Synthesis of 5′-*O*-(2-Azido-2-deoxy-α-D-glycosyl)nucleosides and Their Antitumor Activities

by **Gui-Sheng Zhang**, **Jie Chen**, **Ji-Mei Min**, and **Li-He Zhang***

National Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100083, P.R. China

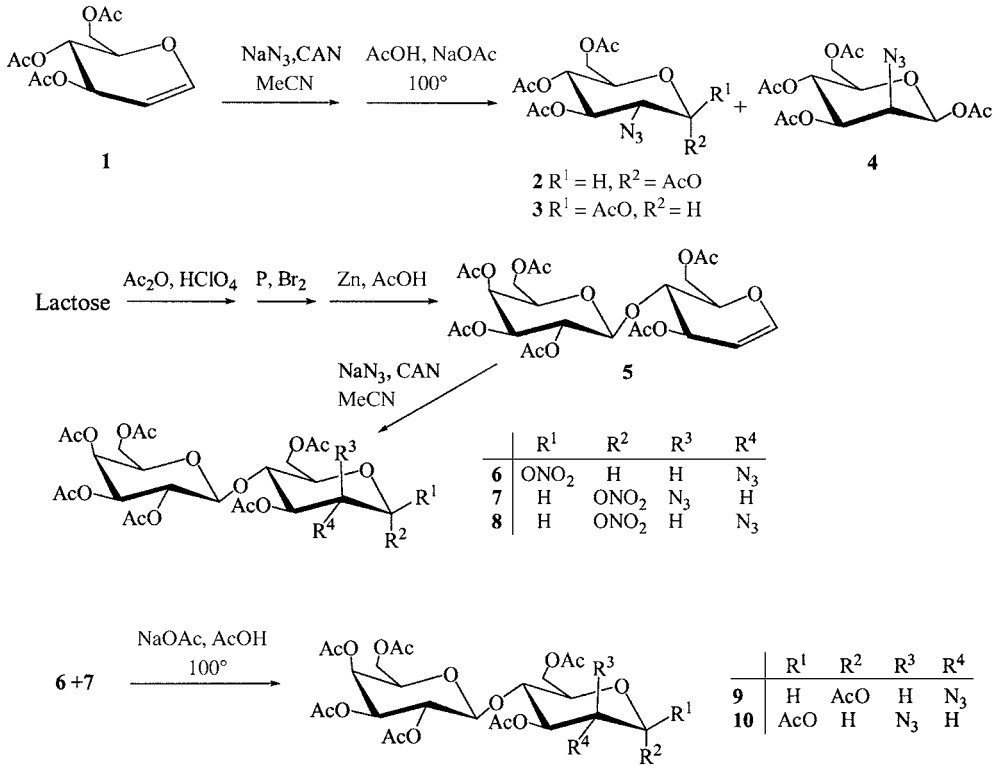
The 1,3,4,6-tetra-*O*-acetyl-2-azido-2-deoxy-β-D-mannopyranose (**4**) or the mixture of 1,3,6-tri-*O*-acetyl-2-azido-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-mannopyranose (**10**) and the corresponding α-D-glucopyranose-type glycosyl donor **9**/**10** reacted at room temperature with protected nucleosides **12**–**15** in CH_2Cl_2 solution in the presence of $BF_3 \cdot OEt_2$ as promoter to give 5′-*O*-(2-azido-2-deoxy-α-D-glycosyl)nucleosides in reasonable yields (*Schemes 2* and *3*). Only the 5′-*O*-(α-D-mannopyranosyl)nucleosides were obtained. Compounds **21**, **28**, **30**, and **31** showed growth inhibition of HeLa cells and hepatoma Bel-7402 cells at a concentration of 10 μM *in vitro*.

1. Introduction. – Nucleoside analogues play an important role in antiviral and anticancer chemotherapy. Among numerous nucleoside analogs, the nucleosides connected to oligosaccharides have received much attention owing to their profound biological activities. There are many carbohydrate receptors on the cell surface; *e.g.*, the asialoglycoprotein receptor exists on the surface of hepatocytes and can bind to terminal galactose residues [1]. Some activities of glycoproteins related to the attachment, migration, proliferation of cancer cells, and the repeating units of polysaccharides have been investigated for the prevention of tumor metastasis [2]. It has been found that many natural antibiotics possessing significant antitumor and antiviral activities contain *O*-glycosylated nucleoside substructures [3–5]. It would be interesting to study whether the glycosyl residue could be used as a targeting moiety towards glycosyl-binding proteins. In this way, some glycosylated antitumor or antiviral nucleoside analogues might be expected to have a higher therapeutic index together with lesser side effects and toxicity. We have reported the syntheses of galactosyl phosphate diester derivatives of nucleoside [6], lactosyl phosphate diester derivatives of nucleoside [7], and 5′-*O*-glycosylnucleosides [8]. It was found that the galactosyl phosphate diesters of arabinosylcytosine were active in the human cytomegalovirus (HCMV) assay. The IC_{50} of some compounds for anti-HCMV activity were 0.1–0.2 μM [6]. Amino and azido groups are potential active groups in many nucleoside analogues possessing bioactivities, such as AZT, ezomycin A_1, and liposidomycin C, *etc*. [9]. We report here the investigation of the synthesis and antitumor activity of nucleoside analogues containing azido-oligosaccharides.

2. Results and Discussion. – Glycal is a very versatile synthetic intermediate and has proven to be useful in the synthesis of glycoconjugates. The common method for the synthesis of 2-azido-2-deoxy-sugars consists of the introduction of an azido group at

C(2) of a per-*O*-acetylglycal [10–14] by addition of sodium azide in the presence of cerium(IV) ammonium nitrate (CAN); subsequently, the C(1)-nitro group can be substituted by an acetoxy group *via* the reaction with AcOH and NaOAc at 100°. This is illustrated by the conversion of **1** to **2**–**4** (see *Scheme 1* and below). However, the azido-nitration usually yields a product mixture that is difficult to separate. Thus, 3,4-di-*O*-acetyl-2,6-anhydro-5-deoxy-D-*lyxo*-hexo-5-enonate gave an inseparable mixture of azido nitrates on treatment with CAN and sodium azide in MeCN at −15° under N_2 [14]; after treatment with NaOAc in glacial AcOH, the NMR spectrum of the corresponding azido acetate mixture indicated the presence of α-D-glucose, β-D-glucose, and α-D-mannose-type anomers in the ratio 5:2:1. In the case of hexa-*O*-acetyl-D-lactal (**5**), the three possible products **6**–**8** were obtained, namely of the D-glucose and D-mannose type, respectively, depending on the different orientation of the azido group at C(2) (*Scheme 1*). *Arnap* and *Lönngren* [12] reported that compounds **6** and **7** were obtained in the ratio 8:1. The D-mannose-type product **7** was the minor component in the mixture of these isomers.

