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Studies on Aminosugars. XXIX. Syntheses of Nucleosides of 3-Amino-3-deoxy-3-*C*-hydroxymethyl-β-D-ribofuranose[1]

Hiroaki YANAGISAWA, Mitsuhiro KINOSHITA, and Sumio UMEZAWA

Department of Applied Chemistry, Faculty of Engineering, Keio University, Koganei-shi, Tokyo

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Reduction of 3-acetamido-3-*C*-carboxy-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose-γ-lactone (**1**) with lithium aluminum hydride or sodium borohydride followed by acetylation gave 3-acetamido-3-*C*-acetoxymethyl-5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (**2**). Hyrdolysis of **2** followed by *N*-phthaloylation and *O*-acetylation gave 3-*C*-acetoxymethyl-5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-phthalimido-α-D-ribofuranose (**7**), which was acetolyzed and chlorinated to give acylglycosyl chloride (**9**). Condensation of **9** with 6-benzamidopurine followed by aminolysis afforded 9-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl)adenine (**11**). 6-dimethylaminopurine, guanine, cytosine and uracil derivatives were similarly synthesized.

In a previous paper[2] we reported the syntheses of branched aminonucleosides which have a new branched amino sugar moiety, 3-amino-3-*C*-carboxy-3-deoxy-D-ribose. As an extension of this work, the syntheses of 9-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl)adenine (**11**), 9-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl)-6-dimethylaminopurine (**14**), 9-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl)guanine (**16**), 1-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl)cytosine (**18**) and 1-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl)uracil (**20**) are described in the present paper.

It has been found that substitution of 3′-hydroxy group or 3′-hydrogen atom of the sugar moiety of ribonucleosides with some substituents often gives rise to biological activities, *i.e.*, 3′-deoxyadenosine (cordycepin),[3] 9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)-6-dimethylaminopurine[4] and 3′-amino-3′-de-

1) Part XLII of "Studies on Antibiotics and Related Substances" by Sumio Umezawa. A part of this paper was read at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1970. (Abstracts of Papers of the Meeting, Vol. III, p. 1572).

2) H. Yanagisawa, M. Kinoshita, S. Nakada, and S. Umezawa, This Bulletin, **43**, 246 (1970).

3) K. G. Cunningham, W. Manson, F. S. Spring, and S. H. Hutchinson, *Nature*, **166**, 949 (1950).

4) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 1 (1955).

oxyadenosine[5] have antitumor activities and 3′-*C*-methyladenosine and 3′-*C*-methylcytosine[6] show antiviral activities. In this connection we were interested in transforming the 3′-*C*-carboxyl group of 3′-amino-3′-*C*-carboxy-3′-deoxy-D-ribose moiety in the aminonucleosides[2] to other substituents. We carried out the reduction of the 3′-*C*-carboxyl group to 3′-*C*-hydroxymethyl group.

Synthesis of Sugar Moiety. 3-Acetamido-3-*C*-carboxy-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose-γ-lactone[2] (**1**) was reduced in tetrahydrofuran with lithium aluminum hydride and the reduction product was acetylated with acetic anhydride-pyridine to afford 3-acetamido-3-*C*-acetoxymethyl-5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (**2**). It has recently been reported that α-amino and α-acylamino esters were reduced with sodium borohydride to afford the corresponding α-amino and α-acylamino alcohols, respectively, in good yields.[7] The reduction of **1** with sodium borohydride also gave **2** in a good yield.

Compound **2** was treated with a mixture of concentrated sulfuric acid, acetic anhydride and acetic acid in order to obtain the corresponding acetyl sugar which was required for the preparation of nucleoside. The product, whose tlc showed a single spot, had an IR-absorption at 1669 cm^{-1} (amide I), but no absorption at 3300—3500 (NH) and 1500—1600 cm^{-1} (amide II). The NMR spectrum of the product showed the presence of four acetyl groups and the absence of N–H proton. These observations and the result of elemental analysis suggested that the structure of the product is 1,2,5-tri-*O*-acetyl-3-deoxy-α-D-ribofuranose-3-spiro-2′-(*N*-acetylaziridine) (**3**). The assignment was also supported by the following reaction. Product **3** was treated with acetic acid as a nucleophile[8] to afford 3-acetamido-1,2,5-tri-*O*-acetyl-3-*C*-acetoxymethyl-3-deoxy-α-D-ribofuranose (**4**) whose structure was confirmed by elemental analysis, IR spectrum [3380 (NH), 1680 (amide I) and 1545 cm^{-1} (amide II)] and NMR spectrum [N–H proton (τ 3.54) and five acetyl groups]. Aziridine formation between 3-amino and 3-*C*-hydroxymethyl groups was also observed on the acetolysis of 3-acetamido-5-*O*-benzyl-3-*C*-benzyloxymethyl-3-deoxy-1,2-*O*-isopropyridene-α-D-ribofuranose (**5**) derived from **2**. The product was assigned as 1,2-di-*O*-acetyl-5-*O*-benzyl-3-deoxy-α-D-ribofuranose-3-*C*-spiro-2′-(*N*-acetylaziridine) (**6**) on the basis of elemental analysis, IR spectrum [1667 cm^{-1} (amide I), no absorption of N–H stretching and amide II] and NMR spectrum (single benzyl group and no N–H proton).

Since the amide-hydrogen in 3-acetamido group of **2** was very reactive in acidic media as described above, the acetamido group of **2** should be favorable for replacement by phthalimido group in order to prevent aziridine formation. Deacetylation of **2** with barium hydroxide followed by phthaloylation with phthalic anhydride-pyridine and *O*-acetylation afforded 3-*C*-acetoxymethyl-5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-phthalimido-α-D-ribofuranose (**7**). The NMR spectrum of **7** revealed the presence of two conformers which might be caused by a steric interaction between the bulky phthalimido group, isopropylidene group and acetoxymethyl group. Acetolysis of **7** afforded 3-*C*-acetoxymethyl-1,2,5-tri-*O*-acetyl-3-phthalimido-D-ribofuranose (**8**). Treatment of **8** with hydrogen chloride in ether gave 3-*C*-acetoxymethyl-2,5-di-*O*-acetyl-1-chloro-3-deoxy-D-ribofuranose (**9**), which was immediately used in the next condensation reaction without purification because of its instability.

