Nucleosides. XXI.[1] Preparative Routes to Nucleosides Derived from 4-Amino-4-deoxy-β-D-glucopyranose[2]

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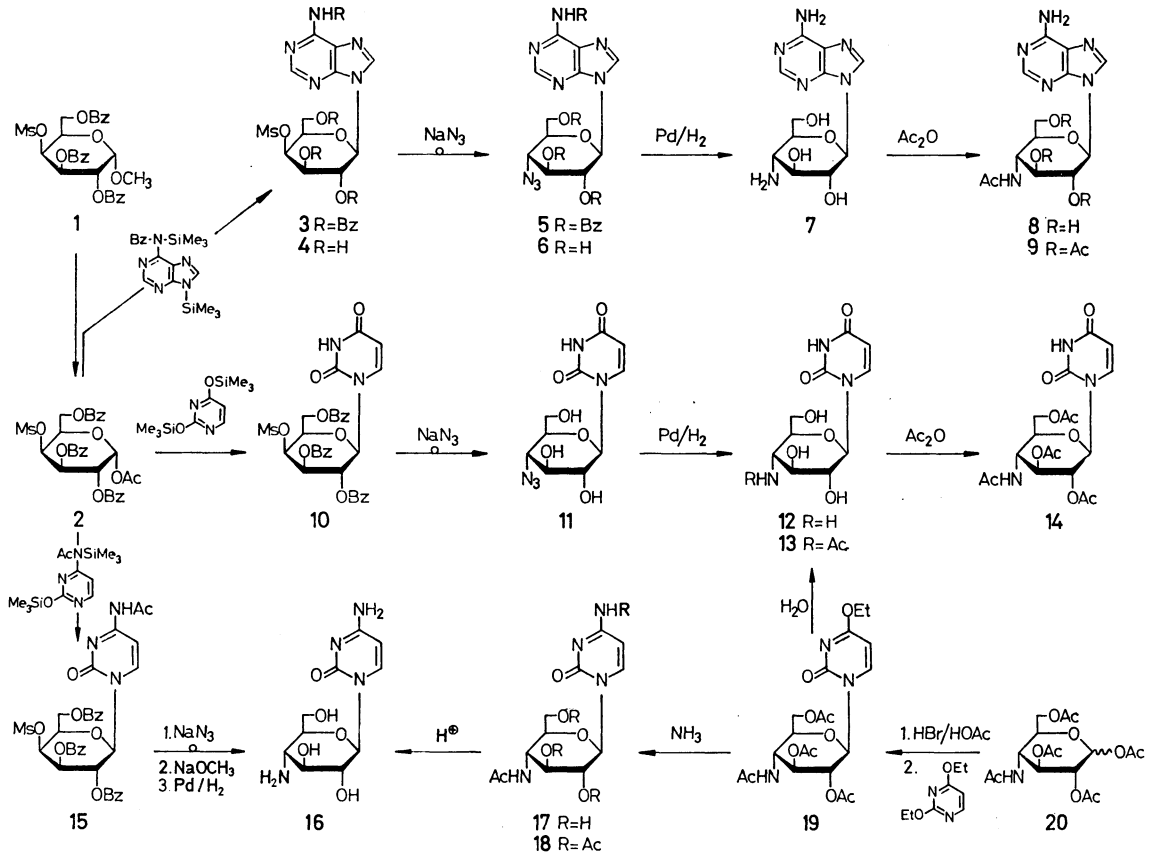
Four-step syntheses for the 4′-amino-4′-deoxy-β-D-glucopyranosyl nucleosides of adenine (**7**), uracil (**12**) and cytosine (**16**) from a readily accessible galactose derivative (**2**) are described, in overall yields of 41—47%. The reaction sequence, used, involved (i) stannic chloride catalyzed nucleosidations of **2** with the bis-trimethylsilyl derivatives of N^6-benzoyladenine, uracil and N^4-acetylcytosine, (ii) displacement of the 4′-sulfonyloxy groups in **3**, **10**, and **15** by azide, (iii) de-*O*-benzoylation and (iv) hydrogenation. An alternate route to **12** and **16**, comprising nucleosidation of tetraacetyl-4-acetamido-4-deoxy-D-glucopyranose (**20**) *via* the classical Hilbert-Johnson approach proved feasable, yet inferior with respect to yields and accessibility of educts. The structures and configurations assigned followed from the synthetic route as well as from spectroscopic data, particularly from the acetyl resonances of the peracetylated nucleosides **9**, **14**, and **18**, which are in excellent agreement with those of the respective glucosyl- and 3-acetamido-3-deoxy-glucosyl analogs (Table).

