Synthesis of 2,4-Dideoxy-β-D-*erythro*-hexopyranosyl Nucleosides

Koen Augustyns, Jef Rozenski, Arthur Van Aerschot, Gerard Janssen, and Piet Herdewijn*

Laboratory of Medicinal Chemistry, Rega Institute, Minderbroedersstraat 10, B-3000 Leuven, Belgium

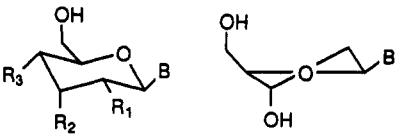
Received July 16, 1992 (Revised Manuscript Received March 8, 1993)

The synthesis of 1-(2,4-dideoxy-β-D-*erythro*-hexopyranosyl)thymine (**12**)[1] was accomplished using two different synthetic routes. It was obtained starting either from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose or from tri-*O*-acetyl-D-glucal. The other modified nucleosides, with either a cytosine, guanine, or adenine moiety, were synthesized using the second reaction scheme. Deoxygenation reactions were accomplished with the (2,4-dichlorophenoxy)thiocarbonyl derivatives generated in situ.

Introduction

The ability of synthetic oligonucleotides of a defined sequence to disrupt the biological function of mRNA or DNA in a sequence-specific manner is well-known as the antisense or antigene modulation of gene expression.[2] This approach can be used to examine the role of a specific gene in a complex biological environment, but it also has therapeutic potential against infectious diseases and diseases evolving from abnormal expression of genes. A striking example is cancer induction. It is possible that tumor development might be controlled by inactivation of growth-stimulatory factors under the control of oncogenes. A serious drawback, however, is the rapid enzymatic degradation of natural oligonucleotides. Therefore, the synthetic challenge lies in the development of synthetic constructs which are enzymatically stable, but still apt to form stable duplexes with natural mRNA or DNA. Our main interest is the development of oligonucleotides with replacement of the natural pentofuranosyl sugar by a hexopyranosyl sugar. Therefore, we synthesized a series of dideoxy-D-*erythro*-hexopyranosyl nucleosides, which were used as building blocks for the incorporation into oligonucleotides (Figure 1).

The synthesis and properties of oligonucleotides containing 2,3-dideoxy-β-D-*erythro*-hexopyranosyl nucleosides **1** was reported elsewhere.[3] Recently, oligonucleotides containing the same carbohydrate moiety were described also by Eschenmoser. These constructs were, however, used to serve other purposes, namely to investigate why nature choose pentose and not hexose nucleic acids.[4] The synthesis of the 3,4-dideoxy-β-D-*erythro*-hexopyranosyl nucleoside analogue **2** and its incorporation into oligonucleotides are straightforward and are reported elsewhere.[1] The structure of the 2,4-dideoxy-β-D-*erythro*-hexose analogue **3** resembles more closely the structure of the natural deoxyribose nucleoside **4**,[5] and therefore, we became interested in the properties of oligonucleotides containing this hexose nucleoside. Also from an antiviral point of view it was interesting to synthesize these new



1 R_1=R_2=H, R_3=OH
2 R_2=R_3=H, R_1=OH
3 R_1=R_3=H, R_2=OH

4

B = nucleic acid base

Figure 1.

nucleoside analogues. Until now, no hexose nucleosides have been found to be a substrate for cellular or viral kinases and, hence, to exert an antiviral effect. The synthesis of **3**, however, is less straightforward than the synthesis of **1** and **2**. We synthesized **3** starting from D-glucose by performing two deoxygenation reactions at C-2 and C-4 and one inversion of the configuration at C-3. Two different synthetic routes starting from easily available carbohydrate precursors were investigated and compared. The outcome of the sugar–base condensation reaction leading to the nucleoside analogues proved to be very susceptible to the reaction conditions used. Yields are higher with pyrimidine bases than with purine bases. Longer reaction times lead to the preponderant formations of the thermodynamically favored β-anomer.

Results and Discussion

The first reaction scheme (Scheme I) starts from the commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Inversion of configuration at C-3[6] and benzylation yielded the starting material **5** (overall yield 68%). Removal of the isopropylidene functions with 80% HOAc resulted in a complex mixture of monoacetates, as also described for the deprotection of the di-*O*-cyclohexylidene derivative.[7] Therefore, the crude 3-*O*-benzyl-D-allose was deacetylated with ammonia before benzoylation to give **6** in 40% yield. ^{1}H NMR analysis proved crystalline **6** to be a β-D-pyranose in a $^4C_1$ conformation. The same conformation was reported for 1,2,4,6-tetra-*O*-acetyl-3-*O*-benzyl-D-allopyranose[7] and 1,2,4,6-tetra-*O*-benzoyl-3-*O*-methyl-D-allopyranose.[8] Sugar–base condensation of **6** with silylated thymine under standard Vorbrüggen

(1) Full details on oligonucleotide synthesis and properties is published elsewhere: Augustyns, K.; Vandendriessche, F.; Van Aerschot, A.; Busson, R.; Urbanke, C.; Herdewijn, P. *Nucleic Acids Res.* **1992**, *20*, 4711–4716. A preliminary communication on the synthesis of **12** has been published: Augustyns, K.; Van Aerschot, A.; Herdewijn, P. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 945–948.

(2) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543–584.

(3) Augustyns, K.; Van Aerschot, A.; Urbanke, C.; Herdewijn, P. *Bull. Soc. Chim. Belg.* **1992**, *101*, 119–130.

(4) (a) Eschenmoser, A. *Nachr. Chem. Tech. Lab.* **1991**, *39*, 795–807. (b) Eschenmoser, A.; Dobler, M. *Helv. Chim. Acta* **1992**, *75*, 218–259.

(5) De Winter, H. et al. Manuscript in preparation.

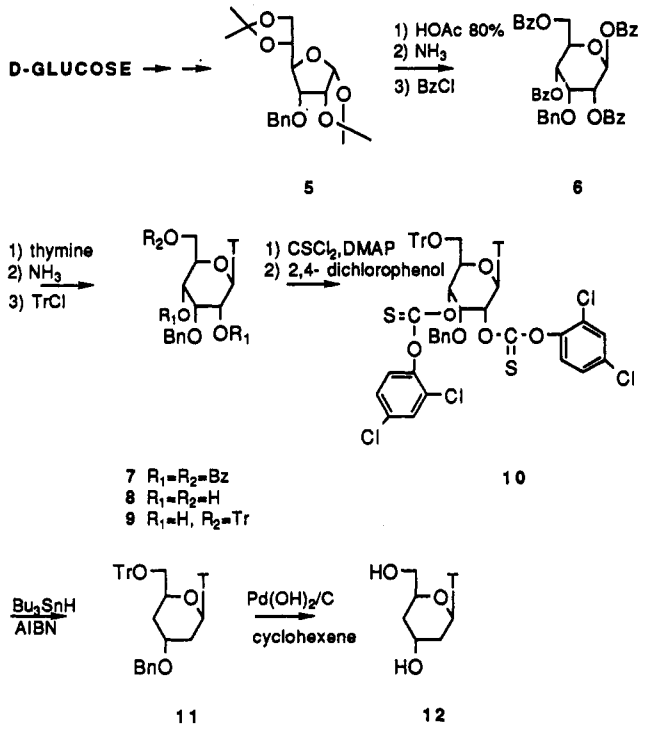
(6) Baker, D. C.; Horton, D.; Tindall, C. G., Jr. *Carbohydr. Res.* **1972**, *24*, 192–197.

(7) Dick, W. E., Jr.; Weisleder, D.; Hodge, J. E. *Carbohydr. Res.* **1975**, *42*, 55–63.

(8) Haga, M.; Takano, M.; Tejima, S. *Carbohydr. Res.* **1972**, *21*, 440–446.