Synthesis of Nucleosides. Condensation of **9** with benzamidopurine was carried out in the presence of mercuric cyanide and Drierite in nitromethane[9] to afford 6-benzamido-9-(3′-*C*-acetoxymethyl-2′,5′-di-*O*-acetyl-3′-deoxy-3′-phthalimido-D-ribofuranosyl)adenine (**10**).[10] By a similar procedure **9** was condensed with 6-chloropurine, N^2-acetylguanine,[11] and N^4-acetylcytosine[12] to afford 9-(3′-*C*-acetoxymethyl-2′,5′-di-*O*-acetyl-3′-deoxy-3′-phthalimido-D-ribofuranosyl)-6-chloropurine (**12**),[10] 9-(3′-*C*-acetoxymethyl-2′,5′-di-*O*-acetyl-3′-deoxy-3′-phthalimido-β-D-ribofuranosyl)-N^2-acetylguanine (**15**) and N^4-acetyl-1-(3′-*C*-acetoxymethyl-2′,5′-di-*O*-acetyl-3′-deoxy-3′-phthalimido-β-D-ribofuranosyl)-cytosine (**17**), respectively. Although the condensation of **9** with uracil by the mercuric cyanide-nitromethane method and Hilbert-Johnson method[13] was unsuccessful, the desired condensation product, 1-(3′-*C*-acetoxymethyl-2′,5′-di-*O*-acetyl-3′-phthalimido-β-D-ribofuranosyl)uracil (**19**) was obtained with the use of trimethylsilyl method[14] in which 2,4-*O*-bis-(trimethylsilyl)-uracil[15] was used as an activated base.

Positions of the base-sugar linkages in the blocked nucleosides **10**, **12**, **15**, **17**, and **19** were determined by UV spectrometry. The condensation reaction of N^2-acetylguanine with **9** gave predominantly N-9 substituted product.[16] The NMR spectra of the condensation products showed that they were anomeric mixtures except in the case of **19**. The blocked nucleoside of uracil was shown to be the β-anomer

5) B. R. Baker, R. E. Schaub, and H. M. Kissman, *J. Amer. Chem. Soc.*, **77**, 5911 (1955).

6) E. Walton, S. R. Jenkins, R. F. Nut, and F. W. Holly, *J. Med. Chem.*, **12**, 306 (1969).

7) H. Seki, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 1948 (1967).

8) 5,6-Epimino-L-idofuranose and L-altrofuranose are attacked by nucleophiles and the aziridine rings are opened exclusively in the terminal positions. *Cf.* H. Saeki and E. Ohki, *ibid.*, **16**, 2471 (1968).

9) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).

10) The structures of compounds **10**, **12**, and **13**, are represented in Fig. 1 by their β-anomer structures for the sake of convenience.

11) Z. A. Shabarova, Z. P. Polyakova, and M. A. Prokofev, *Zh. Obshch. Khim.*, **29**, 215 (1959).

12) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, **1956**, 2384.

13) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 4489 (1930).

14) T. Nishimura, B. Shimizu, aad I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1471 (1964).

15) T. Nishimura and I. Iwai, *ibid.*, **12**, 352 (1964).

16) S. R. Jenkins, F. W. Holly, and E. Walton, *J. Org. Chem.*, **30**, 2851 (1965).

