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C-4′-BRANCHED-CHAIN SUGAR NUCLEOSIDES SYNTHESIS OF ISOMERS OF PSICOFURANINE

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ABSTRACT

Photoamidation of 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose (**1**) afforded 3-*O*-acetyl-4-*C*-carbamoyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**2**) and 3-*O*-acetyl-3-*C*-carbamoyl-1,2:5,6-di-*O*-isopropylidene-D-α-allofuranose (**3**) in 65 and 26% yields respectively (based on consumed **1**). Treatment of **2** with 5% hydrochloric acid in methanol yielded the spiro lactone **5**, which was deacetylated to yield **7**. Reduction of **5** with sodium borohydride afforded 4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-gulofuranose (**9**) in 79% yield. Oxidation of **9** with sodium metaperiodate afforded a dialdose that was reduced with sodium borohydride to give 4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (**11**) in 88% yield. Treatment of the acetate **12**, derived from **11**, with trifluoroacetic acid, followed by acetylation, afforded the branched-chain sugar acetate **14**. Condensation of the glycosyl halide derived from **14** with N^6-benzoyl-N^6,9-bis(trimethylsilyl)adenine yielded an equimolar anomeric mixture of protected nucleosides **15** and **16** in 40% yield. Treatment of the latter compounds with sodium methoxide in methanol afforded 9-[4-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]-adenine (**17**) and the α-D anomer **18**. The structure of **3** was determined by correlation with the known 5,3′-hemiacetal of 3-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α,α′-D-*ribo*-pentodialdose (**25**).

DISCUSSION

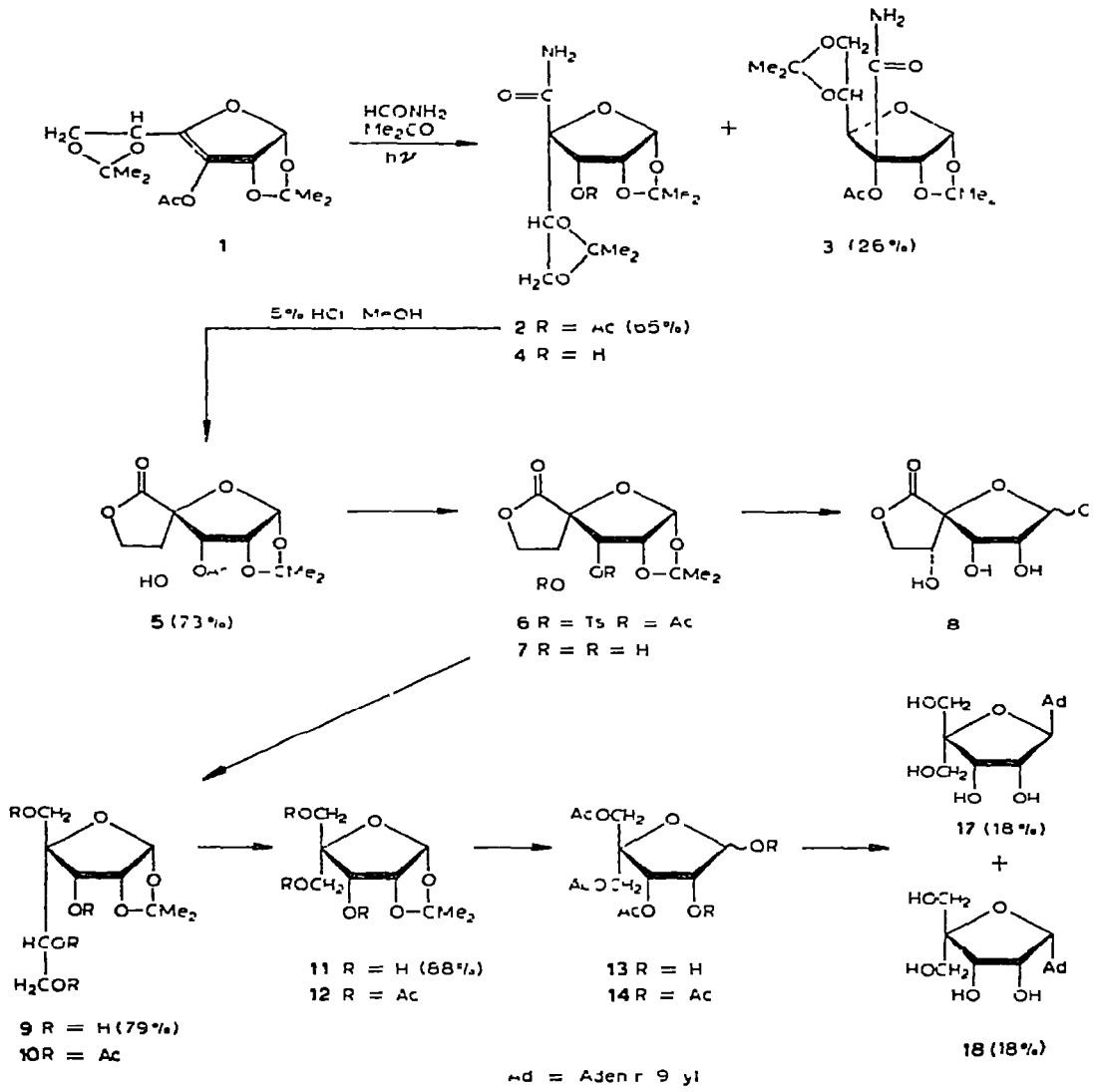
In continuation of our studies on the chemistry of branched-chain sugar nucleosides[1] that are analogues of the naturally occurring nucleosides and nucleoside antibiotics, we now report the application of photoamidation[2] to a disubstituted 3-enofuranose to afford novel 3-*C*- and 4-*C*-(branched-chain)-carbamoyl sugars. Conversion of the carbamoyl group of the latter sugars into a hydroxymethyl group permitted the synthesis of a 4-*C*-(branched-chain) sugar having two hydroxymethyl groups at C-4 of the furanose ring. From this intermediate, 4′-*C*-(branched-chain) sugar nucleosides[3] were synthesized that are isomers of psicofuranine[4].

