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GLYCOSYL* α-AMINO ACIDS

PART III. SYNTHESIS OF D- AND L-2-(1,2:5,6-DI-*O*-ISOPROPYLIDENE-α-D-GALACTOFURANOS-3-YL)GLYCINE

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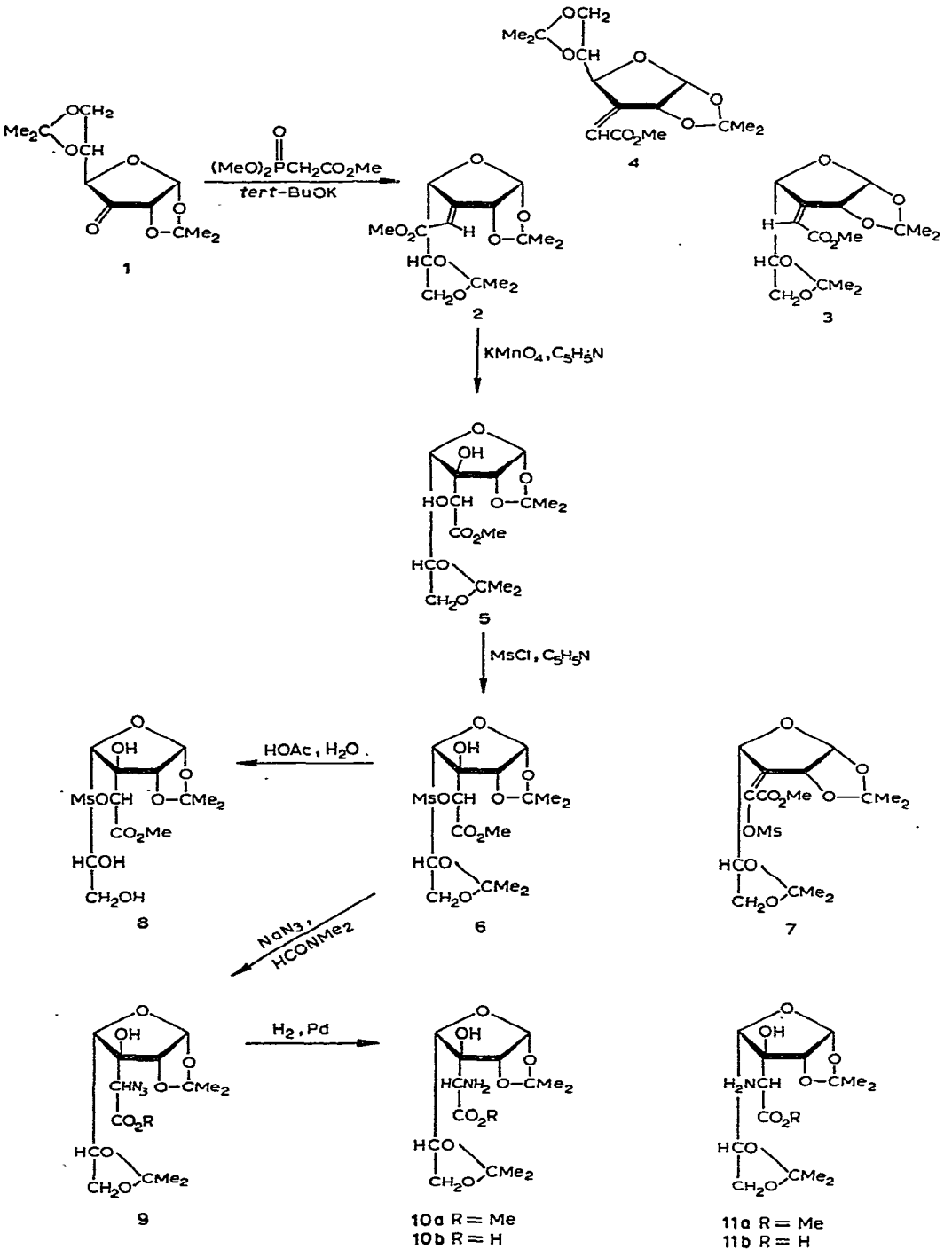
ABSTRACT

Stereospecific hydroxylation of (*E*)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-(methoxycarbonylmethylene)-α-D-*xylo*-hexofuranose (**2**) with potassium permanganate in pyridine afforded pure 3-*C*-[(*R*)-hydroxy(methoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**5**) in 55% yield. Mesylation of the diol **5** in pyridine yielded the monomethanesulfonate **6** and, in addition, a small proportion of an unsaturated, exocyclic sulfonate **7**. Treatment of **6** with sodium azide in *N*,*N*-dimethylformamide and reduction of the resultant α-azido ester **9** afforded methyl D- (and L-) 2-(1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranos-3-yl)glycinate, (**11a**) and (**10a**), respectively. Basic hydrolysis of **11a** and **10a** yielded D- and L-2-(1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranos-3-yl)glycine (**11b**) and (**10b**), respectively. The structures of the glycosyl α-amino acids were correlated with that of L-alanine by circular dichroism.