Scheme 1



We performed the azido-nitration/acetolysis sequence with tri-*O*-acetyl-D-glucal **1** and obtained the azido acetates **2**/**3** and **4** (*Scheme 1*). However, when the glycosyl donors **2**/**3** (D-glucose type) or **4** (D-mannose type) were treated with glycosyl receptor

12 (see below), only the reaction of the D-mannose-type glycosyl donor **4** proceeded in good yield. Thus, the azido-nitration conditions were optimized to increase the formation of D-mannose-type isomer **4** from **1**. The ratio of the isomeric azido nitrate precursors of **2**–**4** varied with temperature, and the D-mannose-type precursor of **4** was the major product at room temperature. Therefore, **1** was treated with CAN and sodium azide at room temperature under Ar, and the crude azido nitrates were then treated with anhydrous NaOAc in AcOH at 100° to give a mixture **2**/**3**/**4** in a ratio of *ca.* 1.75 : 1.00 : 2.12 (by ^{1}H-NMR). After chromatography (silica gel), **4** and **2**/**3** were obtained in 26.6 and 27% yields, respectively. Similarly, **5** prepared from lactose [15] was submitted to the same azido-nitration/acetolysis procedure; the mixture **6**/**7** could be separated from **8** by chromatography after the reaction. Then, the mixture **6**/**7** was treated with NaOAc in AcOH at 100° to give **9**/**10** (*ca.* 1 : 1.1 by ^{1}H-NMR) in 18.4% yield from lactose (*Scheme 1*). The mixture **9**/**10** could not be separated by chromatography.

The protected nucleosides **12**–**15** [16][17] were glycosylated with donor **4** or **9**/**10** in CH_2Cl_2 solution at room temperature in the presence of $BF_3 \cdot Et_2O$ (*Schemes 2* and *3*). No reaction occurred when the mixture **2**/**3** was treated with **12**–**15** by this same procedure. With donor **4**, glycosylnucleosides **16**–**19** were obtained from **12**–**15** in 86.5, 65.0, 51.0, and 79.7% yield, respectively (*Scheme 2*). Of the mixture **9**/**10**, only the D-mannose-type glycosyl donor **10** reacted with **12**–**15** to give the corresponding glycosyl nucleosides **24**–**27** in 46.7, 42.6, 83.0, and 65.2% yield, respectively (*Scheme 3*); the unreacted **9** could be recovered from the reaction mixture. No reaction occurred when the recovered **9** was resubmitted to the same procedure. The NMR data of compounds **16**–**19** and **24**–**27** confirmed the α-D-configuration (see *Table 1*) [13][18] of the glycosyl bonds formed in above reaction. It is suggested that the formation of **16**–**19** and **24**–**27** occurs *via* an S_N1 mechanism through an oxacarbenium cation as the reaction intermediate, and the α-D-selectivity of the mannosylation is the result of a steric effect of the axial substituent at C(2), and the steric hindrance leads to the failure of the reactions of glycosyl donors **2**/**3** or **9** with the nucleosides.

Table 1. *^{1}H-NMR Coupling Constants* $J(1'',2'')$ *and ^{13}C-NMR Chemical Shifts of Glycosylnucleosides* **16**–**19** *and* **24**–**27** *in* $CDCl_3$

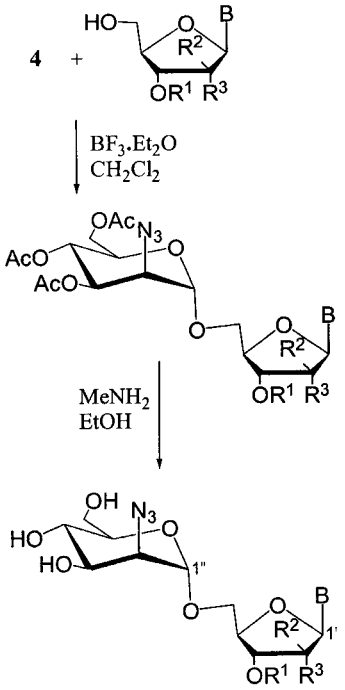
	16	**17**	**18**	**19**	**24**	**25**	**26**	**27**
$J(1'',2'')$ [Hz]	1.5	*s*	*s*	1.5	2.0	1.5	1.75	2.0
δ(C(1'')) [ppm]	98.21	98.14	98.12	98.16	98.19	98.18	97.97	97.96

The protected glycosylation products **16**–**19** and **24**–**27** were treated with 25–30% $MeNH_2$ in abs. EtOH at room temperature to give the target compounds **20**–**23** (*Scheme 2*) and **28**–**31** (*Scheme 3*), respectively.

The results indicate that the reactivity of the D-mannose-type glycosyl donors **4** and **10** lead to a convenient and efficient approach to the synthesis of azido-oligoglycosyl-nucleosides with the advantages of mild conditions, easy workup, high selectivity, and reasonable yields.

Compounds **20**–**23** and **28**–**31** were evaluated for their antitumor activities by cell-culture bioassay. Compounds **21**, **28**, and **30** showed inhibition of the growth of Hela

Scheme 2



12 R^1 = Ac, R^2 = H, R^3 = AcO, B = uracil-1-yl
13 R^1 = Ac, R^2 = H, R^3 = AcO, B = N^4-acetylcytosin-1-yl
14 R^1 = Ac, R^2 = R^3 = H, B = thymin-1-yl
15 R^1 = Bz, R^2 = BzO, R^3 = H, B = N^4-benzoylcytosin-1-yl

16 R^1 = Ac, R^2 = H, R^3 = AcO, B = uracil-1-yl
17 R^1 = Ac, R^2 = H, R^3 = AcO, B = N^4-acetylcytosin-1-yl
18 R^1 = Ac, R^2 = R^3 = H, B = thymin-1-yl
19 R^1 = Bz, R^2 = BzO, R^3 = H, B = N^4-benzoylcytosin-1-yl

20 R^1 = H, R^2 = H, R^3 = OH, B = uracil-1-yl
21 R^1 = H, R^2 = H, R^3 = OH, B = cytosin-1-yl
22 R^1 = H, R^2 = R^3 = H, B = thymin-1-yl
23 R^1 = H, R^2 = OH, R^3 = H, B = cytosin-1-yl

cells by 31.92, 42.41, and 37.86%, respectively, at a concentration of 10 μM, and compound **31** indicated a 46.05% growth inhibition of hepatoma Bel-7402 cells at a concentration of 10 μM (*Table 2*).