The aminoacyl-4-aminohexosyl-cytosine antibiotics gougerotin and blasticidin S, both elaborated by streptomyces species found in Japan,[3,4] have been the subject of intense chemical and biochemical investigations,[5] the main stimulus stemming from their inhibition of protein biosynthesis at the peptide chain elongation stage.[6] As a result, the structures of these antibiotics have been unequivocally established,[7] total synthesis for both have been advanced[16,17] and their structure-activity relationships have been assessed on the basis of the presently available structural analogs.[18] However, number and variety of the structural types being rather limited, these minimal functional group and spatial requirements for inhibition of transpeptidation[18] need to be further substantiated in order to elicit persuasive conclusions with respect to the molecular architecture of the ribosomal binding site. To provide this corroborative evidence, the synthesis of a systematic series of structural analogs, modified in nucleobase, aminosugar unit and aminoacid component, was deemed essential, which on biological evaluation are more likely to produce results of biological significance than previous studies, mainly directed towards the total syntheses of the natural products.[19] By consequence, synthetic work on purine and pyrimidine nucleosides derived from 4-amino-4-deoxy-hexoses was initiated.[15,20] In this paper, we present the results of our synthetic studies on 4′-amino-4′-deoxy-β-D-glucopyranosyl nucleosides, providing with the synthesis of **7** the first purine nucleoside in this series, as well as preparative procedures for the respective uracil (**12**) and cytosine nucleosides (**16**), that are alternate or considerably improved over those already known.[14,15,21]

Choice of Methods. Of the newer nucleosidation procedures available,[22] the most recently advanced[23] "Friedel-Crafts catalyzed trimethylsilyl procedure" was considered the most propitious for the preparation of pyrimidine as well as purine nucleosides[1] allowing utilization of a per-*O*-acyl-glycose rather than the 1-halide. As the sugar precursor to be nucleosidated, a suitably blocked derivative of 4-amino-4-deoxy-D-glucopyranose, *e.g.* its pentaacetate **20**, might be surmised to provide a very direct access to 4-aminoglucosyl nucleosides. However, whilst this approach can be realized as shown by the conversion of **20** to **19** (*vide infra*), it appears to be of limited general applicability for several reasons; *e.g.* the educt is encumbered by conceivable ring contraction to the pyrrolidinose form during nucleosidation and difficulties may arise in removing an *N*-acetyl group in purine nucleosides. Hence, a more suitable starting sugar for Friedel-Crafts catalyzed *N*-glycosidations was required and found in 1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-α-D-galactopyranose (**2**), readily accessible in crystalline form and good yield (79%) from its methyl glycoside **1**[24] by acetolysis in the presence of boron trifluoride-etherate.[25]

Adenine Nucleosides (3—9). When 1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-α-D-galactose (**2**) was allowed to react with a slight excess of *N*-benzoyl-*N*,9-bis(trimethylsilyl)adenine in the presence of stannic chloride (12 hr/60 °C in dichloroethane), the protected nucleoside **3** could be isolated by a simple workup procedure in reasonable yield (59%). Subsequent removal of the *O*- and *N*-benzoyl groups with sodium methoxide/methanol afforded the highly crystalline 4′-*O*-mesyl-derivative **4**. Of the two compounds, **3** and **4**, respectively, **3** was found to give a more uniform reaction mixture when subjected to azidolysis with sodium azide in hexamethyl phosphoric triamide (8 hr/80 °C). The protected azidonucleoside **5** formed in this way was directly debenzoylated, to afford in an overall yield (**3**→**6**) of 78% the 4′-azidoglucosyl-adenine **6**. Subsequent hydrogenation over 10% palladium on carbon proceeded smoothly to give in the form of colorless prisms the desired 4′-amino-4′-deoxy-β-D-glucopyranosyl-adenine (**7**)—the hitherto first purine nucleoside of a 4-aminohexose. It was further characterized by its 4′-acetamido derivative **8** as well as its peracetate **9**, each clearly exhibiting the NMR characteristics required for the *gluco*-configuration (*cf.* Table).

Of particular relevance in this context appears to be the overall yield for the four step reaction sequence **2**→**3**→**5**→**6**→**7**, which is 42%, and, hence, may be the method of choice for the preparation of other 4-amino-hexosyl-purines, should their synthesis be required.



Uracil Nucleosides (10—14). Whilst stannic chloride catalyzed nucleosidations of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose with silylated pyrimidines may readily be performed at room temperature,[23] it was found advantageous to use somewhat more forcing conditions (12 hr, 60 °C) for the *N*-glycosidation of *O,O*-bis(trimethylsilyl)uracil with the hexose derivative **2**, particularly when performing the reaction on rather larger scale. In this way, a crystalline product was obtained in 83% yield, comprising according to tlc an approximate 10: 1 mixture of the β-nucleoside **10** and a second component, most probably the N^3-isomer. The latter, however, was readily removed by recrystallization to afford the protected galactosyl-uracil **10** in a yield of 71%. Displacement of the mesyloxy group in **10** by sodium azide in hexamethyl phosphoric triamide (5 hr, 80 °C) followed by de-*O*-benzoylation with sodium methoxide gave the 4'-azidoglucosyl nucleoside **11** (72%). The subsequent hydrogenation over 10% palladium on carbon readily afforded 4'-amino-4'-deoxy-β-D-glucosyl-uracil **12** (81%), which was further characterized by an amorphous *N*-acetate (**13**) and its crystalline tetraacetyl derivative **14.**

Prior to the availability of the "Friedel-Crafts catalyzed silyl procedure" we had followed another approach for the preparation of the pyrimidine nucleosides **13** and **18**,[15] which expectedly gave inferior results with respect to accessibility of the starting sugar and the yield in the nucleoside synthesis: nucleosidation of peracetylated 4-aminoglucosyl bromide *via* the classical Hilbert-Johnson procedure.[26] Accordingly, 4-acetamido-1,2,3,6-tetra-*O*-acetyl-4-deoxy-D-glucopyranose (**20**) in the form of a sirupy 9: 1 α/β-mixture,[27] was converted into the corresponding 1-bromo sugar by treatment with 40% hydrogen bromide in glacial acetic acid, which *in situ* was reacted with diethoxypyrimidine. The ethoxypyrimidinone nucleoside **19** was readily obtained from the reaction mixture, yet the yield was far from satisfactory (36%, based on **20**). The subsequent hydrolysis with methanolic hydrochloric acid, however, proceeded smoothly affording **13** in 84% yield.

