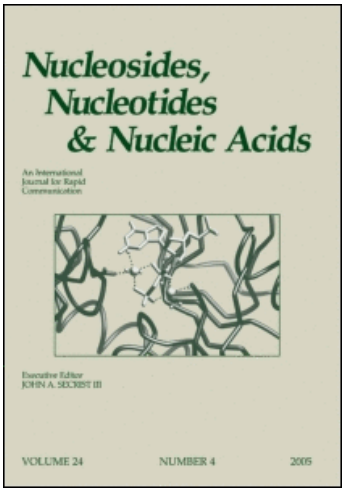


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Antiviral Evaluation of 4'-*C*-Azidomethyl-β-D-Ribofuranosyl Purine and Pyrimidine Nucleosides

Jean-François Griffon[a]; Audrey Dumas[a]; Richard Storer[ab]; Jean-Pierre Sommadossi[c]; Gilles Gosselin[a]
[a] Idenix Pharmaceuticals, Medicinal Chemistry Laboratory, Montpellier, France [b] Summit PLC, Abingdon, Oxfordshire, United Kingdom [c] Idenix Pharmaceuticals, Cambridge, Massachusets, USA

To cite this Article Griffon, Jean-François , Dumas, Audrey , Storer, Richard , Sommadossi, Jean-Pierre and Gosselin, Gilles(2009) 'Synthesis and Antiviral Evaluation of 4'-*C*-Azidomethyl-β-D-Ribofuranosyl Purine and Pyrimidine Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 28: 5, 435 — 449
To link to this Article: DOI: 10.1080/15257770903044531
URL: http://dx.doi.org/10.1080/15257770903044531

Nucleosides, Nucleotides and Nucleic Acids, 28:435–449, 2009

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770903044531

Taylor & Francis
Taylor & Francis Group

SYNTHESIS AND ANTIVIRAL EVALUATION OF 4′-*C*-AZIDOMETHYL-β-D-RIBOFURANOSYL PURINE AND PYRIMIDINE NUCLEOSIDES

Jean-François Griffon,[1] Audrey Dumas,[1] Richard Storer,[1,2] Jean-Pierre Sommadossi,[3] and Gilles Gosselin[1]

[1]*Idenix Pharmaceuticals, Medicinal Chemistry Laboratory, Montpellier, France*
[2]*Summit PLC, Abingdon, Oxfordshire, United Kingdom (Current address)*
[3]*Idenix Pharmaceuticals, Cambridge, Massachusets, USA*

□ *In the search for inhibitors of the replication of RNA viruses, including hepatitis C virus (HCV), the hitherto unknown 4′-C-azidomethyl-β-D-ribofuranosyl nucleosides of the five naturally occurring nucleic acid bases have been synthesized and their antiviral properties examined. These 4′-C-branched nucleosides were stereospecifically prepared by glycosylation of purine and pyrimidine aglycons with a suitable peracylated 4-C-azidomethyl-D-pentofuranose sugar, followed by removal of the protecting groups. The prepared compounds were tested for their activity against several viruses, but they did not show an antiviral effect.*

Keywords 4′-*C*-Azidomethyl-β-D-ribofuranosyl nucleosides; RNA viruses; HCV

INTRODUCTION

RNA viruses of the family *Flaviviridae* are the agents of numerous widespread and often severe diseases. Among these viruses, we can mention the members of the genus *Flavivirus*, including yellow fever virus (YFV) which is still a leading cause of hemorrhagic fever and related mortality (up to 50%) worldwide, the dengue virus (DEN) which is increasing in prevalence in the tropical and subtropical areas of the world, and the West Nile virus (WNV) emerging in North America.[1] Infections resulting

Received 2 March 2009; accepted 1 April 2009.
In honor of and in celebration of Morris J. Robins' 70th birthday.
The authors would like to thank Michel Liuzzi (Idenix Senior Director Virology, Laboratorio Cooperativo Idenix-Università di Cagliari, Italy) and his collaborators for the biological results.
Address correspondence to Gilles Gosselin and Jean-François Griffon, Laboratoires Idenix Sarl, Cap Gamma, 1682 rue de la Valsiere, B.P. 50001, 34189, Montpellier, Cedex 4, France. E-mail: gosselin.gilles@idenix.com; griffon.j-f@idenix.com

