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SYNTHESIS OF BRANCHED-CHAIN SUGARS BY REACTION OF GLYCOSULOSES WITH α-METALATED ISOCYANOACETIC ESTERS[1]

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ABSTRACT

Addition of ethyl isocyanoacetate in strongly basic medium to the glycosuloses 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**) and 1,2-*O*-isopropylidene-5-*O*-trityl-D-*erythro*-pentos-3-ulose (**2**) gave the unsaturated derivatives (*E*)- and (*Z*)-3-deoxy-3-*C*-ethoxycarbonyl(formylamino)methylene-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3** and **4**), and (*E*)-3-deoxy-3-*C*-ethoxycarbonyl-(formylamino)methylene-1,2-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranose (**5**). In weakly basic medium, ethyl isocyanoacetate and **1** gave 3-*C*-ethoxycarbonyl(formylamino)methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**12**) in good yield. The oxidation of **3** and **4** with osmium tetraoxide to 3-*C*-ethoxalyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**17**), and its subsequent reduction to 3-*C*-(*R*)-1′,2′-dihydroxyethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**18**) and its (*S*) epimer (**19**) and to 3-*C*-(*R*)-ethoxycarbonyl(hydroxy)methyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**21**) and its (*S*) epimer (**22**) are described. Hydride reductions of **12** yielded the corresponding 3-*C*-(1-formylamino-2-hydroxyethyl), 3-*C*-(2-hydroxy-1-methylaminoethyl), and 3-*C*-(*R*)-ethoxycarbonyl(methylamino)methyl derivatives (*13*, *14* and *16*). Catalytic reduction of **3** and **4** yielded the 3-deoxy-3-*C*-(*R*)-ethoxycarbonyl-(formylamino)methyl derivative **6** and its 3-*C*-(*S*) epimer. Further reduction of **6** gave 3-deoxy-3-*C*-(*R*)-(1-formylamino-2-hydroxyethyl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**23**) which was deformylated with hydrazine acetate to 3-*C*-(*R*)-(1-amino-2-hydroxyethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**24**). The configurations of the branched-chains in **16**, **21**, and **22** were determined by o.r.d.

INTRODUCTION

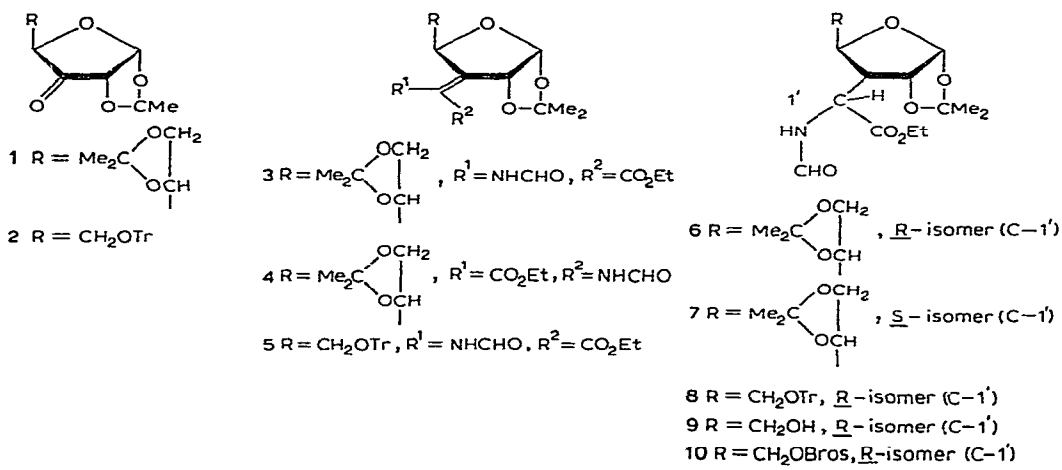
The antiviral and cytostatic properties of branched-chain nucleosides of which the substituents on C-3′ are modified[2] have led to considerable interest in the synthesis of carbohydrates with branching at C-3. For this reason, the use of modified Wittig reagents on ketoses, and especially on 3-uloses, for the preparation[3] of a large number of unsaturated, branched-chain carbohydrates has proved very useful. The unsaturated compounds can be employed[4] for the synthesis of novel, saturated,

branched-chain carbohydrates and nucleosides. Schöllkopf[5] has pointed out that C=C bonds can be formed, not only by using Wittig reagents, but also by reacting α-metalated isocyanoacetic esters with ketones and aldehydes. The products are β-substituted α-formylacrylates which can enter into a wide range of reactions. It has also been shown[6] that the correct choice of conditions for this reaction makes it possible to isolate the 4-alkoxycarbonyl-2-oxazoline intermediates which, under the influence first of strong base and then acid, rearrange to form α-formylacrylates.

We now report the preparation and some reactions of novel, saturated and unsaturated carbohydrates obtained from suitably protected uloses and ethyl isocyanoacetate in the presence of base, and the development of a facile method for the preparation of carbohydrates bearing (*R*)-α-amino acid derivatives as branched chains. As only very low yields of carbohydrates bearing (*S*)-α-amino acid branched-chains could be prepared by this route, the method of choice for the preparation of these (*S*)-compounds remains that of Rosenthal[4].

RESULTS AND DISCUSSION

Ethyl isocyanoacetate reacted with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**) in tetrahydrofuran containing an equivalent of sodium hydride to give, after neutralization, a 9:1 mixture of the unsaturated compounds **3** and **4** in 70% yield. When a mixture of 1,2-*O*-isopropylidene-5-*O*-trityl-D-*erythro*-pentos-3-ulose (**2**) and one equivalent of sodium hydride in tetrahydrofuran was treated with ethyl isocyanoacetate, only the *E* isomer **5** could be isolated subsequently.