In comparing the preparative utility of the three synthetic routes by which 4-aminoglucosyl-uracil now has been prepared, the four step conversion of **2** into **12** in a 41% overall yield appears to be an appreciable improvement over the alternate five step sequence from the much less accessible galactosyl-uracil (overall yield: 31%[21]). The classical Hilbert-Johnson approach **20**→**19**→**13**→**12**, however, is unexpectedly inferior to either one of the two others.

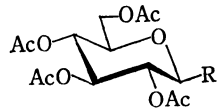
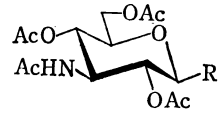
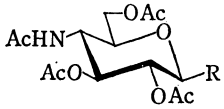
Cytosine Nucleosides (15—18). Whilst a conversion of galactoside **1** into nucleoside **15** *via* the glycosyl bromide of **1** and its condensation with N^4-acetylcytosine has already been described,[14] the high yield (95%) reported for the two steps was based on the pyrimidine precursor, and amounts to only 47% when based on the more precious sugar component. A superior procedure appears to be the nucleosidation of the acetolysis product of **1** with N^4,*O*-bis(trimethylsilyl)-N^4-acetylcytosine in the presence of stannic chloride (12 hr/60 °C in dichloroethane) affording crystalline **15** with a yield of 85% in the nucleosidation step **2**→**15** (62% from **1**). Since the conversion **15**→**16** is readily accomplished by the three step sequence azidolysis→deacetylation→hydrogenation,[14] 4'-amino-

4′-deoxy-β-D-glucosyl-cytosine can now be prepared from a readily accessible galactose derivative (**2**) in an overall yield of 47%.

An alternate route to **16**, elaborated earlier, proved to be of less preparative utility (21% overall yield): the classical Hilbert-Johnson nucleosidation of 4-amino-glucose peracetate (**20**→**19**) followed by aminolysis to **17** and de-*N*-acetylation (**17**→**16**). Nevertheless, a sample prepared in this way, which was subsequently *N*-acylated with BOC-blocked sarcosyl-seryl-azide[15] has provided the first biologically active analogue[31] of the nucleoside antibiotic gougerotin.

Structural and Configurational Assignments. Whilst the mode of preparation in itself provides conclusive proof for structure and configuration of the nucleosides described, corroborative evidence is readily derived from NMR data. However, except for the anomeric proton (*cf.* Table 1), the chemical shifts and coupling patterns of the pyranoid ring protons are not extractable from 60 MHz spectra without extensive decoupling. Much more conveniently, the configurations are ascertained by the chemical shifts of the acetyl resonances of per-acetylated nucleosides on the basis of the "acetyl resonance rule" elaborated for cyclitols,[32] hexopyranoses[33] and hexopyranosyl nucleosides.[33,34] As is apparent from the data collected in Table 1, neither one of the glucopyranosyl nucleosides (II—III), their 3′-amino-analogs (V—VII) or their 4′-amino counterparts (**9**, **14**, **18**, and **19**) exhibited signals attributable to an axially oriented acetoxy group (below τ 7.95 in DMSO-d_6). Equally distinct is the presence of an equatorial acetamido function in the 3′-aminoglucosyl nucleosides V—VII as well as their 4′-amino analogs, appearing as a signal in the τ 8.20—8.24 range, nicely separated from the others. Noteworthy is also the low field resonances for the cytosine nucleosides III and VI, originating from the N^4-acetyl group in the aglycon, as well as the highfield signals, at τ 8.30 and 8.31

Table 1. NMR-Data in DMSO-d_6 and rotations of peracetyl-β-D-glucopyranosyl-nucleosides

Sugar moiety	R[a]		Chemical shifts in τ units[b] H-1′	a-OAc	e-OAc 6′-OAc	e-NHAc	$[\alpha]_D$ (solvent, °C)
	U	(I)	4.03	—	7.98(2) 8.04 8.08	—	+4 (MeOH, 23)[c]
	U(O⁴-Et)	(II)	3.98	—	7.99(2) 8.04 8.12	—	+36 ($CHCl_3$, 26)[d]
	C(N⁴-Ac)	(III)	3.94	—	7.88[e] 7.97(2) 8.02 8.11	—	+38 ($CHCl_3$, 23)[d]
	A(N⁶-Bz)	(IV)	?	—	?	—	+6 ($CHCl_3$, 10)[f]
	U	(V)	4.01	—	7.98 8.02 8.11	8.23	−9 ($CHCl_3$, 24)[g]
	C(N⁴-Ac)	(VI)	3.97	—	7.89[e] 8.00 8.12	8.23	+12 (MeOH, 23)[g]
	A	(VII)	3.91	—	8.00 8.03 8.30	8.24	−36 ($CHCl_3$, 24)[h]
	U	(**14**)	4.15	—	8.00 8.06 8.10	8.21	+11 (MeOH, 23)
	U(O⁴-Et)	(**19**)	4.02	—	7.99 8.03 8.14	8.20	+46 (MeOH, 23)
	C(N⁴-Ac)	(**18**)	3.09	—	7.89[e] 8.01 8.05 8.09	8.23	+28 (DMF, 23)
	A	(**9**)	3.98	—	8.03(2) 8.31	8.22	+6 ($CHCl_3$, 20)

