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9-[3-ACETAMIDO-3-*C*-(CARBOXYMETHYL)-3-DEOXY-3^2,2-LACTONE-α (AND β)-D-XYLOFURANOSYL]ADENINE- ANALOGS OF THE NUCLEOSIDE MOIETY OF THE POLYOXINS*

ALEX ROSENTHAL AND MURRAY RATCLIFFE

Department of Chemistry, The University of British Columbia, Vancouver, B.C. V6T 1W5 (Canada)

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ABSTRACT

Treatment of (*Z*)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-(methoxycarbonyl)-methylene-α-D-*ribo*-hexofuranose (**1**) with a mixture of sodium azide, hydrazoic acid, and *N*,*N*-dimethylformamide afforded 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-(methoxycarbonyl)methyl-α-D-glucofuranose (**3**) and 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-[2-diazo(methoxycarbonyl)methyl]-α-D-glucofuranose (**4**) in 80 and 7% yields, respectively. Treatment of **1** with sodium azide in *N*,*N*-dimethylformamide gave **4** in 45% yield. Reduction of **3** or **4** with hydrogen over palladium afforded 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-(methoxycarbonyl)methyl-α-D-glucofuranose (**5**) in quantitative yield. Oxidation of the *N*-acetyl diol **8**, derived from **7**, with sodium metaperiodate yielded a dialdose that was reduced with sodium borohydride to give **9** in 90% yield. Benzoylation of **9** afforded 3-acetamido-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-(methoxycarbonyl)methyl-α-D-xylofuranose (**10**). Treatment of **10** with trifluoroacetic acid, followed by acetylation, yielded 3-acetamido-1-*O*-acetyl-5-*O*-benzoyl-3-*C*-carboxymethyl-3-deoxy-β-(and α)-D-xylofuranose-3^2,2-lactones (**12** and **13**) in 75 and 25% yields, respectively. Condensation of the glycosyl bromide, derived from **12**, with 6-*N*-benzoyl-6-*N*,9-bis(trimethylsilyl)adenine afforded an anomeric mixture of protected nucleosides **14** and **15** in 50% yield. Treatment of the latter compounds with sodium methoxide in methanol yielded 9-[3-acetamido-3-*C*-(carboxymethyl)-3-deoxy-3^2,2-lactone-β-D-xylofuranosyl]adenine (**16**) and the α-D anomer **17** in 79 and 65% yields, respectively.

INTRODUCTION

In continuation of our studies on the chemistry of branched-chain sugar nucleosides[1] that are analogues of the naturally occurring nucleoside antibiotics[2], we now report conjugate addition of hydrazoic acid to the carbon–carbon double bond of an unsaturated, branched-chain sugar to afford the expected azido product,

*Part of a series: Branched-chain glycos-3-yl β-amino acids. The term "glycosyl" is used in an extended sense, through C-3.

and in addition, an unexpected amino diazo addition-product. From the former product, 3'-*C*-(branched-chain) amino acid nucleosides, that are analogues of the nucleoside moiety of the polyoxins[3], were synthesized.

In the carbohydrate field, there have been a few reports dealing with the synthesis of azido sugars by conjugate addition of hydrazoic acid to unsaturated carbohydrates. Conjugate 1,4-addition of hydrazoic acid to ethyl 6-*O*-tolylsulfonyl-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose afforded an epimeric mixture of 2-azido glycosides[4]. Treatment of methyl 6-*O*-benzoyl-3,4-dideoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose with sodium azide in acetic acid yielded methyl 4-azido-6-*O*-benzoyl-3,4-dideoxy-α-D-*erythro*-hexopyranosid-2-ulose[5]. Treatment of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose with mercuric azide in hot 50% aqueous tetrahydrofuran afforded, after reductive demercuration, 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-glucofuranose[6].