from these viruses are important examples of emerging diseases. We can also mention a member of the genus *Hepacivirus*, namely hepatitis C virus (HCV) which is a causative agent of chronic liver disease, estimated to affect over 170 million people worldwide.[2] Currently, no specific antiviral drugs are available for the prevention or the treatment of infections caused by the majority of RNA viruses. Perhaps the only exception is represented by HCV; current therapy for chronic hepatitis C consists of pegylated interferon-α and the nucleoside analogue ribavirin. However, such standard therapy is poorly tolerated and has limited efficacy, with no more than 45% and 52% response rates among patients infected with the most prevalent HCV genotypes 1 and 4.[3] Therefore, there is an urgent need for more efficient and better tolerated anti-HCV agents, as well as for specific and selective treatments against a higher number of RNA virus infections. The unique RNA-dependant RNA polymerase (RDRP) is essential for replication of RNA viruses, and recent progress have been made in the development of inhibitors of the HCV RDPR.[4] In this regard, we had investigated sugar-modified ribonucleoside analogues and discovered that compounds possessing a β-methyl substituent at the 2′-position of the D-ribose moiety are potent and broad-spectrum anti-RNA virus agents.[5] Among them, and although no longer in development, valopicitabine,[6] an orally bioavailable prodrug of 2′-*C*-methylcytidine (Figure 1) was the first HCV nucleoside polymerase inhibitor to demonstrate proof-of-concept in the clinic by achieving reduction in plasma HCV RNA.[7] More recently, orally biovailable prodrugs (R7128[8] and R1626[9]) of two other branched nucleoside analogues inhibiting HCV replication, namely 2′-deoxy-2′-fluoro-2′-*C*-methylcytidine (PSI-6130)[10] and 4′-azidocytidine (R1479)[11] (Figure 1), have been evaluated in clinical studies for the treatment of chronic hepatitis C.

In continuation of our interest in 4′-*C*-branched nucleoside derivatives,[12] here we focused on the synthesis and antiviral evaluation studies of the hitherto unknown 4′-*C*-azidomethyl-β-D-ribofuranosyl nucleosides bearing the five naturally occurring nucleic acid bases and two modified purines (Figure 1).

RESULTS AND DISCUSSION

Chemistry

It was anticipated that the title β (trans-1′,2′) 4′-*C*-azidomethyl-D-ribofuranosyl nucleoside compounds could be synthesized by condensation of a suitably protected 4-*C*-azidomethyl-D-ribofuranose with the purine and pyrimidine bases. In accord with the Baker's rule,[13] a 2-*O*-acyl-4-*C*-azidomethyl-D-ribofuranose was required for preferential or exclusive formation of the β nucleoside anomers. As starting sugar, we

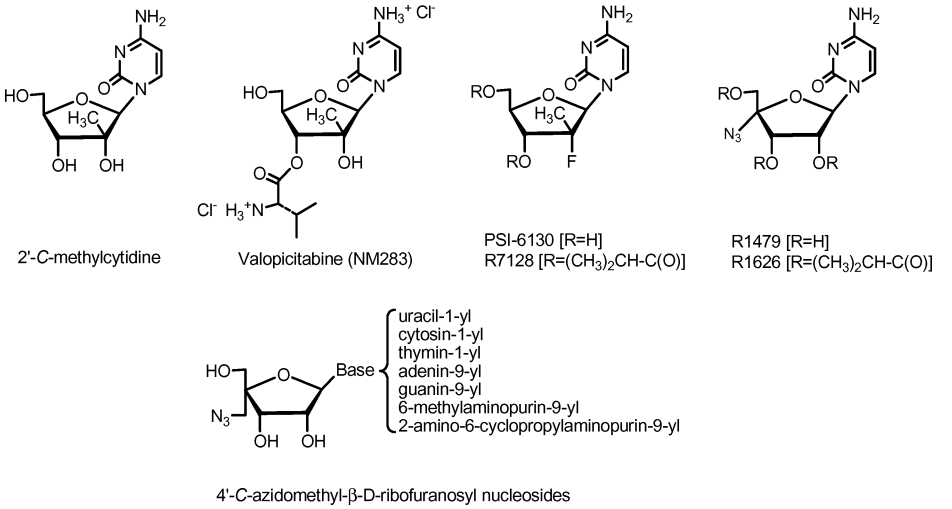
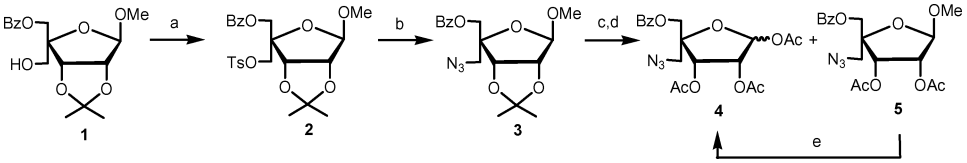