DISCUSSION

In continuation of studies[1] on the synthesis of branched-chain glycosyl α-amino acids that are structural analogs of the sugar moiety of the polyoxins[2–6] we now report the synthesis of two substituted D-galactofuranose analogs having an L- and D-α-amino acid moiety attached by a carbon–carbon linkage to C-3 of the furanosyl ring. The rationale for this synthesis has been outlined previously[1,7] and the present work arose as a consequence of an unexpected epimerization at C-4 of the sugar discovered during application of the Wittig reaction to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[8] (**1**). When ketose **1** was treated with phosphonoacetic acid trimethyl ester in the presence of potassium *tert*-butoxide in *N*,*N*-dimethylformamide at room temperature the main products were (*Z*)- and (*E*)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-(methoxycarbonylmethylene)-α-D-*ribo*-hexofuranose[9] (**4**), together with a variable yield (5–12%) of a 5:1 mixture of (*E*)- and (*Z*)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-(methoxycarbonylmethylene)-α-D-*xylo*-hexofuranose (**2**) and (**3**) respectively. The yield of the *xylo*-unsaturated sugars appears to be dependent upon the purity of the potassium *tert*-butoxide. With absolutely pure, anhydrous base

*Used in an extended sense, through the indicated, non-anomeric carbon atom.


(MeO)2PCH2CO2Me
tert-BuOK
KMnO4, C5H5N
MsCl, C5H5N
HOAc, H2O
NaN3, HCONMe2
H2, Pd
1
2
3
4
5
6
7
8
9
10a R = Me
10b R = H
11a R = Me
11b R = H

the yield of isomerized product is negligible, whereas with base containing an appreciable quantity of *tert*-butyl alcohol a 12% yield of **2** and **3** was obtained. No attempt was made to determine if the latter yield was optimal. Interestingly, other investigators[10] have encountered isomerized products during the treatment, with bases, of cyano sugars having exocyclic unsaturation.

The (*E*)-*xylo* unsaturated sugar (**2**) was readily obtained pure by crystallization of the mixture of **2** and **3** from *n*-hexane. The structure of **2** was assigned from its n.m.r. spectrum and on mechanistic considerations (discussed later). In the (*E*)-isomer (**2**), H-4 is under the deshielding influence[11] of the ester group, and thus exhibits a pair of doublets at lower field (τ 4.60) than the (*Z*)-isomer (**3**) (τ 5.32 having $J_{1',4}$ 1.8 Hz and $J_{4,5}$ 6 Hz). Furthermore, in the (*Z*)-isomer, H-2 and the ester group are *cis* to each other, causing deshielding of H-2 to τ 3.6 ($J_{1,2}$ 3.6 Hz, $J_{1',2}$ 1.2 Hz), in contrast to the much higher τ value of H-2 of the (*E*)-isomer (5.15, $J_{1,2}$ 4.0 Hz, $J_{1',2}$ 0.75 Hz).

Stereospecific *cis*-dihydroxylation of the pure (*E*)-isomer (**2**) with potassium permanganate in pyridine at −10° afforded crystalline 3-*C*-[(*R*)-hydroxy(methoxycarbonyl)methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (**5**) in 55% yield. Application of the same oxidation conditions to the mixture of unsaturated esters **2** and **3** afforded a mixture of diols from which **5** could be obtained by crystallization from ethanol. The diol corresponding to the stereospecific oxidation of **3** could not be detected by t.l.c., nor could it be isolated. As previously[1], the structure of the diol **5** was assigned on the basis of negative circular dichroism[13], and from the rationale of approach of the permanganate ion from the side[12] of **2** the less sterically hindered residue. Therefore, the diol **5** is suggested to be 3-*C*-[(*R*)-hydroxy(methoxycarbonyl) methyl]-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose.