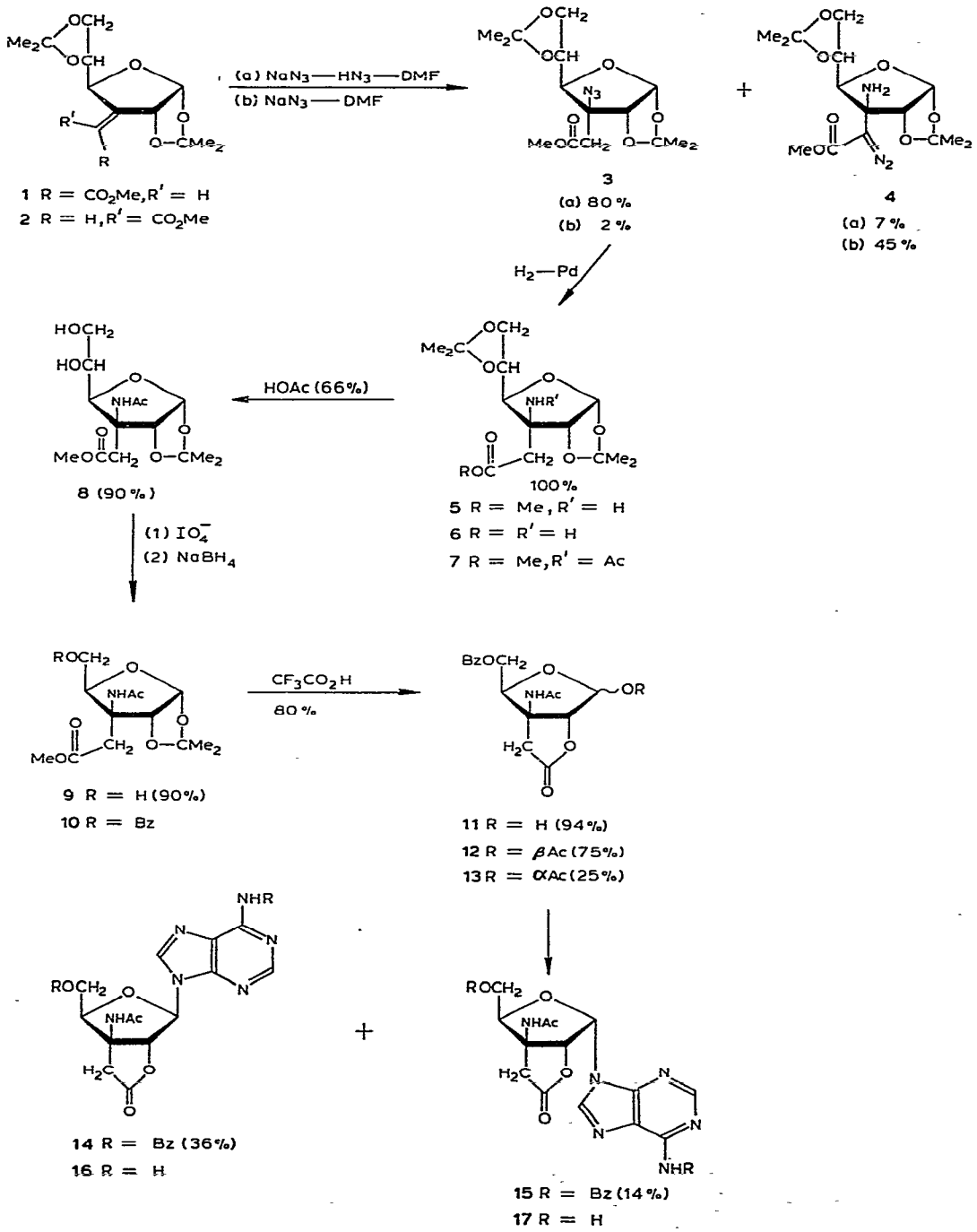
Phenyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside underwent 1,2-addition with hydrazoic acid in acetonitrile to yield phenyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside[7].

RESULTS AND DISCUSSION

When a solution of (*Z*)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-(methoxycarbonyl)methylene-α-D-*ribo*-hexofuranose[8] (**1**) was allowed to react with an excess of sodium azide and hydrazoic acid in *N*-*N*-dimethylformamide for 5 days at 55°, a mixture of two products **3** and **4** was obtained, together with unreacted starting material **1**. Chromatographic separation of the mixture of products on silica gel with 2:1 benzene–ethyl acetate afforded pure **1**, together with **3** and **4**, in 80 and 7% yields, respectively. When **1** was allowed to react with sodium azide only, products **3** and **4** were obtained in 2 and 45% yields, respectively. The (*E*) isomer **2** failed to react with sodium azide and hydrazoic acid.

Assignment of structures **3** and **4** to the products was made on the basis of i.r., n.m.r., u.v., and mass-spectral studies. The i.r. spectrum of **3** revealed the presence of the azide group, absorbing at 2137 cm^{-1}. The n.m.r. spectrum of **3** showed the presence of an AB quartet at δ 3.04 ($J = 18$ Hz) which was assigned to the methylene protons of the chain branch. The i.r. spectrum of **4** revealed the presence of an amine group, absorbing at 3350 and 3410 cm^{-1}, and a diazo ester group[9], absorbing at 1685 and 2101 cm^{-1}. The u.v. spectrum of **4** confirmed the presence of the α-diazo ester group, absorbing at 269 nm. The n.m.r. spectrum of **4** exhibited a two-proton, broad singlet at δ 2.05, which disappeared upon the addition of D_2O, thus confirming the presence of a primary amine group. The high-resolution mass spectra of **3** and **4** revealed peaks at *m/e* 342 (loss of methyl) and at 314 (loss of methyl and nitrogen), respectively. Huisgen and co-workers[9] have reported that treatment of a 1,2,3-triazoline-4-methylcarboxylate with triethylamine afforded a 3-amino-2-diazo methyl carboxylate.