By treating **3**, **4**, or **5** with Raney nickel in refluxing ethanol for 30 min, it was possible to obtain the respective hydrogenation products (**6**, **7**, or **8**). The trityl group of **8** could be removed by hydrogenolysis over Adams' catalyst in acetic acid, and the product was used to prepare the crystalline *p*-bromobenzenesulphonate **10**, which was

amenable to X-ray analysis. The analysis showed[7] that **10** was 5-*O*-*p*-bromobenzenesulphonyl-3-deoxy-3-*C*-(*R*)-ethoxycarbonyl(formylamino)methyl-1,2-*O*-isopropylidene-α-D-ribofuranose and, assuming that cis hydrogenation of **5** had taken place, it follows that **5** must have *E* stereochemistry. The 5,6-*O*-isopropylidene group of the allose derivative **6** was removed under controlled, acidic conditions to give a glycol which was cleaved with periodate. The resulting aldehyde was reduced with sodium borohydride, and the product was reacted with *p*-bromobenzenesulphonyl chloride in pyridine to give a substance identical to **10**. This result established that ethyl isocyanoacetate and strong base react with the oxo sugars **1** and **2** to give, as major products, unsaturated carbohydrates with *E* stereochemistry.

The low-field n.m.r. spectrum of **3** in deuteriochloroform at 34° exemplified the complex spin–spin coupling pattern which can arise from the partial double-bond character of the amide [C(O)–N] bond. It could be seen that the *N*-formyl group existed in solution as a mixture of cis and trans isomers, as the formyl proton appeared as two broad peaks each integrating for one half of a proton at τ 1.86 (*s*) and 1.52 (*d*, J_{trans} 11 Hz). The latter signal collapsed to a singlet on addition of D_2O and, simultaneously, a broad absorption band (τ 0.90–1.20), assigned to the NH proton, disappeared.

At 0°, the broad absorption band (τ 0.90–1.20) assignable to NH was resolved into two signals τ 0.83 (*d*, J_{trans} 11 Hz) and 0.96 (*s*), whereas the peaks of the two formyl proton species at τ 1.86 (*s*) and 1.52 (*d*, J_{trans} 11 Hz) were much sharper. The rest of the spectrum at 0° also showed more fine structure than the spectrum obtained at 34°, with doublets now appearing as double doublets, and the triplets and quartet appearing as double triplets and a double quartet.

The cis and trans proton signals of the secondary *N*-formyl group could not be detected in deuteriomethyl sulphoxide at 30°.

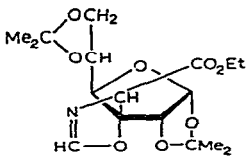
The *Z* isomer **4** in deuteriochloroform at 10° showed cis and trans coupling constants between the secondary amino and formyl protons similar to those observed for **3**, again illustrating the diamagnetic anisotropy caused by the hindered, internal rotation of the amide moiety.

As the low-field n.m.r. region of **5** was obscured by the resonances of the aromatic protons, the cis–trans forms of the amide moiety could not be distinguished.

A mixture of the 4-ethoxycarbonyl-2-oxazoline **11** and the branched-chain allose derivative **12** was formed when ethyl isocyanoacetate was reacted with the oxo sugar **1** in the presence of ethanolic sodium cyanide. The presence of **11** in the crude reaction mixture was indicated by i.r. data, namely $\nu_{max}^{CHCl_3}$ 3515, 3410 (OH and NH), 1730 (ester), 1685 (amide), and 1640 cm^{-1} (oxazoline ring)[6], but the compound could not be purified because attempted chromatography led to hydrolysis to form the branched-chain compound **12**.

Reduction of **12** with one equivalent of lithium aluminium hydride gave the formamido-alcohol **13**, and with excess sodium bis(2-methoxyethoxy)aluminium hydride gave the *N*-methylamino-alcohol **14**. Periodate cleavage of **14** and reduction of the reaction mixture with sodium borohydride gave 1,2:5,6-di-*O*-isopropylidene-

α-D-allofuranose[17] and the known[9] branched-chain derivative **15**, in low yield, to prove that **12** is a substituted allose and not a substituted glucose derivative.



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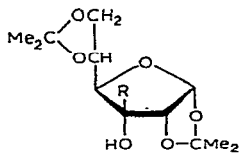


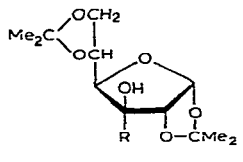
12 R = CH(NHCHO)CO$_2$Et

13 R = CH(NHCHO)CH$_2$OH

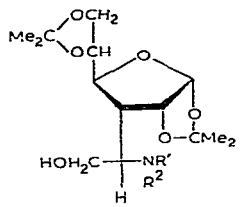
14 R = CH(NHCH$_3$)CH$_2$OH

15 R = CH$_2$OH

16 R = CH(NHCH$_3$)CO$_2$Et



17 R = COCO$_2$Et
18 R = CHOHCH$_2$OH (R)
19 R = CHOHCH$_2$OH (S)
20 R = CH$_2$OH
21 R = CHOHCO$_2$Et (R)
22 R = CHOHCO$_2$Et (S)



23 R^1 = CHO, R^2 = H
24 R^1 = R^2 = H
25 R^1,R^2 = *o*-HOPhCH=

The configuration at C-1′ of **12**, and consequently of **13** and **14**, follows from the observation that all L-amino acids, except the cyclic amino acid proline, give positive Cotton-effect curves[10]. Diborane in tetrahydrofuran reduced **12** to the *N*-methylamino ester **16** which exhibited a negative Cotton effect at ~203 nm. The sign of the Cotton effect indicates that **12**, and therefore **13** and **14**, has a side chain with the *R* configuration.