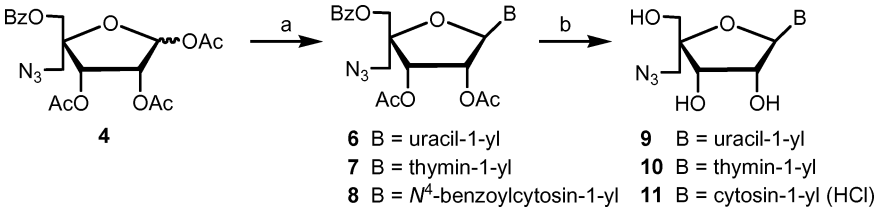
FIGURE 1 Examples of nucleoside analogues with anti-HCV activity and structures of 4′-*C*-azidomethyl-*β*-D-ribofuranosyl nucleosides.

decided to use the syrupy 1,2,3-tri-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-*α*/*β*-D-ribofuranose (**5**), hitherto unknown and specially prepared for our present purpose. In this regard, 5-*O*-benzoyl-4-*C*-hydroxymethyl-2,3-*O*-isopropylidene-1-*O*-methyl-*β*-D-ribofuranose (**1**)[14] was synthesized first in 6 steps from D-ribose by implementing at each step convenient published procedures.[14,15] Introduction of the azido function at the 6-position of **1** was performed *via* the displacement of a 6-*O*-*p*-toluenesulfonyl function (intermediate **2**) by sodium azide to afford **3** in 68% yield (Scheme 1).



SCHEME 1 Reagents and conditions: (a) *p*-toluenesulfonyl chloride, pyridine, 25°C; (b) sodium azide, DMF, 150°C; (c) 85% acetic acid, 110°C; (d) acetic anhydride, 4-dimethylaminopyridine, pyridine, 25°C; (e) acetic acid, acetic anhydride, conc. sulfuric acid, 25°C.

Cleavage of the 2,3-*O*-isopropylidene protecting group of **3** with 85% acetic acid at 110°C, followed by acetylation with acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine led to a mixture of the expected 1,2,3-tri-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-*α*/*β*-D-ribofuranose (**4**) and of the corresponding methyl-*β*-D-ribofuranoside **5**, the latter resulting from the single cleavage of the 2,3-acetonide during the acidic treatment. After separation of **4** from **5**, the methyl-*β*-D-ribofuranoside **5** was subjected to an acetolysis which allowed to obtain **4** with an 80% overall yield from **3**.



SCHEME 2 Reagents and conditions: (a) silylated uracil, thymine or N^4-benzoylcytosine, TMSOTf; 1,2-dichloroethane, 25°C; (b) methanolic ammonia, 25°C.

Glycosylations were carried out by various procedures which, except for the cytosine nucleoside, did not require prior protection of the heterocyclic bases. Thus, in the pyrimidine series, condensation of **4** respectively with silylated uracil, thymine and N^4-benzoylcytosine was performed in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) under Vorbrüggen conditions[16] to afford the corresponding fully acylated 4′-*C*-azidomethyl-β-D-ribofuranosyl nucleosides **6–8** in yields around 50% (Scheme 2).

Compounds **6–8** were deprotected with saturated methanolic ammonia to give the target pyrimidine 4′-*C*-azidomethyl-β-D-ribofuranosyl nucleosides **9–11**.