The configuration of C-3 of compounds **3** and **4** was assigned on the basis of



circular dichroism (c.d.) and on chemical studies. Hydrogenation of **3** and **4** over paladium-on-charcoal yielded the branched-chain β-amino ester **5**, thus proving

that the configuration at C-3 of compounds **3** and **4** was the same. The n.m.r. spectrum of **5** (see Experimental section) confirmed the presence of a β-amino ester sugar. The c.d. spectrum of **3** revealed a negative peak, absorbing at 294 nm. Thus, on the basis of the azide octant-rule[10], it might be surmised that compound **3** has the *gluco* configuration. Although previous workers[11,12] have assigned the configuration of the chiral carbon atom adjacent to the azido group of pyranoid sugars through analysis of their c.d. spectra, no similar study of furanose azides has been reported. We therefore sought confirmation of the validity of the azide octant-rule by measuring the c.d. spectra of two furanose azides. As expected, the c.d. spectra of 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofurancse[13] and of 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[14] revealed opposite Cotton effects, which were in agreement with the azide octant-rule. When an *N*-acetyl compound **10**, derived from **5**, was hydrolyzed with trifluoroacetic acid, a 3^2,2-lactone was obtained, thus confirming that **5** must possess the *gluco* configuration (this chemical proof is described in greater detail in the latter part of the discussion).

Hydrolysis of **5** with sodium hydroxide in aqueous methanol afforded 3-amino-3-*C*-(carboxymethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) in 85% yield. An i.r. peak at 3200–2600 cm^{-1} established the presence of the carboxyl group in **6**. The p.m.r. spectrum of **6** showed a broad singlet resonating at δ 2.0–2.2 that disappeared upon addition of D_2O, thus establishing the presence of an amino group in **6**.

Acetylation of the amino ester **5** afforded the 3-acetamido derivative **7**, in quantitative yield. Selective hydrolysis of **7** with 66% acetic acid removed the 5,6-*O*-isopropylidene group to afford **8** in 90% yield. Treatment of the latter compound with sodium metaperiodate, followed by reduction of the resulting aldehyde, yielded the alcohol **9**. Benzoylation of **9** with benzoyl chloride in pyridine yielded 3-acetamido-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-(methoxycarbonyl)methyl-α-D-xylo-furanose (**10**) in an overall 45% yield from **1**. Hydrolysis of the latter compound with 80% aqueous trifluoroacetic acid afforded the γ-lactone **11** in 94% yield. Acetylation of **11** yielded the anomeric acetates **12** and **13** in 90% yield, and these were separated by column chromatography on silica gel using 5:5:1 benzene–ethyl acetate–ethanol as developer.

Confirmation that the methyl ester **10** was converted into the 3^2,2-lactone **11** was provided by the following evidence. The n.m.r. spectra of **11**, **12**, and **13** revealed the absence of the methyl group of the methyl ester. The two acetyl peaks present were assigned to the *N*-acetyl group at δ 2.15 and to the anomeric *O*-acetyl group at δ 2.05. The i.r. spectra of **12** and **13** revealed the presence of a carbonyl peak at 1800 cm^{-1}, which was attributed to the γ-lactone functionality[15]. Elemental analysis of the lactones **12** and **13** were in agreement with their structures. The n.m.r. spectrum of the β acetate **12** and α anomer **13** revealed the presence of H-1 doublets at δ 6.18 (J = 1 Hz) and at δ 6.59 (J = 5 Hz). The conversion of the methyl ester **10** into the γ-lactone **11** thus provided proof that **10** had the *xylo* configuration.

The γ-lactones **12** and **13** were allowed to react with hydrogen bromide in

acetic acid and dichloromethane to yield 3-acetamido-5-*O*-benzoyl-3-*C*-(carboxymethyl)-3-deoxy-α-D-xylofuranosyl bromide-3^2,2-lactone. The latter compound was immediately condensed with N^6-benzoyl-N^6,9-bis(trimethylsilyl)adenine for 25 min at 170° according to a known procedure[16] to afford, after column chromatography on silica gel with 5:5:1 dichloromethane–ethyl acetate–ethanol as developer, a β,α mixture of protected nucleosides **14** and **15** in 36 and 14% yields, respectively. The coupling constants of H-1′ (0.8 and 4 Hz) of the protected nucleosides **14** and **15**, respectively, permitted the β assignment to **14** and α to **15**. Treatment of the protected nucleosides with sodium methoxide in methanol gave, in high yield, the free, branched-chain nucleoside amino acids **16** and **17**. The site of glycosylation[17] was established as N^9, as both nucleosides exhibited u.v. maxima at 205 and 258 nm. Although the coupling constants of H-1′ (2 and 4 Hz) of the free nucleosides were too close in value to permit assignment of their anomeric configuration, the appreciable difference in their H-1′ chemical shifts (δ 6.2 and 6.55) strongly indicated that the anomer **17** having H-1′ at lower field should be the α nucleoside. Corroboration of the assignment of anomeric configuration to **16** and **17** was based on their c.d.[18] spectra. The β nucleoside **16** exhibited a negative c.d. curve, whereas the α anomer **17** gave a positive c.d. curve. Therefore, compound **16** must be 9-[3-acetamido-3-*C*-(carboxymethyl)-3-deoxy-3^2,2-lactone-β-D-xylofuranosyl]adenine and **17** must be the α anomer. Interestingly the γ-lactone of the α nucleoside **17** was hydrolyzed by water at 60–70°. The p.m.r. spectrum of **17** in D_2O showed a doublet at δ 6.55 that, upon heating the n.m.r. tube for 2–3 min to 60–70°, disappeared and a new doublet at δ 6.7 appeared. These doublets were assigned to H-1′ of the nucleoside γ-lactone and to the 3′-*C*-(carboxymethyl)nucleoside, respectively. An analog of the branched-chain glycosyl amino acid **5** has been recently reported[19].