Oxidation of the olefins **3** or **4** with osmium tetraoxide gave the α-keto-ester **17** in good yield, showing that they differ only in their substitution patterns around the double bond. As **3** is the *E* isomer, **4** must be the *Z* isomer. Although it could reasonably be assumed that attack by the oxidant would take place from the less-hindered side of the unsaturated sugars (**3** and **4**), the configuration at C-3 of the α-keto-ester **17** was firmly established as follows. Reduction of **17** with lithium aluminium hydride gave an epimeric mixture of **18** and **19**. These two epimers could be separated by column chromatography, and each reacted with periodate to give an aldehyde which yielded the known[13] branched-chain derivative **20** on reduction with borohydride.

Reduction of **17** with sodium borohydride gave an epimeric mixture of the hydroxy-esters (**21** and **22**), which was also fractionated by column chromatography. The configuration of each isomer was then determined by comparison of its o.r.d. spectrum with that of L-lactic acid[13]. It was shown that the faster-moving compound (**21**) had the *R*, and the slower-moving compound (**22**) the *S*, configuration at the branched-chain asymmetric carbon atom. Reduction of **21** with lithium aluminium hydride gave a compound identical to **19**, which therefore must be 3-*C*-(*S*)-1′,2′-dihydroxyethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, and **18** must be the isomer with the *R* configuration at C-1′.

Some reactions of hydride reagents with **6** were also investigated. Lithium aluminium hydride reacted with **6** to give the partially reduced product **23**. The *N*-formyl group in **23** was hydrolyzed with hydrazine acetate[12] to give the primary amino compound **24**, from which an *N*-salicylidene derivative **25** was prepared. The o.r.d. curve of **25** displayed a positive Cotton effect, which is usually associated with the *S* configuration of a carbon atom bearing the *N*-salicylidene moiety[14]. As the *R* configuration had already been established for the side chain of **10** and therefore for the side chain of **25** by X-ray analysis[7], this salicylidene derivative is another example of those sugar derivatives for which Inouye[15] has found that the correlation between the sign of the Cotton effect and configuration no longer holds. He has pointed out that intramolecular hydrogen-bonding, and not only configuration, probably also plays a role in determining the sign and strength of the Cotton effects of these salicylidene derivatives.

The preparation of nucleosides from **3** will be reported elsewhere.

EXPERIMENTAL

General methods. — M.p.'s were determined with a Kofler hot-stage apparatus. I.r. spectra were measured with a Perkin–Elmer model 257 spectrophotometer, and n.m.r. spectra were recorded on a Varian HA-100 instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard, unless otherwise stated. Chemical shifts are given on the τ-scale. Optical rotations were measured on solutions in chloroform with a Bendix-NPL Automatic Polarimeter Type 143 (*c* 1.0±0.3). Mass spectra were determined with an A.E.I. MS-9 spectrometer, using the direct-insertion technique and an ionizing voltage of 70 eV. O.r.d. and c.d. spectra were determined at 20° in a 1-cm cell with a Jasco J-20 automatic recording spectropolarimeter. All solvent extracts were dried (Na_2SO_4), and solvent was then removed below 50° *in vacuo*. T.l.c. and p.l.c. were performed on silica gel GF_{254} (Merck); spots were detected with u.v. light at 254 nm, with iodine vapour, or with cerium(IV) sulphate. Silica gel for column chromatography refers to Merck reagent.

(E)-*3-Deoxy-3-C-ethoxycarbonyl(formylamino)methylene-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose* (**3**). — To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[16] (**1**; 3.8 g, 15 mmoles) and ethyl isocyanoacetate (1.69 g, 15 mmoles) in dry tetrahydrofuran (50 ml) at 0°, sodium hydride (720 mg, 15 mmoles; 50% suspension in oil, washed with hexane) was slowly added with stirring. The reaction mixture was then left at 25° for 6 h. The tetrahydrofuran was removed, and water (200 ml) and acetic acid (2 ml) were added to the residue. The solution was extracted with chloroform (3 × 100 ml), and the extract was washed with aqueous sodium hydrogen carbonate and concentrated to leave a mixture of **3** and **4** as an oil (3.1 g) which partially crystallized on standing. Fractional crystallization from acetone–hexane gave compound **3** (2.5 g) as colourless needles, m.p. 130–132°, $[\alpha]_D^{25}$ +148°, $\nu_{max}^{CHCl_3}$ 3280 (NH), 1720 (ester), and 1695 cm^{-1} (amide). Mass spectrum: *m/e* 371 (M^+), 356 ($M^+ - 15$). N.m.r. data [$(CD_3)_2SO$]: τ 0.2 (*s*, exchanges with D_2O,

N*H*), 1.98 (*s*, C*H*O), 4.21 (*d*, $J_{1,2}$ 4 Hz, H-1), 4.56 (*d*, $J_{2,1}$ 4 Hz, H-2), 4.81 (*d*, $J_{4,5}$ 4 Hz, H-4), 5.88 (*q*, *J* 7 Hz, CH_3–CH_2), 5.90–6.80 (*m*, H-5,6,6'), 8.40–9.20 (*m*, $2CMe_2$, –CH_2CH_3).

Anal. Calc. for $C_{17}H_{25}NO_8$: C, 55.0; H, 6.8; N, 3.8. Found: C, 55.2; H, 6.8; N, 3.9.