In previous communications[5,6] we reported that photoamidation of mono-

substituted enoses led to selective carbamoylation at the unsubstituted carbon atom As examples, photoamidation of 3-deoxy-1,2 5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose[5] and 1,2,4,6-tetra-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranose[6] afforded 3-*C*-(branched-chain)-carbamoyl sugars It was therefore envisaged that photoamidation of a disubstituted 3-enofuranose might yield both 3-*C*- and 4-*C*-(branched-chain)-carbamoyl sugars

When a mixture of 3-*O*-acetyl-1,2 5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose[7] (**1**), formamide *tert*-butyl alcohol, and acetone was irradiated for 48–72 h according to a procedure previously described[5], a mixture of two carbamoylation products **2** and **3** was obtained, together with unreacted starting material **1** Chromatographic separation of this mixture on silica gel with 10 10 1 benzene–ethyl acetate–ethanol as developer afforded the readily recoverable **1** in pure form, together with **2** and **3** in 65 and 26% yields, respectively (based on consumed **1**) Surprisingly, no photo-produced hydroxyisopropyl adduct was obtained from the disubstituted enose **1**, but a monosubstituted enose[5] afforded both types of photo adducts The type of product and the point of attachment of the carbamoyl group to the furanose ring of **2** and **3** was readily deduced from analysis of the i r and p m r spectra of the products I r peaks at 3500, 3400, and 1695 cm^{-1} established the presence of a carbamoyl group[8] in compounds **2** and **3** The p m r spectrum (see Experimental section) of **2** clearly showed a single H-3 methine proton resonating at τ 4 66, thus indicating that the carbamoyl group is located at C-4 of **1** The H-2 atom of **2** gave a quartet at τ 5 18 (having $J_{1\ 2} = 4$ and $J_{2\ 3} = 5\ 5$ Hz), which collapsed to a doublet on irradiation of H-3 1,2-*O*-Isopropylideneglycofuranoses having H-2 and H-3 *cis*-disposed have couplings[9] of >2 5 Hz, and therefore, H-3 of **2** must be *cis* to the H-2 The absence of a hydrogen atom at C-4 precluded the use of p m r spectroscopy to deduce the configuration of **2** at C-4

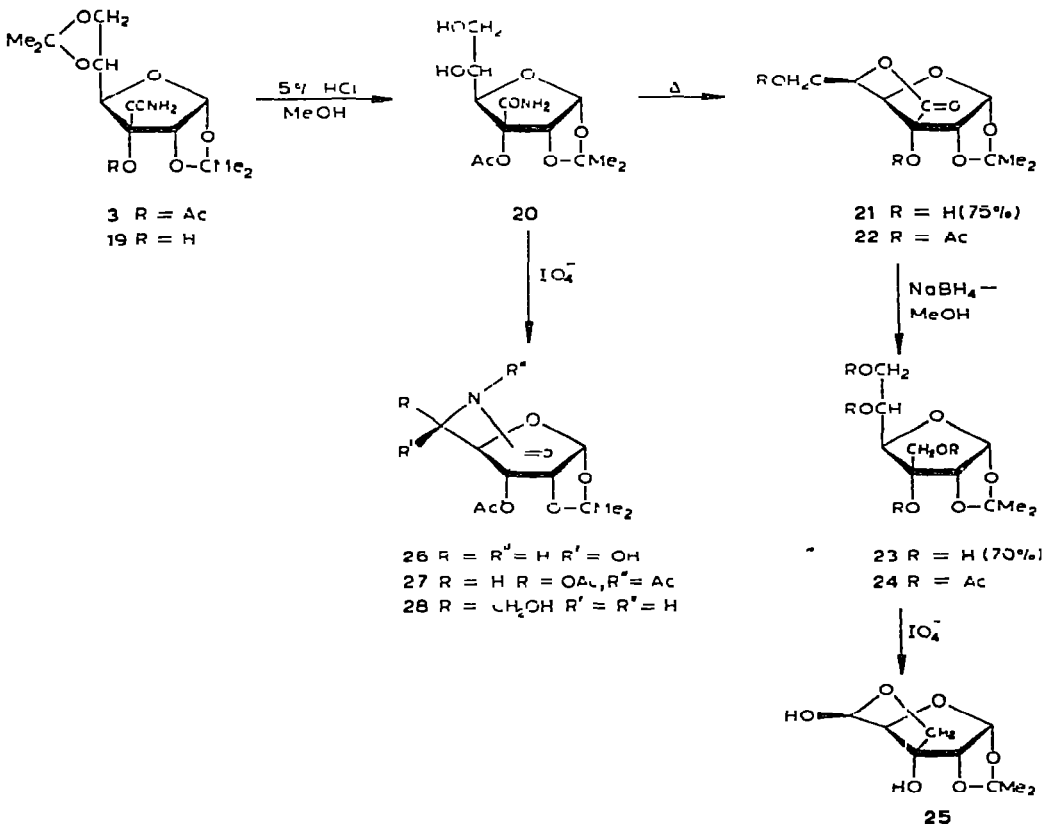
Acid-catalyzed hydrolysis of **2** resulted in a facile elimination of the amide group, because of participation by the hydroxyl group in the hydrolysis step[10–12], and afforded the interesting spiro-lactone sugar **5** in 73% yield Compound **5** exhibited strong i r peaks at 1750 and 1795 cm^{-1}, the latter was attributed to the γ-spiro lactone functionality[8] Previous workers[13] have assigned the configuration of the chiral carbon atom adjacent to the carbonyl group of lactones through analysis of their circular dichroism (c d) spectra Deacetylation of **5** afforded (90% yield) the spiro lactone **7**, which gave a strong, negative, c d maximum at 225 nm, therefore it was inferred that C-4 of **7** had the (*R*)-configuration Because spiro lactones might not follow the same rules as monocyclic γ-lactones, an unequivocal method of assigning the C-4 configuration of **5** was considered essential With this in view, compound **5** was converted into the *p*-toluenesulfonate **6**, which was then subjected to X-ray crystallographic analysis[14] This analysis revealed that the configuration at C-4 was actually (*S*), and therefore, compound **2** must be 3-*O*-acetyl-4-*C*-carbamoyl-1,2 5,6-di-*O*-isopropylidene-α-D-gulofuranose The utilization of compound **5** in the synthesis of isomers of psicofuranine will be dealt with after the proof of structure of the minor carbamoylation product **3** has been described