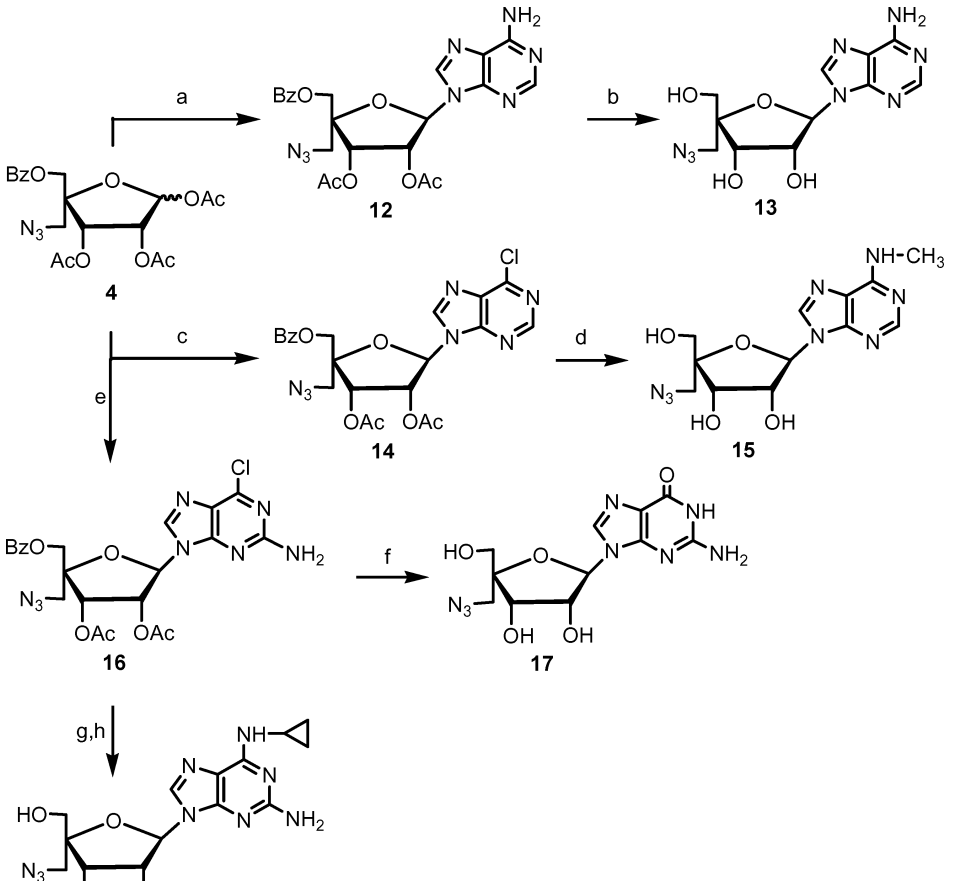
In the purine series (Scheme 3), **4** was condensed with: i) adenine in the presence of tin(IV) chloride in acetonitrile at room temperature following the Saneyoshi procedure[17] to afford **12** in 50% yield; ii) 6-chloropurine in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and TMSOTf in acetonitrile at 60°C, affording the crude intermediate **14,** which directly was treated with methylamine in water to give **15** in an overall 76% yield; iii) silylated 2-amino-6-chloropurine under Vorbrüggen condition[16] to afford **16** in 42% yield.

4′-Azidomethyladenosine (**13**) was obtained in a near quantitative yield by stirring **12** with saturated methanolic ammonia at room temperature overnight. 4′-Azidomethylguanosine (**17**) was obtained in 31% yield by refluxing the 2-amino-6-chloropurine nucleoside **16** with 2-mercaptoethanol and sodium methoxide in methanol, as described in oxaselenolane nucleoside series.[18] Finally, treatment of **16**, successively with saturated methanolic ammonia at 25°C and with cyclopropylamine in ethanol at reflux, afforded the 4′-*C*-azidomethyl-2-amino-6-cyclopropylaminopurine β-D-ribofuranonucleoside **18** in 64% yield.

Structural assignments for all the hitherto unknown 4′-*C*-azidomethyl-β-D-ribofuranosyl nucleosides **9–11**, **13**, **15**, **17**, and **18** are based on elemental analysis, mass spectra and on their physical properties.

Antiviral Evaluations

The 4′-*C*-azidomethyl-β-D-ribofuranosyl nucleosides **9–11**, **13**, **15**, **17**, and **18** were evaluated in cell-based assays (following methods described



SCHEME 3 Reagents and conditions: (a) adenine, tin(IV) chloride, acetonitrile, 25°C; (b) methanolic ammonia, 25°C; (c) 6-chloropurine, DBU, TMSOTf, acetonitrile, 60°C; (d) 40% methylamine in water, 25°C; (e) silylated 2-amino-6-chloropurine, TMSOTf, toluene, 110°C; (f) 2-mercaptoethanol, sodium methoxide, methanol, 65°C; (g) methanolic ammonia, 25°C; (h) cyclopropylamine, ethanol, reflux.

in[5c]) against viruses representative of three genera of the ssRNA$^+$ Flaviviridae, that is, Pestivirus (bovine virus diarrhoea virus), Flavivirus (Yellow Fever, Dengue and West Nile viruses) and Hepacivirus (HCV). They were also tested against a virus representative of another ssRNA$^+$ family, Retroviridae (HIV-1), against a virus representative of a ssRNA$^-$ families, Paramyxoviridae (RSV), and finally against a virus representative of DNA families, that is, Hepadnaviridae (HBV). Unfortunately, all the compounds showed neither antiviral activity nor cytotoxicity at the highest concentration tested (generally 100 μM).