(Z)-*3-Deoxy-3-*C-*ethoxycarbonyl(formylamino)methylene-1,2:5,6-di-*O-*isopropylidene-α-*D-*glucofuranose* (**4**). — The mother liquors from the fractional crystallization of **3** were evaporated to leave an oil (600 mg), which was eluted from silica gel (50 g) with benzene–hexane–acetone (10:7:4) to afford crystalline **3** (300 mg) and **4** (250 mg) which crystallized from acetone–hexane as colourless plates, m.p. 101–102°, $[\alpha]_D^{20}$ +278°, $\nu_{max}^{CHCl_3}$ 3390 (NH), 1720 (sh, ester) and 1695 cm^{-1} (amide). Mass spectrum: *m/e* 371 (M^+), 356 (M^+-15). N.m.r. data (34°): τ 1.77 (*s*, C*H*O), 2.14 (*s*, N*H*), 4.03 (*d*, $J_{1,2}$ 4.5 Hz, H-1), 4.53 (*s*, broad, H-4), 4.68 (*d*, $J_{2,1}$ 4.5 Hz, H-2), 5.78 (*q*, *J* 7 Hz, CH_3–CH_2), 5.80–6.60 (*m*, H-5,6,6'), 8.40–8.80 (*m*, $2CMe_2$, –CH_2CH_3). At 10°, the one-proton signal at τ 1.77 was resolved into two signals for C*H*O at τ 1.62 (*d*, $J_{CHO,NH\,trans}$ 12 Hz) and 1.82 (*s*, $J_{CHO,NH\,cis}$ <2 Hz). The amido-proton singlet at τ 2.14 was also resolved into two signals for N*H* at τ 2.02 (*d*, $J_{NH,CHO\,trans}$ 13 Hz) and 2.14 (*d*, $J_{NH,CHO\,cis}$ <2 Hz).

Anal. Calc. for $C_{17}H_{25}NO_8$: C, 55.0; H, 6.8; N, 3.8. Found: C, 54.8; H, 6.6; N, 3.5.

(E)-*3-Deoxy-3-*C-*ethoxycarbonyl(formylamino)methylene-1,2-*O-*isopropylidene-5-*O-*trityl-α-*D-*ribofuranose* (**5**). — Reaction of the glycosulose **2** (1.72 g, 4 mmoles), ethyl isocyanoacetate (452 mg, 4 mmoles), and sodium hydride (50% in oil; 200 mg, 4.1 mmoles) at 0° in tetrahydrofuran (20 ml), and work-up as for the preparation of **3** and **4**, gave **5** as an oil which crystallized from methanol as colourless needles (1.74 g), m.p. 184–186°, $[\alpha]_D^{25}$ +158°, $\nu_{max}^{CHCl_3}$ 3390 (NH) and 1690 cm^{-1} (broad, CO). Mass spectrum: *m/e* 243 (Ph_3C^+). N.m.r. data: τ 2.00–3.30 (15 aromatic H, N*H*, C*H*O), 3.92 (*d*, $J_{1,2}$ 4 Hz, H-1), 4.32 (*d*, $J_{2,1}$ 4 Hz, H-2), 4.82 (broad *s*, H-4), 5.68 (*q*, *J* 7 Hz, CH_3–CH_2), 6.40–7.00 (*m*, H-5,5'), 8.2–9.0 (*m*, CMe_2), 8.69 (*t*, *J* 7 Hz, CH_3–CH_2).

Anal. Calc. for $C_{32}H_{33}NO_7$: C, 70.7, H, 6.1; N, 2.6. Found: C, 70.9; H, 6.2; N, 2.6.

*3-Deoxy-3-*C-(R)-*ethoxycarbonyl(formylamino)methyl-1,2:5,6-di-*O-*isopropylidene-α-*D-*allofuranose* (**6**). — A suspension of **3** (1 g) and freshly prepared Raney nickel (10 g) in ethanol (50 ml) was heated under reflux for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated to give a syrup (0.9 g) which crystallized from acetone–hexane as colourless plates, m.p. 146–147°, $[\alpha]_D^{23}$ +71°, $\nu_{max}^{CHCl_3}$ 3410 (NH), 1740 (ester), and 1685 cm^{-1} (amide). Mass spectrum: *m/e* 358 (M^+-15). N.m.r. data: τ 1.77 (*s*, C*H*O), 2.96 (*d*, $J_{NH,1'}$ 10 Hz, disappears with Et_3N–D_2O, N*H*), 4.26 (*d*, $J_{1,2}$ 4 Hz, H-1), 4.68 (*dd*, $J_{NH,1'}$ 10 Hz, $J_{1',3}$ 5 Hz, collapses to a *d*, $J_{1',3}$ 5 Hz, on addition of Et_3N–D_2O, H-1'), 5.32 (*t*, $J_{2,1} = J_{2,3} =$ 4 Hz, H-2), 5.77 (*q*, *J* 7 Hz, CH_3–CH_2), 5.88–6.12 (*m*, H-4,5,6,6'), 7.40 (*q*, $J_{3,2}$ 4.5, $J_{3,4}$ 9.0, $J_{3,1'}$ 4.5 Hz, H-3), 8.43 (*s*, CH_3), 8.60 (*s*, CH_3), 8.67 (*s*, $2CH_3$), 8.71 (*t*, CH_3–CH_2).

Anal. Calc. for $C_{17}H_{27}NO_8$: C, 54.7; H, 7.3; N, 3.8. Found: C, 54.4; H, 7.4; N, 3.8.

*3-Deoxy-3-*C-(S)-*ethoxycarbonyl(formylamino)methyl-1,2:5,6-di-*O-*isopropylidene-α-*D-*allofuranose* (**7**). — Hydrogenation of **4**, using the method employed to obtain **6** from **3**, gave **7** as an oil $[\alpha]_D^{23}$ +76°. Mass spectrum: *m/e* 373 (M^+), 358 (M^+-15). N.m.r. data: τ 1.79 (*s*, C*H*O), 2.98 (*d*, $J_{NH,1'}$ 6.5 Hz, N*H*), 4.28 (*d*, $J_{1,2}$ 4.0 Hz, H-1), 4.94 (*t*, $J_{1',3} = J_{1',NH}$ 6.5 Hz, H-1'), 5.32 (*t*, $J_{2,1} = J_{2,3} = 4.0$ Hz, H-2), 5.64–6.12 (*m*, H-4,5,6,6', CH_3–CH_2), 7.43 (*o*, $J_{3,2}$ 4.5, $J_{3,4}$ 9, $J_{3,1'}$ 6.7 Hz, H-3), 8.54 (*s*, $2CH_3$), 8.64 (*s*, CH_3), 8.70 (*t*, *J* 7 Hz, CH_3CH$_2$), 8.72 (*s*, CH_3).