First-order analysis of the p m r spectrum of **3** revealed that the carbamoyl group was attached to C-3 The doublet at τ 4 67 for H-2 collapsed to a singlet when the H-1 doublet (at τ 4 12) was irradiated The absence of coupling between H-2 and H-3 indicated that either these hydrogen atoms were *trans* oriented, or there was no hydrogen atom on C-3 The latter supposition was proved correct by a chemical proof of structure Attempted selective hydrolysis of **3** with 5% hydrochloric acid in methanol (the same conditions that converted amide **2** into the spiro lactone **5**) gave a diol **20** having an amide group Surprisingly, however, when the diol **20** was subjected to pyrolysis at 150°, acetamide and a γ-lactone (**21**) were produced The latter com-

pound exhibited a strong i r peak at 1790 cm^{-1} and gave a positive c d maximum The p m r spectrum of the acetate **22** (derived from **21**) showed a one-proton singlet at τ 5 21 that was assigned to H-4 The absence of coupling between H-4 and H-5 suggested that the lactone ring must be above the furanose ring and C-3 must have the (*R*)-configuration This supposition was corroborated as follows Reduction of the γ-lactone **21** with sodium borohydride in methanol afforded the tetrol **23** in 70% yield The $[\alpha]_D$ value of **23** agreed with the optical rotation of 3-*C*-(hydroxymethyl) 1,2-*O*-isopropylidene-α-D allofuranose, a compound recently reported by Paulsen and co-workers[15] Cleavage of the 5,6-diol of **23** with periodate afforded an aldehyde that cyclized intramolecularly to form the dialdose **25** in 30% yield This dialdose had the same physical data ($[\alpha]_D$ and p m r spectrum) as those reported for a similar compound recently reported[15 16] The α-configuration of **25** at C-5 was indicated by the fact that H-5 exhibited a one-proton singlet at τ 4 6 Thus, compound **25** must be the 5,3′-hemiacetal of 3-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α,α′-D-*ribo*-pentodi aldose, and compound **3** must be 3-*O*-acetyl-3-*C*-carbamoyl-1,2 5,6-di-*O*-isopro pylidene-α-D-allofuranose

Prior attempts at structural proof of the diol amide **20** by periodate-cleavage



studies afforded two compounds (**26** and **28**) which were separated by chromatography on silica Acetylation of **26** afforded **27** The p m r spectrum of **27** showed three methyl resonances at τ 7 48, 7 82, and 7 89 which were assigned to two *O*-acetyl groups and one *N*-acetyl group The H-4 and H-5 atoms of **27** exhibited singlets at τ 5 44 and 3 38, respectively, thus indicating that H-4 and H-5 were *trans*-oriented Thus **26** must be the aminal of 3-*O*-acetyl-3-*C*-carbamoyl-1 2-*O*-isopropylidene-α α'-D-*ribo*-pentodialdose, and **27** is the 3′,5-*N* acetyl carbolactam

Analyses of the mass spectrum of the second pyrrolidone product (**28**) indicated that the diol **20** had not been cleaved by periodate, as the molecular weight of **28** was 286 9960 The fragmentation pattern of **28** showed the loss of water and of acetic acid, thus indicating that the acetate group and H-4 were *cis*-oriented The i r spectrum of **28** confirmed the presence of an hydroxyl group and NH functionality The p m r spectrum showed the presence of eight protons in addition to the methyl groups There were two exchangeable protons, resonating at τ 6 1 and 6 4 The former resonated as a broad doublet having $J = 12$ Hz and the latter gave a very broad singlet A one-proton unresolved quartet at τ 4 43 having $J = 12$ Hz collapsed to a sharp doublet having $J = 4$ 5 Hz upon the addition of deuterium oxide The large coupling constant of 12 Hz was attributed to NH–H-5 coupling Irradiation of the doublet (after D_2O exchange) at τ 4 43 collapsed the doublet at τ 5 38 to a singlet Thus the two signals at τ 4 43 and 5 38 may be attributed to H-5 and H-4, respectively As the configuration of C-4 was known and since $J_{4,5} = 4$ 5 Hz, it is evident that H-4 and H-5 are *cis*-oriented[9] A doublet at τ 5 05 ($J = 11$ Hz) and a second doublet (partially overlapping the doublet at τ 5 38) at τ 5 3 showing the same coupling constant, were assigned to the two C-6 protons, thus confirming that no cleavage of the diol had taken place Clearly, ring closure from N to C-5 had occurred but to account for the large $J_{4,5}$ coupling, the surprising inference must be made that inversion at C-5 had been effected in the process The only explanation that these authors can offer for this unexpected result is that the nitrogen atom attacked the periodate ester at C-5 (before cleavage of the diol was effected) with concomitant inversion at C-5 It is, therefore, tentatively suggested that compound **28** is 3-*O*-acetyl-3-*C*-carboxyl-1,2-*O*-isopropylidene-α-D-talofuranose 3′,5-lactam

The following part of the discussion deals with the utilization of the spiro lactone **5** in the synthesis of isomers of psicofuranine Reduction of the spiro lactone **7**, derived from **5** by deacetylation, with sodium borohydride in methanol–water afforded the branched-chain sugar **9** in 79% yield The tetrol **9** was characterized as its tetraacetate **10** Cleavage of the 5,6-diol of **9** with sodium metaperiodate followed by reduction of the resulting aldehyde with sodium borohydride in methanol afforded 4-*C*-(hydroxymethyl)-1 2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (**11**) in 88% yield Acetylation of **11** with acetic anhydride in pyridine yielded the triacetate **12** in 90% yield Treatment of **12** with 80% aqueous trifluoroacetic acid afforded an α,β-anomeric mixture of branched-chain sugars **13**, which was acetylated to yield an anomeric mixture (4 1 ratio of β to α anomers) of branched-chain sugar acetates **14** in 80% yield Treatment of the furanosyl acetates **14** with a mixture of hydrogen bromide–

acetic acid, and dichloromethane for 1 h at room temperature afforded a glycosyl bromide that was immediately condensed at 130–135° with N^6-benzoyl-N^6,9-bis-(trimethylsilyl)adenine according to a fusion procedure previously described[16] to yield, after column chromatography, an equimolar, anomeric mixture of protected 4′-*C*-(branched-chain) nucleosides (**15** and **16**) in 40% yield Although the coupling constants of H-1′ (4 and 5 8 Hz) of the protected nucleosides were too close in value to permit assignment of their anomeric configuration, the appreciable difference in their H-1′ chemical shifts (τ 3 36 and 3 73) strongly indicated that the anomer **16** having H-1′ at lower field should be the α-nucleoside Treatment of the acetylated nucleosides with sodium methoxide in methanol gave, in high yield, the free, branched-chain-sugar nucleosides **17** and **18** The site of glycosylation[18] was established as N-9, as both nucleosides exhibited u v maxima at 258 nm The assignment of anomeric configuration to **17** and **18** was based on their c d [19] spectra Compound **18** exhibited a strongly positive c d curve, whereas **17** gave a negative one The p m r spectra of **17** and **18** clearly showed doublets for H-1′ at τ 3 59 and 3 31, having $J_{1',2} = 2\ 5$ and 6 5 Hz, respectively The much larger value of $J_{1',2}$ for compound **18** than for **17** further corroborated the assignment of anomeric configuration of the 4′-*C*-(branched-chain) nucleosides Therefore, compound **17** must be 9-[(4-*C*-hydroxymethyl)-β-D-*erythro*-pentofuranosyl]adenine and **18** the α-anomer 9-[4-*C*-(Hydroxymethyl)-α-L-*threo*-pentofuranosyl]adenine has been synthesized recently by a different sequence of reactions[20]