CONCLUSION

A series of hitherto unknown 4′-*C*-azidomethyl-β-D-ribofuranosyl nucleosides were synthesized and evaluated against a broad range of RNA viruses

(including HCV) and against a DNA virus (HBV). All compounds were found inactive and non cytotoxic in all antiviral assays. Several factors could be responsible for their inactivity. Their inability to enter cells or to serve as substrates for intracellular enzymes catalyzing phosphorylation, as well as a lack of inhibition of viral polymerases by their triphosphate forms, would account for their lack of antiviral activity.

EXPERIMENTAL

All reactions were performed with reagent-grade materials and solvents under an atmosphere of nitrogen. Evaporation of the solvent was carried out in a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Büchi B-545 apparatus and are uncorrected. The UV absorption spectra were recorded on an Uvikon XS spectrophotometer (99–9089). ^{1}H-NMR spectra were run at room temperature in DMSO-d_6 or $CDCl_3$ with a Bruker AC 200, 250, or 400 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual peak (DMSO-d_6) set at δ_H 2.49 or ($CDCl_3$) set at δ_H 7.26 ppm. Deuterium exchange, decoupling experiments or 2D-COSY spectra were performed in order to confirm proton assignments. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quadruplet), br (broad), m (multiplet), p (pseudo). All J-values are in Hz. FAB mass spectra were recorded in the positive- (FAB > 0) or negative- (FAB < 0) ion mode on a JEOL JMS DX 300 mass spectrometer; the matrix was a mixture (50:50, v/v) of glycerol and thioglycerol (GT). IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR. Elemental analyses were carried out by the "Service de Microanalyses du CNRS, Division de Vernaison" (France) or by the "Laboratoire de Mesures Physiques, Université Montpellier 2" (France). Thin layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbency or by charring after immersion in a solution of $(NH_4)_2SO_4$ (150 g) in EtOH-H_2SO_4-water (300:30:450 mL) with heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385) or LiChroprep RP-18 (40–63 μm, Merck Art. 1.13900.0250) at atmospheric pressure.

4-*C*-Azidomethyl-5-*O*-benzoyl-2,3-*O*-isopropylidene-1-*O*-methyl-β-D-ribofuranose (3)

To a solution of **1**[14] (18.8 g, 55.5 mmol) in anhydrous pyridine (280 mL) under argon was added *p*-toluenesulfonyl chloride (21.3 g, 111.7 mmol). The reaction mixture was stirred overnight at room temperature. Ice-cold water was added (20 mL) and the reaction was diluted with methylene chloride (400 mL). The organic layer was washed with aqueous

hydrochloric acid (1N, 250 mL), with water (250 mL) and then dried over sodium sulfate and evaporated under reduced pressure to give the crude tosylate **2** which was purified by silica gel column chromatography [eluent: stepwise gradient of diethyl ether (10–20%) in petroleum ether] to give **2** (25.1g, 92%) as a pale yellow solid. To a solution of **2** (25.1 g, 551.0 mmol) in dry DMF (360 mL) was added sodium azide (16.6 g, 254.8 mmol). The reaction mixture was refluxed for 2 days, cooled to room temperature, diluted with ice-cold water (300 mL) and extracted with methylene chloride (3 × 200 mL). The combined organic layers were washed with a saturated aqueous sodium hydrogen carbonate solution (200 mL), with water (5 × 200 mL), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of diethyl ether (0–10%) in petroleum ether] to afford pure **3** (12.7 g, 68%) as a yellow oil.

^{1}H-NMR (DMSO-d_6): δ 8.1–7.5 (m, 5H, C_6H_5CO), 5.04 (s, 1H, H-1), 5.46 (dd, 2H, H-2 and H-3, J = 17 Hz, J = 6.0 Hz); 4.34 (dd, 2H, H-5, H-5′, J = 20.0 Hz, J = 11.5 Hz), 3.69 (pt, 2H, H-6′, H-6′), 3.27 (s, 3H, OCH_3), 1.49 (s, 3H CH_3), 1.32 (s, 3H CH_3); (matrix GT): FAB > 0 *m/z* 363 $(M+H)^+$, 332 $(M\text{-}OCH_3)^+$, 105 $(C_6H_5CO)^+$ FAB < 0 *m/z* 121 $(C_6H_5CO_2)^-$; IR (neat) 2106 cm^{-1} (N_3).