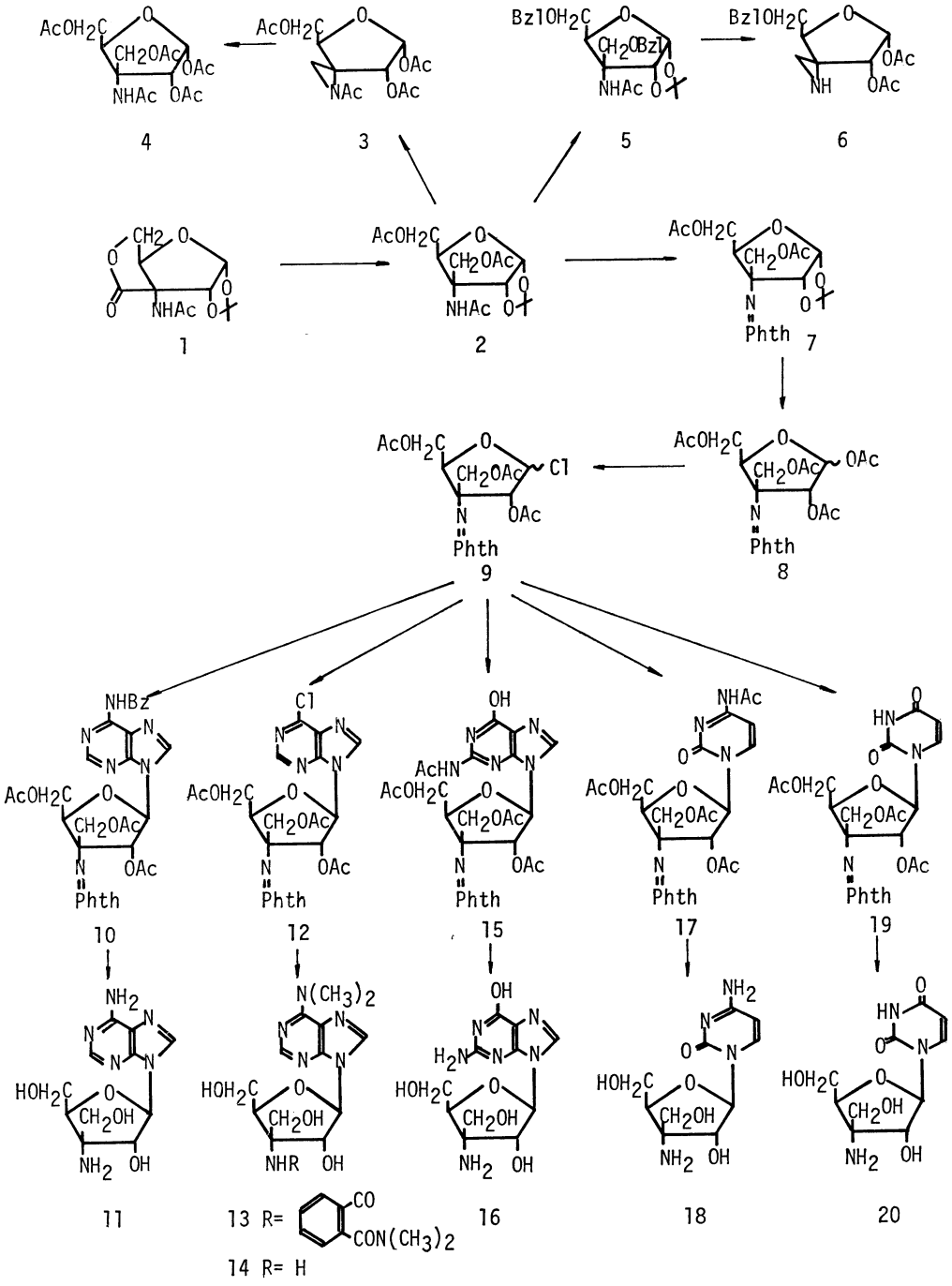

Fig. 1

(**19**). β-Anomer (**15**) was isolated from the anomeric mixture by preparative layer chromatography and β-anomer (**17**) by recrystallization. The blocked nucleoside (**10**)[10] was deacetylated and dephthaloylated with *n*-butylamine-methanol[17] to afford an anomeric mixture of 9-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-D-ribofuranosyl)adenine, from which β-anomer (**11**) was isolated. Other blocked nucleosides **15**, **17**, and **19** were similarly deblocked to afford 9-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl) guanine (**16**) and 1-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl)cytosine (**18**) and 1-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-β-D-ribofuranosyl)uracil (**20**), respectively. The blocked nucleoside (**12**)[10] was treated with dimethylamine-methanol to afford 9-[3′-deoxy-3′-(*o*-*N*,*N*-dimethylcarbamoyl)benzamido-3′-*C*-hydroxymethyl-D-ribofuranosyl]-6-dimethylaminopurine (**13**).[10] The product (**13**)[10] was then dephthaloylated with *n*-butylamine-methanol to afford an anomeric mixture of 9-(3′-amino-3′-deoxy-3′-*C*-hydroxymethyl-D-ribofuranosyl)-6-dimethylaminopurine, from which β-anomer (**14**) was isolated by recrystallization.

The NMR spectra of the amino nucleosides **11**, **14**, **16**, **18**, and **20** showed that they contain no anomer.

17) L. Goodman and J. W. Marsico, *J. Med. Chem.*, **6**, 413 (1963).

Their anomeric configurations were determined to be β on the basis of their ORD curves. In general, pyrimidine β-D-nucleosides show positive and purine β-D-nucleosides negative Cotton effects.[18] The ORD curves of the purine nucleosides **11**, **14** and **16** showed negative Cotton effects and those of the pyrimidine nucleosides **18** and **20** showed positive ones. This indicates that all the synthetic branched aminonucleosides have β-configurations.

Examination of the antiviral activity of the branched aminonucleosides (**11**, **14**, **16**, **18** and **20**) is in progress. Compound **11**, namely the 3'-amino-3'-hydroxymethyl derivative of adenosine, has been found to exhibit weak inhibition against *vaccinia Dairen*.

Experimental

Thin layer chromatography (tlc) and preparative layer chromatography (plc) were carried out with the use of silica gel (Daiichi Pure Chemicals Co., Inc.). The prepared plates were activated at 110°C for 1 hr. The spray reagent was 10% sulfuric acid. Silica gel column chromatography was carried out with the use of WAKO-GEL C-200 (Wako Pure Chemical Industries, Ltd.). NMR spectra were taken with a Varian A-60D spectrometer at a frequency of 60 MHz in deuteriochloroform, deuteriodimethyl sulfoxide and deuterium oxide with tetramethylsilane and sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Melting point determination was carried out on a micro hot stage and not corrected.

*3-Acetamido-3-C-acetoxymethyl-5-O-acetyl-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**2**).* *a) Reduction of **1** with Lithium Aluminum Hydride*: A solution of **1** (2.55 g) in tetrahydrofuran (20 m*l*) was added dropwise to a suspension of lithium aluminum hydride (0.99 g) in tetrahydrofuran (24 m*l*) under ice-cooling and stirring for 15 min. The mixture was then stirred in an ice bath for 3 hr and at room temperature for 3 hr. To the reaction mixture was added ethyl acetate (20 m*l*) and 20% aqueous isopropanol (20 m*l*) under ice-cooling and the mixture was stirred at room temperature for 30 min. Isopropanol (150 m*l*) was added to the reaction mixture and the precipitates were separated by centrifuging and washed with isopropanol (80 m*l*×4). The supernatant layer and washings were evaporated to dryness. To the residue was added pyridine (45 m*l*) and acetic anhydride (30 m*l*) and the mixture was kept at room temperature for 15 hr. The reaction mixture was evaporated with toluene, the residue being dissolved in 1 N hydrochloric acid (40 m*l*) and ethyl acetate (80 m*l*). The organic layer was separated, washed with water (20 m*l*) and aqueous sodium bicarbonate solution (20 m*l*) successively, dried over sodium sulfate and evaporated. Trituration of the syrupy residue with diisopropyl ether afforded **2** as a colorless crystal; yield 2.06 g (61.5%). The analytical sample was purified by recrystallization from ethyl acetate-diisopropyl ether: mp 135—136°C; $[\alpha]_D^{23}$+74° (*c* 1.7, ethanol); ν_{max}^{Nujol} 3350, 1743, and 1683 cm^{-1}; τ^{CDCl_3} 3.87 (s, N–H), 4.09 (d, H-1, $J_{1,2}$=4.0 Hz), 7.90 (s, two $OCOCH_3$), 7.98(s, $NCOCH_3$), 8.43 and 8.62 [=$C(CH_3)_2$].