The i.r. spectrum of the n.m.r. sample of **17** after heating, cooling, and subsequent removal of the solvent at low temperature, revealed a broad absorption-band between 2800–2400 cm^{-1} that is typical of a free acid. Presumably, the heterocyclic base of the α nucleoside **17** participated in the hydrolysis of the γ-lactone ring. Similar treatment of the β nucleoside **16** with D_2O did not hydrolyze the γ-lactone. Fusion of the nucleoside containing the free carboxymethyl group at 160° converted it into the lactone nucleoside **17**.

EXPERIMENTAL

General. — Solutions were dried with anhydrous sodium sulfate and evaporated under diminished pressure. Column chromatography was performed on t.l.c.-grade Silica Gel H without binder (Merck) 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 (unless otherwise stated) with tetramethylsilane as internal standard (set at δ = 0) by using a Varian A-60 or Varian XL-100 spectrometer. I.r. spectra were recorded on a Perkin–Elmer 337 spectrometer. Mass spectra were performed with a HMS-9 spectrometer and circular-dichroism measurements were performed with a Jasco J-20

automatic recording spectropolarimeter at room temperature. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter. Hydrazoic acid solutions were prepared according to the procedure of H. Wolff[20]. All melting points are corrected. Elemental analyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

*Treatment of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-*(Z)*-3-C-(methoxycarbonyl)-methylene-α-*D*-ribo-hexofuranose* (**1**) *with hydrazoic acid and sodium azide. — Procedure A.* A solution of **1** (10 g), sodium azide (5 g), hydrazoic acid (70 ml of a 1.6M solution of HN_3 in chloroform), and redistilled, anhydrous *N,N*-dimethylformamide (400 ml) was stirred for 5 days at 55°. The solvent was then evaporated to a syrup that was diluted with saturated aqueous sodium chloride (100 ml). The aqueous suspension was extracted with dichloromethane (2 × 100 ml) and the combined organic extracts were dried and evaporated to yield a bright-yellow syrup (11 g). This syrup was chromatographed on t.l.c.-grade silica gel (51 × 7 cm) with 2:1 benzene–ethyl acetate as developer, to afford starting material **1** (1 g), 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-(methoxycarbonyl)methyl-α-*D*-glucofuranose **3**, 9 g, 80%), and 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*[1-diazo-(methoxycarbonyl)methyl]-α-*D*-glucofuranose **4**, 0.8 g, 7%).

Distillation of **3** at 110–115° and 0.5 torr gave an analytical sample; $[\alpha]_D^{25}$ −25° (*c* 1, chloroform); ν_{max}^{film} 2137 (N_3), 1745 cm^{-1} (CO_2CH_3); c.d. $\Delta\varepsilon$ −0.035 (α_{max} 294 nm, water), $[\theta]_{294}^{30}$ −118°; n.m.r. ($CDCl_3$): δ 5.95 (d, 1, $J_{1,2}$ 3.8 Hz, H-1) 5.07 (d, 1, H-2), 3.9 (s, 3, CH_3), 3.04 (q, 2, J_{AB} 18 Hz, H-1 protons), 1.79, 1.48, and 1.40 (3s, 12, CH_3). Irradiation at δ 5.95 collapsed the doublet at δ 5.07 to a singlet.

Anal. Calc. for $C_{15}H_{23}N_3O_7$: C, 50.42; H, 6.49; N, 11.76. Found: C, 50.53; H, 6.32; N, 11.30.

Distillation of **4** at 120–130° and 0.5 torr gave an analytical sample; $[\alpha]_D^{25}$ +16.2° (*c* 0.13, chloroform); ν_{max}^{film} 3410, 3350 (NH_2), 2101 (= N_2), 1685 cm^{-1} (CO_2CH_3); λ_{max}^{MeOH} 269 (ε 7630), 213 nm (ε 5380); n.m.r. ($CDCl_3$): δ 5.88 (d, 1, $J_{1,2}$ 4 Hz, H-1), 4.5 (d, 1, H-2), 3.79 (s, 3, CH_3), 2.05 (s, 2, NH_2, exchanges with D_2O), 1.50, 1.41, 1.37, and 1.30 (4s, 12, CH_3). Irradiation at δ 5.88 collapsed the doublet at 6.45 to a singlet.