EXPERIMENTAL

General methods — Irradiations were performed as described previously[5] Solutions were dried with anhydrous sodium sulfate and evaporated under diminished pressure Column chromatography was performed on t l c -grade Silica Gel G without binder (Mondray) under a pressure of 4–8 lb in^{-2} with flow rates of 70–140 ml/h P m r spectra were determined in chloroform-*d* solution with Me_4Si as internal standard by using a Varian HA-100 spectrometer Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter Circular dichroism measurements were performed with a Jasco J-20 automatic recording spectropolarimeter at room temperature I r spectra were recorded on a Perkin–Elmer 337 spectrometer

Elemental analyses were obtained from Mr Borda of the Microanalytical Laboratory of the University of British Columbia

Irradiation of 3-O-acetyl-1,2 5,6-di-O-isopropylidene-α-D-erythro-hex-3-enose (**1**) — A solution of **1** (10 g) in anhydrous formamide (30 ml), *tert*-butanol (15 ml), and acetone (15 ml) was irradiated[5] for 48–72 h After concentrating the solution to remove *tert*-butanol and acetone (at 30 torr and 50°), the resulting mixture was diluted with saturated aqueous sodium chloride (200 ml) The resulting mixture was extracted with dichloromethane (7 × 150 ml) The combined extracts were concentrated to 200 ml and washed with saturated aqueous sodium chloride (50 ml), dried, and evaporated to a syrup (11 g) This syrup was chromatographed on t l c-grade

silica gel (40 × 11 cm), with 10 10 1 benzene–ethyl acetate–ethanol as developer, to afford starting material **1** (5 g), the amide **2** (3 75 g, 65%), and the amide **3** (1 55 g, 26%)

Compound **2** was recrystallized from ether–petroleum ether (b p 30–60°), m p 163–164°, $[\alpha]_D^{26}$ +54 5° (*c* 4 5, chloroform), ν_{max}^{Nujol} 3500, 3400 and 1695 cm^{-1} ($CONH_2$), n m r ($CDCl_3$) τ 3 45 (d 1, $J_{1,2}$ 3 5 Hz, H-1), 4 66 (d, 1 $J_{2,3}$ 5 5 Hz, H-3), 5 18 (q, 1, H-2), 5 22 (t, 1, $J_{5,6}$ 6 5 Hz, H-5), 5 86 (m, 2, H-6, H-6′) 7 86 (s, 3, OAc), 8 40 8 60, 8 62 and 8 64 (4 s, 12, CH_3) Irradiation at τ 4 66 produced a doublet at τ 5 18

Anal Calc for $C_{15}H_{23}NO_8$ C, 52 17, H, 6 71, N, 4 06 Found C, 52 56, H, 6 86, N, 3 76

Compound **3** was crystallized from chloroform, m p 68–70° $[\alpha]_D^{24}$ +57 4° (*c* 1 16, chloroform), ν_{max}^{film} 3450 and 1690 cm^{-1} ($CONH_2$), n m r ($CDCl_3$) τ 3 57 (broad s, 2, $CONH_2$, exchanges with D_2O), 4 12 (d 1, $J_{1,2}$ 4 Hz H-1) 4 67 (d, 1, H-2), 5 5 (m, 1, H-5), 7 9 (s, 3, OAc), 8 45, 8 5, and 8 62 (3 s, 12, CH_3)

Anal Calc for $C_{15}H_{23}NO_8$ C 52 17, H, 6 71 N, 4 06 Found C, 51 97, H, 6 70, N, 3 93

4-C-Carbamoyl-1,2 5,6-di-O-isopropylidene-α-D-gulofuranose (**4**) — Compound **2** (0 3 g) was dissolved in anhydrous methanol (10 ml) containing a catalytic amount of sodium methoxide After 2 h, the solution was decationized with IR-120 (H^+) resin, and evaporated The resulting syrup (0 24 g 93%) was crystallized from ethyl ether–petroleum ether (b p 30–60) to afford pure **4**, m p 65°, $[\alpha]_D^{26}$ −1 3° (*c* 1 28, chloroform), n m r ($CDCl_3$) τ 3 2, 3 7 (2 broad s, 2, $CONH_2$) 4 18 (d, 1, $J_{2,3}$ 2 Hz H-1), 8 4, and 8 6 (2 s 12, CH_3) (N m r data were unobtainable following addition of D_2O)

Anal Calc for $C_{13}H_{21}NO_6$ C, 51 48, H 6 98 N 4 62 Found C, 51 26, H, 6 92, N, 4 54

3-O-Acetyl-3-C-carboxyl-1,2-O-isopropylidene-α-D-gulofuranose 4′,6-lactone (**5**) — Compound **2** (0 5 g) was dissolved in methanol (25 ml) containing 5% of aqueous hydrochloric acid (2 5 ml) This solution was stirred at room temperature for 12 h, neutralized with Amberlite IR-45 (OH^-) resin, and evaporated to a syrup (0 46 g) Column chromatography on t l c -grade silica (15 × 2 cm) packed and eluted with 10 10 1 benzene–ethyl acetate–ethanol afforded **5** (0 31 g, 73%), which was recrystallized from ethyl ether–petroleum ether (b p 30-60°), m p 142–143°, $[\alpha]_D^{25}$ +35 6° (*c* 1 0, chloroform), $\nu_{max}^{CHCl_3}$ 3550 (OH), 1795 (γ-lactone), and 1750 cm^{-1} (OAc), n m r ($CDCl_3$) τ 3 94 (d, 1, $J_{1,2}$ 3 5 Hz, H-1), 4 95 (d, 1, $J_{2,3}$ 4 8 Hz, H-3), 5 02 (q, 1, H-2), 5 15 (m, 1, H-5), 5 64 (m, 2, H-6, H-6′), 7 25 (broad s, OH, exchanges in D_2O), 7 89 (s, 3, OAc), 8 41, and 8 70 (2 s, 6 CH_3)