0022-3263/93/1958-2977$04.00/0

Scheme I



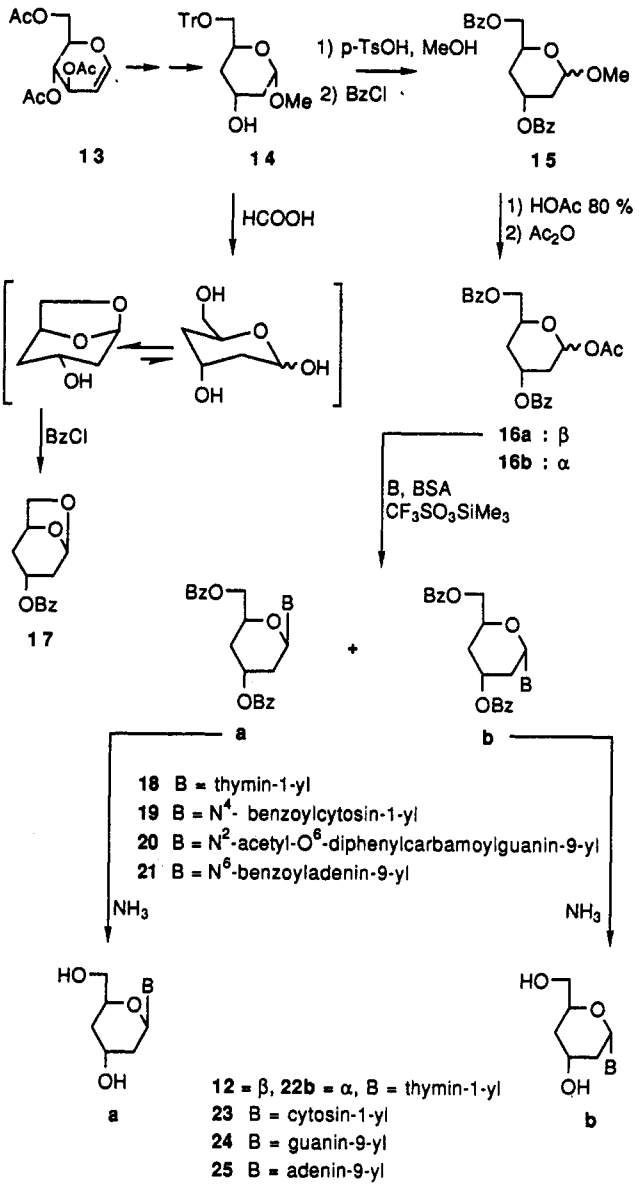
Bz = benzoyl, T = thymine, DMAP = 4-dimethylaminopyridine, AIBN = 2,2'-azobisisobutyronitrile

conditions[9] yielded 80% of compound **7**. Deprotection with methanolic ammonia (**8**, 95%) and selective protection of the primary hydroxyl with a trityl group afforded **9** (84%).

Classical deoxygenation reactions at C-2′ and C-4′ met with difficulties. Deoxygenation with Bu_3SnH of the methoxy(thiocarbonyl) or the phenoxy(thiocarbonyl) derivatives resulted in complex mixtures from which the desired compound **11** was isolated with great difficulty and in very low yields. This problem was solved by using a phenoxy(thiocarbonyl) group substituted with electron-withdrawing groups. As reported by Barton,[10] these groups increase the radicophilicity of the thione group and hence increase the speed of the desired fragmentation, while reducing side reactions. We prepared the 2,4-dichlorophenoxythiocarbonyl derivative **10** from **9**, with thiophosgene and 2,4-dichlorophenol. Deoxygenation of **10** went smoothly with Bu_3SnH (3 equiv) in benzene at reflux temperature (1.5 h). Less byproducts are formed using this procedure, although the yield is still not spectacular (48%). Cleavage of both the trityl and benzyl group was accomplished by transfer hydrogenation affording **12** in 53% yield.

Because of the low yields and the difficult deoxygenations, a different synthetic approach to prepare 2,4-dideoxy-D-*erythro*-hexopyranosyl nucleoside analogues was explored (Scheme II). Methyl 2,4-dideoxy-6-*O*-trityl-β-D-*erythro*-hexopyranoside (**14**) was obtained in five steps starting from tri-*O*-acetyl-D-glucal (**13**).[11] Detritylation of **14** with formic acid followed by benzoylation resulted in the formation of the 1,6-anhydro compound **17** (40%)

Scheme II



(Scheme II). Also, treatment of **14** with HOAc 80% followed by benzoylation or vice versa resulted in the formation of the same compound **17**. The equilibrium between the free hexose and the 1,6-anhydrohexose in acid medium is clearly shifted towards the anhydro form.[12] The equatorial orientation of the C-3 substituent in the 1,6-anhydro form favours the formation of **17**. However, detritylation of **14** with a catalytic amount of p-toluenesulfonic acid in methanol, followed by benzoylation gave a mixture of α and β anomers **15** (90%, 1/3). Partial anomerization of the methoxy group under these reaction circumstances is a common observation.[11b] Treatment of the mixture of anomers **15** with 80% HOAc followed by acetylation afforded 62% of β-**16a** and 7% of α-anomer **16b**.

One-pot sugar–base condensation[13] (Scheme II) of **16a** with thymine, BSA (bis(trimethylsilyl)acetamide), and $CF_3SO_3SiMe_3$ (1:2:6:1.3) afforded an α/β mixture of **18**. The β-anomer **18a** is thermodynamically favored over the α-anomer **18b**. Extension of the reaction time from 6 to 16 h at room temperature turned the α/β ratio from 1/2.5

(9) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255.
(10) Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2619–2622.
(11) (a) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439–1441. (b) Yang, Y.; Falck, J. R. *Tetrahedron Lett.* **1982**, *23*, 4305–4308.
(12) Cerny, M.; Stanek, J., Jr. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23–177.
(13) Wright, G. E.; Dudycz, L. W. *J. Med. Chem.* **1984**, *27*, 175–181.

to 1/8 with the same total isolated yield. It thus seemed that the α-anomer is gradually converted to the β-anomer. This preponderance of the β-anomer was also observed by Robins[14] in the synthesis of 2-deoxy-D-*ribo*-hexopyranosyl nucleoside analogues. Almost the same α/β ratio (1/7) was obtained after sugar–base condensation of **16a** with N^4-benzoylcytosine affording **19a** and **19b**. For the synthesis of the guanine analogue the fully protected N^2-acetyl-O^6-(diphenylcarbamoyl)guanine[15] was used affording exclusively the N-9 isomer. Thus, **20a** and **20b** were obtained (α/β = 1/5) although in a low total yield (41%). The synthesis of the protected adenosine analogue was less successful yielding only 30% of the β-anomer **21a** after a very long reaction time. Increase in temperature and prolonged reaction time both gave even lower yields. Deprotection of **18–21** with methanolic ammonia (Scheme II) afforded nucleoside analogues **22–25**.

1-(2,4-Dideoxy-β-D-*erythro*-hexopyranosyl)thymine (**12**), obtained from both reaction schemes, was completely identical by ^{1}H NMR, ^{13}C NMR, UV, and MS. Neighboring group participation of the 2′-benzoyloxy function during sugar–base condensation reaction explains the exclusive formation of the β-anomer following the first reaction scheme.[9] Crystallographic studies on analogous pyranosyl nucleosides[14,16] indicated the preferential equatorial orientation of the aglycon moiety. This means that the β-nucleoside adopts a $^4C_1$ conformation and the α-nucleoside a $^1C_4$ conformation. The H-1′ of both the α- and β-nucleoside is axially oriented and therefore gives an identical double doublet in the ^{1}H NMR spectrum when 2′-deoxynucleosides are considered ($J_{1',2'ax} \approx 11$ Hz, $J_{1',2'eq} \approx 2$ Hz). However, the equatorial orientation of H-3′ in the β-nucleosides (small coupling constant, downfield shift) and the axial orientation of H-3′ in the α-nucleosides (large coupling constant, upfield shift) gives a clear distinction between both compounds. This difference is observed with the protected (**18a,18b**) and unprotected (**12,22b**) nucleosides as well as with other bases (**19–21, 23–25**). The N^9-glycosylation (and not N^7-glycosylation) of the purine nucleosides was deduced from the ^{13}C NMR and from the UV spectra, both for guanine and adenine. These data correspond with the reported literature data.[17–21]

Conclusion

The synthesis of 1-(2,4-dideoxy-β-D-*erythro*-hexopyranosyl)thymine (**12**) was accomplished by two different synthetic routes from commercially available carbohydrate precursors. In the first route 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was used as the starting material, and **12** was obtained in 12 steps with an overall yield of 3%. Tri-*O*-acetyl-D-glucal (**13**) was the precursor in the second route, which afforded **12** in 11 steps (overall yield = 14%). The higher yield convinced us to select the second route to synthesize the nucleoside analogues (**23a, 24a, 25a**). These new nucleoside analogues do not show antiviral activity. They are, however, useful building blocks for the synthesis of hexose nucleic acids.[1]

Experimental Section

Melting points were determined with a Buchi–Tottoli apparatus and are uncorrected. Ultraviolet spectra were recorded with a Philips PU8740 UV/vis scanning spectrophotometer. The NMR spectra were determined with a JEOL FX 90Q spectrometer. Chemical ionization mass spectra (CIMS) and liquid secondary ion mass spectra (LSIMS) were obtained using a Kratos Concept 1H mass spectrometer. Elemental analyses were carried out at the University of Konstanz. Column chromatography was performed on silica gel (0.060–0.200 mm). Pyridine was dried by distillation after refluxing with KOH. Dichloromethane and acetonitrile were refluxed with calcium hydride and distilled. Dichloroethane (P_2O_5), benzene and toluene (Na), and methanol (Mg,I_2) were refluxed with a drying agent prior to distillation.