Table 2. *Percentage of Growth Inhibition of HeLa Cells and Hepatoma Bel-7402 Cells by Glycosylnucleosides* **20**–**23** *and* **28**–**31** *at a Concentration of 10* μM[a])

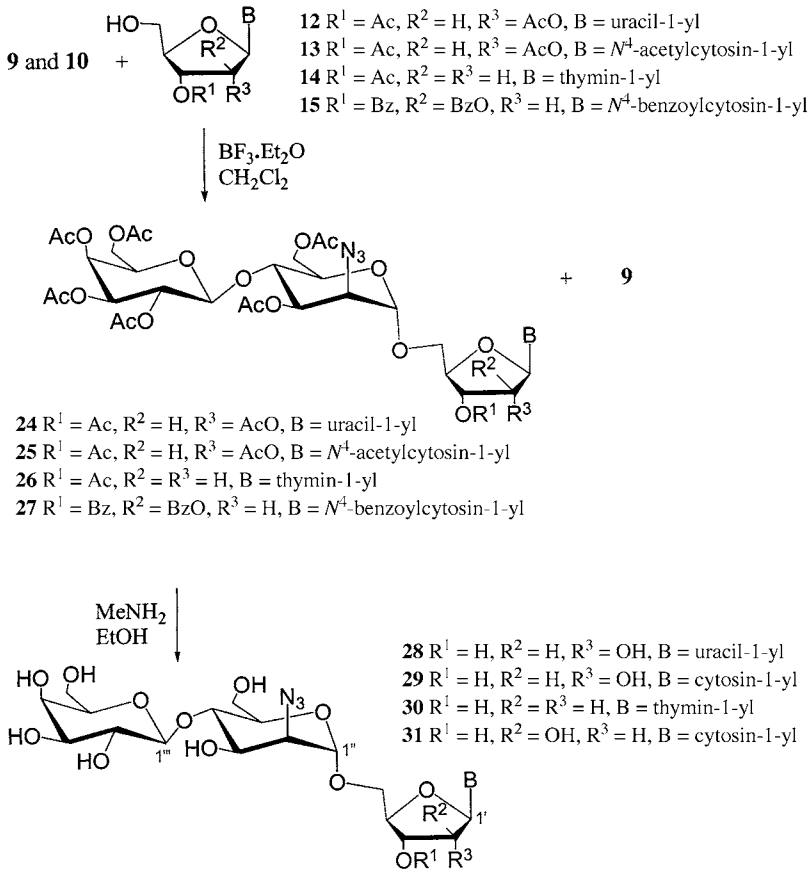
	20	**21**	**22**	**23**	**28**	**29**	**30**	**31**
HeLa	4.03	31.92	6.86	0.10	42.41	16.26	37.86	16.28
Bel-7402	7.48	4.96	6.19	6.71	13.76	4.33	20.07	46.05

[a]) HeLa and Bel-7402 cells were seeded in 96-well culture plates at a concentration of 5000/well. After overnight culture, the compounds were dissolved in sterilized phosphate-buffered saline and added to the well. After 5 h incubation at 37°, the inhibition of the cell growth was measured by the MTT method [19].

Experimental Part

1. *General.* CC = Column chromotography. TLC: silica gel *GF-254* (*Qing Dao Chemical Company*, China) plates with detection by UV, or charting with 5% phosphomolybdic acid hydrate in EtOH. Optical rotations: *Perkin-Elmer 243B* polarimeter. IR Spectra: *DE-983G* spectrophotometer; KBr pellets; in cm^{-1}. NMR Spectra: *Varian VXR-300* or *Varian INOVA-500*; δ in ppm rel. to $SiMe_4$ as an internal standard *J* in Hz. MS: *PE SCLEX-QSTAR* and *Autospec UltimaETOF* spectrometers; in *m/z*.

Scheme 3



2. *1,3,4,6-Tetra*-O-*acetyl-2-azido-2-deoxy-β*-D-*mannopyranose* (**4**). A soln. of **1** (2.11 g, 7.7 mmol) in dry MeCN (100 ml) was added to a mixture of CAN (12.65 g, 28.1 mmol) and NaN_3 (0.75 g, 11.5 mol) in MeCN (30 ml), which was cooled in an ice-salt bath, with vigorous stirring under Ar. Then, the mixture was kept for 24 h at r.t. Et_2O (100 ml) and ice-cold H_2O (50 ml) were added, and the org. phase was washed with H_2O (3 × 50 ml) and evaporated to give a syrup (2.2 g).

A soln. of the above syrup (2.1 g) in AcOH (15 ml) containing anh. NaOAc (1.0 g) was heated at 100° for 2 h and then cooled. The mixture was extracted with CH_2Cl_2 (100 ml), the extract washed with H_2O, aq. $NaHCO_3$ soln., and H_2O, dried ($MgSO_4$), and evaporated: syrup (1.87 g) containing **2**, **3**, and **4** (*ca.* 1.75 : 1.00 : 2.12 by ^{1}H-NMR ($CDCl_3$): 6.21 (*d*, *J*(1,2) = 3.54, H–C(1) of **2**); 5.80 (*d*, *J*(1,2) = 8.55, H–C(1) of **3**); 5.96 (*d*, *J*(1,2) = 1.43, H–C(4) of **4**). The syrup was purified by CC (silica gel, petroleum ether (60–90°)/AcOEt 4 : 1): **2**/**3** (753 mg, 27% from **1**) and **4** (743 mg, 26.6% from **1**). **2**/**3**: ^{1}H-NMR ($CDCl_3$): 6.30 (*d*, *J*(1,2) = 3.55, H–C(1) of **2**); 5.56 (*d*, *J*(1,2) = 8.55, H–C(1) of **3**). **4**: ^{1}H-NMR ($CDCl_3$): 6.12 (*d*, *J*(1,2) = 1.3, H–C(1)).

3. *1,3,6-Tri*-O-*acetyl-2-azido-2-deoxy-4*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl)-α*-D-*glucopyranose* (**9**) *and 1,3,6-Tri*-O-*acetyl-2-azido-2-deoxy-4*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl)-β*-D-*mannopyranose* (**10**). Lactose (5.86 g, 32.52 mmol) was treated according to a published method [15] to give a syrup **5** (13.3 g). The crude **5** in MeCN (50 ml) was added to a mixture of CAN (31.85 g, 70.7 mmol) and NaN_3 (2.25 g, 34.5 mmol) in MeCN (30 ml), which was cooled in an ice-salt bath, with vigorously stirring under Ar. Then, the mixture was kept for 24 h at r.t. Et_2O (250 ml) and ice-cold H_2O (50 ml) were added, and the org. phase was

washed with H_2O (3 × 50 ml) and evaporated. The residue was purified by CC (silica gel, petroleum ether (60–90°)/AcOEt 3:2): **8** and **6/7**.

The mixture **6/7** obtained above in AcOH (60 ml) containing anh. NaOAc (4.0 g) was heated at 100° for 2 h and then cooled. The mixture was extracted with CH_2Cl_2 (300 ml), the extract washed with H_2O, aq. $NaHCO_3$ soln., and H_2O, dried ($MgSO_4$), and evaporated, and the syrup obtained was purified by CC (silica gel, petroleum ether (60–90°)/AcOEt 4:1): **9/10** (3.7 g, 18.4% from lactose) (*ca.* 1.0:1.1 by ^{1}H-NMR ($CDCl_3$): 6.14 (*d*, *J*(1,2) = 3.9, H–C(1) of **9**); 5.86 (br., H–C(1) of **10**).