Treatment of **5** with methanesulfonyl chloride in pyridine at room temperature resulted in the expected monosulfonate **6** in 60% yield. In addition to **6**, the unusual dehydrated methanesulfonate (**7**) was obtained in 30% yield after chromatography. Compound **7** was present before chromatography, and does not appear to be an artifact of the separation process. Because **6** decomposed if left for several days at room temperature it required use soon after isolation unless it was stored at low temperature. Similarly, compound **6** decomposed when treated with 65% acetic acid to give several products, some of which decolorized potassium permanganate spray; these were formed in addition to the expected product (**8**) in which the 5,6-*O*-isopropylidene group had been selectively removed.

Treatment of **6** with sodium azide in *N*,*N*-dimethylformamide under anhydrous conditions at 60° in the dark gave the expected displacement-product **9**. Immediate reduction of the latter with hydrogen over 5% palladium on charcoal in anhydrous benzene[1] yielded the D- and L-α-amino esters (**11a**) and (**10a**) in 38 and 9.5% yields, respectively. The azido-ester **9** underwent reduction considerably more slowly than did the epimeric azido-ester having the *gluco* configuration, taking 7 h in the former and 1.25 h in the latter case, possibly because of steric hindrance to the reduction of **9**.

The proposed reason for the non-stereospecificity in the sulfonate displacement

and subsequent formation of both possible amino esters has been previously discussed[1]. It is thought to result from two competing displacement-mechanisms, one via the intermolecular SN2 mechanism to afford the amino ester having the opposite configuration from the starting diol. The second mechanism invokes intramolecular displacement of the sulfonate by the tertiary hydroxyl group to give an epoxide, followed by opening of the epoxide at the exocyclic position by azide to yield an α-amino ester having the same configuration as the starting diol.

The configurations of the resultant α-amino esters were assigned from evidence of c.d. studies on the esters and the free amino acids obtained after basic hydrolysis.[14] Methyl L-2-(1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranos-3-yl)glycinate exhibited an intense positive Cotton effect at 204 nm in 95% ethanol. Conversely, methyl D-2-(1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranos-3-yl)glycinate exhibited an intense positive Cotton effect at 206 nm in 95% ethanol, in contrast to the positive Cotton effects observed with other L-amino acids[14].

Hydrolysis of **11a** and **10a** in 1.25% aqueous methanolic sodium hydroxide followed by deionization afforded in high yield the crystalline amino acids D- and L-2-(1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranos-3-yl)glycine, **11b** and **10b**, respectively. The c.d. spectra of these compounds revealed intense Cotton effects of the same sign as the corresponding α-amino esters, when determined in 0.5M hydrochloric acid in 95% ethanol at a wavelength of 210 nm, thus supporting the configurational assignments for **10a** and **11a**.

EXPERIMENTAL

General. — P.m.r. spectra were determined in deuteriochloroform solution with Me_4Si as the internal standard by using a Varian XL-100 spectrometer. Optical rotations were measured at ambient temperature with a Perkin–Elmer Model 141 automatic polarimeter. The c.d. measurements were performed on a Jasco J-20 and a J-5 automatic recording spectropolarimeter at room temperature, and i.r. spectra were recorded on a Perkin–Elmer 337 spectrometer. Column chromatography was performed on t.l.c. grade silica gel, without binder, under a pressure of 4–8 lb. in^{-2} and flow rates of 70–140 ml h^{-1}; t.l.c. on Silica Gel G was used to monitor all reactions. Melting points were determined on a Leitz microscope heating-stage, model 350, and are corrected. Chemical analyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

(E)- *and* (Z)-*3-Deoxy-1,2:5,6-di*-O-*isopropylidene-3*-C-(*methoxycarbonyl*)-*methylene-α*-D-ribo-*hexofuranose* (**4**) *and* (E)- *and* (Z)-*3-deoxy-1,2:5,6-di*-O-*isopropylidene-3*-C-(*methoxycarbonyl*)*methylene-α*-D-xylo-*hexofuranose* (**2**) *and* (**3**). — According to the previously published procedure[1] the anhydrous ketose **1**, (20 g) was treated with phosphonoacetic acid trimethyl ester (17.5 g) and potassium *tert*-butoxide (9.5 g) in *N,N*-dimethylformamide (60 ml). The product (17.9 g) was chromatographed on silica gel (Davison, 60–200 mesh, column dimensions:45 × 7.5cm) with 4:1 benzene–ethyl acetate as developer. The more-mobile zone (**4**, yield 11.0 g, 45%) has been pre-