1,2,4,6-Tetra-*O*-benzoyl-3-*O*-benzyl-β-D-allopyranose (6). A solution of 31.4 g (120.6 mmol) of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[6] in DMF (100 mL) was added dropwise at room temperature to a solution of NaH (5.31 g of a 60% suspension in oil, 132.7 mmol) in 100 mL of DMF. After being stirred for 2 h, the mixture was cooled on an ice bath, and a solution of 22.79 g (132.7 mmol) of benzyl bromide in DMF (50 mL) was added dropwise. Stirring was continued for 2 h at room temperature, water was added, and the mixture was evaporated. Extraction ($CHCl_3/H_2O$), drying, and evaporation of the organic layer and purification by flash column chromatograph [(1) CH_2Cl_2, (2) CH_2Cl_2–MeOH (99:1), (3) CH_2Cl_2–MeOH (97:3)] yielded 37.76 g (107.9 mmol, 90%) of 3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) as an oil. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48; N, 27.40. Found: C, 64.97; H, 7.52; N, 27.23.

A solution of 37.76 g (107.9 mmol) of **5** in 80% acetic acid (400 mL) was stirred for 3.5 h at room temperature and for 1 h under reflux. After evaporation and coevaporation (four times) with toluene, the residue was treated with concentrated ammonia (200 mL) for 1.5 h. The solution was concentrated and purified by column chroamtography (CH_2Cl_2–MeOH (9:1)) yielding 28.36 g (105 mmol, 97%) of 3-*O*-benzyl-D-allose. Pyridine was repeatedly evaporated from this compound, followed by the addition of pyridine (400 mL), cooling to 0 °C, and treatment with 122 mL (1050 mmol) of benzoyl chloride. This mixture was stirred for 2 h at 0 °C and for 21 h at room temperature. Water was added at 0 °C, the volatiles were removed by evaporation, and the residue was dissolved in CH_2Cl_2 (600 mL). This organic layer was washed twice with aqueous HCl (200 mL, 1 N) and seven times with 200 mL of a saturated sodium bicarbonate solution, dried, evaporated, and coevaporated with toluene (three times) affording a dark brown residue. The title compound (**6**) was obtained directly from this residue by crystallization from ethyl acetate–ethanol (29.53 g, 43.0 mmol, 40% yield from **5**): mp 181–183 °C; CIMS (NH_3) 704 (MNH_4^+); HRMS calcd for $C_{34}H_{29}O_8$ (M − C_6H_5CO) 565.1862, found 565.1856; ^{1}H NMR ($CDCl_3$) δ 4.35–4.90 (m, 6 H, H-3, H-5, H-6, $CH_2C_6H_5$), 5.42 (dd, 1 H, J = 2.8 and 8.4 Hz, H-2), 5.50 (dd, 1 H, J = 2.9 and 9.6 Hz, H-4), 6.65 (d, 1 H, J = 8.4 Hz, H-1), 7.05–7.70 (m, 17 H, aromatic H), 7.90–8.10 (m, 8 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 63.2 (C-6), 69.4, 71.1, 71.3, 75.1, 75.5 (C-2, C-3, C-4, C-5, $CH_2C_6H_5$), 91.2 (C-1), 127.7, 128.2, 128.4, 129.7, 129.9, 132.9, 133.4, 137.3 (aromatic), 164.9, 166.0 (C=O).

1-(2,4,6-Tri-*O*-benzoyl-3-*O*-benzyl-β-D-allopyranosyl)-thymine (7). Bis(trimethylsilyl)thymine[9] (12 mmol, obtained after refluxing overnight thymine in hexamethyldisilazane in the presence of a catalytic amount of ammonium sulfate) and 6.86 g (10 mmol) of **6** were dissolved in 70 mL of dichloroethane. $SnCl_4$ (1.64 mL, 14 mmol) was added, and the reaction mixture was stirred for 4 h at 40 °C. Then it was diluted with CH_2Cl_2 (100 mL) and poured into a saturated sodium bicarbonate solution (200 mL). The obtained emulsion was filtered over Celite, the layers were separated, and the organic layer was dried and evaporated. Purification by column chromatography [(1) CH_2Cl_2–acetone (97:3), (2) CH_2Cl_2–acetone (95:5), (3) CH_2Cl_2–acetone (93:7)] afforded 5.53 g (8.0 mmol, 80%) of the title compound (**7**) as a white foam: UV (MeOH) λ_{max} = 264 nm (log ε = 4.08);

(14) Nord, L. D.; Dalley, N. K.; McKernan, P. A.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1044–1054.
(15) Robins, M. J.; Zou, R.; Hansske, F.; Madej, D.; Tyrrell, D. L. J. *Nucleosides Nucleotides* **1989**, *8*, 725–741.
(16) De Winter, H. L.; De Ranter, C. J.; Blaton, N. M.; Peeters, O. M.; Van Aerschot, A.; Herdewijn, P. *Acta Crystallogr. Sect. B.* **1992**, *48*, 95–103.
(17) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294–1298.
(18) Chenon, M. T.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4627–4636.
(19) Jenkins, S. R.; Holly, F. W.; Walton, E. *J. Org. Chem.* **1965**, *30*, 2851–2852.
(20) Montgomery, J. A.; Thomas, H. J. *J. Am. Chem. Soc.* **1965**, *87*, 5442–5447.
(21) Kjellberg, J.; Johansson, N. G. *Tetrahedron Lett.* **1986**, *42*, 6541–6544.

CIMS (NH_3) 691 (MH^+); HRMS calcd for $C_{39}H_{34}N_2O_{10}$ (M) 690.2214, found 690.2196; ^1H NMR ($CDCl_3$) δ 1.82 (s, 3 H, CH_3), 4.30–4.95 (m, 6 H, H-3′, H-5′, H-6′, $CH_2C_6H_5$), 5.20–5.50 (m,2 H, H-2′, H-4′), 6.60 (d, 1 H, J = 9.6 Hz, H-1′), 7.00–7.70 (m, 14 H, aromatic H), 7.85–8.15 (m, 7 H, H-6, aromatic H), 8.80 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 12.2 (CH_3), 63.0 (C-6′), 69.0, 70.6, 72.5, 74.6, 75.4 (C-2′, C-3′, C-4′, C-5′, $CH_2C_6H_5$), 78.1 (C-1′), 111.7 (C-5), 150.2 (C-2), 162.9 (C-4), 127.8, 128.2, 128.3, 128.5, 129.5, 129.8, 133.1, 133.6, 134.5, 137.0 (C-6, aromatic), 164.9 and 166.0 (C=O).