4. *Glycosylations of Nucleosides* **12**–**15**: *General Procedure*. A soln. of one of the glycosyl receptors **12**–**15** (50 mg) and 2 equiv. of glycosyl donor **4** or 3 equiv. of **9/10** in a soln. of dry CH_2Cl_2 (5 ml) and $BF_3 \cdot OEt_2$ (0.2 ml) was stirred at r.t. until the disappearance of the glycosyl receptor (TLC monitoring). After cooling in an ice bath and neutralization with sat. $NaHCO_3$ soln., the mixture was extracted with CH_2Cl_2, the org. layer was dried (Na_2SO_4) and evaporated, and the residue purified by CC (silica gel): **16**–**19** or **24**–**27**, resp.

*5′-*O*-(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-mannopyranosyl)uridine 2′,3′-Diacetate* (**16**). Yield 86.5%. White solid. $[\alpha]_D^{18} = -42$ ($c = 0.024$, H_2O). ^{1}H-NMR ($CDCl_3$): 8.67 (*s*, NH); 7.42 (*d*, *J*(5,6) = 8.0, H–C(6)); 6.06 (*d*, *J*(1′,2′) = 5.5, H–C(1′)); 5.97 (*d*, H–C(5)); 4.92 (*d*, *J*(1″,2″) = 1.5, H–C(1″)); 5.45–5.27 (*m*, H–C(3″), H–C(3′), H–C(2′), H–C(4″)); 4.26 (*m*, H_a–C(6″), H–C(4′)); 4.16 (*m*, H–C(2″)); 4.11 (*m*, H_b–C(6″)); 4.01–3.96 (*m*, H–C(5″), H_a–C(5′)); 3.81 (*m*, H_b–C(5′)); 2.12–2.08 (5*s*, 5 AcO). ^{13}C-NMR ($CDCl_3$): 170.64–162.50 (C=O); 150.08 (C(6)); 139.71 (C(4)); 103.92 (C(5)); 98.21 (C(1″)); 87.59 (C(1′)); 80.69 (C(4′)); 72.67 (C(3′)); 71.22 (C(3″)); 69.95 (C(2′)); 69.40 (C(5″)); 66.69 (C(5″)); 65.09 (C(4″)); 62.01 (C(6″)); 60.92 (C(2″)); 20.73 (*Me*CO). ESI-TOF-MS: 664.0792 ([*M* + Na]$^+$).

*N^4-Acetyl-5′-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-mannopyranosyl)cytidine 2′,3′-Diacetate* (**17**): Yield 65%. Colorless. $[\alpha]_D^{18} = +4.4$ ($c = 0.031$, $CHCl_3$). IR: 2111.15 (N_3). ^{1}H-NMR ($CDCl_3$): 10.01 (br., AcN*H*); 7.90 (*d*, *J*(5,6) = 6.5, H–C(6)); 7.56 (*d*, H–C(5)); 6.12 (*d*, *J*(1′,2′) = 1.5, H–C(1′)); 5.38 (*m*, H–C(2′), H–C(3′)); 5.35 (*dd*, *J*(3″,4″) = 10.0, *J*(4″,5″) = 12.0, H–C(4″)); 5.27 (*dd*, *J*(2″,3″) = 8.5, H–C(3″)); 4.91 (*s*, H–C(1″)); 4.31 (br., H–C(4′)); 4.23 (*m*, 1 H, H_a–C(6″)); 4.15 (*m*, H–C(2″)); 4.05 (*m*, H_b–C(6′)); 3.96 (*m*, H_a–C(5′), H–C(5″)); 3.84 (*m*, H_b–C(5′)); 2.27–2.04 (6*s*, 18 H, 5 AcO, 1 *Ac*NH). ^{13}C-NMR ($CDCl_3$): 170.64–163.16 (6 C=O); 144.26 (C(6)); 98.14 (C(1″)); 97.74 (C(5)); 89.03 (C(1′)); 80.53 (C(4′)); 73.62 (C(3′)); 71.00 (C(3″)); 69.64 (C(2′)); 69.18 (C(5″)); 66.52 (C(5′)); 65.23 (C(4″)); 61.96 (C(6″)); 60.91 (C(2″)); 24.87 (*Me*CONH); 20.66–20.39 (5 *Me*CO). ESI-TOF-MS: 681.3033 ([*M* − 1]$^+$).

*5′-*O*-(3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-mannopyranosyl)thymidine 3′-Acetate* (**18**): Yield 51.0%. White solid. $[\alpha]_D^{18} = -52.9$ ($c = 0.021$, H_2O). ^{1}H-NMR ($CDCl_3$): 9.04 (*s*, NH); 7.23 (*s*, H–C(6)); 6.31 (*m*, H–C(1′)); 5.59–5.25 (*m*, H–C(4″)); H–C(3′), H–C(3″)); 4.94 (*s*, H–C(1″)); 4.27–4.22 (*m*, H_a–C(6″)); 4.17–4.15 (*m*, H_b–C(6″), H_a–C(5′)); 4.07–4.04 (*m*, H–C(2″), H–C(4′)); 3.92 (*m*, H–C(5″)); 3.74 (*m*, H_b–C(5′)); 2.25 (*m*, 2 H–C(2′)); 2.12–1.93 (5*s*, 4 AcO, Me). ^{13}C-NMR ($CDCl_3$): 170.73–163.43 (4 C=O), 150.32 (C(4)); 134.65 (C(6)); 111.61 (C(5)); 98.12 (C(1″)); 86.68 (C(1′)); 84.7 (C(4′)); 82.89 (C(3′)); 74.27 (C(3″)); 69.44 (C(5″)); 67.78 (C(5′)); 65.20 (C(4″)); 62.08 (C(6″)); 61.17 (C(2″)); 37.08 (C(2′)); 20.89 (4 *Me*CO); 12.56 (Me). ESI-TOF-MS: 598.2132 ([*M* + 1]$^+$), 620.1924 ([*M* + Na]$^+$).

*N^4-Benzoyl-1-[2,3-di-*O*-benzoyl-5-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-*D*-mannopyranosyl)-β-*D*-arabinofuranosyl]cytosine* (**19**): Yield 79.7%. White solid. $[\alpha]_D^{18} = +18.5$ ($c = 0.024$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 8.75 (br., PhN*H*); 8.18–7.38 (*m*, 15 arom. H); 8.08 (*d*, *J*(5,6) = 8.0, H–C(6)); 7.84 (*dd*, H–C(5)); 6.61 (*d*, *J*(1′,2′) = 4.5, H–C(1′)); 6.05 (*dd*, *J*(2′,3′) = 2.0, H–C(2′)); 5.59 (br., H–C(3′)); 5.35 (*m*, H–C(4′), H–C(3″)); 4.99 (*d*, *J*(1″,2″) = 1.5, H–C(1″)); 4.38 (*dd*, *J*(3″,4″) = 8.5, *J*(4″,5″) = 5.0, H–C(4″)); 4.28 (*m*, H_a–C(6″)); 4.18 (*m*, H_a–C(5′)); 4.12 (*m*, H_b–C(6″), H–C(5″), H–C(2″)); 4.03 (*m*, H_b–C(5′)); 2.09, 2.07, 2.00 (3*s*, 3 AcO). ^{13}C-NMR ($CDCl_3$): 170.68–162.51 (6 CO); 145.18 (C(6)); 133.95–127.53 (12 C, Ph); 98.16 (C(1″)); 97.27 (C(5)); 85.50 (C(1′)); 81.18 (C(4′)); 75.21 (C(3′)); 70.88 (C(3″)); 68.94 (C(2′), C(5″)); 66.96 (C(5′)); 65.64 (C(4″)); 62.01 (C(6″)); 61.13 (C(2″)); 20.67–20.48 (3 *Me*CO). ESI-TOF-MS: 869.0676 ([*M* + 1]$^+$), 891.0727 ([*M* + Na]$^+$).