Anal Calc for $C_{12}H_{16}O_8$ C, 50 00 H, 5 59 Found C, 49 90, H, 5 51

4-C-Carboxyl-1,2-O-isopropylidene-α-D-gulofuranose 4′,6-lactone (**7**) — Compound **5** (0 04 g) was dissolved in anhydrous methanol (1 ml) containing a catalytic amount of sodium methoxide After 15 min at room temperature, the solutions was decationized with Rexyn RG-51 (H^+) resin Evaporation of the filtrate gave crystalline

7 (32 mg 90%) Recrystallization of the product from ethanol gave pure **7**, m p 171-173° $[\alpha]_D^{25}$ −13 6° (*c* 0 65, chloroform), ν_{max}^{Nujol} 3500, 3450 (OH), and 1775 cm^{-1} (γ-lactone), c d $\Delta\varepsilon$ −0 759 (λ_{max} 225 nm, *c* 0 0045, methanol), $[\theta]_{225}^{30}$ −2507, n m r [$CDCl_3$ and $(CD_3)_2CO$] τ 3 95 (d, 1, $J_{1,2}$ 3 8 Hz, H-1), 5 03 (d, 1, $J_{2,3}$ 3 5 Hz, H-3) 5 53 (q, 1, H-2), 8 39, and 8 62 (2 s, 6, CH_3)

Anal Calc for $C_{10}H_{14}O_7$ C, 48 78, H, 5 73 Found C, 48 45, H, 5 62

3-O-Acetyl-4-C-carboxyl-1,2-O-isopropylidene-5-O-tosyl-α-D-gulofuranose 4',6 lactone (**6**) — Compound **5** (50 mg) was dissolved in anhydrous pyridine (1 ml) at 0° *p*-toluenesulfonyl chloride (66 mg) was added, and the resulting solution was heated for two days at 50° The cooled mixture was diluted with ice–water (5 ml) and extracted with dichloromethane (2 × 10 ml) The combined organic extracts were washed with saturated, aqueous sodium hydrogencarbonate (10 ml), dried and evaporated to afford a syrup (80 mg) T l c (developed with 4 1 benzene–ethyl acetate) of the product indicated the presence of some starting material Chromatography of the mixture on t l c -grade silica (23 × 1 cm) developed with the same solvent afforded the pure sulfonate **6** (37 mg) in 61% yield (based on starting material consumed) Recrystallization of the product from benzene gave an analytical sample, m p 160 5-161°, $[\alpha]_D^{-6}$ −48 9° (*c* 0 62 chloroform), n m r ($CDCl_3$) τ 2 05 (m, 2 H-2', H-5'), 2 6 (m, 2, H-3', H-5'), 3 93 (d, 1, $J_{1,2}$ 3 7 Hz, H-1), 4 38 (q, 1, $J_{5,6}$ 2 Hz, H-5), 4 82 (d, 1, $J_{2,3}$ 4 5 Hz, H-3), 4 99 (q, 1, H-2), 5 46 (m, 2, H-6, H-6'), 7 58 (s 3, CH_3), 7 88 (s, 3, OAc), 8 4, and 8 67 (2 s, 6, CH_3)

Anal Calc for $C_{19}H_{22}O_{10}S$ C, 51 58, H, 5 01 Found C, 51 43, H, 4 82

4-C-Carboxyl-α-(and β)-D-gulofuranose 4',6-lactone (**8**) — Compound **7** (20 mg) was dissolved in 80% aqueous trifluoroacetic acid (0 5 ml) and the solution was stirred for 15 min at room temperature after which time toluene (2 × 2 ml) was evaporated from the solution to afford a mixture of α and β-anomers of **8** (12 mg, 75%), ν_{max}^{film} 1770 cm^{-1} (γ-lactone) n m r [$(CD)_3CO$ and D_2O] 4 70 (1, d, $J_{1,2}$ 4 Hz, H-1 α) and 4 85 (1, d, $J_{1\beta,2}$ 1 5 Hz, H-1 β)

Anal Calc for $C_7H_{10}O_7$ C, 40 78 H, 4 89 Found C, 40 61 H, 4 93

3-C-Carbamoyl-1,2 5,6-di-O-isopropylidene-α-D-allofuranose (**19**) — 3-*O*-Acetyl-3-*C*-carbamoyl-1,2 5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**, 0 10 g) was deacetylated as described for the preparation of **4**, to afford compound **19** (80 mg, 90%), m p 156–157 , $[\alpha]_D^{26}$ −1 75° (*c* 0 6, chloroform), $\nu_{max}^{CHCl_3}$ 3575 (OH) 3450, 3300, and 1700 cm^{-1} ($CONH_2$), n m r ($CDCl_3$) τ 3 05, 3 6 (2 broad s, NH_2), 4 0 (d, 1, $J_{1,2}$ 3 9 Hz, H-1), 5 34 (d, 1, H-2), 6 5 (s, 1, OH, exchanges in D_2O), 8 44, 8 60, 8 64, and 8 7 (4 s, 12, CH_3)

Anal Calc for $C_{13}H_{21}NO_7$ C, 51 48, H, 6 98, N, 4 62 Found C, 51 50, H, 6 79, N, 4 60

3-O-Acetyl-3-C-carbamoyl-1,2-O-isopropylidene-α-D-allofuranose (**20**) — Compound **3** (0 60 g) in methanol (50 ml) and 5% aqueous hydrochloric acid (1 ml) was kept for 10 h at room temperature The solution was then neutralized with Amberlite IR-45 (OH^-) resin and evaporated to yield **20** (0 49 g, 93%) as a syrup, $[\alpha]_D^{26}$ +114 4° (*c* 1, chloroform) $\nu_{max}^{CHCl_3}$ 3500–3300 (OH), 3200, 1695 ($CONH_2$), and 1750 cm^{-1}

(OAc), n m r ($CDCl_3$) τ 3 52 (broad s, 2, NH_2), 4 1 (d, 1, $J_{1,2}$ 4 2 Hz, H-1), 4 2 (d, 1 H-2), 7 84 (s, 3, OAc), 8 48, and 8 66 (2 s, 6, CH_3)

3,5-Di-O-acetyl-3-C-carboxyl-1,2-O-isopropylidene-α-D-allo-pentodialdofuranose 3′,5-N-acetyllactam (**21**) *and 3-O-acetyl-3-C-carboxyl-1,2-O-isopropylidene-β-L-talofuranose 3′,5-lactam* (**28**) — Compound **20** (30 mg) in methanol (1 ml) was added to water (2 ml) containing sodium hydrogencarbonate (10 mg), and sodium metaperiodate (20 mg) The resulting solution was stirred for 15 min at room temperature, after which time dichloromethane (2 ml) was added and the resulting mixture was filtered Evaporation of the filtrate yielded a syrup (30 mg) that was chromatographed on t l c -grade silica gel (12 × 1 cm) developed with 1 1 benzene–ethyl acetate to afford 3-*O*-acetyl-3-*C*-carboxyl-1,2-*O*-isopropylidene-α-D-*allo*-pentodialdofuranose 3′,5-lactam (**26**, 13 mg) and 3-*O*-acetyl-3-*C*-carboxyl-1 2-*O*-isopropylidene-β-L-talofuranose 3′ 5-lactam (**28**)