Anal. Calc. for $C_{17}H_{27}NO_8$: C, 54.7; H, 7.3; N, 3.8. Found: C, 54.6; H, 7.3; H, 3.9.

*3-Deoxy-3-*C-(R)-*ethoxycarbonyl(formylamino)methyl-1,2-*O-*isopropylidene-5-*O-*trityl-α-*D-*ribofuranose* (**8**). — A suspension of **5** (1.09 g) and Raney nickel (10 ml, settled suspension) in ethanol was treated as for **6** to give an oil from which a trace of triphenylmethane was removed by crystallization from acetone–hexane to give colourless needles of **8** (530 mg), m.p. 171–173°, $[\alpha]_D^{22}$ +57°, $\nu_{max}^{CHCl_3}$ 3420 (NH), 1740 and 1720 cm^{-1} (CO), Mass spectrum: *m/e* 468 (M^+-Ph). N.m.r. data: τ 1.85 (*s*, CHO), 2.30–2.90 (*m*, Ph_3C), 3.13 (broad *d*, disappears on addition of D_2O–Et_3N, $J_{NH,1'}$ 10 Hz, N*H*), 4.11 (*d*, $J_{1,2}$ 4 Hz, H-1), 5.22 (*q*, $J_{1',3}$ 5 Hz, collapses to *d* with D_2O–Et_3N, H-1'), 5.29 (*t*, $J_{1,2} = J_{2,3} = 4$ Hz, H-2), 5.81 (*q*, *J* 7 Hz, CH_3–CH_2), 5.85 (*m*, H-4), 6.48 (*q*, $J_{5',5''}$ 10, $J_{5',4}$ 3 Hz, H-5'), 6.88 (*q*, $J_{5'',5'}$ 10, $J_{5'',4}$ 3 Hz, H-5''), 7.14 (*m*, H-3), 8.48 (*s*, CH_3), 8.69 (*s*, CH_3), 8.75 (*t*, J 7 Hz, CH_3–CH_2).

Anal. Calc. for $C_{32}H_{35}NO_7$: C, 70.4; H, 6.5; N, 2.6. Found: C, 70.6; H, 6.5; N, 2.6.

*5-O-p-Bromobenzenesulphonyl-3-deoxy-3-*C-(R)-*ethoxycarbonyl(formylamino)-methyl-1,2-*O-*isopropylidene-α-*D-*ribofuranose* (**10**). — (*a*) A solution of **8** (408 mg) in glacial acetic acid (25 ml) was hydrogenated over Adams' catalyst (115 mg) at 20 p.s.i. for 4 days at 20°. Elution of the product from silica gel (10 g) with methanol–chloroform (1:15) separated unchanged starting material and triphenylmethane from an oil **9** (175 mg), *m/e* 288 (M^+-15) (Calc. for $C_{13}H_{21}NO_7$: M 303). The unpurified oil **9** was dissolved in dry pyridine (2 ml) containing *p*-bromobenzenesulphonyl chloride (125 mg), and the mixture was kept at 20° for 20 h before being poured into ice–water (50 ml). The product was extracted with chloroform in the usual manner, purified by p.l.c. on silica gel with ethyl acetate, and crystallized from acetone–hexane to give **10** as colourless needles, m.p. 141–142°, $[\alpha]_D^{23}$ +29°. These crystals were used for an X-ray analysis[7].

Anal. Calc. for $C_{19}H_{24}BrNO_9S$: C, 43.7; H, 4.6; N, 2.7. Found: C, 43.9; H, 4.7; N, 2.8.

(*b*) To a solution of **3** (1 g) in methanol (30 ml), 10% sulphuric acid (3 ml) was added, and the mixture was kept at room temperature for 3 h, then neutralized with aqueous sodium hydroxide, and evaporated. The residue was dissolved in methanol, and the solvent was again evaporated to leave the crystalline 5,6-diol (0.55 g), M^+ 333

(calc. for $C_{14}H_{23}NO_8$: M 333). To a well-stirred solution of the foregoing compound (0.5 g) in water (3 ml), sodium metaperiodate (320 mg, 1 mol.) was added, and the reaction was monitored with potassium iodide–starch paper. When all the periodate had disappeared, the mixture was extracted with chloroform (5 × 30 ml). Evaporation of the extract gave an oil (374 mg), a solution of which in ethanol (5 ml) was treated with sodium borohydride (200 mg) during 10 min. After stirring for 1 h, water (50 ml) was added, and the mixture was kept overnight before extraction with chloroform (5 × 50 ml). The solvent was removed, and the oily residue (311 mg) was eluted from silica gel (10 g) with chloroform–methanol (19:1) to give **9** as an oil (115 mg), which was sulphonylated in the usual manner to give a product identical to **10** described in (*a*).

3-C-Ethoxycarbonyl(formylamino)methyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**12**). — A solution of ethyl isocyanoacetate (2.9 g, 60 mmoles) in ethanol (50 ml) was added to a suspension of sodium cyanide (5 g) and **2** (15.2 g, 60 mmoles) in ethanol (10 ml), and the mixture was stirred at room temperature for 18 h. The solvent was evaporated to leave a syrup which was extracted with carbon tetrachloride (200 ml). Evaporation of the extract left an oil (24 g) containing two compounds (t.l.c.). The faster moving compound could not be purified as part of it was hydrolysed to the slower moving compound on attempted chromatography. The i.r. spectrum of the mixture showed peaks at $\nu_{max}^{CHCl_3}$ 3515, 3410 (NH and OH), 1730, 1685 (ester and amide), and 1640 cm^{-1} (C=N). The presence of the last absorption band indicated[6] that the mixture contained the 2-oxazoline **11**.

