acetate–chloroform (1:1). Recrystallization of the product from ethyl acetate–hexane gave the title mixture (**32**) of epimers (6.58 g, 82%), m.p. ~69–80°; ν_{max} 3400 (NH), and 1735 and 1685 cm^{-1} (CO). N.m.r. data: τ 1.80 (bs, 1 H, sharpens on addition of D_2O, CHO), 3.40 (m, 1 H, disappears on addition of D_2O, NH), 4.15 and 4.19 (2 d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.26–5.49 (m, 2 H, simplifies on addition of D_2O, H-2,6), 5.70–5.92 (m, 3 H, H-4, OCH_2Me), 6.36 and 6.42 (2 d, 1 H, $J_{3,4}$ 3 Hz, H-3), 6.60 and 6.62 (2 s, 6 H, 2 OMe), 7.64–8.01 (m, 2 H, H-5,5'), 8.55 and 8.71 (2 s, 6 H, 2 Me), and 8.74 (t, 3 H, OCH_2Me).

Anal. Calc. for $C_{14}H_{23}NO_7$: C, 53.2; H, 7.4; N, 4.4. Found: C, 53.2; H, 7.3; N, 4.4.

REFERENCES

1 L. Hough and A. C. Richardson, in W. Pigman and D. Horton (Eds.), *The Carbohydrates*, Vol. 1A, Academic Press, New York, 1972, pp. 113–163; J. Staněk, M. Černý, J. Kocourek, and J. Pacák, *The Monosaccharides*, Academic Press, New York, 1963, pp. 123–174.
2 D. Hoppe and U. Schöllkopf, *Justus Liebigs Ann. Chem.*, 763 (1972) 1–16.
3 A. J. Brink and A. Jordaan, *Carbohydr. Res.*, 34 (1974) 1–13.

4 U. SCHÖLLKOPF, F. GERHARDT, R. SCHRÖDER, AND D. HOPPE, *Justus Liebigs Ann. Chem.*, 766 (1972) 116–129.
5 K. BISCHOFBERGER, A. J. BRINK, O. G. DE VILLIERS, R. H. HALL, AND A. JORDAAN, *J. Chem. Soc., Perkin Trans. 1*, (1977) 1472–1476.
6 R. H. HALL, K. BISCHOFBERGER, S. J. EITELMAN, AND A. JORDAAN, *J. Chem. Soc., Perkin Trans. 1*, (1977) 743–753.
7 R. H. HALL, K. BISCHOFBERGER, S. J. EITELMAN, AND A. JORDAAN, *J. Chem. Soc., Perkin Trans. 1*, (1977) 2236–2241.
8 D. HOPPE, *Angew. Chem. Int. Ed. Engl.*, 13 (1974) 789–804; U. SCHÖLLKOPF, *ibid.*, 9 (1970) 763–773.
9 D. HORTON AND F. O. SWANSON, *Carbohydr. Res.*, 14 (1970) 159–171.
10 J. S. BRIMACOMBE AND O. A. CHING, *Carbohydr. Res.*, 8 (1968) 82–88.
11 J. C. A. BOEYENS, A. J. BRINK, R. H. HALL, A. JORDAAN, AND J. A. PRETORIUS, *Acta Crystallogr. Sect. B*, 33 (1977) 3059–3066.
12 J. KOVAR AND H. H. BAER, *Can. J. Chem.*, 51 (1973) 1801–1811.
13 G. C. BARRETT, *Amino-Acids, Pept., Proteins*, 7 (1967) 1, and earlier volumes.
14 J. GIGG AND R. GIGG, *J. Chem. Soc., C*, (1966) 82–86.
15 J. YOSHIMURA, T. IIDA, H. WAKAI, AND M. FUNABASHI, *Bull. Chem. Soc. Jpn.*, 46 (1973) 3207–3209.
16 J. G. BUCHANAN, *Int. Rev. Sci., Org. Chem. Ser. One*, 7 (1973) Chapter 2.
17 R. J. SUHADOLNIK, *Nucleoside Antibiotics*, Wiley, New York, 1970, Chapter 5.