viously characterized. The less-mobile zone (2.8 g, 12%) was shown to consist of two new unsaturated sugars (**2** and **3**) in a ratio of 5:1 as shown by n.m.r. The major isomer crystallized readily from the mixture in *n*-hexane, and is tentatively assigned the structure **2**: m.p. 68.0–69.0°, $[\alpha]_D^{29} -67.0°$ (*c* 1, chloroform); τ ($CDCl_3$) 3.86 (d.d, 1, $J_{1',2}$ 0.5 Hz, $J_{1',4}$ 2 Hz, H-1')*, 4.13 (d, 1, $J_{1,2}$ 4 Hz, H-1), 4.60 (d.d, 1, $J_{4,5}$ 6.5 Hz, H-4), 5.15 (d.d, 1, H-2), 5.43 (q, 1, $J_{5,6}$ 6.5 Hz, H-5), 6.10 (d, 2, H-6), 6.25 (s, 3, CO_2CH_3). Irradiation at τ 4.13 collapsed the double doublet at τ 5.15 to a doublet (*J* 0.5 Hz), and similarly irradiation at τ 4.60 collapsed the signal at τ 3.86 to a narrow doublet (*J* 0.5 Hz).

Anal. Calc. for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 57.23; H, 6.95.

3-C-[(R)-hydroxy(methoxycarbonyl)methyl]-1,2:5,6-di-O-isopropylidene-α-D-galactofuranose (**5**). — Oxidation of pure **2** (1.71 g) in water (20 ml) and pyridine (40 ml) was conducted as previously described[1] at −10°, with potassium permanganate (0.95 g) in water (40 ml) added dropwise as oxidant. The reaction mixture was extracted with chloroform (6 × 150 ml), and the combined organic extracts were washed with water, dried (sodium sulfate), and evaporated to yield a pale-yellow syrup (1.04 g, 55%) that crystallized on trituration with ethanol. An analytical sample of **5** was prepared by recrystallization from ethanol; m.p. 145.5–146.5°, $[\alpha]_D^{29} -12.0°$ (*c* 1, chloroform); c.d. (*c* 0.3, ethanol) $[\theta]_{202} -1930$, $[\theta]_{210} -2340$ (trough), $[\theta]_{220} -1730$, $[\theta]_{230}$ 0, $[\theta]_{237}$ 780 (peak), $[\theta]_{250}$ 0; τ^{CDCl_3} 4.12 (d, 1, $J_{1,2}$ 4 Hz, H-1), 5.32 (d.t, 1, $J_{5,6}$ 8 Hz, $J_{5,4}$ 6 Hz), 5.40 (d, 1, H-2), 5.68 (d, 1, $J_{1',1'-OH}$ 9 Hz, collapses to a singlet on D_2O addition, H-1'), 5.82–6.25 (multiplet, 2, H-6), 6.06 (s, 1, 3-OH, exchanges in D_2O), 6.14 (s, 3, CO_2Me), 6.33 (d, 1, 1'-OH, exchanges in D_2O).

Anal. Calc. for $C_{15}H_{24}O_9$: C, 51.72; H, 6.94. Found: C, 51.58; H, 7.07.

1,2:5,6-Di-O-isopropylidene-3-C-[(R)-methylsulfonyloxy(methoxycarbonyl)methyl]-α-D-galactofuranose (**6**) *and 3-deoxy-1,2:5,6-di-O-isopropylidene-3-C-[methylsulfonyloxy(methoxycarbonyl)methylene]-α-D-xylofuranose* (**7**). — Methanesulfonyl chloride (0.1 g) was added dropwise to a solution of **5** (83 mg) in pyridine (5 ml) at 0°. After stirring the mixture overnight at room temperature, chloroform (10 ml) and ice–water (10 ml) were added, and the resultant aqueous phase was extracted with chloroform (4 × 10 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (10 ml) and water (10 ml), dried (sodium sulfate), and evaporated under diminished pressure to afford a yellow syrup (120 mg). The product was chromatographed under a pressure of 8 lb. in^{-2} on a column of t.l.c.-grade silica gel (25 g) packed and eluted with 3:7 benzene–ethyl acetate, to afford two pure compounds.

Compound **7** (29 mg, 30%) was recrystallized from ethanol; m.p. 154–155°, $[\alpha]_D^{22} -8°$ (*c* 0.5, dichloromethane); τ^{CDCl_3} 4.08 (d, 1, $J_{1,2}$ 4.0 Hz, H-1), 4.57 (d, 1, $J_{4,5}$ 6.5 Hz, H-4), 4.67 (d, 1, H-2), 5.43 (d.d, 1, $J_{5,6}$ 6.5 Hz, $J_{5,6'}$ 7.2 Hz, H-5), 6.10 (s, 3, CO_2Me), 6.12 (multiplet, 2, H-6), 6.64 (s, 3, SO_2Me).