a) Abbreviations used=uracilyl-1; U(O⁴-Et)=4-ethoxypyrimidinonyl-1; C(N⁴-Ac)=N⁴-acetylcytosinyl-1; A=adeninyl-9; A(N⁶-Bz)=N^6-benzoyladeninyl-9. b) Except for compound VI (P. Emig, Techn. Hochschule Darmstadt, unpublished results) the NMR data for I—III, V and VII are derived from Ref. 33. c) T. Ueno, Techn. Hochschule Darmstadt, unpublished results. d) G. E. Hilbert and E. F. Jansen, *J. Amer. Chem. Soc.*, **58**, 60 (1936). e) N⁴-Acetyl resonance of the cytosine moiety. f) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965). g) S. Takei and Y. Kuwada, *Chem. Pharm. Bull.*, **16**, 944 (1965). h) J. Beranek, H. A. Friedman, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **2**, 188 (1965).

respectively, for the adenine derivatives VII and **9** (*cf.* Table 1). Those clearly arise from the 2'-acetoxy resonances, being in the range of diamagnetic shielding by the purine moiety, since similar upfield shifts have been observed for other purine nucleosides with an equatorial pyranoid 2'-acetoxy function.[33] In the pyrimidine nucleosides, this diamagnetic shielding is expectedly[33] lower, giving rise to resonances that are only shifted by approximately 0.1 ppm towards higher field (τ 8.08—8.14).

The results clearly demonstrate that examination of the acetyl resonances in DMSO-d_6 provides a reliable, convenient method for configurational assignments in the hexopyranosyl nucleoside field, when taking into consideration the predictable shielding effects by purine and pyrimidine nucleobases. Converse conclusions reached by Cushley *et al.*[35] have later been shown[36] invalid, being based, in part, on incorrect configurational assignments.

Whilst configuration and conformation of the sugar moiety may readily be elicited from NMR data, the orientation of nucleobase to the sugar is less clear. An attempt was made to obtain some, though admittedly limited information on this from the rotational values of the peracetylated nucleosides. Since replacement of an acetoxy by an acetamido group does not substantially affect rotations,[37] the sign and magnitude of the nucleosides in the Table 1 would be excepted to be at least very similar, if the sugar-nucleobase orientations are identical. However, as is clearly apparent from the data in the Table, they vary within too wide a range as to allow even limited conclusions on this matter.

Experimental

Melting points were determined on a Bock Monoskop, and are uncorrected. Spectra were recorded on Perkin-Elmer 125 (IR), Perkin-Elmer 137 (UV), and Varian A-60A (NMR) instruments.

Thin layer chromatography (tlc) on Kieselgel F_{254} plastic sheets (Merck, Darmstadt) was used throughout to monitor the reactions and to ascertain the purity of the products; developers employed (A) ethyl acetate–chloroform (1:1); (B) ethyl acetate–ethanol–water (15:2:1). The spots were visibilized by UV, by iodine vaporing, or by spraying with 80% aqueous sulfuric acid and charring at 110 °C for 5 min. Column chromatography was carried out on silica gel of 70—230 mesh ("Kieselgel 60", Merck, Darmstadt).

1-O-Acetyl-2,3,6-tri-O-benzoyl-4-O-mesyl-α-D-galactopyranose (2). To a solution of 30.0 g (51 mmol) of methyl 2,3,6-tri-*O*-benzoyl-4-*O*-mesyl-α-D-galactopyranoside (**1**)[28] in 600 ml of acetic anhydride 30 ml of BF_3–etherate in ether was added, and the mixture was heated to 60 °C for 12 hr, followed by gradually stirring into ice–water (3 l). After 2 hr, the solution was neutralized by careful addition of solid $NaHCO_3$, and subsequently extracted with two 500 ml portions of dichloromethane. The organic phase was dried over Na_2SO_4 and evaporated to dryness to yield a residue, which after charcoal treatment in methanol (500 ml), was recrystallized from the minimum amount of methanol: 24.2 g (79%), mp 143—144 °C; $[\alpha]_D^{20}$ +92° (*c* 1, $CHCl_3$); NMR ($CDCl_3$) τ 1.8—2.8 (m, 15, $3C_6H_5$), 3.35 (narrow [4 Hz] m, H-1), 4.12 (narrow m [4 Hz], H-2 and H-3), 4.41 (m [4 Hz], 1, H-4), 6.90 (s, 3, OMs), 7.83 (s, 3, OAc).

Found: C, 58.42; H, 4.63; S, 5.16%. Calcd for $C_{30}H_{28}O_{12}S$: C, 58.82; H, 4.61; S, 5.22%.