The mixture (5.2 g), together with chloroform (50 ml) and water (2 ml), was stirred with silica gel (column-chromatography grade) for 72 h, then filtered, and evaporated to leave a crystalline residue (5 g) containing only the slower moving compound. Recrystallization from benzene gave colourless crystals of **12**, m.p. 132–134°, $[\alpha]_D^{20}$ +21°, $\nu_{max}^{CHCl_3}$ 3510, 3405 (OH, NH), 1730 (ester), and 1685 cm^{-1} (amide). Mass spectrum: *m/e* 389 (M^+), 374 (M^+-15), 356 (M^+-H_2O-15). N.m.r. data: τ 1.80 (*s*, C*H*O), 2.91 (*d*, $J_{NH,1'}$ 6 Hz, disappears on addition of D_2O–Et_3N, N*H*), 4.33 (*d*, $J_{1,2}$ 4 Hz, H-1), 5.36 (*d*, $J_{2,1}$ 4 Hz, H-2), 5.38 (*d*, $J_{1',NH}$ 6 Hz, H-3), 5.60–6.40 (*m*, CH_3CH_2, H-4,5,6,6') 6.63 (*s*, disappears on addition of D_2O–Et_3N, O*H*), 8.30–8.90 (*m*, $4CH_3$, CH_3–CH_2).

Anal. Calc. for $C_{17}H_{27}NO_9$: C, 52,4; H, 7.0; N, 3.6. Found: C, 52.1; H, 7.1; N, 3.6.

3-C-(1-Formylamino-2-hydroxyethyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**13**). — A solution of **12** (396 mg; 1.02 mmoles) in dry ether (50 ml) was treated with lithium aluminium hydride (58 mg; 1.53 mmoles), and the mixture was stirred at room temperature for 2 h. M Sodium hydroxide (1 ml) was added and stirring was continued until a clear solution was obtained. The mixture was then filtered and the solvent was removed to give an oily product (300 mg), which was eluted from silica gel (30 g) with chloroform–methanol (10:1) to afford **13** (210 mg) which, after crystallization from acetone–hexane, was obtained as colourless plates, m.p. 159°, $[\alpha]_D^{22}$ +4°, $\nu_{max}^{CHCl_3}$ 3350 (broad) (NH and OH), 1625 cm^{-1} (amide).

Anal. Calc. for $C_{15}H_{25}NO_8$: C, 51.9; H, 7.3; N, 4.0. Found: C, 51.9; H, 7.3; N, 4.0.

3-C-(2-Hydroxy-1-methylaminoethyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**14**) *and 3-C-hydroxymethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose* (**15**). — A solution of **12** (2.2 g) in dry benzene (100 ml) was treated with sodium bis-(2-methoxyethoxy)aluminium hydride (10 ml, 70% solution in benzene), and the mixture was refluxed for 20 h. Ethyl acetate (10 ml) and water (10 ml) were added and all solvent was removed to leave a residue, which was dissolved by heating with sodium hydroxide (6 g) in water (10 ml) for 3 min at 60°. The cooled mixture was extracted with chloroform (5 × 50 ml), and the extract was evaporated to leave **14** (1.5 g) as an oil, *m/e* 318 ($M^+ - 15$) (calc. for $C_{15}H_{27}NO_7$: *M* 333), $\nu_{max}^{CHCl_3}$ 3530, 3350 cm^{-1} (NH and OH). As some decomposition of the oil took place on silica gel, it was not further purified but was dissolved in ethanol–water (1:1, 50 ml) and treated with sodium metaperiodate (0.8 g, ~0.8 equiv.). When the periodate was consumed (30 min, sodium iodide–starch paper), sodium borohydride (1 g) was added and stirring was continued for 10 min. Acetone (10 ml) was then added and the mixture was evaporated *in vacuo* to leave a residue which was extracted with chloroform (5 × 50 ml). Evaporation of the extract left an oil (580 mg) which was eluted from silica gel (20 g) with chloroform–methanol (19:1) to give, first, 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose [200 mg, identical (m.p., m.m.p., R_F) with an authentic sample[17]], and then an oil (94 mg). Elution of this oil from silica gel (10 g) with acetone–benzene (1:1) afforded **15** as an oil which gave fine, colourless needles, m.p. 74°, when it was covered with hexane. The crystals were identical (mass spectrum, R_F) with an authentic sample prepared by another route[9].

Phosgene (0.2 ml, 12.5% in benzene) was added at 0° to a solution of **15** (30 mg) in dry benzene (5 ml) containing pyridine (1 ml), and the solution was kept at room temperature for 30 min. The mixture was poured into ice–water (10 ml) and extracted with chloroform (4 × 5 ml), and the extract was evaporated. Traces of pyridine were removed from the residue by distillation of toluene (2 × 5 ml) therefrom. The product crystallized from acetone–hexane as colourless needles, m.p. 114–115°, which were identical (m.p., m.m.p., mass spectrum, R_F, i.r. and X-ray powder data) to authentic[9] $3,3^1$-*O*-carbonyl-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose.

3-C-(R)-Ethoxycarbonyl(methylamino)methyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**16**). — A solution of **12** (970 mg) in tetrahydrofuran (50 ml) was saturated with diborane by bubbling a mixture of the reagent and nitrogen through the solution (with exclusion of air and moisture). The reaction mixture was left at room temperature for 4 h and then poured into ice-cold, aqueous sodium hydroxide (8%, 50 ml). Hydrogen peroxide (30%, 10 ml) was added, and stirring was continued for 10 min before the addition of ice–water (100 ml) and extraction with chloroform (4 × 100 ml). The combined extracts were washed with cold water (2 × 50 ml) and evaporated to leave an oil (850 mg), which was eluted from silica gel (25 g) with chloroform–methanol (25:1) to give **16** as an oil which crystallized from hexane as colourless needles, m.p. 88–89°, $[\alpha]_D^{22}$ +9°, $\nu_{max}^{CHCl_3}$ 3510, 3320 (OH and NH), and