Compound **26** (12 mg) in anhydrous pyridine (1 ml) and acetic anhydride (1 ml) was kept for 10 h at room temperature The mixture was then evaporated to dryness The residue was dissolved in dichloromethane (2 ml) and extracted with water (1 ml), and the organic layer was dried and evaporated to afford crystalline 3,5-di-*O*-acetyl-3-*C*-carboxyl-1 2-*O*-isopropylidene-α-D-*allo*-pentodialdofuranose 3′,5-*N*-acetyllactam (**27**), m p 118–120 , $[\alpha]_D^{30}$ −20 6 (*c* 0 12, chloroform) $\nu_{max}^{CHCl_3}$ 1770 and 1720 (CONCO), and 1750 cm^{-1} (OAc), n m r ($CDCl_3$) τ 3 38 (s, 1, H-5), 4 14 (d, 1, $J_{1,2}$ 4 Hz, H-1), 4 8 (d, 1, H-2), 5 44 (s, 1, H-4) 7 48 (s, 3, NAc), 7 82, 7 89 (2 s, 6, OAc), 8 42, and 8 62 (2 s, 6, CH_3)

Anal Calc for $C_{15}H_{19}NO_9$ C 50 42 H, 5 36, N, 3 92 Found C, 50 77, H 5 49, N, 3 66

Compound **28** was recrystallized from carbon tetrachloride–ethyl ether, m p 128–129°, $[\alpha]_D^{26}$ −71° (*c* 0 1, chloroform), $\nu_{max}^{CHCl_3}$ 1750 (OAc) and 1720 cm^{-1} (γ-lactam), n m r ($CDCl_3$) τ 4 12 (d, 1, $J_{1,2}$ 3 6 Hz, H-1), 4 43 (q, 1, $J_{NH,5}$ 12 Hz, H-5), 5 05 (d, 1, $J_{6,6}$ 11 Hz, H-6), 5 19 (d, 1, H-2), 5 3 (d, 1, H-6′), 5 38 (d, 1, $J_{4,5}$ 4 5 Hz, H-4), 6 1 (broad d, 1, exchanges in D_2O, N-H), 6 4 (broad s, 1, exchanges in D_2O, OH), 7 80 (s, 3, OAc), 8 2, and 8 55 (2 s, 6, CH_3) D_2O exchange collapsed the quartet at τ 4 43 to a doublet Irradiation at τ 4 12 collapsed the doublet at τ 5 19 to a singlet Irradiation at τ 4 43 collapsed the doublet at τ 5 38 to a singlet

Anal Calc for $C_{12}H_{17}NO_7$ $0.5H_2O$ C 48 64, H, 6 12, N, 4 72 Found C, 48 35, H, 5 81, N, 4 38 Molecular weight by mass spectrometry 286 996 $C_{12}H_{17}NO_7$ requires 287 100 $M^+ + 1$ 288 099 required 288 108

3-C-Carboxyl-1,2-O-isopropylidene-α-D-allofuranose 3′,5-lactone (**21**) — Compound **20** (0 09 g) was placed in a short-path distillation apparatus (bulb to bulb) and heated to 140–150° at 0 2 torr until distillation of a syrup ceased Crystals formed at the mouth of the exit tube were heated with warm air to force them into the exit Separation of the exit tube from the collection bulb afforded pure acetamide (13 mg), m p 81–82°, (lit m p 82 3°) The syrup (57 mg, 79%) in the collection bulb was recrystallized from ethanol to give pure **21**, m p 129–132°, $[\alpha]_D^{26}$ +29° (*c* 0 64, chloroform), $\nu_{max}^{CHCl_3}$ 3600–3400 (OH) and 1790 cm^{-1} (γ-lactone), c d $\Delta\varepsilon$ +0 673

(λ_{max} 230 nm, *c* 0 0036, methanol), $[\theta]^{30}_{230}$ +2223, n m r ($CDCl_3$) 4 11 (d, 1, $J_{1,2}$ 4 Hz, H-1), 5 28 (d, 1, H-2), 6 04 (broad s, 2, OH, exchanges in D_2O), 8 4, and 8 6 (2 s, 6, CH_3)

Anal Calc for $C_{10}H_{14}O_7$ C, 48 78, H, 5 73 Found C, 48 97, H, 5 60

3,6-Di-O-acetyl-3-C-carboxyl-1,2-O-isopropylidene-α-D-allofuranose 3',5-lactone (**22**) — A solution of compound **21** (50 mg) in pyridine (1 ml) and acetic anhydride (0 5 ml) was kept for 24 h at room temperature After evaporation, the resulting residue was dissolved in dichloromethane (2 ml) and washed with water (1 ml) The organic solution was dried and evaporated to a syrup (64 mg, 95%) that crystallized from benzene–petroleum ether (b p 30–60°), m p 116 5–117°, $[\alpha]_D^{26}$ +6 4° (*c* 0 26, chloroform), n m r ($CDCl_3$) τ 4 05 (d, 1 $J_{1,2}$ 4 Hz, H-1), 4 87 (d, 1, H-2), 5 21 (s, 1, H-4), 5 38 (q, 1, $J_{5,6}$ 6 Hz, H-5), 5 62 (m, 2, H-6, H-6'), 7 8, 7 86 (2 s, 6, OAc), 8 42, and 8 58 (2 s, 6, CH_3) [Lit [21,22] gives m p 113–113 5°, $[\alpha]_D^{21}$ +6 2° (*c* 1 7, chloroform)] and [m p 115 3–115 8°, $[\alpha_D^{21}$ +6° (*c* 0 3, chloroform)], respectively

Anal Calc for $C_{14}H_{18}O_9$ C, 50 91, H, 5 49 Found C, 50 93, H, 5 48

3-C-(Hydroxymethyl)-1,2-O-isopropylidene-α-D-allofuranose (**23**) — Compound **21** (42 mg) was dissolved in methanol (1 ml) and water (1 ml) containing sodium borohydride (11 mg) The resulting mixture was kept for 24 h at room temperature and then neutralized with Rexyn RG-51 (H^+) resin, filtered, and the resulting solution evaporated to a syrup Methanol (3 × 5 ml) was evaporated from this syrup and the residue was dissolved in ethyl acetate, filtered, and the solvent removed by evaporation to give **23** as a syrup (0 03 g, 70%), $[\alpha]_D^{25}$ +28 4° (*c* 0 67, chloroform) (lit [15] $[\alpha]_D^{20}$ +30° in chloroform)