Adenine Nucleosides (3—9). 9-(2',3',6'-Tri-O-benzoyl-4'-O-mesyl-β-D-galactopyranosyl)-N⁶-benzoyladenine (3): To a solution of 3.0 g (4.9 mmol) of 4-*O*-mesylgalactose **2** in 1,2-dichloroethane (75 ml) was added 6 g of molecular sieve[38] and 1.5 ml of stannic chloride. After 30 min standing 2.0 g (5.2 mmol) of N^6-benzoyl-N^6,9-bis(trimethylsilyl)adenine[39,40] was added and the mixture was heated to 60 °C for 12 hr under careful exclusion of moisture. The molecular sieve was removed and the solution, after dilution with dichloromethane (75 ml), was extracted with aqueous sodium bicarbonate (2×100 ml) and washed with water (2×100 ml). Drying (Na_2SO_4) and evaporation to dryness followed by repeated reevaporations from methanol, left a sirup, which was crystallized by dissolving in benzene (120 ml), removal of some insoluble material, and gradual addition of cyclohexane (*ca.* 100 ml): 2.3 g (59%) of a colorless, amorphous product, uniform by tlc (A); $[\alpha]_D^{20}$ −17° (*c* 1, $CHCl_3$); NMR ($CDCl_3$) τ 1.26 and 1.52 (two 2 H-s, H-2 and H-8), 1.8—2.8 (broad m, 20, $4C_6H_5$), 3.65 (m, 2, H-1' and H-4'), 6.83 (s, 3, OMs).

Found: C, 60.45; H, 4.26; N, 8.83; S, 3.97%. Calcd for $C_{40}H_{33}N_5O_{11}S$: C, 60.67; H, 4.20; N, 8.85; S, 4.05%.

9-(4'-O-Mesyl-β-D-galactopyranosyl)adenine (4): To 1.0 g of tetrabenzoyl derivative **3** in methanol (20 ml) was added 1 ml of 5 M methanolic sodium methoxide with cooling, and the mixture was stored in a refrigerator overnight. The crystals, which had separated, were filtered off (0.35 g). From the mother liquor a second crop (0.1 g) was obtained by deionization with a strongly acidic ion exchange resin (Merck I), evaporation to dryness and trituration with little methanol. Both fractions were recrystallized from little water: 0.28 g (58%) of **4** as needles of mp 216—218 °C (decomp.); $[\alpha]_D^{20}$ +9° (*c* 0.6, H_2O); NMR (DMSO-d_6) τ 6.67 (s, 3, OMs).

Found: C, 37.97; H, 4.68; N, 18.49; S, 8.41%. Calcd for $C_{12}H_{17}N_5O_7S$: C, 38.30; H, 4.57; N, 18.66; S, 8.53%.

9-(4'-Azido-4'-deoxy-β-D-glucopyranosyl)adenine (6): To a solution of 10.0 g (12.6 mmol) of galacto-mesylate **3** in hexamethyl phosphoric acid triamide (50 ml) was added sodium azide (4.2 g, 5 molar equiv.) and the mixture was heated to 80 °C with vigorous stirring for 8 hr, followed by pouring into ice–water (2 l). The precipitate was collected, washed with water and subjected to treatment with activated carbon in methanol (150 ml). Evaporation to dryness, filtration with water and drying gave 9-(2',3',6'-tri-*O*-benzoyl-4'-azido 4'-deoxy-β-D-glucopyranosyl)-N^6-benzoyladenine (**5**) as an amorphous, colorless product (9.0 g), showing only traces of an impurity (tlc in A). Due to difficulties encountered in crystallization attempts from the usual solvents, the product was directly subjected to debenzoylation with sodium methoxide (4 ml of a 5 M methanolic solution) in methanol (100 ml) by storing for 24 hr at ambient temperature. Some product had crystallized and was isolated after standing overnight in a refrigerator: 2.60 g (60%) of mp 231—233 °C (decomp.). The mother liquor was deionized (Merck I resin) and evaporated to dryness *in vacuo* to give, from a concentrated methanolic solution, a second crop (0.77 g) Total yield on crude **6**: 3.37 g (78%); mp 229—231 (decomp.). For analytical data, a 200 mg portion was recrystallized from a small amount of water; mp 236—238 °C (decomp.); $[\alpha]_D^{20}$ +46° (*c* 1, dimethylformamide); IR (KBr) N_3 at 2100 cm^{-1}; NMR (DMSO-d_6 +D_2O) τ 1.84 and 1.99 (two 1 H-s, H-2 and H-8), 4.67 (d, 1, $J_{1,2}$=8.5 Hz, H-1').

Found: C, 39.00; H, 4.39; N, 32.98%. Calcd for $C_{11}H_{14}N_8O_4 \cdot H_2O$: C, 38.82; H, 4.74; N, 32.93%.

9-(4'-Amino-4'-deoxy-β-D-glucopyranosyl)adenine (7): To a

prehydrogenated suspension of 500 mg 10% Pd/C in water (100 ml) was added a solution of 2.0 g (6.3 mmol) of azido-nucleoside **6**, and the hydrogenation was continued. After 2 hr, tlc in B showing the absence of starting material, the catalyst was removed followed by concentration to dryness and several reevaporations from methanol, which induced crystallization: 1.70 g (90%) of **7**, crystallizing with 1 mol of methanol in colorless prisms, decomposing from 200 °C on, after sintering around 160 °C; $[\alpha]_D^{20}$ +12° (*c* 1, H_2O).

Found: C, 43.67; H, 6.00; N, 25.54. Calcd for $C_{11}H_{16}N_6O_4 \cdot CH_3OH$: C, 43.90; H, 6.14; N, 25.60%.