Found: C, 52.37; H, 6.93; N, 4.26%. Calcd for $C_{15}H_{23}NO_8$: C, 52.17; H, 6.71; N, 4.06%.

*b) Reduction of **1** with Sodium Borohydride*: A solution of sodium borohydride (8.9 g) in 50% aqueous ethanol (110 m*l*) was added to a solution of **1**(14.1 g) in ethanol(83 m*l*) and the mixture was refluxed for 15 hr. The reaction mixture was evaporated with toluene to remove a trace of water. Pyridine (120 m*l*) and acetic anhydride (90 m*l*) was added to the residue and the mixture was stirred vigorously at room temperature for 3 hr. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate (200 m*l*) and water (200 m*l*). The organic layer was successively washed with water, aqueous potassium bisulfate solution and aqueous sodium bicarbonate solution. The dried organic layer was evaporated and the residue was triturated with diisopropyl ether to afford **2**: yield 12.5 g (67.5%); mp 135—136°C (from ethyl acetate-diisopropyl ether).

*1,2,5-Tri-O-acetyl-3-deoxy-α-D-ribofuranose-3-C-spiro-2'-(N-acetylaziridine) (**3**).* To a solution of **2** (1.15 g) in a mixture of acetic acid (8 m*l*) and acetic anhydride (8 m*l*) was added dropwise concentrated sulfuric acid (0.8 m*l*) and the mixture was allowed to stand at room temperature for 12 hr. The reaction mixture was shaken with 10% aqueous sodium acetate (40 m*l*) and dichloroethane (20 m*l*). The aqueous layer was further extracted with dichloroethane (10 m*l*×3). The combined extracts were washed with aqueous potassium bicarbonate solution (20 m*l*), dried over sodium sulfate and evaporated to give **3** as a syrup; yield 710 mg (65%). The analytical sample was purified by silica gel column chromatography (ethyl acetate-benzene 1 : 1); $[\alpha]_D^{23}$+61° (*c* 2.1, ethanol); ν_{max}^{Film} 1743, 1669 cm^{-1}; τ^{CDCl_3} 4.43 (d, H-1, $J_{1,2}$=3.2 Hz), 4.64 (d, H-2), 7.86, 7.88, 7.89 and 7.99 (s, $COCH_3$).

Found: C, 50.93; H, 5.77; N, 4.45%. Calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25%.

*3-Acetamido-1,2,5-tri-O-acetyl-3-C-acetoxymethyl-3-deoxy-α-D-ribofuranose (**4**).* A solution of **3** (60 mg) in acetic acid (1.5 m*l*) was heated at 55°C for 5 hr, and then evaporated with toluene. The residual syrup was purified through a silica gel column (10 g, 24×1 cm). Elution with ether acetate-benzene (1 : 1 and 3 : 1) afforded **4** as a glass: yield 55 mg (78%); $[\alpha]_D^{22}$ +13° (*c* 2.3, ethanol); ν_{max}^{KBr} 3380, 1753, 1680, and 1545 cm^{-1}; τ^{CDCl_3} 3.54 (s, N–H), 3.86 (d, H-1, $J_{1,2}$=2.7 Hz), 4.46 (d, H–2), 7.83, 7.87, 7.88, 7.93 and 7.97 (s, $COCH_3$).

Found: C, 49.78; H, 5.91; N, 3.64%. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95; N, 3.60%.

*3-Acetamido-5-O-benzyl-3-C-benzyloxymethyl-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**5**).* To a solution of sodium (110 mg) dissolved in methanol (6 m*l*) was added **2** (505 mg) and the resulting solution was refluxed for 30 min. After addition of a small amount of ethyl acetate, the solution was evaporated to dryness. The residue was dissolved in anhydrous dimethylformamide (8 m*l*) and to the solution was added freshly dried barium oxide (2.04 g), barium hydroxide octahydrate (0.87 g) and benzyl bromide (2.8 m*l*) under ice-cooling. The mixture was stirred in an ice-bath for 2 hr and then at room temperature for 18 hr. After addition of dichloroethane (20 m*l*) to the reaction mixture, the precipitates were filtered off with a hyflo super cell pad. The filtrate was concentrated to 3—4 m*l* and was diluted with ethyl acetate (15 m*l*). The resulting slurry was warmed, and the precipitates were again filtered off and washed with ethyl acetate. The filtrate and washings were evaporated and the residue was placed on a silica gel column (20 g, 1.8×18 cm) and eluted with benzene-ethyl acetate (3 : 1),

18) J. T. Yang, and T. Samejima, *J. Amer. Chem. Soc.*, **85**, 4039 (1963); T. L. V. Ulbricht, J. P. Jennings, P. M. Scopes, and W. Klyne, *Tetrahedron Lett.*, **1964**, 695; T. Nishimura, B. Shimizu, and I. Iwai, *Biochim. Biophys. Acta*, **157**, 221 (1968).

The eluent containing **5** was evaporated to dryness: a syrup, yield 570 mg (88%); $[\alpha]_D^{17}$ +42° (*c* 3.2, ethanol); ν_{max}^{Film} 3285 and 1654 cm^{-1}; τ^{CDCl_3} 2.70 (s, two C_6H_5), 3.84 (s, N–H), 4.23 (d, H-1, $J_{1,2}$=3.6 Hz), 5.19 (d, H-2), 5.51 (s, two benzyl CH_2), 8.10 (s, N–$COCH_3$), 8.48 and 8.68 [s, =$C(CH_3)_2$].

Found: C, 67.81; H, 6.81; N, 3.34%. Calcd for $C_{25}H_{31}NO_6$: C, 68.00; H, 7.08; N, 3.17%.