Anal. Calc. for $C_{15}H_{23}N_3O_7$: C, 50.42, H, 6.49; N, 11.76. Found: C, 50.71; H, 6.25; N, 11.71.

Procedure B. Treatment of compound **1** *with sodium azide.* A solution of **1** (4.4 g) and sodium azide (3.5 g) in anhydrous, redistilled *N,N*-dimethylformamide (250 ml) was stirred for 5 days at 55°. The mixture was processed as described in procedure A to yield a yellow syrup (3.5 g). This syrup was chromatographed on t.l.c.-grade silica gel (27.6 cm) with 2:1 benzene–ethyl acetate as developer to afford starting material **1** (1.97 g), compound **3** (0.20 g, 2%), and compound **4** (2.2 g, 45%).

*3-Amino-3-deoxy-1,2:5,6-*O*-isopropylidene-3-*C*-(methoxycarbonyl)methyl-α-*D*-glucofuranose* (**5**). — A solution of **3** (0.9 g) in methanol (5 ml) was added to pre-hydrogenated 5% palladium-on-charcoal (0.15 g) in methanol (50 ml). This mixture was hydrogenated at atmospheric pressure for 12–15 h. (until all starting material

had been consumed, as evidenced by t.l.c. with 1 : 1 benzene–ethyl acetate as developer). After removal of catalyst by filtration, the solvent was evaporated to yield syrupy **5** (0.8 g, 96%). Distillation of this syrup at 135–140° and 0.5 torr gave an analytical sample: $[\alpha]_D^{26}$ +39.7° (*c* 1.07, chloroform); ν_{max}^{film} 3400–3100 (NH_2), 1740 (CO_2CH_3), 1650–1550 cm^{-1} (NH_2); n.m.r. ($CDCl_3$): δ 5.85 (d, 1, $J_{1,2}$ 3.7 Hz, H-1), 4.53 (d, 1, H-2), 3.67 (s, 3, CH_3) 2.8 (q, 2, $J_{A,B}$ 18 Hz, H-1) 1.76 (s, 2, NH_2, exchanges with D_2O), 1.48, 1.40, 1.32, and 1.29 (4s, 12, CH_3). Irradiation at δ 5.85 collapsed the doublet at δ 4.53 to a singlet.

Anal. Calc. for $C_{15}H_{25}NO_7$: C, 54.37, H, 7.60; N, 4.23. Found: C, 54.59; H, 7.68, N, 4.50.

*3-Amino-3-*C*-(carboxymethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (**6**). — A solution of **5** (55 mg), methanol (2 ml), and 4% sodium hydroxide in methanol (1 ml) was boiled for 30 min under reflux. The solution was then decationized with Rexyn RG-51 (H^+) resin and evaporated to give crystalline **6** (40 mg, 85%). Sublimation of **6** at 210° and 0.5 torr gave an analytical sample: $[\alpha]_D^{25}$ +25° (*c* 0.12 chloroform); ν_{max}^{Nujol} 3200–2600 (CO_2H), 1640 cm^{-1} (C = O); n.m.r. ($CDCl_3$): δ 5.9 (d, 1, $J_{1,2}$ 3.9 Hz, H-1), 4.5 (d, 1, H-2), 3.70 (q, 2, $J_{A,B}$ 8 Hz, H-1's), 2.0–2.2 (broad s, 2, NH_2, exchanges with D_2O), 1.45, 1.38, 1.31, and 1.22 (4s, 12, CH_3).

Anal. Calc. for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41; Found: C, 52.97; H. 7.15; N, 4.20.

*3-Acetamido-3-deoxy-1,2:5,6-*di-*O-isopropylidene-3-*C*-(methoxycarbonyl)methyl-α-*D*-glucofuranose* (**7**). — A solution of compound **6** (2 g) in anhydrous pyridine (20 ml) and acetic anhydride (2 ml) was stirred for 20 h at room temperature. The solution was poured into ice–water (20 ml) and stirred for 10 min, and then extracted with dichloromethane (2 × 50 ml). The dried, organic solution was evaporated to a solid (2.2 g, 98%). Sublimation of **7** at 120° and 0.5 torr afforded an analytical sample: $[\alpha]_D^{26}$ +22.8° (*c* 1.05, chloroform); ν_{max}^{film} 3500, 3400, 1695 (–CONH–), 1740 cm^{-1} (CO_2CH_3); n.m.r. ($CHCl_3$): δ 6.2 (s, 1, NH), 6.08 (d, 1, $J_{1,2}$ 4 Hz, H-1), 5.32 (d, 1, H-2), 3.71 (s, 3, CO_2CH_3), 3.0 (s, 2, H-1 protons), 2.0 (s, 3, NAc), 1.55, 1.48, and 1.38 (s, 12, CH_3).