3-C-(Acetoxymethyl)-5,6-di-O-acetyl-1,2-O-isopropylidene-α-D-allofuranose (**24**) — Compound **23** (10 mg) was acetylated as described for the preparation of **22**, to afford **24** (15 mg, 100%) Distillation of **24** at 140° and 0 2 torr gave an analytical sample, $[\alpha]_D^{28}$ +25 1° (*c* 1 1, chloroform), n m r ($CDCl_3$) τ 4 22 (d, 1, $J_{1,2}$ 4 1 Hz, H-1), 4 72 (m, 1), 7 86, 7 92 (2 s, 9, OAc), 8 4, and 8 6 (2 s, 6, CH_3)

Anal Calc for $C_{16}H_{24}O_{10}$ C, 51 06, H, 6 43 Found C, 51 31, H, 6 40

5,3'-Hemiacetal of 3-C-hydroxymethyl-1,2-O-isopropylidene-α,α'-D-ribo-pentodialdose[15] (**25**) — Compound **23** (43 mg) was dissolved in water (1 ml) at 0° and sodium metaperiodate (5 mg) in water (1 ml) was added After 20 min, the mixture was concentrated to approximately 1 ml, diluted with saturated, aqueous sodium chloride (1 ml) and extracted with dichloromethane (2 × 2 ml) The dried organic solution was evaporated to a syrup (1 5 mg, 30%), $[\alpha]_D^{28}$ +73° (*c* 0 1, chloroform), (lit [15] $[\alpha]_D^{20}$ +68°, chloroform), n m r ($CHCl_3$), τ 4 08 (d, 1, $J_{1,2}$ 3 9 Hz, H-1), 4 6 (s, 1, H-5), 5 55 (d, 1, H-2), 5 74 (1, s, H-4), 6 05 (d, 2, J_{AB} 10 Hz, CH_2), 8 39 and 8 59 (2 s 6 CH_3)

4-C-(Hydroxymethyl)-1 2-O-isopropylidene-α-D-gulofuranose (**9**) *and 4-C-(acetoxymethyl)-3,5,6-tri-O-acetyl-1,2-O-isopropylidene-α-D-gulofuranose* (**10**) — To a solution of the 4-(*S*)-6-spiro-γ-lactone **7** (0 4 g) in methanol (16 ml) was added sodium borohydride (0 04 g) After stirring the solution for 12 h at room temperature, it was neutralized with Rexyn RG-51 (H^+) resin, filtered evaporated, and methanol

(2 × 20 ml) was evaporated from the filtrate to afford **9** as a clear syrup (0 26 g, 79%), $[\alpha]_D^{26}$ +15° (*c* 1 1, methanol), n m r [$(CD_3)_2CO$] τ 4 17 (d, 1, $J_{1,2}$ 4 Hz, H-1), 5 28 (q 1, $J_{2,3}$ 5 8 Hz, H-2), 5 58 (d, 1, H-3), 5 8 (q, 1, $J_{5,6}$ 4 Hz, $J_{5,6'}$ 7 Hz, H-5), 6 1 (s, 2, CH_2), 4 4 (m, 2, H-6, H-6'), 8 4, 8 6 (2 s, 6, CH_3) The 4-*C*-(hydroxymetnyl) sugar **9** was further characterized as its tetraacetate **10**

A solution of **9** (20 mg) in anhydrous pyridine (1 ml) and acetic anhydride (0 75 ml) was kept for 10 h at room temperature and then evaporated The residue was dissolved in dichloromethane (5 ml) and washed with water (2 ml) The organic solution was dried and evaporated to afford 4-*C*-(acetoxymethyl)-3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-gulofuranose (**10**, 30 mg, 90%) An analytical sample of **10** was obtained by distillation at 150° and 0 5 torr, $[\alpha]_D^{26}$ +44 3° (*c* 2 6, chloroform), n m r ($CDCl_3$) τ 4 19 (d, 1, $J_{1,2}$ 4 Hz, H-1), 4 36 (q, 1, $J_{5,6}$ 2 6 Hz, $J_{5,6'}$ 7 7 Hz, H-5), 4 83 (d, 1, $J_{2,3}$ 6 Hz, H-3), 5 15 (q, 1, H-2), 5 45 (q, 1, $J_{6,6'}$ 12 Hz, H-6), 5 83 (s, 2, CH_2), 5 93 (q, 1, H-6'), 7 82, 7 90, 7 98 (3 s, 12, OAc), 8 39, 8 63 (2 s, 6, CH_3)

Anal Calc for $C_{18}H_{26}O_{11}$ C, 51 67, H, 6 26 Found C, 51 27, H, 6 40

4-C-(Hydroxymethyl)-1,2-O-isopropylidene-α-D-erythro-pentofuranose (**11**) *and* (**12**) — A solution of **9** (324 mg) in methanol (6 ml) was added to a mixture of sodium metaperiodate (140 mg) and sodium hydrogencarbonate (20 mg) in water (6 ml) After 1 h, t l c with 5 1 ethyl acetate–ethanol showed the reaction to be complete, and ethylene glycol (0 1 ml) was added, followed by sodium borohydride (35 mg) After 30 min, acetone (0 5 ml) was added and the solution was evaporated to yield **11** as a syrup (0 25 g, 88%), $[\alpha]_D^{28}$ +7° (*c* 0 1, methanol)

Compound **11** (0 25 g) was acetylated with acetic anhydride (3 ml) and pyridine (10 ml) After 10 h at room temperature, the solution was evaporated and the residue dissolved in dichloromethane (10 ml), and the organic solution was washed with water (5 ml) The organic solution was then dried and evaporated to afford the triacetate **12** (337 mg, 90%) An analytical sample of **12** was obtained by distillation at 155–160° and 0 5 torr, $[\alpha]_D^{26}$ +47 6° (*c* 0 76, chloroform), n m r ($CDCl_3$) τ 4 13 (d, 1, $J_{1,2}$ 4 Hz, H-1), 4 85 (d, 1, $J_{2,3}$ 5 8 Hz, H-3), 5 16 (q, 1, H-2), 5 55 (q, 2, J_{AB} 11 Hz, H-5, H-5'), 5 81 (q, 2, J_{AB} 12 Hz, H-5'', H-5''), 7 87, 7 92 (2 s, 9, OAc), 8 4, 8 67 (2 s, 12, CH_3)