*5′-*O*-[3,6-Di-*O*-acetyl-2-azido-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-α-*D*-mannopyranosyl]uridine 2′,3′-Diacetate* (**24**): Yield 46.7%. Yellow solid. $[\alpha]_D^{18} = +27.2$ ($c = 0.035$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 8.87 (*s*, NH); 7.44 (*d*, *J*(5,6) = 6.0, H–C(6)); 6.09 (*d*, *J*(1′,2′) = 6.5, H–C(1′)); 5.97 (*dd*, H–C(5)); 5.40 (*dd*, H–C(3′)); 5.38 (*dd*, H–C(4‴)); 5.30–5.28 (*m*, H–C(3‴), H–C(2′)); 5.17 (*dd*, H–C(2‴)); 4.99 (*dd*, H–C(3‴)); 4.85 (*d*, *J*(1″,2″) = 2.0, H–C(1″)); 4.59 (*d*, *J*(1‴,2‴) = 8.50, H–C(1‴)); 4.46 (*m*, H_a–C(6‴)); 4.25–4.16 (*m*, H–C(4′), H_b–C(6‴), H_a–C(6″)); 4.11–4.07 (*m*, H–C(2″), H_b–C(6″)); 4.02–4.01 (*m*, H–C(4″), H–C(5‴)); 3.98–3.94 (*m*, H–C(5″), H_a–C(5′)); 3.81 (*m*, H_b–C(5′)); 2.26–1.97 (8*s*, 8 AcO); ^{13}C-NMR ($CDCl_3$): 170.54–162.60 (8 C=O); 150.41 (C(4)); 139.67 (C(6)); 103.98 (C(5)); 101.15 (C(1‴)); 98.19 (C(1″)); 87.10 (C(1′)); 80.76 (C(4′)); 73.75 (C(4′)); 72.60 (C(2′)); 71.03 (C(3″), C(3‴)); 70.59 (C(5″)); 70.52

(C(3′)); 69.97 (C(5‴)); 68.89 (C(2‴)); 67.19 (C(5′)); 66.82 (C(4‴)); 62.03 (C(6‴)); 61.12 (C(2″)); 60.92 (C(6″)); 20.81–20.25 (*Me*CO). ESI-TOF-MS: 930.0867 ($[M+1]^+$).

N^4-*Acetyl-5′*-O-*[3,6-di*-O-*acetyl-2-azido-2-deoxy-4*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl)-α*-D-*mannopyranosyl]cytidine 2′,3′-Diacetate* (**25**): Yield 42.6%. Yellow solid. $[\alpha]_D^{18} = +36.33$ ($c = 0.033$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 9.01 (br., AcN*H*); 7.87 (*d*, *J*(5,6) = 7.5, H–C(6)); 7.55 (*dd*, H–C(5)); 6.16 (*d*, *J*(1′,2′) = 4.0, H–C(1′)); 5.40–5.30 (*m*, H–C(3″), H–C(4‴), H–C(3′), H–C(2′)); 5.15 (*dd*, H–C(2‴)); 4.99 (*dd*, H–C(3‴)); 4.85 (*d*, *J*(1″,2″) = 1.5, H–C(1″)); 4.58 (*d*, *J*(1‴,2‴) = 8.0, H–C(1‴)); 4.42 (*m*, H_a–C(6‴)); 4.31 (*m*, H–C(4′)); 4.19–4.14 (*m*, H_a–C(6″), H_b–C(6‴)); 4.11–4.07 (*m*, H–C(2″), H_b–C(6″)); 4.02–3.94 (*m*, H–C(5″), H–C(4″), H–C(5‴), H_a–C(5′)); 3.82 (*m*, H_b–C(5′)); 2.15–1.97 (9*s*, 8 AcO, *Ac*NH). ^{13}C-NMR ($CDCl_3$): 170.52–162.60 (9 C=O); 144.42 (C(6)); 101.141 (C(1‴)); 98.18 (C(1″)); 97.552 (C(1′)); 88.94 (C(5)); 80.71 (C(4′)); 73.94 (C(4″)); 73.67 (C(2′)); 71.04 (C(3″)); 70.89 (C(3‴)); 70.59 (C(5‴)); 70.26 (C(3′)); 69.79 (C(5‴)); 68.93 (C(2‴)); 66.95 (C(5′)); 66.81 (C(4‴)); 62.06 (C(6‴)); 61.09 (C(2″)); 60.96 (C(6″)); 24.97 (*Me*CONH); 20.82–20.34 (*Me*CO). ESI-TOF-MS: 971.0698 ($[M+1]^+$), 993.0771 ($[M+Na]^+$).

5′-O-*[3,6-Di*-O-*acetyl-2-azido-2-deoxy-4*-O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl)-α*-D-*mannopyranosyl]thymidine 3′-Acetate* (**26**): Yield 83%. White solid. $[\alpha]_D^{18} = +26.4$ ($c = 0.024$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 8.59 (*s*, NH); 7.22 (*s*, H–C(6)); 6.33 (*m*, H–C(1′)); 5.37 (*m*, H–C(4‴)); 5.31 (*m*, H–C(3‴)); 5.22 (*m*, H–C(3′)); 5.15 (*dd*, H–C(2‴)); 4.98 (*dd*, H–C(3‴)); 4.88 (*d*, *J*(1″2″) = 1.75, H–C(1″)); 4.57 (*d*, *J*(1‴,2‴) = 7.50, H–C(1‴)); 4.45 (*m*, H_a–C(6‴)); 4.21–3.88 (*m*, H–C(4′), H_b–C(6‴), H_a–C(6″), H–C(2″), H_b–C(6″), H–C(4″), H–C(5‴), H–C(5″), H_a–C(5′)); 3.68 (*m*, H_b–C(5′)); 2.40–2.10 (*m*, H–C(2′)); 2.15–1.93 (8*s*, 7 AcO, Me). ^{13}C-NMR ($CDCl_3$): 170.49–163.22 (7 C=O); 150.17 (C(4)); 134.69 (C(6)); 111.62 (C(5)); 101.58 (C(1‴)); 97.97 (C(1″)); 84.57 (C(1′)); 83.01 (C(4′)); 74.34 (C(3′)); 74.11 (C(4″)); 71.26 (C(3″)); 70.94 (C(3‴)); 70.72 (C(5‴)); 70.01 (C(5″)); 69.04 (C(2‴)); 67.66 (C(5′)); 66.73 (C(4‴)); 61.93 (C(6‴)); 61.17 (C(6‴)); 61.02 (C(2″)); 36.96 (C(2′)); 20.86–20.49 (7 *Me*CO); 12.49 (Me). ESI-TOF-MS: 886.1050 ($[M+1]^+$), 908.0852 ($[M+Na]^+$).