9-(4'-Acetamido-4'-deoxy-β-D-glucopyranosyl)adenine (8): To a stirred suspension of **7** (100 mg) in methanol (10 ml) was added 1 ml of acetic anhydride, giving gradually a clear solution. After 5 hr at room temperature (tlc in B showed the reaction to be complete), the mixture was evaporated to dryness followed by two reevaporations from ethanol. The residue was filtered with ethanol to give **7** as a hygroscopic (after drying over P_2O_5), solid product, containing 1 mol of acetic acid; NMR (D_2O) τ 1.63 and 1.83 (two 1 H-s, H-2 and H-8), 4.33 (d, 1, $J_{1',2'}$=9 Hz, H-1'), 7.86 (s, 3, acetic acid of crystallization), 7.91 (s, 3, NHAc).

Found: C, 44.94; H, 5.55; N, 21.39%. Calcd for $C_{13}H_{18}N_6O_5 \cdot CH_3COOH$: C, 45.22; H, 5.57; N, 21.10%.

9-(4'-Acetamido-2',4',6'-tri-O-acetyl-4'-deoxy-β-D-glucopyranosyl) adenine (9): To a pyridine solution (2 ml) of **8** (100 mg) was added 1 ml of acetic anhydride with cooling and stirring and the mixture was then kept at room temperature for 3 hr. Concentration to dryness *in vacuo* (finally 0.1 mm, bath temperature 25 °C), followed by reevaporations from water and ethanol–water (1:1) gave a sirup which on trituration with ether solidified. Filtration afforded 100 mg (63%) of an amorphous product, uniform by tlc (in B); $[\alpha]_D^{20}$ +6° (*c* 1, $CHCl_3$); NMR (DMSO-d_6) τ 1.60 and 1.80 (two 1 H-s, H-2 and H-8), 2.00 (d, 1, J=8 Hz, 4'-NH), 2.71 (s, 2, 6-NH_2), 3.98 (d, 1, $J_{1',2'}$=9 Hz, H-1'), 4.25 (t, 1, $J_{1',2'}=J_{2',3'}$= 9 Hz, H-3'), 5.88 (m, 4, H-4', H-5', and 6'-CH_2), acetyl resonances *cf.* Table 1.

Found: C, 49.00; H, 5.56; N, 17.89%. Calcd for $C_{18}H_{24}N_6O_8$C: 49.14; H, 5.21; N, 18.10%.

Uracil Nucleosides. 1-(2',3',6'-Tri-O-benzoyl-4'-O-mesyl-β-D-galactopyranosyl)uracil (10): To a solution of 20.0 g (32.7 mmol) of 4-*O*-mesyl-galactose **2** in 1,2-dichlorethane was added 40 g of molecular sieve,[38] followed, after standing for 30 min, by the addition of stannic chloride (10 ml) and *O,O*-bis(trimethylsilyl)uracil[39,41] (11.0 g, 1.3 molar equiv.). The mixture was heated to 60 °C for 12 hr, and subsequently treated with saturated sodium bicarbonate solution (2×500 ml) and water (2×500 ml). The organic layer was dried (Na_2SO_4), concentrated to dryness and reevaporated twice from methanol. The residue was dissolved in hot ethanol (150 ml), from which it crystallized: 18.4 g of product, mp 189—190 °C, that, according to tlc in B, was contaminated with approximately 10% of another product (N^3-isomer) of lower R_f-value. The latter, being scarcely soluble in ethanol, was removed by one recrystallization from this solvent, affording 15.5 g (71%) of **10** as needles of mp 204—206 °C (lit,[21] 207—208 °C); UV (MeOH) and NMR data ($CDCl_3$) correlated well with those reported by Kondo and Goto[21] for their product, obtained by another route.

Found: C, 57.87; H, 4.19; N, 4.26; S, 4.71%. Calcd for $C_{12}H_{28}N_2O_{12}S$: C, 57.83; H, 4.25; N, 4.22; S, 4.82%.

1-(4'-Azido-4'-deoxy-β-D-glucopyranosyl)uracil (11): A mixture of 12.0 g (18 mmol) of mesyl-nucleoside **10**, 6.6 g (5 molar equiv.) of sodium azide and 45 ml of hexamethyl phosphoric triamide was stirred at 80—90 °C for 5 hr, followed by pouring into ice-water (1 l). The solid precipitate was filtered off, dried over P_2O_5 and directly subjected to de-*O*-benzoylation by dissolution in methanol (110 ml), containing 5 ml of 5 M methanolic sodium methoxide, and storage at room temperature overnight. The mixture was then deionized by a strongly acidic resin (Merck I) and evaporated to dryness, followed by several reevaorations from 1:1 methanol–water, which induced crystallization. Filtration with methanol yielded 3.3 g (72%) of **11** as colorless crystals of mp 226—228 °C (decomp.); lit,[21]: 226 °C (decomp.).