1-(3-*O*-Benzyl-β-D-allopyranosyl)thymine (8). A solution of 5.48 g (7.94 mmol) of **7** in methanolic ammonia was stirred for 48 h at room temperature. After evaporation and purification by column chromatography [(1) CH_2Cl_2–MeOH (9:1), (2) CH_2Cl_2–MeOH (85:15)] 2.86 g (7.57 mmol, 95%) of the title compound (**8**) was obtained as a white foam: UV (MeOH) λ_{max} = 265 nm (log ϵ = 4.01); ^1H NMR (DMSO-d_6) δ 1.80 (s, 3 H, CH_3), 3.40–4.10 (m, 6 H, H-2′, H-3′, H-4′, H-5′, H-6′), 4.48 (t, 1 H, 6′OH), 4.84 (s, 2 H, $CH_2C_6H_5$), 5.00 (d, 1 H, J = 5.2 Hz, OH), 5.25 (d, 1 H, J = 4.8 Hz, OH), 5.74 (d, 1 H, J = 9.0 Hz, H-1′), 7.25–7.55 (m, 6 H, H-6, aromatic H), 11.2 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 12.2 (CH_3), 61.2 (C-6′), 67.5, 68.5, 74.7, 77.1 (C-2′, C-3′, C-4′, $CH_2C_6H_5$), 80.0, 80.9 (C-1′, C-5′), 109.6 (C-5), 127.3, 127.5, 128.2, 139.7 (aromatic), 137.1 (C-6), 151.3 (C-2), 163.9 (C-4).

1-(3-*O*-Benzyl-6-*O*-trityl-β-D-allopyranosyl)thymine (9). A mixture of 2.86 g (7.57 mmol) of **8** and 2.53 g (9.08 mmol) of trityl chloride in pyridine (50 mL) was kept for 64 h at room temperature. The mixture was concentrated and partitioned (CH_2Cl_2, saturated sodium bicarbonate solution). The organic layer was dried, evaporated, and coevaporated twice with toluene. The residue was purified by column chromatography [(1) CH_2Cl_2–MeOH (99:1), (2) CH_2Cl_2–MeOH (98:2), (3) CH_2Cl_2–MeOH (97:3)] yielding 3.96 g (6.39 mmol, 84%) of the title compound (**9**) as a foam: UV (MeOH) λ_{max} = 266 nm (log ϵ = 4.00); ^1H NMR ($CDCl_3$) δ 1.88 (s, 3 H, CH_3), 2.35 (m, 1 H, OH), 3.35 (d, 2 H, H-6′), 3.45–4.05 (m, 4 H, H-2′, H-4′, H-5′, OH), 4.18 (br s, 1 H, H-3′), 4.92 (d, 2 H, J = 5.5 Hz, $CH_2C_6H_5$), 5.92 (d, 1 H, J = 9.0 Hz, H-1′), 7.05–7.60 (m, 21 H, H-6, aromatic H); ^{13}C NMR ($CDCl_3$) δ 12.3 (CH_3), 63.9 (C-6′), 69.4, 70.8, 75.1, 75.9 (C-2′, C-3′, C-4′, $CH_2C_6H_5$), 79.3, 80.7 (C-1′, C-5′), 87.0 (Ph_3C), 111.3 (C-5), 127.1, 127.8, 127.9, 128.5, 137.9, 143.5 (aromatic), 135.1 (C-6), 151.2 (C-2), 163.3 (C-4).

1-[3-*O*-Benzyl-2,4-bis-*O*-[(2,4-dichlorophenoxy)(thiocarbonyl)]-6-*O*-trityl-β-D-allopyranosyl]thymine (10). A mixture of 4.97 g (8.02 mmol) of **9** and 7.84 g (64.2 mmol) of 4-(dimethylamino)pyridine in CH_2Cl_2 (150 mL) was treated with 1.29 mL (16.04 mmol) of thiophosgene at −40 °C. The mixture was kept for 100 min at a temperature between −40 and −20 °C. Then, 5.23 g (32.08 mmol) of 2,4-dichlorophenol was added, and the reaction mixture was stirred for 10 min at room temperature. After this solution was washed with 300 mL of cold 1 M KH_2PO_4, the aqueous layer was extracted twice with CH_2Cl_2 (200 mL). The combined organic layers were washed with 20 mL of a saturated sodium chloride solution, dried, evaporated, and purified by column chromatography [(1) hexane, (2) hexane–EtOAc (9:1), (3) hexane–EtOAc (7:3), (4) hexane–EtOAc (65:35)] yielding 5.21 g (5.06 mmol, 63%) of the title compound (**10**) as a white foam. This compound still contains contaminants. It was, however, very difficult to obtain a pure sample because of the presence of similar eluting unknown contaminants: UV (MeOH) λ_{max} = 266 nm (log ϵ = 3.99); ^1H NMR ($CDCl_3$) δ 1.97 (s, 3 H, CH_3), 3.25–3.65 (m, 2 H, H-6′), 4.35–4.75 (m, 1 H, H-5′), 4.83 (br s, 2 H, $CH_2C_6H_5$), 4.98 (br s, 1 H, H-3′), 5.50–5.80 (m, 2 H, H-2′, H-4′), 6.48 (d, 1 H, J = 9.6 Hz, H-1′), 6.70–7.60 (m, 27 H, H-6, aromatic H), 9.10 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 12.4 (CH_3), 62.4 (C-6′), 72.4, 73.3, 75.4, 77.6, 77.9, 78.9, (C-1′, C-2′, C-3′, C-4′, C-5′, $CH_2C_6H_5$), 86.6 (Ph_3C), 111.6 (C-5), 134.9 (C-6), 150.2 (C-2), 163.4 (C-4), 191.4, 191.6 (C=S) + aromatic signals.

1-(3-*O*-Benzyl-2,4-dideoxy-6-*O*-trityl-β-D-*erythro*-hexopyranosyl)thymine (11). Nitrogen was bubbled through a solution of 5.21 g (5.06 mmol) of **10** in benzene (60 mL) for 20 min. After 0.33 g (2.02 mmol) of 2,2′-azobis(2-methylpropionitrile) and 4.20 mL (15.20 mmol) of tri-*n*-butyltin hydride were added, the mixture was refluxed for 100 min. The volatiles were removed by evaporation, and the residue was purified by column chromatography [(1) hexane, (2) hexane–EtOAc (65:35), (3) hexane–EtOAc (3:2)] affording 1.44 g (2.45 mmol, 48%) of the title compound (**11**) as a white foam: UV (MeOH) λ_{max} = 264 nm (log ϵ = 3.99); ^1H NMR ($CDCl_3$) δ 1.45–2.35 (m, 4 H, H-2′, H-4′), 1.96 (s, 3 H, CH_3), 2.90–3.30 (m, 2 H, H-6′), 4.01 (br s, 1 H, H-3′), 4.15–4.45 (m, 1 H, H-5′), 4.58 (d, 2 H, J = 2.6 Hz, $CH_2C_6H_5$), 6.13 (dd, 1 H, J = 1.7 and 10.7 Hz, H-1′), 7.15–7.55 (m, 21 H, H-6, aromatic H), 8.65 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 12.4 (CH_3), 31.9 and 34.6 (C-2′, C-4′), 66.4 (C-6′), 70.3, 70.8, 72.8 (C-3′, C-5′, CH_2C_6H-5), 78.5 (C-1′), 110.6 (C-5), 126.9, 127.6, 128.3, 128.6, 143.8 (aromatic), 135.4 (C-6), 149.6 (C-2), 163.3 (C-4).

1-(2,4-Dideoxy-β-D-*erythro*-hexopyranosyl)thymine (12). Method A. A solution of 1.35 g (2.30 mmol) of **11** in cyclohexene (50 mL) and ethanol (25 mL) was degassed with nitrogen for 20 min, and 0.30 g of 20% $Pd(OH)_2$ on carbon was added. This mixture was refluxed for 23 h, after which TLC analysis (CH_2Cl_2–MeOH (9:1)) showed incomplete reaction. Therefore, another 0.90 g of 20% $Pd(OH)_2$ on carbon was added in three portions over a total refluxing time of 71 h. After being cooled to room temperature, the mixture was filtered and the residue was washed with ethanol. The combined filtrate was evaporated and purified by column chromatography [CH_2Cl_2–MeOH (9:1)] yielding 314 mg (1.23 mmol, 53%) of the title compound (**12**) as a white foam. An analytical sample was obtained after crystallization from acetone: mp 227–229 °C dec; UV (MeOH) λ_{max} = 266 nm (log ϵ = 4.00); (0.01 N NaOH) λ_{max} = 266 nm (log ϵ = 3.79); CIMS (NH_3) 257 (MH^+), 274 (MNH_4^+); HRMS calcd for $C_{11}H_{16}N_2O_5$ (M) 256.1059, found 256.1056; ^1H NMR (DMSO-d_6) δ 1.15–2.00 (m, 4 H, H-2′, H-4′), 1.79 (s, 3 H, CH_3), 3.39 (d, 2 H, J = 4.4 Hz, H-6′), 3.80–4.10 (m, 1 H, H-5′), 4.21 (br s, 1 H, H-3′), 4.63 (t, 1 H, J = 4.8 Hz, 6′OH), 4.94 (br s, 1 H, 3′OH), 5.94 (dd, 1 H, J = 2.6 and 11.0 Hz, H-1′), 7.55 (s, 1 H, H-6), 11.25 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 12.2 (CH_3), 33.6, 36.5 (C-2′, C-4′), 63.1 (C-3′), 64.4 (C-6′), 74.1 (C-5′), 77.4 (C-1′), 109.7 (C-5), 137.0 (C-6), 150.4 (C-2), 164.0 (C-4).