1730 cm^{-1} (ester). Mass spectrum: *m/e* 360 (M^+-15), 342 (M^+-15-H_2O), and 302 (M^+-CO_2Et). N.m.r. data: τ 4.46 (*d*, $J_{1,2}$ 4 Hz, H-1), 5.26 (*d*, $J_{2,1}$ 4 Hz, H-2), 5.30–6.30 (*m*, H-4,5,6,6', CH_2CH_3), 6.46 (*s*, H-1'), 7.00–8.00 (broad, disappears with D_2O, N*H*), 7.58 (*s*, NCH_3), 8.30–8.80 (*m*, $4CH_3$, CH_2CH_3). O.r.d. (*c* 7.5×10^{-4}, methanol): $[\phi]_{195}$ −4230°, $[\phi]_{202}$ −5470°, $[\phi]_{210}$ −4480°, $[\phi]_{220}$ −3130°, $[\phi]_{230}$ −1250°, $[\phi]_{250}$ −310°, $[\phi]_{260}$ 0.

Anal. Calc. for $C_{17}H_{29}NO_8$: C, 54.5; H, 7.8; N, 3.7. Found: C, 54.4; H, 7.9, N, 3.8.

3-C-Ethoxalyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**17**). — To a solution of **3** (2.707 g, 7.3 mmoles) in dry pyridine (50 ml) osmium tetraoxide (3 g, 11.8 mmoles) was added, and the mixture was stirred for 24 h. Sodium metabisulphite (6 g) dissolved in water (90 ml) was added to the dark solution and stirring was continued for 1 h. The mixture was poured into ice–water (300 ml) and extracted with chloroform (5 × 50 ml). The combined extracts were washed successively with cold 3M hydrochloric acid (3 × 50 ml), saturated, aqueous sodium hydrogen carbonate (2 × 50 ml), and water (3 × 50 ml). Removal of the solvent gave **17** as an oil (2.593 g, 98%).

An analytical sample, prepared by distillation (0.01 mmHg) of **17** in a micro-distillation tube, had $[\alpha]_D^{22}$ +76°, $\nu_{max}^{CHCl_3}$ 3510 (OH), 1745 (CO_2Et), and 1715 cm^{-1} (CO). Mass spectrum: *m/e* 345 (M^+-15). N.m.r. data: τ 3.99 (*d*, $J_{1,2}$ 4 Hz, H-1), 5.08 (*d*, $J_{4,5}$ 7 Hz, H-4), 5.39 (*d*, $J_{2,1}$ 4 Hz, H-2), 5.65 (*q*, *J* 7 Hz, CH_3CH_2), 5.72–6.06 (*m*, H-5,6), 8.50 (*s*, CH_3), 8.62 (*t*, *J* 7 Hz, CH_3CH_2), 8.64 (*s*, CH_3), 8.71 (*s*, $2CH_3$).

Anal. Calc. for $C_{16}H_{24}O_9$: C, 53.3; H, 6.7. Found: C, 53.3; H, 6.8.

Oxidation of **4** (116 mg) with osmium tetraoxide (100 mg), as described for **3**, also gave **17** as an oil (94 mg).

3-C-(R)-1',2'-Dihydroxyethyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**18**) *and its* (*1'S*)*-epimer* (**19**). — A solution of the α-keto-ester **17** (242 mg) in dry ether (10 ml) was treated at room temperature with lithium aluminium hydride (240 mg). After 2 h, excess reagent was destroyed with ethyl acetate (1 ml). The solution was then shaken with aqueous potassium hydroxide (5%, 20 ml) and extracted with chloroform (5 × 20 ml). The combined extracts were washed with water (1 × 20 ml) and evaporated to give a mixture (200 mg) of two compounds (t.l.c.). Elution of the mixture from silica gel (10 g) with methanol–chloroform (1:20) gave, first, **18** (90 mg) and then **19** (90 mg).

Compound **18** was obtained as an oil $[\alpha]_D^{23}$ +25° (*c*, 3.9). Mass spectrum: *m/e* 305 (M^+-15). N.m.r. data: τ 4.15 (*d*, $J_{1,2}$ 3.8 Hz, H-1), 5.55 (*d*, $J_{2,1}$ 3.8 Hz, H-2), 5.63–6.16, (*m*, H-1',2',4,5,6,6'), 8.51–8.75 (*m*, $2CMe_2$).

Anal. Calc. for $C_{14}H_{24}O_8$: C, 52.5, H, 7.6. Found: C, 52.7; H, 7.7.

Compound **19** crystallized from acetone–hexane as colourless needles, m.p. 92–93°, $[\alpha]_D^{23}$ +20°. Mass spectrum: *m/e* 305 (M^+-15). N.m.r. data: τ 4.16 (*d*, $J_{1,2}$ 3.8 Hz, H-1), 5.54 (*d*, $J_{2,1}$ 3.8 Hz, H-2), 5.63–6.19 (*m*, H-1',2',4,5,6,6'), 8.50–8.78 (*m*, $2CMe_2$).

Anal. Calc. for $C_{14}H_{24}O_8$: C, 52.5; H, 7.6. Found: C, 52.8; H, 7.7.

The preparation of **20** *from* **19** *and* **18**. — A solution of **19** (135 mg, 0.4 mmole) in methanol (10 ml) was treated in the dark with an aqueous solution of sodium metaperiodate (90 mg, 0.42 mmole) until potassium iodide–starch paper gave a negative test. Water (25 ml) was added and the mixture was extracted with chloroform (3 × 25 ml). The extract was evaporated to give an oil (94 mg), $\nu_{max}^{CHCl_3}$ 1773 cm^{-1} (C=O), which was not purified but was dissolved in dry ether (10 ml) and was treated with lithium aluminium hydride (20 mg). Work-up of this reaction mixture, as for the preparation of **18** and **19**, gave an oil (88 mg) which crystallized from acetone–hexane to give **20** containing one mole of acetone, m.p. 86–87° (lit.[11] m.p. 84–86°), which was identical (mass spectrum, R_F) to authentic[13] 3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**20**).