1-(4'-Amino-4'-deoxy-β-D-glucopyranosyl)uracil (12): *A. Form Azidonucleoside 11 by Hydrogenation*:[42] To a prehydrogenated suspension of 500 mg 10% Pd/C in 1:1 water–ethanol (100 ml) was added 2.0 g (6.8 mmol) of azide **11** in 20 ml of water, and the hydrogenation was continued. After 3 hr, tlc in B showing the absence of starting material, the catalyst was removed followed by evaporation to dryness *in vacuo*. Trituration of the residue with ethanol gave a crystalline product, which was filtered after standing in a refrigerator overnight: 1.52 g (81%) of colorless crystals, mp 241—243 °C (decomp.); mp, UV (MeOH), NMR (D_2O) and analytical data corresponded well with those reported for a product from another route.[21]

B. From 4'-Acetamido-nucleoside 13 by Deacetylation: A solution of sirupy **13** (680 mg, 2.15 mmol) in 4 M hydrochloric acid was refluxed for 3 hr, followed, after cooling down, by deionization with a strongly basic resin (Merck III), which was thoroughly washed on removal. The filtrate was subjected to charcoal treatment and subsequently evaporated to dryness, yielding a residue which crystallized on several reevaporations from ethanol. Filtration with ethanol and recrystallization from the same solvent gave 410 mg (65%) of **12** as colorless crystals, identical in all respects with the product described under A.

1-(4'-Acetamido-4'-deoxy-β-D-glucopyranosyl)uracil (13): *A. From Ethoxypyrimidinone-Nucleoside 20 by Hydrolysis*: A solution of 750 mg (1.5 mmol) of **20** in 8% methanolic hydrochloric acid (30 ml) was kept at ambient temperature for 24 hr followed by concentration *in vacuo* and repeated reevaporations of the residue from methanol. The yellowish sirup was purified on a silica gel column by elution with methanol to yield, after drying for 2 hr at 60 °C and 0.1 mm, 476 mg of amorphous **13** (84%), homogeneous by tlc (B), $[\alpha]_D^{23}$ +8° (*c* 1, CH_3OH); the product could not be crystallized from the usual solvents.

Found: C, 45.64; H, 5.52; N, 13.10%. Calcd for $C_{12}H_{17}N_3O_7$: C, 45.71; H, 5.44; N, 13.33%.

B. De-O-acetylation of Tetraacetate 14: To a solution of 440 mg (1 mmol) of **14** in methanol (15 ml) was added 0.2 ml of N methanolic sodium methoxide and the mixture was kept overnight at ambient temperature. Deionization with Dowex 50 (H^+) and concentration to dryness followed by repeated reevaporations from ethanol left a sirup, which was subjected to a small silica gel column and eluted with methanol. After evaporation to dryness *in vacuo* (finally 0.1 mm): 240 mg (76%) of **14** a colorless sirup, identical with respect to tlc (in B), IR and NMR data with the product described under A.

1-(4'-Acetamido-2',3',6'-tri-O-acetyl-4'-deoxy-β-D-glucopyranosyl)uracil (14): To aminoglucosyl-uracil **12** (430 mg, 1.5 mmol) in pyridine (10 ml) was added with stirring 4 ml of acetic anhydride. After 15 hr at ambient temperature, the clear solution was evaporated to dryness *in vacuo* (finally 0.1 mm) followed by coevaporations with water, water–ethanol (1:1) and ethanol. The resulting sirup was dissolved in a small amount of methanol from which **14** crystallyzed gradually. Filtration after standing overnight in a refrigerator and drying at 60 °C/0.1 mm for 3 hr afforded 470 mg (68%) of

14 as colorless crystals of mp 260—263 °C (decomp.)[43]; $[\alpha]-$ +11° (*c* 1, CH_3OH); NMR (DMSO-d_6) τ 1.35 (s, 1, uracil-NH), 2.01 (broad d, 1, 4'-NH), 2.07 and 4.31 (two 1 H-d, $J_{5,6}$=8.5 Hz, H-5 and H-6), 4.15 (m, 1, H-1'), acetyl resonances *cf.* Table.

Found: C, 48.79; H, 5.15; N, 9.49%. Calcd for $C_{18}H_{23}N_3O_{10}$: C, 48.98; H, 5.25; N, 9.52%.

Treatment of *N*-acetyl derivative **13** with pyridine–acetic anhydride and processing of the mixture in a manner analogous to the one described above gave compound **14** in 74% yield.

*1-(4'-Acetamido-2',3',6'-tri-*O*-acetyl-4'-deoxy-β-*D*-glucopyranosyl)-4-ethoxypyrimidin-2-one (19)*: A solution of 2.30 g (5.9 mmol) of sirupy 1,2,3,6-tetra-*O*-acetyl-4-acetamido-4-deoxy-D-glucopyranose (**20**, α/β-ratio 9: 1)[27] in 40% HBr in glacial acetic acid (15 ml) was kept at ambient temperature for 3 hr. The mixture was then diluted with chloroform (200 ml) and extracted successively with cold water (2×100 ml), saturated sodium bicarbonate solution (2×100 ml) and water, followed by drying of the organic phase (Na_2SO_4). After filtration, the solution was added to 4.0 g (4 molar equiv.) of 2,4-diethoxypyrimidine and the solvent was removed *in vacuo*. The resulting mixture was then heated for 12 hr on a water-bath at 60 °C. After cooling down, *n*-hexane (200 ml) was added, resulting in a brownish precipitate. The hexane, containing the excessive diethoxypyrimidine, was removed by decantation, followed by another *n*-hexane extraction and discoloration of the residue in benzene solution with activated charcoal. Addition of *n*-hexane to the filtrate till beginning turbidity and standing in a refrigerator gave a first crop of crude **20**, successive further additions of *n*-hexane to the respective mother liquors a second and third. Recrystallization of the combined fractions by dissolution in the minimum amount of methanol and addition of water afforded 1.07 g (36%) of **20**, mp 118—120 °C (after sintering around 110 °C); $[\alpha]_D^{23}$ +46° (*c* 1, CH_3OH), +59° (*c* 1, $CHCl_3$); NMR (DMSO-d_6) τ 1.81 and 3.93 (two 1 H-d, $J_{5,6}$=7.5 Hz, H-5 and H-6), 2.10 (d, 1, $J_{4',NH}$=9 Hz, NH), 4.02 (m, 1, halfwidth 9 Hz, H-1'), 4.68 (m, 2, H-3' and H-2'), 5.63 and 8.71 (2H-q and 3H-t, J=7 Hz, OCH_2CH_3), 5.9 (m, 4, H-4', H-5', and 6'-CH_2), acetyl resonances *cf.* Table 1; acetyl resonances in $CDCl_3$ at τ 7.93, 7.97, 8.02, and 8.04.