Method B. **18a** (1.32 g, 2.84 mmol) was treated with methanolic ammonia for 4 days. Evaporation and purification by column chromatography [(1) CH_2Cl_2–MeOH (95:5), (2) CH_2Cl_2–MeOH (9:1)] afforded 0.64 g (2.50 mmol, 88%) of **12**. An analytical sample was obtained after crystallization from ethanol. This compound is by all means (UV, CIMS, ^1H NMR, and ^{13}C NMR) identical to **12** obtained by method A: mp 231–233 °C dec. Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.36; H, 6.23; N, 10.78.

Methyl 3,6-Di-*O*-benzoyl-2,4-dideoxy-D-*erythro*-hexopyranoside (β and α Anomers) (15). Methyl 2,4-dideoxy-6-*O*-trityl-α-D-*erythro*-hexopyranoside (**14**)[11] (2.80 g, 6.93 mmol) was dissolved in 70 mL of methanol containing 0.05% of *p*-toluenesulfonic acid monohydrate. This solution was stirred for 24 h at room temperature, followed by the addition of 0.23 g of solid sodium bicarbonate and stirring for another 30 min. Then, the mixture was filtered and the filtrate was evaporated and coevaporated with pyridine. The residue was dissolved in pyridine (40 mL), and benzoyl chloride (8 mL, 69.3 mmol) was added. After being stirred for 4 h at room temperature, the solution was cooled to 0 °C and water was added. The reaction mixture was concentrated, dissolved in CH_2Cl_2, and washed three times with a saturated sodium bicarbonate solution and once with water. The combined aqueous layer was extracted once more with CH_2Cl_2. The combined organic layers were dried, evaporated, coevaporated with toluene and purified by column chromatography [(1) CH_2Cl_2, (2) CH_2Cl_2–MeOH (99.75:0.25), (3) CH_2Cl_2–MeOH (99.5:0.5)] affording 2.32 g (6.27 mmol, 90%) of the title compound (**15**) as a mixture of the α and β anomers (α/β ≈ 1/3). Although both isomers can be separated, the further reactions were carried out on the α/β mixture.

β Anomer: CIMS (NH_3) 388 (MNH_4^+); HRMS calcd for $C_{21}H_{21}O_6$ (M − H) 369.1338, found 369.1315; ^1H NMR ($CDCl_3$) δ 1.60–2.30 (m, 4 H, H-2, H-4), 3.54 (s, 3 H, OCH_3), 4.15–4.50 (m, 3 H, H-5, H-6), 4.83 (dd, 1 H, J = 2.2 and 9.2 Hz, H-1), 5.59 (quintet, 1 H, J = 3.1 Hz, H-3), 7.30–7.70 (m, 6 H, aromatic H), 8.00–8.25 (m, 4 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 31.7, 35.4 (C-2, C-4), 56.0 (OCH_3), 66.6, 68.4, 69.2 (C-3, C-5, C-6), 99.5 (C-1), 128.2, 128.3, 129.5, 132.8, 133.0 (aromatic), 165.2, 166.1 (C=O).

α Anomer: CIMS (NH_3) 388 (MNH_4^+); HRMS calcd for $C_{20}H_{19}O_5$ (M − OCH_3) 339.1232, found 339.1231; ^1H NMR ($CDCl_3$) δ 1.65–2.20 (m, 4 H, H-2, H-4), 3.42 (s, 3 H, OCH_3), 4.30–4.70 (m, 3 H, H-5, H-6), 4.88 (dd, 1 H, J = 1.6 and 3.5 Hz, H-1), 5.42 (quintet, 1 H, J = 3.3 Hz, H-3), 7.25–7.60 (m, 6 H, aromatic H),

7.95–8.20 (m, 4 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 31.3, 32.6 (C-2, C-4), 54.9 (OCH_3), 62.1, 65.9, 66.9 (C-3, C-5, C-6), 97.6 (C-1), 128.2, 129.5, 132.6, 132.8 (aromatic), 165.8, 166.2 (C=O).

1-*O*-Acetyl-3,6-di-*O*-benzoyl-2,4-dideoxy-D-*erythro*-hexopyranose [β (16a) and α (16b) Anomers]. A solution of 2.31 g (6.24 mmol) of **15** in 80% acetic acid was kept for 5 h at 80 °C. After evaporation, followed by coevaporation with toluene (three times), the residue was dissolved in a mixture of pyridine–acetic anhydride (2:1, 45 mL) and stirred for 72 h at room temperature. After the mixture was cooled to 0 °C, water was added and the mixture was evaporated and coevaporated with toluene. Purification by column chromatography [(1) CH_2Cl_2, (2) CH_2Cl_2–MeOH (99.5:0.5), (3) CH_2Cl_2–MeOH (99:1)] afforded 1.54 g (3.87 mmol, 62%) of the β anomer **16a** and 0.17 g (0.43 mmol, 7%) of the α anomer **16b**. **16a**: CIMS (NH_3) 416 (MNH_4^+); HRMS calcd for $C_{20}H_{19}O_6$ (M – CH_3CO) 355.1182, found 355.1176; ^{1}H NMR ($CDCl_3$) δ 1.70–2.20 (m, 4 H, H-2, H-4), 2.11 (s, 3 H, CH_3), 4.20–4.50 (m, 3 H, H-5, H-6), 5.63 (quintet, 1 H, J = 3.3 Hz, H-3), 6.17 (dd, 1 H, J = 3.1 and 9.5 Hz, H-1), 7.05–7.65 (m, 6 H, aromatic H), 7.75–8.20 (m, 4 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 31.2, 34.2 (C-2, C-4), 66.3, 67.7, 70.3 (C-3, C-5, C-6), 91.1 (C-1), 128.2, 128.4, 129.5, 132.9, 133.1 (aromatic), 165.2, 166.0, 168.8 (C=O).

16b: CIMS (NH_3) 416 (MNH_4^+); HRMS calcd for $C_{20}H_{19}O_6$ (M – CH_3CO) 355.1182, found 355.1158; ^{1}H NMR ($CDCl_3$) δ 1.90–2.50 (m, 4 H, H-2, H-4), 1.98 (s, 3 H, CH_3), 4.35–4.80 (m, 3 H, H-5, H-6), 5.48 (quintet, 1 H, J = 3.0 Hz, H-3), 6.30 (dd, 1 H, J = 1.2 and 3.1 Hz, H-1), 7.25–7.70 (m, 6 H, aromatic H), 7.95–8.25 (m, 4 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3), 30.9, 31.4 (C-2, C-4), 64.4, 65.3, 66.4 (C-3, C-5, C-6), 90.9 (C-1), 128.2, 129.4, 132.9 (aromatic), 165.3, 166.0, 169.0 (C=O).