Anal. Calc. for $C_{16}H_{24}O_{10}S$: C, 47.06; H, 5.92. Found: C, 47.24; H, 5.72.

*H-1' denotes proton on the C-3 side-chain.

Compound **6** (61 mg, 60%) was analyzed as the pure, undistilled syrup as it was unstable on distillation; $[\alpha]_D^{23}+3.4°$ (*c* 0.6, chloroform); τ^{CDCl_3} 4.06 (d, 1, $J_{1,2}$ 4 Hz, H-1), 4.66 (s, 1, H-1'), 5.48 (d, 1, H-2), 5.4–5.6 (m, 1, H-5), 5.90 (d, 1, $J_{4,5}$ 7 Hz, H-4), 5.94–6.35 (m, 2, H-6), 6.12 (s, 3, CO_2Me), 6.83 (s, 3, SO_2Me).

Anal. Calc. for $C_{16}H_{26}O_{11}S$: C, 45.07; H, 6.15. Found: C, 45.14; H, 6.11.

1,2-O-Isopropylidene-3-C-[(R)-methylsulfonyloxy(methoxycarbonyl)methyl]-α-D-galactofuranose (**8**). — To **6** (200 mg) was added 65% aqueous acetic acid (20 ml) and the solution was stirred for 5 h at room temperature (after which time all starting material had been consumed) to afford at least four components, as evidenced by t.l.c. (silica gel, ethyl acetate). The reaction mixture was then evaporated (oil pump) and azeotropically dried with toluene (3 × 5 ml) to yield a mobile syrup (170 mg) which, after column chromatography on t.l.c.-grade silica gel (45 g) (column packed and eluted with ethyl acetate under a pressure of 8 lb.in^{-2} afforded **8** (40 mg, 22%). Recrystallized from ethanol, it had m.p. 119.5–120.0° (decomp.), $[\alpha]_D^{22}+25.5°$ (*c* 0.1, dichloromethane); $\tau^{(D_2O)}$ 3.90 (d, 1, 4 Hz, H-1), 4.34 (s, 1, H-1'), 6.05 (s, 3, CO_2Me), 6.62 (s, 3, SO_2Me), 8.34 (s, 3, Me), 8.62 (s, 3, Me).

Anal. Calc. for $C_{13}H_{22}O_{11}S$: C, 40.41; H, 5.74. Found: C, 40.55; H, 5.71.

Methyl L-*2-(1,2:5,6-di-O-isopropylidene-α-D-galactofuranos-3-yl)glycinate* (**10a**) *and methyl* D-*2-(1,2:5,6-di-O-isopropylidene-α-D-galactofuranos-3-yl)glycinate* (**11a**). — Sulfonate **6** (100 mg) and sodium azide (100 mg) in anhydrous *N,N*-dimethylformamide (7 ml) were stirred in the dark for 40 h at 60° under anhydrous conditions. The reaction mixture was then evaporated to dryness, taken up in dichloromethane, filtered, and evaporated, to afford a clear syrup that was immediately hydrogenated for 7 h in anhydrous benzene with 5% Pd-on-charcoal (50 mg) under hydrogen at 1 atm. Filtration and evaporation of the filtrate afforded a clear syrup (77 mg) that contained two ninhydrin-positive components, R_F 0.52 (major), and R_F 0.31 (minor) (silica gel, 5:5:1 ethyl acetate–dichloromethane–ethanol). No unreacted sulfonate was detected. Column chromatography on t.l.c.-grade silica gel (20 g), packed and eluted with the aforementioned solvent system, under a pressure of 8 lb.in^{-2}, afforded the two pure components.

10a (31 mg, 38%), recrystallized from ethanol had m.p. 158.0–158.5°, $[\alpha]_D^{23}-21°$ (*c* 0.3, chloroform); c.d. (*c* 0.13, 95% ethanol) $[\theta]_{204}$ 4050 (peak), $[\theta]_{210}$ 3880, $[\theta]_{220}$ 0, $[\theta]_{232}-3380$ (trough), $[\theta]_{240}-2160$, $[\theta]_{255}$ 0; τ^{CDCl_3} 4.09 (d, 1, $J_{1,2}$ 4 Hz, H-1), 5.38 (d.t, 1, $J_{5,4}$ 8 Hz, $J_{5,6}$ 8 Hz, $J_{5,6'}$ 6 Hz, H-5), 5.55 (d, 1, H-2), 5.84–6.12 (m, 2, H-6), 6.16 (d, 1, H-4), 6.21 (s, 3, CO_2Me), 6.32 (s, 1, C-1'), 6.9–8.5 (v. broad s, 3, NH_2, OH, exchanges in D_2O).