*1,2-Di-*O*-acetyl-5-*O*-benzyl-3-deoxy-α-*D*-ribofuranose-3-*C*-spiro-2′-(*N*-acetylaziridine) (**6**).* To a solution of **5** (384 mg) in a mixture of acetic acid (3 m*l*) and acetic anhydride (3 m*l*) was added dropwise concentrated sulfuric acid (0.29 m*l*) and the mixture was kept at room temperature for 12 hr. After addition of 10% sodium acetate solution (20 m*l*), the mixture was extracted with dichloroethane (20 m*l*, 5 m*l*×2) and the extracts were washed with water and aqueous potassium bicarbonate solution and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column (10 g, 20×1 cm). Elution with benzene-ethyl acetate (1 : 3 and 1 : 1) gave **6** asasyrup; yield 66 mg (20%); $[\alpha]_D^{17}$+91° (*c* 1.8, ethanol); ν_{max}^{Film} 1746 and 1667 cm^{-1}; τ^{CDCl_3} 2.66 (s, C_6H_5), 4.47 (d, H-1, $J_{1,2}$= 3.4 Hz), 4.70 (d, H-2), 7.94, 7.98 and 8.04 (s, $COCH_3$).

Found: C, 60.91; H, 6.56; N, 3.81%. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71%.

*3-C-Acetoxymethyl-5-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-phthalimido-α-*D*-ribofuranose (**7**).* A mixture of **2** (3.81 g) and barium hydroxide octahydrate (7.62 g) in water (29 m*l*) was refluxed under stirring for 2 hr. Carbon dioxide was passed through the reaction mixture for neutralization. Precipitates were separated by centrifuging and washed with ethanol. The supernatant and washings were evaporated to give a syrup containing colorless crystals. To this was added ethanol (40 m*l*) and the crystals were filtered off and washed with ethanol (10 m*l*). The filtrate and washings were evaporated to afford a syrup (3.01 g). To a solution of the syrup in pyridine (25 m*l*) was added phthalic anhydride (2.46 g) and the mixture was warmed at 50°C for 30 min. Acetic anhydride (25 m*l*) was added and the mixture was further warmed at 50°C for 30 min. The resulting mixture was evaporated and the residue was dissolved in a small amount of benzene and chromatographed on a silical gel column (40 g, 2.8×15 cm). Elution with benzene and benzene-ethyl acetate (10 : 1 and 6 : 1) afforded **7** as a glass: yield 3.34 g (70%). The NMR spectrum of **7** showed that it was a mixture of two conformers (7 : 3) : τ^{CDCl_3} (major) 2.16 (s, C_6H_5), 4.11 (d, H-1, $J_{1,2}$=4.0 Hz), 7.87, 8.01 (s, $COCH_3$), 8.57 and 8.70 [s, –$C(CH_3)_2$]; (minor) 4.07 (d, H-1, $J_{1,2}$=3.9 Hz), 7.87, 7.95 (s, $COCH_3$), 8.57 and 8.67 [s, –$C(CH_3)_2$]; $\nu_{max}^{CHCl_3}$ 1747 and 1725 cm^{-1}; $[\alpha]_D^{17}$+120° (*c* 1.2, ethanol).

Found: C, 58.63; H, 5.66; N, 3.44%. Calcd for $C_{21}H_{23}NO_9$: C, 58.19; H, 5.35; N, 3.23%.

*3-C-Acetoxymethyl-1,2,5-tri-*O*-acetyl-3-deoxy-3-phthalimido-*D*-ribofuranose (**8**).* To an ice-cooled solution of **7** (3.34 g) in a mixture of acetic acid (23 m*l*) and acetic anhydride (23 m*l*) was added concentrated sulfuric acid (1.76 m*l*) under stirring and the mixture was kept at room temperature for 12 hr. The reaction mixture was mixed with powdered sodium acetate trihydrate (18 g) and the resulting slurry was stirred for 30 min. After evaporation at 35°C, the residue was partitioned between water (100 m*l*) and ethyl acetate (70 m*l*). The aqueous layer was further extracted with ethyl acetate (20 m*l*×2). The combined organic layers were washed with aqueous potassium bicarbonate solution (50 m*l*×3) and dried over sodium sulfate. Removal of ethyl acetate and a trace of acetic acid by co-distillation with toluene gave **8** as a glass: yield 2.14 g (58%). An analytical sample was purified by silica gel chromatography with a solvent system, benzene-ethyl acetate (10 : 1) : $[\alpha]_D^{17}$+82° (*c* 2.1, ethanol); $\nu_{max}^{CHCl_3}$ 1750 and 1726 cm^{-1}; τ^{CDCl_3} 2.15 (s, C_6H_4), 3.83 (s, H-1), 4.15 (s, H-2), 7.85, 7.90, 8.06 and 8.08 (s, $COCH_3$).

Found: C, 54.71; H, 4.96; N, 3.04%. Calcd for $C_{22}H_{23}NO_{11}$: C, 55.34; H, 4.86; N, 2.93%.

*3-C-Acetoxymethyl-2,5-di-*O*-acetyl-1-chloro-3-deoxy-*D*-ribofuranose (**9**).* Through a mixture of **8** (2.14 g) and Drierite (2.14 g) in dry ether (100 m*l*) was passed dry hydrogen chloride under ice-salt cooling for 2 hr and the mixture was allowed to stand for 19 hr in a refrigerator. The reaction mixture was evaporated below 30°C and the residual hydrogen chloride was removed by co-distillation with benzene. The TLC of the residue showed that the product **9** (R_f 0.79 with benzene-ethyl acetate 1 : 1) was unstable and a new spot (R_f 0.63) appeared during evaporation. The residue, therefore, was used immediately for the next condensation reaction.

*6-Benzamido-9-(3′-C-acetoxymethyl-2′,5′-di-*O*-acetyl-3′-deoxy-3′-phthalimido-*D*-ribofuranosyl)adenine (**10**).* A solution of **9** [prepared from **8** (2.14 g)] in a small amount of nitromethane was added to a mixture of benzamidopurine (1.07 g), mercuric cyanide (1.14 g) and Drierite (7.00 g) in nitromethane (50 m*l*). After the mixture was refluxed under stirring for 4 hr, the precipitates were filtered off and washed with ethyl acetate. The filtrate and washings were mixed with silica gel (7 g) and evaporated to dryness. The powered residue was placed on a silica gel column (70 g, 2.8×28 cm) and eluted with benzene and benzene-ethyl acetate (1 : 1, 1 : 2 and 1 : 5). The eluent containing **10** was evaporated to afford **10** as an amorphous powder; yield 1.13 g (38%). An analytical sample was obtained by PLC technique with a solvent system, benzene-ethyl acetate (1 : 4) : $[\alpha]_D^{17}$ –31° (*c* 1.39, ethanol); $\nu_{max}^{CHCl_3}$ 1748, 1724, 1610 and 1587 cm^{-1}; λ_{max}^{MeOH} 280 mμ (ε 22300).