Anal Calc for $C_{15}H_{22}O_9$ C, 51 98, H, 6 55 Found C, 52 02, H, 6.40

4-C-(Acetoxymethyl)-1,2,3,5-tetra-O-acetyl-α-(and β)-D-erythro-pentofuranose (**14**) — Compound **12** (0 1 g) was dissolved in 80% aqueous trifluoroacetic acid (1 5 ml) at 0° After 15 min, the solution was evaporated to dryness, the residue was diluted with toluene (2 ml), and the solvent was removed The thoroughly dried residue was dissolved in pyridine (1 ml) and acetic anhydride (0 5 ml), and the solution was kept for 10 h at room temperature The mixture was evaporated and the residue was dissolved in dichloromethane (5 ml) The organic solution was washed with water (2 ml), dried and evaporated to afford **14** as an α,β mixture (90 mg, 80%) An analytical sample of the anomeric mixture was obtained by distillation at 125–130° and 0 5 torr, $[\alpha]_D^{26}$ −21 5° (*c* 0 68, chloroform), n m r ($CDCl_3$) τ 3 6 (d, 1, $J_{1,2}$ 4 Hz, H-1α), 3 8 (s, 1, H-1β), 7 92 (s, 15, OAc)

Anal Calc for $C_{16}H_{20}O_{11}$ C, 49 23, H, 5 68 Found C, 49 27, H 5 80

9 [4-C-(Hydroxymethyl)-α-D erythro-pentofuranosyl]adenine (**18**) *and 9-[4-C-(hydroxymethyl)-β-D-erythro-pentofuranosyl]adenine* (**17**) — An α,β mixture of compound **14** (0 1 g) was dissolved in anhydrous dichloromethane (1 ml), and hydrogen bromide-saturated glacial acetic acid (2 ml) was added at 0° with stirring The flask was sealed and kept for 1 h at room temperature The solution was then evaporated and any remaining acetic acid reoved by successive azeotroping with toluene (2 × 2 ml) under diminished pressure The resulting syrup was immediately dissolved in anhydrous dichloromethane (5 ml) containing N^6-benzoyl-N^6,9-bis(trimethylsilyl)adenine[16] (0 1 g) and the solvent was removed This homogeneous syrup was heated for 30 min to 130–135° at 15 torr T l c with benzene–ethyl acetate–ethanol showed the presence of three charring, u v -absorbing components Chromatography of this mixture on t l c -grade silica (20 × 2 cm), with the aforementioned solvent afforded 9-[4-*C*-(acetoxymethyl)-2,3,5-tri-*O*-acetyl-α-D-*erythro*-pentofuranosyl]-N^6-benzoyladenine (**16**, 29 mg, 20%), 9-[4-*C*-(acetoxymethyl)-2,3,5-tri-*O*-acetyl-β-D-*erythro*-pentofuranosyl]-N^6-benzoyladenine (**15** 29 mg, 20%), and a third, unknown component (7 mg, 5%), n m r for **16** ($CDCl_3$) τ 0 9 (broad s, 1, N^6H), 1 2 (s, 1, H-2), 1 6 (s, 1, H-8) 1 95 (m, 2, *o*-aromatic protons), 2 42 (m, 3, m, *p*-aromatic protons), 3 36 (d, 1, $J_{1',2'}$ 4 Hz, H-1'), 4 42 (d, 1, $J_{2',3'}$ 4 Hz, H-3'), 5 23 (t, 1, H-2'), 7 85, 7 94 (2 s, 12, OAc) Irradiation at τ 3 36 produced a doublet at τ 5 23 Irradiation at τ 5 23 produced singlets at τ 3 36 and 4 42, n m r for **15** ($CDCl_3$) τ 0 85 (broad s, 1, NH), 1 23 (s, 1, H-2), 1 83 (s, 1, H-8), 2 0 (m, 2 *o*-aromatic protons), 2 61 (m, 3, *p,m*-aromatic protons), 3 73 (d, 1, $J_{1',2'}$ 5 8 Hz, H-1') 3 83 (unresolved q, 1, $J_{2',3'}$ 5 5 Hz, H-2'), 4 1 (d, 1, H-3'), 5 58 (m 4), 7 87, 7 93, 7 95, and 7 99 (4 s, 12 OAc)

To a solution of compound **16** (0 02 g) in methanol (1 ml) was added a catalytic amount of sodium methoxide and the solution was kept for 24 h The solution was decationized with Rexyn RG-51 (H^+) resin and evaporated to give a residue that was dissolved in water treated with charcoal, and filtered through sintered glass Evaporation of the aqueous solution gave 9-[4-*C*-(hydroxymethyl)-α-D-*erythro*-pentofuranosyl]adenine (**18**) which was recrystallized from water, m p 262–263 5°, $[\alpha]_D^{26}$ +7° (*c* 0 1, water), $\lambda_{max}^{H_2O}$ 258 nm (ε 9700) c d $\Delta\varepsilon$ +0 448 (λ_{max} 255 nm, *c* 0 0001, water), $[\theta]_{295}^{30}$ +1480, n m r (D_2O) τ 1 07 (s, 1, H-2), 1 15 (s, 1, H-8), 3 31 (d, 1, $J_{1',2'}$ 6 5 Hz, H-1'), and 4 41 (q, 1, $J_{2',3'}$ 4 Hz, H-2')

Anal Calc for $C_{11}H_{15}N_5O_5 \cdot 2H_2O$ C, 39 64, H, 5 75 N, 21 01 Found C 39 75, H, 6 13, N, 21 30

Compound **15** was deacetylated as just described for **18**, to afford **17** as a hard glass, $[\alpha]_D^{28}$ +1° (*c* 0 1, water) $\lambda_{max}^{H_2O}$ 258 nm (ε 7,860), c d $\Delta\varepsilon$ −0 335 (λ_{max} 255 nm, *c* 0 0001, water), $[\theta]_{295}^{30}$ −1650 n m r (CD_3OD) τ 1 5 (s, 1, H-2), 1 67 (broad s, 2, NH_2), 1 77 (s, 1, H-8), 3 59 (d, 1, $J_{1',2'}$ 2 5 Hz, H-1'), and 4 21 (d, 1, $J_{2',3'}$ 6 Hz H-3')

Anal Calc for $C_{11}H_{15}N_5O_5$ C, 44 44, H, 5 09, N 23 56 Found C, 44 75 H, 5 43, N, 23 33

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