Anal. Calc. for $C_{17}H_{27}NO_8$: C, 54.68, H, 7.29; N, 3.75. Found: C, 54.76; H, 7.25; N, 3.88.

*3-Acetamido-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-(methoxycarbonyl) methyl-α-*D*-xylofuranose* (**10**). — A solution of **7** (2.1 g) in 66% acetic acid (5 ml) was stirred for 23 h at room temperature. Toluene (25 ml) was distilled from the solution to yield a light-yellow syrup (1.8 g), R_F 0.13, with 5:5:1 benzene–ethyl acetate–ethanol as developer. Distillation of the diol **8** at 150–160° and 0.5 torr gave pure **8** in near-quantitative yield: $[\alpha]_D^{26}$ +51.5° (*c* 1.14, chloroform); $\nu_{max}^{CHCl_3}$ 3600–3400 (OH), 1735 (CO_2CH_3), and 1675 cm^{-1} (NAc); n.m.r. ($CDCl_3$): δ 6.68 (s, 1, NH), 5.87 (d, 1, $J_{1,2}$ 6.2 Hz, H-1), 4.88 (d, 1, H-2), 2.02 (s, 3, NAc), 1.45, and 1.27 (s, $2CH_3$). A solution of **8** (1.7 g) in methanol (40 ml) was added to a mixture of sodium metaperiodate (1.09 g) and saturated sodium hydrogencarbonate solution (2 ml), and water (70 ml). After 15 min, a drop of ethylene glycol was added, followed by

sodium borohydride (120 mg) and the resulting solution was stirred for 0.5 h. The solution was then filtered through sintered glass and the solvent evaporated to yield a residue that was taken up in water (25 ml) and extracted with dichloromethane (4 × 100 ml). The combined organic solution was dried and evaporated to yield a hard glass (1.3 g, 85%). Distillation of this glass at 150–160° and 0.5 torr gave pure **9**; $[\alpha]_D^{26}$ +19.0° (*c* 1.44, chloroform); $\nu_{max}^{CHCl_3}$ 3600 (OH), 3400 (NH), 1735 (CO_2CH_3), and 1685 cm^{-1} (NAc); n.m.r. ($CDCl_3$): δ 7.68 (s, 1, NH, exchanges with D_2O), 5.85 (d, 1, $J_{1,2}$ 4 Hz, H-1), 5.07 (d, 1, H-2), 3.65 (s, 3, CH_3), 1.99 (s, 3, NAc), 1.48, and 1.3 (s, 6, CH_3). Compound **9** (1.2 g) was benzoylated with benzoyl chloride (0.5 ml) in anhydrous benzene (15 ml) and pyridine (1 ml). After stirring for 8 h at room temperature, the solution was passed through a short column of alumina (5 g). The eluate was evaporated to yield **10** (1.39 g), R_F 0.25 on silica gel with 10:10:1 benzene–ethyl acetate–ethanol, as developer. A minor impurity was present. Chromatographic separation on t.l.c.-grade silica gel (23 × 3 cm) eluted with 10:10:1 benzene–ethyl acetate–ethanol as developer afforded pure **10** (1.08 g) in an overall yield of 50% based on **7**. An analytical sample of **10** was obtained by distillation at 200–210° and 0.5 torr; $[\alpha]_D^{26}$ +28.4° (*c* 1.1, chloroform); $\nu_{max}^{CHCl_3}$ 3500–3300 cm^{-1} (NH); n.m.r. ($CDCl_3$): δ 8.2–7.9 (m, 2, *o*-aromatic protons), 7.6–7.4 (m, 3, *p,m*-aromatic protons), 6.61 (broad s, 1, NH), 5.95 (d, 1, $J_{1,2}$ 3.5 Hz, H-1), 5.08 (d, 1, H-2), 5.62 (s, 3, CH_3), 5.29 (s, 2, H-1^1), 1.92 (s, 3, OAc), 1.52, and 1.35 (2s, 6, CH_3).

Anal. Calc. for $C_{20}H_{25}NO_8$: C, 58.96; H, 6.19; N, 3.44. Found: C, 58.60; H, 6.30; N, 3.21.