Found: C, 58.56; H, 4.70; N, 13.13%. Calcd for $C_{32}H_{28}N_6O_{10}$: C, 58.53; H, 4.30; N, 12.81%.

*9-(3′-Amino-3′-deoxy-3′-C-hydroxymethyl-β-*D*-ribofuranosyl)adenine (**11**).* A solution of **10** (1.13 g) in a mixture of methanol (30 m*l*) and *n*-butylamine (10 m*l*) was refluxed for 19 hr. After evaporation of the resulting solution to dryness, ethyl acetate (50 m*l*) was added to the residue and the mixture was allowed to stand overnight in a refrigerator. The colorless precipitates (440 mg) were separated by filtration and recrystallized from 10% aqueous methanol (20 m*l*): yield 140 mg (27%); mp 230°C; $[\alpha]_D^{14}$ –60° (*c* 1.1, water); RD[19] (c 0.015, water) at 20°C; $[\Phi]_{300}$ –800°, $[\Phi]_{278}$ –1900° (tr); $\lambda_{max}^{H_2O}$ 259mμ (ε 17100), $\lambda_{max}^{0.1NHCl}$ 257 mμ (ε 16100), $\lambda_{max}^{0.1NNaOH}$ 260 mμ (ε 16700); τ^{D_2O} 1.89, 2.17 (s, H-2 and H-8), 4.12 (d, H-1′, $J_{1',2'}$=7.2 Hz) and 5.39 (d, H-2′).

Found: C, 44.91; H, 5.65; N, 28.29%. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37%.

*6-Chloro-9-(3′-C-acetoxymethyl-2′,5′-di-*O*-acetyl-3′-deoxy-3′-phthalimido-*D*-ribofuranosyl)purine (**12**).* A solution of **9** [prepared from **8** (3.46 g)] in a small amount of nitromethane was added to a mixture of 6-chloropurine (1.12 g), mercuric cyanide (1.84 g) and Drierite (10 g) in nitromethane (90 m*l*) under refluxing and stirring. The nitromethane (20 g) was distilled off and the residue was refluxed under stirring for 2 hr. The precipitates were filtered off and washed with ethyl acetate. The filtrate and washings were evaporated with silica gel (7 g) to dryness. The pow-

19) ORD were determined on a JASCO ORD/UV-5 recording spectropolarimeter.

dered residue was placed on a silica gel column (150 g, 3.3×30 cm) and eluted with benzene and benzene-ethyl acetate (10 : 1, 3 : 1, 2 : 1 and 1 : 1), successively. The eluent containing **12** was evaporated to afford a glass; yield 1.92 g (46.3%); λ_{max}^{MeOH} 242 and 266 mμ.

*6-Dimethylamino-9-[3'-deoxy-3'-(o-N,N-dimethylcarbamoyl)-benzamido-3'-C-hydroxymethyl-D-ribofuranosyl]purine (**13**).*[10] A solution of **12** (1.92 g) in 20% dimethylamine-methanol (20 ml) was refluxed for 3.5 hr. The reaction mixture was evaporated to dryness with silica gel (4 g). The powdered residue was placed on a silica gel column (90 g, 2.5×33 cm) and eluted with ethyl acetate and ethyl acetate-ethanol (4 : 1), successively. The eluent containing **13**[10] was evaporated to afford a glass (**13**)[10]; yield 1.18 g (70%). Further purification of the product (200 mg) was carried out by PLC (5 sheets of 0.5 mm×20×20 cm plate) to afford an analytical sample (130 mg): $[\alpha]_D^{20}$ −34° (*c* 3.0, methanol); ν_{max}^{KBr} 3350 and 1596 cm^{-1}; λ_{max}^{MeOH} 275 mμ (ε 20000). The NMR spectrum showed that **13** was an anomeric mixture (β/α=3.5/1): τ^{CD_3OD} (β anomer) 1.73, 1.77 (s, H-2 and H-8), 3.93 (d, H-1', $J_{1',2'}$=7.6 Hz), 4.94 (d, H-2'), 6.50 [s, purine N(CH_3)$_2$], 6.85, 7.07 [s, phthaloyl N(CH_3)$_2$]; τ^{CD_3OD} (α anomer) 4.08 (d, H-1', $J_{1',2'}$=4.3 Hz), 6.52 [s, purine N(CH_3)$_2$], 6.92, 7.17 [s, phthaloyl N(CH_3)$_2$].

Found: C, 54.03; H, 6.45; N, 18.94%. Calcd for $C_{23}H_{29}N_7O_6\cdot 1/2\ H_2O$: C, 54.33; H, 5.93; N, 19.27%.

*6-Dimethylamino-9-(3'-amino-3'-deoxy-3'-C-hydroxymethyl-β-D-ribofuranosyl)purine (**14**).* A solution of **13** (200 mg) in 50% *n*-butylamine-methanol (12 ml) was refluxed for 2 days. After evaporation, the residue was partitioned between water (10 ml) and ethyl acetate (10 ml). The aqueous layer was separated, washed with ethyl acetate (10 ml×7) and evaporated to dryness. The NMR spectrum of the glassy residue revealed that it was an anomeric mixture (β/α=3.5/1). The β-anomer (**14**) was separated as crystals from the methanolic solution of the anomeric mixture; yield 62 mg (48%). An analytical sample was obtained by further recrystallization from methanol: mp 172—174°C; $[\alpha]_D^{23}$ −68° (c 2.0, water); RD (*c* 0.017, water) at 20°C, $[\Phi]_{310}$ −800° $[\Phi]_{296}$ −1700° (tr); ν_{max}^{KBr} 3340 and 1600 cm^{-1}; $\lambda_{max}^{H_2O}$ 275.5 mμ (ε 20100), $\lambda_{max}^{0.1NHCl}$ 268 mμ (ε 20000) and $\lambda_{max}^{0.1NNaOH}$ 276 mμ (ε 19600); τ^{D_2O} 1.89, 2.13 (s, H-2 and H-8), 4.06 (d, H-1', $J_{1',2'}$=7.6 Hz), 5.34 (d, H-2') and 6.87 [s, purine N(CH_3)$_2$].