1,6-Anhydro-3-*O*-benzoyl-2,4-dideoxy-β-D-*erythro*-hexopyranose (17). Methyl 2,4-dideoxy-6-*O*-trityl-α-D-*erythro*-hexopyranoside (14)[11] (157 mg, 0.39 mmol) was dissolved in formic acid (20 mL), followed by immediate evaporation and coevaporation with toluene. The resulting residue was dissolved in pyridine (5 mL), and 0.5 mL of benzoyl chloride was added. After being stirred overnight, the reaction mixture was cooled to 0 °C and water was added. After evaporation, the residue was dissolved in CH_2Cl_2 and washed with a saturated sodium bicarbonate solution (twice) and water. The organic layer was dried, evaporated, coevaporated with toluene, and purified by column chromatography (CH_2Cl_2) yielding 36 mg (0.15 mmol, 40%) of the title compound (**17**) as an oil: CIMS (NH_3) 235 (MH^+), 252 (MNH_4^+); HRMS calcd for $C_{13}H_{14}O_4$ (M) 234.0892, found 234.0886; ^{1}H NMR ($CDCl_3$) δ 1.60–2.55 (m, 4 H, H-2, H-4), 3.65–4.10 (m, 2 H, H-6), 4.65 (br s, 1 H, H-5), 5.25–5.75 (m, 2 H, H-1, H-3), 7.25–7.70 (m, 3 H, aromatic H), 7.90–8.20 (m, 2 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 35.2, 37.7 (C-2, C-4), 66.0, 68.1, 72.8 (C-3, C-5, C-6), 100.8 (C-1), 128.2, 129.4, 132.8 (aromatic), 165.5 (C=O).

1-(3,6-Di-*O*-benzoyl-2,4-dideoxy-D-*erythro*-hexopyranosyl)-thymine [β (18a) and α (18b) Anomers]. (A) A mixture of 250 mg (0.63 mmol) of **16a**, 158 mg (1.26 mmol) of thymine, and 0.94 mL (3.77 mmol) of bis(trimethylsilyl)acetamide (BSA) in dichloroethane (10 mL) was refluxed for 15 min. After the mixture was cooled to 0 °C, 160 μL (0.82 mmol) of $CF_3SO_3SiMe_3$ was added under nitrogen to the resulting clear solution. The reaction mixture was kept for 1 h at 0 °C and for 5 h at room temperature. Then it was diluted with CH_2Cl_2 (100 mL) and poured into a saturated sodium bicarbonate solution (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried, evaporated, and purified by column chromatography (hexane–EtOAc (3:2)) yielding 78 mg (0.17 mmol, 22%) of the α anomer **18b** and 191 mg (0.41 mmol, 55%) of the β anomer **18a**.

(B) A mixture of 1.59 g (4 mmol) of **16a**, 1.01 g (8 mmol) of thymine, and 6 mL (24 mmol) of BSA in dichloroethane (50 mL) was refluxed for 15 min. After the mixture was cooled to room temperature, 1.01 mL (5.2 mmol) of $CF_3SO_3SiMe_3$ was added under nitrogen to the resulting clear solution. The reaction mixture was kept for 16 h at room temperature. Extraction as above and purification by column chromatography [(1) hexane–EtOAc (4:1), (2) hexane–EtOAc (3:2)] yielded 0.16 g (0.34 mmol, 9%) of the α anomer **18b** and 1.32 g (2.84 mmol, 71%) of the β anomer **18a**.

18a: UV (MeOH) λ_{max} = 265 nm (log ε = 4.02); CIMS (NH_3) 465 (MH^+), 482 (MNH_4^+); HRMS calcd for $C_{20}H_{19}O_5$ (M – B) 339.1232, found 339.1254; ^{1}H NMR ($CDCl_3$) δ 1.65–2.45 (m, 4 H, H-2′, H-4′), 1.92 (s, 3 H, CH_3), 4.30–4.70 (m, 3 H, H-5′, H-6′), 5.65 (t, 1 H, J = 2.2 Hz, H-3′), 6.24 (dd, 1 H, J = 2.2 and 10.6 Hz, H-1′), 7.23 (s, 1 H, H-6), 7.35–7.70 (m, 6 H, aromatic H), 7.95–8.25 (m, 4 H, aromatic H), 9.50 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 12.3 (CH_3), 31.0, 34.5 (C-2′, C-4′), 66.2, 67.3 (C-3′, C-6′), 71.9 (C-5′), 78.1 (C-1′), 111.2 (C-5), 128.2, 128.4, 129.5, 133.0, 133.2 (aromatic), 134.7 (C-6), 149.8 (C-2), 163.4 (C-4), 165.2, 166.0 (C=O).

18b: UV (MeOH) λ_{max} = 266 nm (log ε = 4.00); CIMS (NH_3) 465 (MH^+), 482 (MNH_4^+); HRMS calcd for $C_{20}H_{19}O_5$ (M – B) 339.1232, found 339.1257; ^{1}H NMR ($CDCl_3$) δ 1.70–2.65 (m, 4 H, H-2′, H-4′), 1.91 (s, 3 H, CH_3), 4.30–4.85 (m, 3 H, H-5′, H-6′), 5.55 (m, 1 H, H-3′), 6.20 (dd, 1 H, J = 2.6 and 10.1 Hz, H-1′), 7.25 (s, 1 H, H-6), 7.35–7.70 (m, 6 H, aromatic H), 7.90–8.20 (m, 4 H, aromatic H), 9.30 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 12.2 (CH_3), 30.9, 35.4 (C-2′, C-4′), 64.3, 66.2 (C-3′, C-6′), 71.0 (C-5′), 76.8 (C-1′), 111.0 (C-5), 128.2, 129.4, 129.5, 133.0 (aromatic), 134.9 (C-6), 149.8 (C-2), 163.3 (C-4), 165.2, 166.0 (C=O).

1-(3,6-Di-*O*-benzoyl-2,4-dideoxy-D-*erythro*-hexopyranosyl)-*N*⁴-benzoylcytosine [β (19a) and α (19b) Anomers]. A mixture of 1.59 g (4 mmol) of **16a**, 1.72 g (8 mmol) of N^4-benzoylcytosine, and 6 mL (24 mmol) of BSA in dichloroethane (50 mL) was refluxed for 20 min. After the mixture was cooled to room temperature, 1.01 mL (5.2 mmol) of $CF_3SO_3SiMe_3$ was added under nitrogen to the resulting clear solution. The reaction mixture was kept for 16 h at room temperature, diluted with CH_2Cl_2 (200 mL), and poured into a sodium bicarbonate solution (7%, 200 mL). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was dried, evaporated, and purified by column chromatography [(1) CH_2Cl_2, (2) CH_2Cl_2–CH_3CN (9:1), (3) CH_2Cl_2–CH_3CN (85:15)] affording 1.24 g (2.24 mmol, 56%) of the β anomer **19a** and 0.18 g (0.33 mmol, 8%) of the α anomer **19b**.

19a: UV (MeOH) λ_{max} = 304 nm (log ε = 3.98), λ_{max} = 261 nm (log ε = 4.38), λ_{min} = 290 nm (log ε = 3.92); CIMS (NH_3) 554 (MH^+); HRMS calcd for $C_{31}H_{27}N_3O_7$ (M) 553.1849, found 533.1903; ^{1}H NMR ($CDCl_3$) δ 1.55–2.70 (m, 4 H, H-2′, H-4′), 4.30–4.70 (m, 3 H, H-5′, H-6′), 5.67 (t, 1 H, J = 2.2 Hz, H-3′), 6.35 (dd, 1 H, J = 2.2 and 11.0 Hz, H-1′), 7.25–7.70 (m, 10 H, H-5, aromatic H), 7.75–8.25 (m, 7 H, H-6, aromatic H), 9.00 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 31.2, 35.2 (C-2′, C-4′), 66.1, 67.2 (C-3′, C-6′), 72.1 (C-5′), 80.0 (C-1′), 97.1 (C-5), 127.5, 128.4, 128.7, 129.6, 133.0, 133.1 (aromatic), 143.7 (C-6), 153.7 (C-2), 162.0 (C-4), 165.2, 166.0, 166.9 (C=O).

19b: UV (MeOH) λ_{max} = 302 nm (log ε = 3.99), 261 nm (log ε = 4.39), λ_{min} = 290 nm (log ε = 3.89); CIMS (NH_3) 554 (MH^+); HRMS calcd for $C_{24}H_{21}N_3O_5$ (M – C_6H_5COOH) 431.1481, found 431.1466; ^{1}H NMR ($CDCl_3$) δ 1.80–2.90 (m, 4 H, H-2′, H-4′), 4.30–4.85 (m, 3 H, H-5′, H-6′), 5.55 (m, 1 H, H-3′), 6.23 (dd, 1 H, J = 3.1 and 8.8 Hz, H-1′), 7.25–7.65 (m, 10 H, H-5, aromatic H), 7.85–8.20 (m, 7 H, H-6, aromatic H); ^{13}C NMR ($CDCl_3$) δ 31.0, 35.3 (C-2′, C-4′), 64.6, 65.9 (C-3′, C-6′), 70.9 (C-5′), 79.0 (C-1′), 96.9 (C-5), 127.6, 128.2, 128.4, 128.8, 129.4, 129.6, 133.1 (aromatic), 143.8 (C-6), 153.8 (C-2), 162.0 (C-4), 165.2, 166.0, 166.9 (C=O).