Similar treatment of compound **18** also gave **20**.

3-C-(R)-Ethoxycarbonyl(hydroxy)methyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**21**) *and its* (S)*-epimer* (**22**). — A solution of sodium borohydride (250 mg; 6.6 mmoles) in ethanol (50 ml) was added dropwise to a stirred solution of the α-keto-ester **17** (2.3706 g; 6.6 mmoles) in ethanol (50 ml). After stirring for an additional 2 h at room temperature, the solvent was removed *in vacuo* and the residue was extracted with chloroform. The extract was evaporated to yield a mixture (2.3 g) of two compounds (t.l.c.) as an oil. Elution of this oil from silica gel with chloroform–methanol (19:1) yielded a faster moving compound **21** as an oil (950 mg), and another fraction (590 mg) which consisted of a mixture of both compounds. After repeated chromatography, the slower moving compound **22** was obtained pure (10 mg) as an oil.

Compound **21** had $[\alpha]_D^{20}$ +38°; o.r.d. data (*c* 1.09×10^{-4}, ethanol): $[\Phi]_{210}$ +3820, $[\Phi]_{217}$ 0, $[\Phi]_{220}$ −1660, $[\Phi]_{230}$ −3570, $[\Phi]_{240}$ −1910, $[\Phi]_{250}$ −1330, $[\Phi]_{260}$ −660, $[\Phi]_{270}$ −330, $[\Phi]_{280}$ 0. Mass spectrum: *m/e* 347 ($M^+ - 15$).

Anal. Calc. for $C_{16}H_{26}O_9$: C, 53.0; H, 7.2. Found: C, 52.8; H, 7.1.

Compound **22** had $[\alpha]_D^{20}$ +31°; o.r.d. data (*c* 0.88×10^{-4}, ethanol): $[\Phi]_{225}$ 0, $[\Phi]_{230}$ +2220, $[\Phi]_{240}$ +3130, $[\Phi]_{250}$ +2880, $[\Phi]_{260}$ +2350, $[\Phi]_{270}$ +1980, $[\Phi]_{280}$ +1890. Mass spectrum: *m/e* 347 ($M^+ - 15$).

Reduction of **21** (113 mg) with lithium aluminium hydride (20 mg) in dry ether (20 ml), using the procedure described for the preparation of **18** and **19** from **17**, gave an oil (88 mg) which crystallized from acetone–hexane as colourless needles, and was identical (m.p., m.m.p., $[\alpha]_D$, R_F) to **19**.

3-Deoxy-3-C-(R)-(1-formylamino-2-hydroxyethyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**23**). — A solution of **6** (966 mg; 2.6 mmoles) in dry ether (25 ml) was treated at room temperature with lithium aluminium hydride (147 mg; 3.9 mmoles). After 3 h, excess reagent was destroyed with ethyl acetate (1 ml), and the mixture was shaken with aqueous potassium hydroxide (5%, 25 ml) and extracted with chloroform (7 × 25 ml). The combined extracts were washed with water (25 ml) and evaporated to give an oil (855 mg), which was eluted from silica gel (100 g) with chloroform–methanol (19:1) to give an oil (550 mg; 65%). Crystallization from hexane–acetone gave **23** as colourless needles, m.p. 95–97°, $[\alpha]_D^{22}$ +26°.

Anal. Calc. for $C_{15}H_{25}NO_7$: C, 54.4; H, 7.6; N, 4.2. Found: C, 54.4; H, 7.6; N, 4.1.

3-Deoxy-3-C-(R)-(*2-hydroxy-1*-N-*salicylideneiminoethyl*)-*1,2:5,6-di*-O-*isopropylidene-α*-D-*allofuranose* (**25**). — A solution of **23** (1.12 g) in ethanol (5 ml) was added to a hydrazine acetate solution (5 ml), prepared by mixing equimolar amounts of hydrazine hydrate and glacial acetic acid[12]. The mixture was stirred at 60° and monitored by t.l.c. (chloroform–methanol, 19:1). After completion of the reaction (30 h), saturated, aqueous sodium hydrogen carbonate (50 ml) was added and organic solvent in the mixture was evaporated. The aqueous solution was extracted with chloroform (6 × 50 ml), and the extract was evaporated *in vacuo* to give **24** as an oil (850 mg; 83%), $\nu_{max}^{CHCl_3}$ 3400 cm^{-1} (NH_2). Mass spectrum: *m/e* 288 ($M^+ - 15$). The oil was not purified but was used directly for the preparation of **25**.

A solution of **24** (817 mg; 2.7 mmoles) in methanol (3 ml) was added to a solution of salicylaldehyde (378 mg; 3.1 mmoles) in methanol (2 ml), and the mixture was heated at ~95° for 15 min and then left overnight at room temperature[18]. The crystalline deposit was recrystallized from acetone–hexane to give **25** as yellow needles (692 mg), m.p. 156–157°, $[\alpha]_D^{22}$ +129°. Electronic spectrum (ethanol): $\log \varepsilon_{410}$ 2.98, $\log \varepsilon_{316}$ 3.45, $\log \varepsilon_{279}$ 3.43, $\log \varepsilon_{257}$ 3.98. O.r.d. (*c* 1.67×10^{-4}, ethanol): $[\Phi]_{340}$ +7320, $[\Phi]_{330}$ +8540, $[\Phi]_{320}$ +6010; $[\Phi]_{310}$ 0; $[\Phi]_{300}$ −3660.

Anal. Calc. for $C_{21}H_{29}NO_7$: C, 61.9; H, 7.2; N, 3.4. Found: C, 61.6; H, 7.0; N, 3.3.

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