*3-Acetamido-1-*O*-acetyl-5-*O*-benzoyl-3-*C*-(carboxymethyl)-3-deoxy-β(and α)-*D*-xylofuranose-3^2,2-lactone* (**12**) and (**13**). — A solution of compound **10** (1 g) in 80% aqueous trifluoroacetic acid (50 ml) was stirred for 1 h at room temperature. The solution was evaporated to yield a residue from which toluene (2 × 25 ml) was evaporated to remove the last traces of acid. The resulting syrup (0.84 g) was acetylated with acetic anhydride (4 ml) and pyridine (6 ml). After 20 h at room temperature, the solution was poured into ice–water (20 ml) and stirred for 20 min. The mixture was extracted with dichloromethane (2 × 50 ml), dried, and evaporated to yield a syrup (0.9 g, 90%). Chromatography of the anomeric mixture on silica gel (29 × 4 cm) with 5:5:1 benzene–ethyl acetate–ethanol as developer afforded the pure α and β-acetates **13** and **12**. An analytical sample of **13** was prepared by distillation at 140–145° and 0.5 torr; $[\alpha]_D^{26}$ + 75° (*c* 0.69, chloroform); $\nu_{max}^{CHCl_3}$ 1800 (γ-lactone) and 1680 cm^{-1} (CONH); n.m.r. ($CDCl_3$); δ 8.2–7.9 (m, 2, *o*-aromatic protons), 7.7–7.4 (m, 3, *p,m'*-aromatic protons), 6.59 (d, 1, $J_{1,2}$ 5 Hz, H-1), 6.25 (broad s, 1, NH, exchanges with D_2O), 5.29 (d, 1, H-2), 5.2 (q, 2, $J_{A,B}$ 18 Hz, H-3^1) 2.15 (s, 3, NAc), and 2.05 (s, 3, OAc).

Anal. Calc. for $C_{18}H_{19}NO_8$: C, 57,29; H, 5.08; N, 3.71. Found: C, 58.60; H, 5.30; N, 3.21.

Distillation of **12** at 150–155° and 0.5 torr gave an analytical sample: $[\alpha]_D^{26}$ −57° (*c* 0.18, chloroform); $\nu_{max}^{CHCl_3}$ (γ-lactone), 1690 cm^{-1} (CONH); n.m.r. ($CDCl_3$): 8.01–8.00 (m, 2, *o*-aromatic protons), 7.6–7.4 (m, 3, *p,m*-aromatic protons), 7.8

(s, 1, NH, exchanges with D_2O), 6.18 (d, 1, $J_{1,2}$ 1 Hz, H-1); 5.07 (d, 1, H-2), 4.80 (t, 1, $J_{4,5} = J_{4,5'}$ 5 Hz, H-4), 4.5 (d, 2, $J_{4,5}$ 5 Hz, H-5 protons), 3.09 (q, 2, J_{AB} 19 Hz, H-3^1), and 1.99 (s, 6, NAc, OAc).

Anal. Calc. for $C_{18}H_{19}NO_8$: C, 57.29; H, 5.08; N, 3.71. Found: C, 57.65; H, 5.34; N, 3.58.

*9-{[3-Acetamido-5-*O*-benzoyl-3-*C*-(carboxymethyl)-3-deoxy-α (and β)-*D*-xylofuranosyl]-3^2,2-lactone}-N^6-benzoyladenine* (**15**) and (**14**). — An α,β mixture of **12** and **13** (150 mg) was dissolved in anhydrous dichloromethane (2 ml), and hydrogen bromide-saturated acetic acid (2 ml) was added at 0° with stirring. The flask was sealed and kept for 2 h at room temperature. The solution was then evaporated, and any remaining acetic acid removed by successive evaporation of toluene (2 × 2 ml) from the residue 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] (0.2 g) and the solvent was removed. This homogenous syrup was then heated for 30 min to 170° at 15 torr. After cooling, ethanol saturated with sodium hydrogencarbonate (10 ml) was added and the resulting suspension filtered through sintered glass. Removal of the solvent under diminished pressure gave a brown syrup (0.2 g). Column chromatography of the product on t.l.c.-grade silica gel (23 × 2 cm) with 5:5:1 dichloromethane–ethyl acetate–ethanol as developer afforded the faster-migrating 9-[3-acetamido-5-*O*-benzoyl-3-*C*-carboxymethyl-3-deoxy-3^2,2-lactone-β-*D*-xylofuranosyl]-N^6-benzoyladenine (**14**, 75 mg, 36%) and 9-[3-acetamido-5-*O*-benzoyl-3-*C*-(carboxymethyl)-3-deoxy-3^2,2-lactone-α-*D*-xylofuranosyl]-N^6-benzoyladenine (**15**, 30 mg, 14%). Recrystallization of **15** from methanol gave an analytical sample; m.p. 154–156°, $[\alpha]_D^{26}$ −13.9° (*c* 0.8, chloroform); λ_{max}^{MeOH} 202 (ε 22,200), 227 (ε 19,900), 277 nm (16,700); $\nu_{max}^{CHCl_3}$ 1800 cm^{-1} (lactone); n.m.r. 9.4 (broad s, 1, NHBZ, exchanges with D_2O), 8.5 (s, 1, H-8), 8.2 (s, 1, NHAc), 8.14 (s, 1, H-2), 8.0–7.8 (m, 4, *o*-aromatic protons), 7.6–7.3 (m, 6, *p*-aromatic protons), 6.88 (d, $J_{1',2'}$ 4 Hz, H-1'); 5.55 (d, 1, H-2'), 5.0 (m, 1, H-4'), 4.8–4.4 (m, 2, H-5' protons), 3.25 (s, 2, methyiene), and 1.94 (s, 3, NAc).