Found: C, 47.85; H, 6.45; N, 25.48%. Calcd for $C_{13}H_{20}N_6O_4$: C, 48.14; H, 6.22; N, 25.91%.

*N^2-Acetyl-9-(3'-C-acetoxymethyl-2',5'-di-O-acetyl-3'-deoxy-3'-phthalimido-β-D-ribofuranosyl)guanine (**15**).* To a mixture of N^2-acetylguanine (866 mg), mercuric cyanide (1.14 g) and Drierite (10 g) in nitromethane (100 ml) was added a solution of **9** [prepared from **8** (2.15 g)] in a small amount of nitromethane under refluxing and stirring. After nitromethane (10 ml) was distilled off, the mixture was refluxed for 2 hr under stirring. The precipitates were filtered off and washed with ethyl acetate and the filtrate and washings were evaporated with silica gel (2 g). The residue was placed on a silica gel column (70 g, 3.5×16 cm) and eluted with benzene, benzene-ethyl acetate (10 : 1, 5 : 1, 2 : 1 and 1 : 2), ethyl acetate and ethyl acetate-isopropanol (10 : 1), successively. Evaporation of the eluent containing **15** afforded the anomeric mixtue of **15** as a glass; yield 1.29 g (47%). The product (473 mg) was subjected to PLC (10 sheets of 0.5 mm×20×20 cm plate) with a solvent system, ethyl acetate-isopropanol (10 : 1). The upper bands with R_f value of 0.43 were collected under UV light (365 mμ) and extracted with ethyl acetate-isopropanol (1 : 1) to afford the β-anomer (**15**) as a glass: yield 211 mg (21%); $[\alpha]_D^{25}$ −5° (*c* 4.2, methanol); ν_{max}^{KBr} 3420, 1755, 1726, 1695 (sh), 1610 and 1562 cm^{-1}; λ_{max}^{MeOH} mμ (ε) 242(19800), 255 (18300), 260(18400) and 282 (14000); τ^{CD_3OD} 1.89 (s, H-8), 2.06 (s, phthaloyl C_6H_4), 4.00 (s, H-1' and H-2'), 7.68, 7.90, 7.96 and 8.14 (s, $COCH_3$).

Found: C, 53.08; H, 4.52; N, 13.42%. Calcd for $C_{27}H_{26}N_6O_{11}$: C, 53.11; H, 4.29; N, 13.71%.

The lower bands on PLC afforded a mixture of anomers (α/β=2/1): yield 97 mg (9.6%); τ^{CD_3OD} (α-anomer) 2.71 (s, H-8), 3.37 (d, H-1', $J_{1',2'}$=5.1 Hz) and 3.95 (d, H-2').

*9-(3'-Amino-3'-deoxy-3'-C-hydroxymethyl-β-D-ribofuranosyl)-guanine (**16**).* A solution of **15** (β anomer, 177 mg) in 50% *n*-butylamine-methanol (10 ml) was refluxed for 20 hr. The product (**16**) was deposited as solid in the reaction mixture, separated by centrifuging and washed with methanol; yield 55 mg. Recrystallization from water gave an analytical sample; mp 230°C (colored) but not fused below 300°C; $[\alpha]_D^{23}$ −25° (*c* 1.6, 0.1 N HCl), RD (*c* 0.025, water) at 20°C, $[\Phi]_{320}$ −500°, $[\Phi]_{310}$ −650°(tr); ν_{max}^{KBr} 3380, 3150, 1690, 1653, and 1595 cm^{-1}; $\lambda_{max}^{H_2O}$ 251 mμ (ε 11900) and 274 mμ (ε 8600)(sh), $\lambda_{max}^{0.1NHCl}$ 256.5 mμ (ε 11400) and 275 mμ (ε 8400)(sh), $\lambda_{max}^{0.1NNaOH}$ 258 mμ (ε 9300) and 269 mμ (ε 9500).

Found: C, 40.31; H, 5.60; N, 25.38%. Calcd for $C_{11}H_{16}N_6O_5\cdot H_2O$: C, 40.00; H, 5.49; N, 25.45%.

*N^4-Acetyl-1-(3'-C-acetoxymethyl-2',5'-di-O-acetyl-3'-deoxy-3'-limido-β-D-ribofuranosyl)cytosine (**17**).* A mixture of *N*^{4}-acetylcytosine (0.875 g), mercuric cyanide (1.45 g) and Drierite (10 g) in nitromethane (120 ml) was heated and nitromethane (20 ml) was distilled off at atmospheric pressure. To the resulting mixture was added a solution of **9** [prepared from **8** (2.74 g)] in a small amount of nitromethane under refluxing and stirring. After the second distillation of nitromethane (10 ml), the reaction mixture was refluxed for 2.5 hr under stirring. The precipitates were filtered off and washed with ethyl acetate. Silica gel (2 g) was added to the combined filtrate and washings and evaporated. The residual powders were placed on a silica gel column (50 g, 3.8×17 cm) and eluted with benzene, benzene-ethyl acetate (2 : 1 and 1 : 2), ethyl acetate and ethyl acetate-isopropanol (10 : 1), successively. The eluent containing **17** was evaporated to afford a crystalline solid (1.46 g, 45%). Pure β-anomer (**17**) was obtained by recrystallization of the crystals from ethanol, the first crop 398 mg and the second 252 mg. Total yield 650 mg (45% from the anomeric mixture); mp 268—273.5°C (sintered); $[\alpha]_D^{20}$ +28° (*c* 2.0, dimethyl sulfoxide); ν_{max}^{KBr} 3420, 3140, 1754, 1725, 1662, 1624 and 1560 cm^{-1}; λ_{max}^{MeOH} 242 mμ (ε 22400) and 299 mμ (ε 9000); τ^{DMSO-d_6} 1.75 (d, H-6, $J_{5,6}$=7.6 Hz), 2.77 (d, H-5), 3.65 (d, H-1', $J_{1',2'}$=5.2 Hz), 4.06 (d, H-2'), 7.82, 7.86, 7.88 and 8.26 (s, $COCH_3$).