N^4-*Benzoyl-1-[*O-*2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl-(1 → 4)*-O-*3,6-di*-O-*acetyl-2-azido-2-deoxy-α*-D-*mannopyranosyl-(1 → 5)-2,3-di*-O-*benzoyl-β*-D-*arabinofuranosyl]cytosine* (**27**). Yield 65.3%. Yellow solid. $[\alpha]_D^{18} = +8.35$ ($c = 0.092$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 8.84 (br. AcN*H*); 8.08 (*d*, *J*(5,6) = 7.5, H–C(6)); 7.85 (*dd*, H–C(5)); 8.16–7.41 (15 arom. H); 6.60 (*d*, *J*(1′,2′) = 3.50, H–C(1′)); 6.03 (*dd*, H–C(2′)); 5.60 (br., H–C(3′)); 5.42–5.38 (*m*, H–C(3″), H–C(4‴)); 5.14 (*dd*, *J*(2‴,3‴) = 10.5, H–C(2‴)); 5.00 (*dd*, H–C(3‴)); 4.93 (*d*, *J*(1″,2″) = 2.0, H–C(1″)); 4.57 (*d*, *J*(1‴,2‴) = 8.0, H–C(1‴)); 4.42–4.39 (*m*, H_a–C(6‴), H–C(4′)); 4.19–4.12 (*m*, H_a–C(6″)), H_b–C(6‴), H_a–C(5′), H_b–C(6″)); 4.02–3.94 (*m*, H–C(5″), H–C(4″), H–C(5‴), H–C(2″), H_b–C(5′)); 2.15–1.97 (6*s*, 6 AcO, AcN). ^{13}C-NMR ($CDCl_3$): 170.52–162.00 (9 C=O); 133.85–127.55 (9 C, Ph); 129.93 (C(6)); 129.63 (C(5)); 101.46 (C(1‴)); 97.96 (C(1″)); 85.55 (C(1′)); 81.16 (C(4′)); 76.44 (C(3′)); 75.09 (C(2′)); 74.47 (C(4″)); 70.90 (C(3″), C(3‴)); 70.59 (C(5‴)); 69.52 (C(5″)); 68.94 (C(2‴)); 66.84 (C(5′)); 66.74 (C(4‴)); 62.06 (C(6‴)); 60.97 (C(6″)); 60.88 (C(2″)); 20.82–20.34 (*Me*CO). ESI-TOF-MS: 1157.0925 ($[M+1]^+$), 1179.0927 ($[M+Na]^+$).

5. *General Procedure for Deprotection*. At r.t., one of the compounds **16**–**19** or **24**–**27** (50 mg) was added to 10 ml of 25–30% $MeNH_2$ in abs. EtOH. After stirring for 8 h, the mixture was evaporated and the residue was submitted to CC (silica gel, CH_2Cl_2/MeOH 10:1 (removal of all impurities), then CH_2Cl_2/MeOH 1:1). The eluted product was purified by reversed-phase CC (short *C-18* column, H_2O): **20**–**23** and **28**–**31**, resp.

5′-O-*(2-Azido-2-deoxy-α*-D-*mannopyranosyl)uridine* (**20**): Yield 83.3%. White solid. $[\alpha]_D^{18} = +66.0$ ($c = 0.015$, H_2O). ^{1}H-NMR (D_2O): 7.76 (*d*, *J*(5,6) = 8.13, H–C(6)); 5.80 (*d*, H–C(5)); 5.77 (*d*, *J*(1′,2′) = 3.8, H–C(1′)); 4.96 (*d*, *J*(1″,2″) = 1.41, H–C(1″)); 4.22–4.19 (*m*, H–C(2′), H–C(3′), H–C(4′)); 3.96 (*dd*, H–C(2″)); 3.90–3.86 (*m*, H_a–C(5′), H–C(3″)); 3.79–3.74 (*m*, H_a–C(6″), H_b–C(5′)); 3.65 (*m*, H_b–C(6″)); 3.54 (*t*, H–C(4″)); 3.42 (*m*, H–C(5″)). ^{13}C-NMR (D_2O): 166.62, 151.84 (C(4), C(2)); 141.86 (C(6)); 102.22 (C(5)); 98.17 (C(1″)); 90.36 (C(1′)); 82.50 (C(3′)); 74.29 (C(2′)); 73.44 (C(5″)); 70.86 (C(3″)); 69.46 (C(4′)); 66.95 (C(4″)); 66.13 (C(5′)); 64.03 (C(2″)); 60.98 (C(6″)). HR-FAB-MS (pos. mode): 432.1306 ($[C_{15}H_{22}O_{10}N_5+H]^+$; calc. 432.1366).

5′-O-*(2-Azido-2-deoxy-α*-D-*mannopyranosyl)cytidine* (**21**): Yield 62.1%. White solid. $[\alpha]_D^{18} = +26.8$ ($c = 0.020$, H_2O). ^{1}H-NMR (D_2O): 7.63 (*d*, *J*(5,6) = 7.50, H–C(6)); 5.81 (*d*, H–C(5)); 5.63 (*s*, H–C(1′)); 4.83 (*s*, H–C(1″)); 4.05 (br., H–C(2′), H–C(3′), H–C(4′)); 3.82–3.63 (*m*, H–C(2″), H_a–C(5′), H–C(3″)); 3.69–3.63 (*m*, H_a–C(6″), H_b–C(5′)); 3.55–3.49 (*m*, H_b–C(6″)); 3.47–3.40 (*m*, H–C(4′)); 3.35 (*m*, H–C(5″)). ^{13}C-NMR (D_2O): 168.77, 160.04 (C(4), C(2)); 143.76 (C(6)); 100.43 (C(5)); 98.30 (C(1″)); 93.31 (C(1′)); 84.35 (C(3′)); 77.02 (C(2′)); 75.71 (C(5″)); 73.16 (C(3′)); 71.52 (C(4′)); 69.25 (C(4″)); 68.23 (C(5′)); 66.34 (C(2″)); 63.24 (C(6″)). HR-FAB-MS (pos. mode): 431.1523 ($[C_{15}H_{23}O_9N_6+H]^+$; calc. 431.1526).