Anal. Calc. for $C_{28}H_{24}N_6O_7 \cdot H_2O$: C, 58.55; H, 4.55; N, 14.61. Found: C, 58.60; H, 4.46, N, 14.77.

Compound **14** was obtained as an amorphous solid; $[\alpha]_D^{30}$ +43.6° (*c* 0.22, methanol); λ_{max}^{MeOH} 202 nm (ε 22,000), 227 (ε 19,400, 278 nm) (ε 16,000); $\lambda_{max}^{CHCl_3}$ 1800 cm^{-1} (lactone); n.m.r. ($CDCl_3$): 9.68 (broad s, 1, NHBz, exchanges with D_2O), 9.26 (broad s, 1, NHAc, exchanges with D_2O), 8.78 (s, 1, H-8) 1.8 (s, 1, H-2); 8.1–7.9 (m, *o*-aromatic protons), 7.7–7.3 (m, 6, *p,m*-aromatic protons), 6.01 (d, 1, $J_{1',2'}$ 0.8 Hz, H-1'), 5.5 (d, 1, H-2'), 4.9 (q, 1, $J_{4',5'}$ 6 Hz, H-4'), 4.4 (m, 2, H-5' protons), 3.42 (q, 2, J_{AB} 18 Hz, H-3^2), and 2.16 (s, 3, NAc).

Anal. Calc. for $C_{28}H_{24}N_6O_7 \cdot H_2O$: C, 58.55; H, 4.55; N, 14.61. Found: C, 58.69; H, 4.43; N, 14.37.

*9-{[3-Acetamido-3-*C*-(carboxymethyl)-3-deoxy-α-*D*-xylofuranosyl]-3^2,2-lactone} adenine* (**17**). — To a solution of compound **15** (100 mg) in anhydrous methanol (4 ml) was added a catalytic amount of sodium methoxide (5 ml of a 0.02mM solution)

and the solution was kept for 20 h. The solution was decationized with Amberlite IRC-50 (H^+) resin and evaporated to a clear syrup that was dissolved in water (3 ml) and extracted with ethyl ether (1 ml). The aqueous layer was evaporated to afford an amorphous solid (40 mg, 65% yield). Compound **17** was recrystallized from methanol; m.p. 162–163°, $[\alpha]_D^{30}$ −37.4° (*c* 0.12, methanol); λ_{max}^{Nujol} 1796 cm^{-1} (γ-lactone); $\lambda_{max}^{H_2O}$ 205 nm (ε 23,300), 258 (ε 14,250): c.d. $\Delta\varepsilon$ +1.0 (λ_{max} 255, water), $[\theta]_{255}^{30}$ +3,300°; n.m.r. (D_2O): 8.2 (2s, 2, H-8, H-2), 6.55 (d, 1, $J_{1',2'}$ 4 Hz, H-1'), 5.55 (d, 1, H-2'), 3.25 (q, 2, $J_{A,B}$ 10 Hz, H-3[1]), and 2.05 (s, 3, NAc).

Anal. Calc. for $C_{14}H_{16}N_6O_5 \cdot MeOH$: C, 47.36; H, 5.28; N, 22.12. Found: C, 47.83; H, 5.29; N, 22.32.

The α nucleoside **17**, contained in the n.m.r. tube, was heated for 2-3 min at 60–70°. The doublet at δ 6.55 (H-1') gradually disappeared and a new doublet at δ 6.7 gradually appeared during the heating.

9-{[3-Acetamido-3-C-(carboxymethyl)-3-deoxy-β-D-xylofuranosyl]-3²,2-lactone} adenine (**16**). — Compound **14** was deacetylated as just described for **15**, to afford the β nucleoside **16** (0.12 g, 79%) which was recrystallized from methanol; m.p. 159–162°, $[\alpha]_D^{28}$ −11° (*c* 0.3, methanol); λ_{max}^{Nujol} 1790 cm^{-1} (γ-lactone), $\lambda_{max}^{H_2O}$ 205 nm (ε 14,800), $\lambda_{max}^{H_2O}$ 258 (ε 11,300); c.d. $\Delta\varepsilon$ −1.0 (λ_{max} 255 nm, water); n.m.r. ($(CD_3)_2CO$): 8.43 (s, 1, H-2), 8.37 (s, 1, H-8), 1.02 (broad s, 1, NH, exchanges with D_2O), 6.2 (d, 1, $J_{1',2'}$ 2 Hz, H-1'), 5.7 (d, 1, H-2'), and 2.2 (s, 3 NAc).

Anal. Calc. for $C_{14}H_{16}N_6O_5 \cdot CH_3OH$: C, 47.36; H, 5.28; N, 22.12. Found: C, 47.85; H, 5.00; N, 22.21.

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