Anal. Calc. for $C_{15}H_{25}O_8N$: C, 51.88; H, 7.25; N, 4.03. Found: C, 51.70; H, 7.18; N, 3.87.

Compound **11a** (8 mg, 9.5%), was obtained pure by recrystallization from ethanol, and was then sublimed at 120° and 0.1 mm Hg; m.p. 175.5–176.5°, $[\alpha]_D^{22}-15.4°$ (*c* 0.5, chloroform); c.d. (*c* 0.15, 95% ethanol) $[\theta]_{204}-3820$, $[\theta]_{206}-4550$ (trough), $[\theta]_{220}-1150$, $[\theta]_{223}$ 0, $[\theta]_{233}$ 3400 (peak), $[\theta]_{252}$ 0; τ^{CDCl_3} 4.05 (d, 1, $J_{1,2}$ 4.0 Hz, H-1), 5.48 (d, 1, H-2), 5.55 (m, 1, H-5), 5.91 (d, 1, $J_{4,5}$ 7 Hz, H-4), 6.08 (d.d, 1, $J_{6,5}$ 6 Hz,

H-6), 6.19 (s, 4, H-1′, CO_2Me), 6.42 (dd, 1, $J_{5,6'}$ 8 Hz, H-6′), 7.1-8.2 (v. broad s, 3, NH_2, OH).

Anal. Calc. for $C_{15}H_{25}NO_8$: C, 51.88; H, 7.25; N, 4.03. Found: C, 52.17; H, 7.15; N, 4.01.

L-*2-(1,2:5,6-di-*O*-isopropylidene-α-*D*-galactofuranos-3-yl)glycine* (**10b**). — The α-amino ester **10a** (28 mg) in 1.25% aqueous methanolic sodium hydroxide (2 ml of 1:1 solution) was stirred for 30 min at room temperature. T.l.c. (silica gel, 5:5:1 dichloromethane–ethyl acetate–ethanol) indicated that the reaction was complete after this time. The solution was then passed through 5 ml of Rexyn RG-51 (H^+) (polystyrenecarboxylic acid-type resin) that had been prewashed with 1% acetic acid and then water until the effluent was neutral. Elution of the column with water, and combination and evaporation of the ninhydrin-positive fractions afforded the crystalline α-amino acid **10b** (24 mg, 89%). An analytical sample was recrystallized from ethanol; m.p. 180–181° (decomp.), $[\alpha]_D^{20} -22.7°$ (*c* 1, ethanol); c.d. (*c* 0.17, 0.5N HCl in 95% ethanol) $[\theta]_{202} +5900$, $[\theta]_{210} +7100$ (peak), $[\theta]_{220} +4540$, $[\theta]_{230} +2560$, $[\theta]_{240} +400$.

Anal. Calc. for $C_{14}H_{23}NO_8$: C, 50.46; H, 6.95; N, 4.20. Found: C, 50.37; H, 6.97; N, 4.10.

D-*2-(1,2:5,6-di-*O*-isopropylidene-α-*D*-galactofuranos-3-yl)glycine* (**11b**). — A solution of **11a** (8 mg) in 1.25% aqueous methanolic sodium hydroxide (1 ml of 1:1 solution) was stirred at room temperature for 30 min (complete reaction by t.l.c., silica gel, 5:5:1 dichloromethane–ethyl acetate–ethanol) and then passed through 5 ml of Rexyn RG-51 (H^+) prewashed as before. Elution as in the preceding experiment afforded the crystalline amino acid **11b** (7 mg, 88%). An analytical sample was recrystallized from methanol; m.p. 214–215° (decomp.), $[\alpha]_D^{22} -13.6°$ (*c* 0.2, 1:1 ethanol–water); c.d. (*c* 0.14, 0.5M HCl in 95% ethanol) $[\theta]_{202} -5240$, $[\theta]_{210} -6420$ (trough), $[\theta]_{220} -4780$, $[\theta]_{230} -1670$.

Anal. Calc. for $C_{14}H_{23}NO_8$: C, 50.46; H, 6.95; N, 4.20. Found: C, 50.21; H, 6.85; N, 4.18.

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