9-(3,6-Di-*O*-benzoyl-2,4-dideoxy-D-*erythro*-hexopyranosyl)-*N*²-acetyl-*O*⁶-(diphenylcarbamoyl)guanine [β (20a) and α (20b) Anomers]. A mixture of 2.15 g (5.54 mmol) of N^2-acetyl-O^6-(diphenylcarbamoyl)guanine[15] and 4.16 mL (16.63 mmol) of BSA in acetonitrile (50 mL) was refluxed for 20 min, evaporated, and dissolved in toluene (30 mL). This resulting clear solution was added to a solution of **16a** (1.84 g, 4.62 mmol) in toluene (30 mL) and stirred for 17 h at room temperature in the presence of 1.26 mL (6.47 mmol) of $CF_3SO_3SiMe_3$. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and poured into a sodium bicarbonate solution (7%, 200 mL). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was dried, evaporated, and purified by column chromatography [(1) CH_2Cl_2, (2) CH_2Cl_2–CH_3CN (9:1), (3) CH_2Cl_2–CH_3CN (85:15)] affording 1.14 g (1.57 mmol, 34%) of the β anomer **20a** and 0.25 g (0.34 mmol, 7%) of the α anomer **20b**.

20a: UV (MeOH) λ_{max} = 227 nm (log ε = 4.72), λ_{max} = 280 nm (log ε = 4.15); LSIMS (*m*-nitrobenzyl alcohol) 727 (MH^+); ^{1}H NMR ($CDCl_3$) δ 1.75–2.55 (m, 4 H, H-2′, H-4′), 2.45 (s, 3 H, CH_3), 4.35–4.70 (m, 3 H, H-5′, H-6′), 5.70 (t, 1 H, J = 2.6 Hz, H-3′), 6.19

(dd, 1 H, J = 4.4 and 9.2 Hz, H-1'), 7.15–7.70 (m, 16 H, aromatic H), 7.90–8.20 (m, 5 H, H-8, aromatic H); ^{13}C NMR ($CDCl_3$) δ 24.8 (CH_3), 31.0, 35.2 (C-2', C-4'), 66.0, 67.1 (C-3', C-6'), 72.1 (C-5'), 78.7 (C-1') + aromatic signals.

20b: UV (MeOH) λ_{max} = 229 nm (log ε = 4.73), λ_{max} = 284 nm (log ε = 4.19); LSIMS (*m*-nitrobenzyl alcohol) 727 (MH^+); ^{1}H NMR ($CDCl_3$) δ 1.95–2.60 (m, 4 H, H-2', H-4'), 2.39 (s, 3 H, CH_3), 4.25–4.80 (m, 3 H, H-5', H-6'), 5.60 (t, 1 H, J = 3.0 Hz, H-3'), 6.13 (t, 1 H, J = 3.1 Hz, H-1'), 7.00–7.80 (m, 16 H, aromatic H), 7.90–8.15 (m, 4 H, aromatic H), 8.30 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$) δ 24.8 (CH_3), 29.8, 30.6 (C-2', C-4'), 64.6, 65.7, 66.4 (C-3', C-5', C-6'), 80.3 (C-1') + aromatic signals.

9-(3,6-Di-*O*-benzoyl-2,4-dideoxy-β-D-*erythro*-hexopyranosyl)-N^6-benzoyladenine (21a). A mixture of 1.65 g (4.15 mmol) of **16a**, 1.19 g (4.98 mmol) of N^6-benzoyladenine, and 3.7 mL (14.9 mmol) of BSA in acetonitrile (50 mL) was kept for 15 min at 50 °C. Then 1.21 mL (6.22 mmol) of $CF_3SO_3SiMe_3$ was added to the clear solution and the resulting mixture was kept for 54 h at 50 °C and for 64 h at room temperature. After dilution with CH_2Cl_2 (200 mL) the mixture was poured into a sodium bicarbonate solution (7%, 200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was dried, evaporated, and purified by column chromatography [(1) hexane–EtOAc (2:3), (2) hexane–EtOAc (3:7)], affording 0.71 g (1.23 mmol, 30%) of the title compound (**21a**): UV (MeOH) λ_{max} = 280 nm (log ε = 4.28); CIMS (2-methylpropane) 578 (MH^+); HRMS calcd for $C_{32}H_{27}N_5O_6$ (M) 577.1961, found 577.1958; ^{1}H NMR ($CDCl_3$) δ 1.90–2.70 (m, 4 H, H-2', H-4'), 4.35–4.75 (m, 3 H, H-5', H-6'), 5.77 (t, 1 H, J = 2.6 Hz, H-3'), 6.35 (t, 1 H, J = 6.6 Hz, H-1'), 7.20–7.70 (m, 9 H, aromatic H), 7.90–8.20 (m, 6 H, aromatic H), 8.23 and 8.77 (2 × s, 2 × 1 H, H-2, H-8), 9.13 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 30.9, 34.7 (C-2', C-4'), 65.9, 67.1 (C-3', C-6'), 71.7 (C-5'), 78.2 (C-1'), 123.0 (C-5), 127.7, 128.1, 128.4, 129.4, 132.3, 132.9, 133.2 (aromatic), 140.5 (C-8), 149.4, 151.2, 152.3 (C-2, C-4, C-6), 164.5, 165.0, 165.9 (C=O).

1-(2,4-Dideoxy-α-D-*erythro*-hexopyranosyl)thymine (22b). **18b** (0.16 g, 0.34 mmol) was deprotected with ammonia in methanol and purified in the same way as for **12** yielding 86 mg (0.34 mmol, 100%) of the title compound (**22b**). An analytical sample was obtained after crystallization from ethanol–ether: mp 179–182 °C dec; UV (MeOH) λ_{max} = 266 nm (log ε = 4.00); (0.01 N NaOH) λ_{max} = 265 nm (log ε = 3.72); CIMS (NH_3) 257 (MH^+), 274 (MNH_4^+); ^{1}H NMR (DMSO-d_6) δ 1.15–2.05 (m, 4 H, H-2', H-4'), 1.79 (s, 3 H, CH_3), 3.40–3.65 (m, 2 H, H-6'), 3.80–4.20 (m, 2 H, H-3', H-5'), 4.70 (t, 1 H, 6'OH), 4.95 (brs, 1 H, 3'OH), 5.78 (dd, 1 H, J = 2.6 and 10.1 Hz, H-1'), 7.64 (s, 1 H, H-6), 11.25 (brs, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 12.4 (CH_3), 34.3, 39.0 (C-2', C-4'), 61.8, 62.4, (C-3', C-6'), 74.2 (C-5'), 76.3 (C-1'), 109.8 (C-5), 137.0 (C-6), 150.7 (C-2), 164.3 (C-4). Anal. Calcd for $C_{11}H_{16}N_2O_5 \cdot {}^1/_{20}H_2O$: C, 51.38; H, 6.31; N, 10.89. Found: C, 51.00; H, 6.25; N, 10.63.