Found: C, 50.99; H, 6.03; N, 8.90%. Calcd for $C_{20}H_{27}N_3O_{10}$: C, 51.17; H, 5.80; N, 8.95%.

*Cytosine-Nucleosides (15—18). 1-(2',3',6'-Tri-*O*-benzoyl-4-*O*-methanesulfonyl-β-*D*-galactopyranosyl)-*N*⁴-acetylcytosine (15)*: To a stirred solution of 4-*O*-mesyl-galactose **2** (4.8 g, 7.8 mmol) in sieve-dried 1,2-dichlorethane (150 ml) was added molecular sieve[38] (5 g), tin tetrachloride (2.4 ml), and, after 15 min, 1.65 g (1.1 molar equiv.) of N^4,*O*-bis(trimethylsilyl)-N^4-acetylcytosine,[39] and the mixture was kept in a bath at 60 °C for 12 hr. After dilution with 300 ml of 1,2-dichloroethane the solution was extracted with saturated sodium hydrogen carbonate (2×200 ml) followed by washing with water (2×200 ml). The organic phase was dried (Na_2SO_4), and evaporated to dryness *in vacuo*, yielding a solid mass that was filtered and thoroughly washed with ethanol: 4.7 g (85%) of **15** as colorless needles, mp 266—268 °C (decomp.) and $[\alpha]_D^{23}$ +38.6° (*c* 1, dimethylformamide). The product was identical with respect to tlc (in A), IR and NMR with a sample prepared by another route.[14]

*1-(4'-Acetamido-4'-deoxy-β-*D*-glucopyranosyl)cytosine (17)*: A solution of ethoxypyrimidinone-nucleoside **19** (2.70 g, 5.46 mmol) in methanol, saturated with ammonia (150 ml), was heated in a pressure bottle for 22 hr at 95 °C. After treatment with charcoal, the mixture was concentrated to dryness followed by several reevaporations from methanol. The solid residue was recrystallized from methanol: 1.13 g (66%) of **17** as colorless crystals of mp 290—292 °C (decomp.) and $[\alpha]_D^{23}$ +34° (*c* 1, H_2O). The product was identical with a sample prepared by *N*-acetylation of **16** with acetic anhydride in methanol, for which mp 317—319 °C (decomp.) and $[\alpha]_D^{26}$ +32° (*c* 1, H_2O) have been reported.[14]

*1-(4'-Amino-4'-deoxy-β-*D*-glucopyranosyl)cytosine (16)*: A solution of 4'-acetamido-nucleoside **17** (540 mg, 1.72 mmol) in 4 M hydrochloric acid was refluxed for 4 hr, followed, after cooling, by deionization with a strongly basic resin (Merck III), which was thoroughly washed on removal. The filtrate was subjected to charcoal treatment and then evaporated to dryness, giving a sirupous residue that gradually crystallized on repeated reevaporations from methanol. Recrystallization from the same solvent afforded 320 mg (69%) of **16** of mp 210 °C and $[\alpha]_D^{23}$ +15° (*c* 1, H_2O).

A sample prepared from mesylate **15** *via* azidolysis, deacylation and hydrogenation[14] had mp, UV, and IR data duplicating those above.

*1-(4'-Acetamido-2',3',6'-tri-*O*-acetyl-4'-deoxy-β-*D*-glucopyranosyl)-*N*⁴-acetylcytosine (18)*: *N*-Acetyl derivative **17** (1.0 g) in 1:1 pyridine–acetic anhydride (1:1) was kept overnight at ambient temperature, followed by evaporation to dryness *in vacuo* (finally 0.1 mm). Trituration of the residue with ethanol induced crystallization to give, after recrystallization from the same solvent 1.1 g (72%) of **18** as needles of mp 295 °C (decomp.); $[\alpha]_{23}^{D}$ +28.1° (*c* 1, dimethylformamide); lit,:[14] mp 293—294 °C; $[\alpha]_{25}^{D}$ +27°; NMR (DMSO-d_6) τ −0.84 (s, 1, N^4–H), 1.56 and 2.75, (two 1 H-d, $J_{5,6}$=7 Hz, H-6 and H-5), 2.18 (d, 1, $J_{4',NH}$=9 Hz, C-4'-NH), 3.90 (m, 1, H-1'), acetyl resonances *cf.* Table 1.

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