Found: C, 55.00; H, 4.53; N, 9.68%. Calcd for $C_{26}H_{26}N_4O_{11}$: C, 54.73; H, 4.59; N, 9.82%.

*1-(3'-Amino-3'-deoxy-3'-C-hydroxymethyl-β-D-ribofuranosyl)cytosine (**18**).* A solution of **17** (277 mg) in 50% *n*-butylamine-methanol (10 ml) was refluxed for 15 hr and then evaporated to dryness. The residue was dissolved in ethyl acetate (10 ml) and kept in a refrigerator. The colorless precipitates were collected by filtration and partitioned between water (10 ml) and ethyl acetate (10 ml). The aqueous layer was washed with ethyl acetate (10 ml×5) and evaporated to dryness; yield 123 mg (96%). An analytical sample was obtained reprecipitation from methanol-ethyl acetate; mp 117—120°C; $[\alpha]_D^{27}$ +29° (*c* 3.6, water); RD (*c* 0.029, water) at 20°C, $[\Phi]_{300}$+2700°, $[\Phi]_{289}$+4800 (pk); ν_{max}^{KBr} 3310, 3180 (sh), 1655, 1636 and 1600 (sh)cm^{-1}; $\lambda_{max}^{H_2O}$ 230 mμ (ε 7900) and 270 mμ (ε 8500), $\lambda_{max}^{0.1NHCl}$ 278.5

mμ (ε 11000), $\lambda_{max}^{0.1NNaOH}$ 231 mμ (ε 6900) and 272 mμ (ε 7800); τ^{D_2O} 2.10 (d, H-6, $J_{5,6}$=7.6 Hz), 3.91 (d, H-5), 4.02 d, H-1′, $J_{1',2'}$=6.0 Hz), 5.69 (d, H-2′).

Found: C, 43.65; H, 6.57; N, 18.55%. Calcd for $C_{10}H_{16}N_4O_5 \cdot CH_3OH$: C, 43.41; H, 6.63; N, 18.41%.

*1-(3′-C-Acetoxymethyl-2′,5′-di-O-acetyl-3′-deoxy-3′-phthalimido-β-D-ribofuranosyl)uracil (**19**).* To a solution of **9** [prepared from **8** (3.31 g)] in benzene (10 ml) was added 2,4-di-*O*-trimethylsilyluracil (5.0 g). The mixture was refluxed for 1 hr under stirring and 2,4-di-*O*-trimethylsilyluracil (3.0 g) was then added to this. After the mixture was refluxed for 2 days under stirring, ethanol (40 ml) was added and the resulting slurry was stirred for 30 min. The precipitates were removed by filtration. Silica gel (3 g) was added to the filtrate and evaporated. The residue was placed on a silica gel column (50 g, 3.8×17 cm) and eluted with benzene, benzene-ethyl acetate (5 : 1, 1 : 1, 1 : 2), successively. Evaporation of the eluent containing **19** afforded a pure sample of **19** as a glass; yield 846 mg (23%); $[\alpha]_D^{26}$ +27° (*c* 3.5, methanol); ν_{max}^{KBr} 3410, 1750 (sh), 1720 and 1635 (sh) cm^{-1}; λ_{max}^{MeOH} 242 mμ (ε 13900) and 257 nμ (ε 11600); τ^{CD_3OD} 2.09 (s, phthaloyl C_6H_4), 2.33 (d, H-6, $J_{5,6}$=7.9 Hz), 4.18 (d, H-1′, $J_{1',2'}$=4.4 Hz), 4.21 (d, H-5), 4.40 (d, H-2′), 7.90, 8.07 and 8.18 (s, $COCH_3$).

Found: C, 54.26; H, 4.77; N, 7.43%. Calcd for $C_{24}H_{23}N_3O_{11}$: C, 54.44; H, 4.38; N, 7.93%.

*1-(3′-Amino-3′-deoxy-3′-C-hydroxymethyl-β-D-ribofuranosyl)uracil (**20**).* A solution of **19** (116 mg) in 50% *n*-butylamine-methanol (10 ml) was refluxed for 18 hr. After evaporation the residue was partitioned between water (6 ml) and ethyl acetate (6 ml). The aqueous layer was washed with ethyl acetate (6 ml×7) and evaporated to afford a crystalline solid. To the residue was added isopropanol (6 ml) and the crystals of **20** were collected by centrifuging; yield 27 mg (45.1%). An analytical sample was obtained by recrystallization from water: mp 257.5°C (sintered), 261.5—262°C (decomp.); $[\alpha]_D^{20}$ +13° (*c* 1.0, 0.1 N HCl): RD (*c* 0.025, water) at 20°C, $[\Phi]_{300}$ +800°, $[\Phi]_{278}$ +2900° (pk); ν_{max}^{KBr} 3440, 3365, 1720 and 1680 cm^{-1}; $\lambda_{max}^{H_2O}$ 261.5 mμ (ε 10300), $\lambda_{max}^{0.1NHCl}$ 261 mμ (ε 10500), $\lambda_{max}^{0.1NNaOH}$ 263 mμ (ε 7600); τ^{D_2O} 2.06 (d, H-6, $J_{5,6}$=8.1 Hz), 4.00 (d, H-1′, $J_{1',2'}$=6.5 Hz), 4.04 (d, H-5), 5.69 (d, H-2′) and 6.31 (s, 3′ $-CH_2$).

Found: C, 44.01; H, 5.66; N, 15.13%. Calcd for $C_{10}H_{15}N_3O_6$: C, 43.95; H, 5.53; N, 15.38%.

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