5′-O-(2-Azido-2-deoxy-α-D-mannopyranosyl)thymidine (**22**): Yield 72.7%. White solid. $[\alpha]_D^{18} = +61.4$ ($c = 0.016$, H_2O). ^{1}H-NMR (D_2O): 7.46 (*s*, H–C(6)); 6.15 (*t*, *J*(1′,2′) = 6.54, H–C(1′)); 4.90 (*s*, H–C(1″)); 4.43 (*dd*, H–C(3′)); 4.07 (*dd*, H–C(4′)); 3.88–3.84 (*m*, H–C(2″), H_a–C(5′), H–C(3″)); 3.76–3.67 (*m*, H_a–C(6″), H_b–C(5′)); 3.64 (*m*, H_b–C(6″)); 3.55 (*dd*, H–C(4″)); 3.42 (*m*, H–C(5″)); 2.33–2.23 (*m*, 2 H–C(2′)); 1.82 (*s*, Me). ^{13}C-NMR (D_2O): 166.76, 151.92 (C(4), C(2)); 137.49 (C(6)); 111.54 (C(5)); 98.33 (C(1″)); 85.91 (C(1′)); 85.27 (C(4′)); 73.41 (C(5″)); 71.11 (C(3′)); 70.82 (C(3″)); 67.97 (C(5″)); 67.17 (C(5′)); 66.99 (C(4″)); 64.14 (C(2″)); 60.96 (C(6″)); 39.28 (C(2′)); 12.11 (Me). HR-FAB-MS (pos. mode): 430.1597 ($[C_{16}H_{24}O_9N_5 + H]^+$; calc. 430.1574).

1-[5-O-(2-Azido-2-deoxy-α-D-Mannopyranosyl)-β-D-arabinofuranosyl]cytosine (**23**): Yield 87.0%. White solid. $[\alpha]_D^{18} = +16.61$ ($c = 0.028$, MeOH). ^{1}H-NMR (D_2O): 7.59 (*d*, *J*(5,6) = 7.50, H–C(6)); 6.04 (*d*, *J*(1′,2′) = 5.4, H–C(1′)); 5.85 (*d*, H–C(5)); 4.87 (*s*, H–C(1″)); 4.26 (*t*, H–C(3′)); 3.99–3.79 (*m*, H–C(2′), H–C(4′), H–C(2″), H_a–C(5′), H–C(3″)); 3.71–3.47 (*m*, H_a–C(6″), H_b–C(5′), H–C(5″), H_b–C(6″), H–C(4″)). ^{13}C-NMR (D_2O): 166.80, 158.13 (C(4), C(2)); 142.99 (C(6)); 98.64 (C(1″)); 96.06 (C(1′)); 86.14 (C(5)); 81.25 (C(3′)); 76.26 (C(2′)); 75.46 (C(5″)); 73.77 (C(3″)); 71.18 (C(4′)); 67.35 (C(4″)); 66.74 (C(5′)); 64.41 (C(2″)); 61.32 (C(6″); HR-FAB-MS (pos. mode): 431.1505 ($[C_{15}H_{23}O_9N_6 + H]^+$; calc. 431.1526).

5′-O-[2-Azido-2-deoxy-4-O-(β-D-galactopyranosyl)-α-D-mannopyranosyl]uridine (**28**): Yield 67.2%. White solid. $[\alpha]_D^{18} = +66.0$ ($c = 0.015$, MeOH). ^{1}H-NMR (D_2O): 7.73 (*d*, *J*(5,6) = 8.0, H–C(6)); 5.77 (*d*, H–C(5)); 5.73 (*d*, *J*(1′,2′) = 3.0, H–C(1′)); 4.93 (*s*, H–C(1″)); 4.31 (*d*, *J*(1‴,2‴) = 7.50, H–C(1‴)); 4.20–4.14 (*m*, H–C(3″), H–C(4‴), H–C(3′)); 3.99–3.96 (*m*, H–C(2′), H–C(2‴)); 3.84 (*dd*, H–C(3‴)); 3.79–3.52 (*m*, H_a–C(6‴), H–C(4′), H_b–C(6‴), H_a–C(6″), H–C(2″), H_b–C(6″), H–C(4″), H–C(5‴), H–C(5″), H_a–C(5′)); 3.38 (*m*, H_b–C(5′)). ^{13}C-NMR (D_2O): 169.08, 154.25 (C(2), C(4)); 144.26 (C(6)); 105.82 (C(5)); 104.53 (C(1‴)); 100.31 (C(1″)); 92.79 (C(1′)); 84.78 (C(3′)); 78.94 (C(5‴)); 78.11 (C(2′)); 76.63 (C(5″)); 75.21 (C(3″)); 74.41 (C(3‴)); 73.68 (C(4′)); 72.03 (C(2‴)); 71.74 (C(4″)); 71.28 (C(5′)); 68.48 (C(4‴)); 65.78 (C(2″)); 63.82 (C(6″)); 62.68 (C(6‴)). HR-FAB-MS (pos. mode): 594.1852 ($[C_{21}H_{32}O_{15}N_5 + H]^+$; calc. 594.1895).

5′-O-[2-Azido-2-deoxy-4-O-(β-D-galactopyranosyl)-α-D-mannopyranosyl]cytidine (**29**): Yield 62.1%. White solid. $[\alpha]_D^{18} = +76.1$ ($c = 0.011$, MeOH). ^{1}H-NMR (D_2O): 7.73 (*d*, *J*(5,6) = 7.5, H–C(6)); 5.91 (*d*, H–C(5)); 5.72 (*d*, *J*(1′,2′) = 2.0, H–C(1′)); 4.93 (*s*, H–C(1″)); 4.31 (*d*, *J*(1‴,2‴) = 8.00, H–C(1‴)); 4.17–4.11 (*m*, H–C(3″), H–C(4‴), H–C(3′)); 3.99–3.95 (*m*, H–C(2′), H–C(2‴)); 3.86–3.51 (*m*, H–C(3‴), H_a–C(6‴), H–C(4′), H_b–C(6‴), H_a–C(6″), H–C(2″), H_b–C(6″), H–C(4″), H–C(5‴), H–C(5″), H_a–C(5′)); 3.38 (*m*, H_b–C(5)). ^{13}C-NMR (D_2O): 166.94, 158.19 (C(2), C(4)); 141.91 (C(6)); 103.80 (C(5)); 98.30 (C(1‴)); 96.42 (C(1″)); 91.42 (C(1′)); 82.39 (C(3′)); 76.95 (C(5‴)); 76.10 (C(2′)); 75.02 (C(5″)); 73.21 (C(3″)); 72.38 (C(3‴)); 71.67 (C(4′)); 70.05 (C(2‴)); 69.54 (C(4′)); 69.27 (C(5′)); 66.36 (C(4‴)); 63.79 (C(2″)); 61.82 (C(6″)); 60.67 (C(6‴)). HR-FAB-MS (pos. mode): 593.2054 ($[C_{21}H_{33}O_{14}N_6 + H]^+$; calc. 593.2055).