1-(2,4-Dideoxy-β-D-*erythro*-hexopyranosyl)cytosine Hydrochloride (23a). A solution of 1.24 g (2.24 mmol) of **19a** in methanolic ammonia was kept for 4 days at room temperature. After evaporation and purification by column chromatography [(1) CH_2Cl_2–MeOH (9:1), (2) CH_2Cl_2–MeOH (4:1)] we obtained 0.51 g (2.12 mmol, 94%) of the title compound (**23a**). The compound was converted to its HCl salt and crystallized from methanol–ether: mp 171–174 °C dec; UV (MeOH) λ_{max} = 282 nm (log ε = 4.08), λ_{max} = 213 nm (log ε = 3.96); CIMS (NH_3) 242 (MH^+); ^{1}H NMR (DMSO-d_6, before conversion to the HCl salt) δ 1.10–1.80 (m, 4 H, H-2', H-4'), 3.39 (d, 2 H, J = 4.5 Hz, H-6'), 3.70–4.10 (m, 1 H, H-5'), 4.19 (br s, 1 H, H-3'), 4.40–5.10 (m, 2 H, 3'OH, 6'OH), 5.74 (d, 1 H, J = 7.4 Hz, H-5), 6.01 (t, 1 H, J = 6.6 Hz, H-1'), 7.16 (br s, 2 H, NH_2), 7.60 (d, 1 H, J = 7.4 Hz, H-6); ^{13}C NMR (DMSO-d_6, before conversion to the HCl salt) δ 33.8, 37.3 (C-2', C-4'), 63.3 (C-3'), 64.6 (C-6'), 74.0 (C-5'), 78.2 (C-1'), 94.6 (C-5), 142.1 (C-6), 155.3 (C-2), 165.7 (C-4). Anal. Calcd for $C_{10}H_{15}N_3O_4 \cdot HCl$: C, 43.25; H, 5.81; N, 15.13. Found: C, 43.11; H, 5.77; N, 14.97.

1-(2,4-Dideoxy-α-D-*erythro*-hexopyranosyl)cytosine (23b). **19b** (0.18 g, 0.33 mmol) was deprotected with methanolic ammonia and purified as for **23a** yielding 70 mg (0.29 mmol, 88%) of the title compound (**23b**) as a foam: UV (pH 2) λ_{max} = 282 nm (log ε = 4.05); CIMS (2-methylpropane) 242 (MH^+); ^{1}H NMR (DMSO-d_6) δ 1.10–2.20 (m, 4 H, H-2' H-4'), 3.45–3.65 (m, 2 H, H-6'), 3.85–4.20 (m, 2 H, H-3', H-5'), 4.73 (t, 1 H, 6'OH), 4.96 (d, 1 H, 3'OH), 5.71 (d, 1 H, J = 7.5 Hz, H-5), 5.78 (dd, 1 H, J = 1.8 and 8.8 Hz, H-1'), 7.14 (br s, 2 H, NH_2), 7.66 (d, 1 H, J = 7.5 Hz, H-6); ^{13}C NMR (DMSO-d_6) δ 34.2, 37.7 (C-2', C-4'), 61.1, 62.2 (C-3', C-6'), 73.8 (C-5'), 76.2 (C-1'), 94.0 (C-5), 141.2 (C-6), 154.8 (C-2), 165.6 (C-4).

9-(2,4-Dideoxy-β-D-*erythro*-hexopyranosyl)guanine (24a). A mixture of 1.14 g (1.57 mmol) of **20a** in methanolic ammonia was kept for 4 days at room temperature, followed by evaporation. The residue was dissolved in H_2O (100 mL) and washed with ether (5 × 50 mL). Concentration of the aqueous layer afforded 0.43 g (1.53 mmol, 97%) of the title compound (**24a**). An analytical sample was obtained after recrystallization from H_2O: mp slowly decomposes at 250 °C; UV (MeOH) λ_{max} = 255 nm (log ε = 4.09), 271 nm (sh, log ε = 3.94); CIMS (2-methylpropane) 282 (MH^+); HRMS calcd for $C_5H_5N_5O$ (BH) 151.0494, found 151.0489, calcd for $C_6H_9O_2$ (S – H_2O) 113.0602, found 113.0593; ^{1}H NMR (DMSO-d_6) δ 1.40–1.95 (m, 4 H, H-2', H-4'), 3.37 (d, 2 H, J = 4.9 Hz, H-6'), 3.85–4.10 (m, 1 H, H-5'), 4.26 (br s, 1 H, H-3'), 4.69 (t, 1 H, 6'OH), 4.99 (d, 1 H, 3'OH), 5.86 (dd, 1 H, J = 2.2 and 11.4 Hz, H-1'), 6.60 (br s, 2 H, NH_2), 7.89 (s, 1 H, H-8), 10.65 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 33.8, 37.3 (C-2', C-4'), 63.0 (C-3'), 64.4 (C-6'), 74.0 (C-5'), 76.3 (C-1'), 116.4 (C-5), 135.8 (C-8), 151.1 (C-4), 153.9 (C-2), 157.2 (C-6). Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot 1H_2O$: C, 44.15; H, 5.73; N, 23.40. Found: C, 44.23; H, 5.51; N, 23.17.

9-(2,4-Dideoxy-α-D-*erythro*-hexopyranosyl)guanine (24b). **20b** (216 mg, 0.30 mmol) was deprotected and purified as for **24a** affording 60 mg (0.21 mmol, 70%) of almost pure title compound (**24b**). The pure compound was obtained after crystallization from methanol–water: mp slowly decomposes at 250 °C; UV (MeOH) λ_{max} = 255 nm (log ε = 4.14), 271 nm (sh, log ε = 3.99); LSIMS (glycerol) 282 (MH^+); ^{1}H NMR (DMSO-d_6) δ 1.60–2.35 (m, 4 H, H-2', H-4'), 3.45–3.60 (m, 2 H, H-6'), 3.80–4.25 (m, 2 H, H-3', H-5'), 4.70 (br s, 1 H, 6'OH), 5.15 (br s, 1 H, 3'OH), 5.85 (m, 1 H, H-1'), 6.47 (br s, 2 H, NH_2), 8.11 (s, 1 H, H-8), 10.40 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 34.2, 37.3 (C-2', C-4'), 61.4, 62.6 (C-3', C-6'), 71.2 (C-5'), 75.8 (C-1'), 116.5 (C-5), 136.6 (C-8), 151.1 (C-4), 153.5 (C-2), 157.0 (C-6). Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot 1.3H_2O$: C, 43.36; H, 5.82; N, 22.98. Found: C, 43.70; H, 5.73; N, 22.67.

9-(2,4-Dideoxy-β-D-*erythro*-hexopyranosyl)adenine (25a). A solution of 0.71 g (1.23 mmol) of **21a** in methanolic ammonia was kept for 2 days at room temperature. After evaporation and purification by column chromatography [(1) CH_2Cl_2–MeOH (90:10), (2) CH_2Cl_2–MeOH (80:20)], 0.28 g (1.06 mmol, 86%) of the title compound (**25a**) was obtained. An analytical sample was obtained after crystallization from ethanol–acetonitrile: mp 208–210 °C dec; UV (MeOH) λ_{max} = 260 nm (log ε = 4.17); CIMS (2-methylpropane) 266 (MH^+); ^{1}H NMR (DMSO-d_6) δ 1.45–2.11 (m, 4 H, H-2', H-4'), 3.40 (d, 2 H, J = 4.5 Hz, H-6'), 3.90–4.20 (m, 1 H, H-5'), 4.30 (br s, 1 H, H-3'), 4.55–5.20 (m, 2 H, 3'OH, 6'OH), 6.07 (dd, 1 H, J = 1.8 and 11.5 Hz, H-1'), 7.25 (br s, 2 H, NH_2), 8.15 (s, 1 H, H-8), 8.35 (s, 1 H, H-2); ^{13}C NMR (DMSO-d_6) δ 33.8, 37.0 (C-2', C-4'), 62.8 (C-3'), 64.3 (C-6'), 73.7 (C-5'), 76.8 (C-1'), 118.7 (C-5), 139.2 (C-8), 149.2 (C-4), 152.7 (C-2), 156.1 (C-6). Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot {}^1/_{20}H_2O$: C, 49.64; H, 5.72; N, 26.31. Found: C, 49.39; H, 5.73; N, 25.94.

Acknowledgment. A.V.A. is a research associate of the Belgian National Fund of Scientific Research. This work has been supported by grants from the Belgian FGWO (Fonds voor Geneeskundig Wetenschappelijk Onderzoek, project 3.0076.92). We thank Nathalie Pillet for technical assistance and Dominique Brabants and Mieke Vandekinderen for editorial help.

Supplementary Material Available: ^{13}C NMR spectra for compounds **6–10**, **12**, **15–21a**, **23b**, and **24a** and HRMS spectra for compounds **6**, **7**, **12**, **15–19**, **21a**, and **24a** (70 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.