5′-O-[2-Azido-2-deoxy-4-O-(β-D-galactopyranosyl)-α-D-mannopyranosyl]thymidine (**30**): Yield 88.0%. White solid. $[\alpha]_D^{18} = +14.04$ ($c = 0.027$, MeOH). ^{1}H-NMR (D_2O): 7.40 (*s*, H–C(6)); 6.11 (*t*, *J*(1′,2′) = 6.6, H–C(1′)); 4.87 (*d*, *J*(1″,2″) = 1.5, H–C(1″)); 4.63 (*dd*, H–C(4‴)); 4.28 (*d*, *J*(1‴,2‴) = 7.50, H–C(1‴)); 4.01 (*dd*, H–C(3′)); 3.94 (*dd*, H–C(3″)); 3.86 (*dd*, H–C(2‴)); 3.81–3.73 (*m*, H–C(3‴), H_a–C(6‴)); 3.70–3.48 (*m*, H–C(4′), H_b–C(6‴), H_a–C(6″), H–C(2″), H_b–C(6″), H–C(4″), H–C(5‴), H–C(5″), H_a–C(5′)); 3.36 (*m*, H_b–C(5′)); 2.25 (*m*, 2 H–C(2′)); 1.77 (*s*, Me). ^{13}C-NMR (D_2O): 169.20, 154.36 (C(4), C(2)); 139.94 (C(6)); 114.01 (C(5)); 105.83 (C(1‴)); 100.57 (C(1″)); 88.24 (C(1′)); 87.59 (C(3′)); 79.01 (C(5‴)); 78.12 (C(5″)); 75.29 (C(3″)); 74.42 (C(3‴)); 73.73 (C(4′)); 73.36 (C(4″)); 72.05 (C(2‴)); 71.33 (C(5′)); 69.61 (C(4‴)); 65.91 (C(2″)); 63.84 (C(6″)); 62.73 (C(6‴)); 41.58 (C(2′)); 14.51 (Me). HR-FAB-MS (pos. mode): 592.2108 ($[C_{22}H_{34}O_{14}N_5 + H]^+$; calc. 592.2102).

1-[O-β-D-Galactopyranosyl-(1 → 4)-O-2-azido-2-deoxy-α-D-mannopyranosyl-(1 → 5)-β-D-arabinofuranosyl]cytosine (**31**): Yield 91.0%. White solid. $[\alpha]_D^{18} = +37.48$ ($c = 0.021$, MeOH). ^{1}H-NMR (D_2O): 7.63 (*d*, *J*(5,6) = 8.0, H–C(6)); 6.09 (*d*, *J*(1′,2′) = 5.50, H–C(1′)); 5.90 (*dd*, H–C(5)); 4.93 (*d*, *J*(1″,2″) = 1.0, H–C(1″)); 4.32–4.29 (*m*, H–C(1‴), H–C(2′)); 4.05–3.96 (*m*, H–C(3′), H–C(3″), H–C(4‴), H–C(2‴)); 3.86 (*dd*, H–C(3‴)); 3.81–3.59 (*m*, H_a–C(6‴), H–C(4′), H_a–C(6″), H_b–C(6‴), H–C(2″), H_b–C(6″), H–C(5″), H–C(4″), H–C(5‴)); 3.53 (H_a–C(5′)); 3.39 (H_b–C(5′)). ^{13}C-NMR (D_2O): 168.79, 160.14 (C(2), C(4)); 145.04 (C(6)); 105.81 (C(5)); 100.52 (C(1‴)); 98.07 (C(1″)); 88.10 (C(1′)); 83.22 (C(3′)); 78.96 (C(5‴)); 78.29 (C(2′)); 78.11 (C(5″)); 77.41 (C(3″)); 75.24 (C(3‴)); 74.41 (C(4′)); 73.69 (C(2‴)); 72.02 (C(4″)); 71.31 (C(5′)); 68.86 (C(4‴)); 65.82 (C(2″)); 63.83 (C(6″)); 62.70 (C(6‴)). HR-FAB-MS (pos. mode): 593.2053 ($[C_{21}H_{33}O_{14}N_6 + H]^+$; calc. 593.2054).

5. *Antitumor Activity.* Inhibition of tumor-cell growth by the designed compounds was carried out according to published methods [20][21].

This work was supported by the *National Natural Science Foundation of China.*

REFERENCES

[1] G. Ashwell, *Annu. Rev. Biochem.* **1982**, *51*, 531.
[2] R. G. Armugham, T. C.-Y. Hsieh, M. L. Tanzer, R. A. Laine, *Biochim. Biophys. Acta* **1986**, *883*, 112.
[3] M. Takahashi, T. Kagasaki, T. Hosoya, S. Takahashi, *J. Antibiot.* **1993**, *46*, 1643.
[4] S. Takahashi, T. Kinoshita, M. Takabashi, *J. Antibiot.* **1994**, *47*, 95.
[5] T. Nagata, T. WaKayama, M. Asano, T. Segawa, Jap. Pat. JP 66234646 to *Toagosei Chem. Ind. Co., Ltd.*, 1994.
[6] T.-W. Ma, J.-M. Min, L.-H. Zhang, *Carbohydr. Res.* **1994**, *257*, 323.
[7] T.-W. Cai, J.-M. Min, L.-H. Zhang, *Carbohydr. Res.* **1997**, *303*, 113.
[8] Z.-J. Liu, M. Zhou, J.-M. Min, L.-H. Zhang, *Tetrahedron: Asymmetry* **1999**, *10*, 2119.
[9] S. Knapp, *Chem. Rev.* **1995**, *95*, 1859.
[10] R. U. Lemieux, R. M. Ratcliffe, *Can. J. Chem.* **1979**, *57*, 1244.
[11] H. Paulsen, J. P. Lorentzen, *Carbohydr. Res.* **1984**, *133*, C1.
[12] J. Arnap, J. Lönngren, *J. Chem. Soc., Perkin Trans. 1* **1981**, 2070.
[13] Q. Li, H. Li, M. S. Cai, Z. J. Li, R. L. Zhou, *Tetrahedron: Asymmetry* **1999**, *10*, 2675.
[14] E. Darakas, H. Hultberg, K. Leontein, J. Lönngren, *Carbohydr. Res.* **1982**, *103*, 176.
[15] W. N. Haworth, E. L. Hirst, M. M. T. Plant, R. J. W. Reinolds, *J. Chem. Soc.* **1930**, 2644.
[16] M. Smith, D. H. Rammler, I. H. Goldberg, H. G. Khorana, *J. Am. Chem. Soc.* **1962**, *84*, 430.
[17] V. Bhat, B. G. Ugarkar, V. A. Sayeed, N. Kosora, P. A. Domenico, E. Stocker, *Nucleosides Nucleotides* **1989**, *8*, 179.
[18] K. Bock, C. Pedersen, *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.
[19] P. R. Twentyman, M. Luscombe, *Br. J. Cancer* **1987**, *56*, 279.
[20] T. Mosmann, *J. Immunol. Methods* **1983**, *65*, 55.
[21] C. H. Langeveld, C. A. M. Jongenelen, J. J. Heimans, J. C. Stoof, *Cancer Res.* **1992**, *52*, 3994.

Received October 20, 2002