1,2,3-Tri-O-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-α/β-D-ribofuranose (4)

Compound **3** (12,4 g, 34.12 mmol) was suspended in a 85% aqueous acetic acid solution (170 ml). The solution was heated at 110°C for 6 hours. The solvents were removed under vacuum and the residue was successively coevaporated with toluene, absolute ethanol, and pyridine. The oily residue was dissolved in pyridine (190 ml) and acetic anhydride (54.4 ml, 575 mmol) and a catalytic amount of 4-dimethylaminopyridine were added. The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was dissolved with methylene chloride (600 mL) and successively washed with a saturated aqueous sodium hydrogen carbonate solution (300 mL), a 1M hydrochloric acid (300 mL) and water (2 × 500 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography [eluent: stepwise gradient of diethyl ether (30–40%) in petroleum ether] to give 2,3,di-*O*-acetyl-5-*O*-benzoyl-4-*C*-azidomethyl-1-*O*-methyl-β-D-ribofuranose **5** (10.76 g, 77%) and **4** (2.08 g, 14%) as a pale yellow syrup. Compound **5** was further converted to **4** by acetolysis. Thus, to a solution of **5** (10.76 g, 26.44 mmol) in acetic acid (132 mL) and acetic anhydride (13.2 ml) was added conc.H_2SO_4 (0.79 mL). The reaction mixture was stirred overnight at room temperature, cooled to 0°C, neutralized with

solid sodium hydrogen carbonate and extracted with methylene chloride (3 × 250 mL). The combined organic layers were washed with water (500 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on silica gel chromatography [eluent: stepwise gradient of diethyl ether (30–40%) in petroleum ether] to give **4** (9.86 g, 66%). A small fraction of **4** (overall yield, 80%) was repurified on silica gel chromatography [eluent: stepwise gradient of diethyl ether (30–40%) in petroleum ether] in order separate the α and the β anomer.

α anomer: ^{1}H-NMR (DMSO-d_6): δ 8.1–7.5 (m, 5H, C_6H_5CO), 6.41 (d, 1H, H-1, $J_{1,2} = 4.6$ Hz), 5.61 (d, 1H, H-3, $J_{2-3} = 6.5$ HZ), 5.52 (dd, 1H, H-2, $J_{2-3} = 6.5$ Hz, $J_{1,2} = 4.7$ Hz), 4.5–4.4 (dd, 2H, H-5, H-5′, J = 14.9 Hz, J = 11.7 Hz); 3.9–3.5 (dd, 2H, H-6, H-6′, J = 64.5 Hz, J = 13.3 Hz), 2.16 (s, 3H, CH_3CO_2), 2.14 (s, 3H, CH_3CO_2), 2.07 (s, 3H, CH_3CO_2); MS (matrix GT): FAB > 0 *m/z* 376 (M-$CH_3CO_2^-$)$^+$, 105 (C_6H_5CO)$^+$, 43 (CH_3CO)$^+$ FAB < 0 *m/z* 121 ($C_6H_5CO_2$)$^-$, 59 (CH_3CO_2)$^-$.

β anomer: ^{1}H-NMR (DMSO-d_6): δ 8.0–7.5 (m, 5H, C_6H_5CO), 6.09 (s, 1H, H-1), 5.63 (d, 1H, H-3, J = 5.4 Hz), 5.35 (d, 1H, H-2, J = 6.0 Hz), 4.6–4.3 (dd, 2H, H-5, H-5′, J = 33.0 Hz, J = 11.8 Hz); 3.8–3.5 (dd, 2H, H-6, H-6′, J = 44.0 Hz, J = 11.4 Hz), 2.12 (s, 3H, CH_3CO_2), 2.06 (s, 3H, CH_3CO_2), 1.87 (s, 3H, CH_3CO_2); MS (matrix GT): FAB > 0 *m/z* 376 (M-$CH_3CO_2^-$)$^+$, 105 (C_6H_5CO)$^+$, 43 (CH_3CO)$^+$ FAB < 0 *m/z* 121 ($C_6H_5CO_2$)$^-$, 59 (CH_3CO_2)$^-$.

1-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)uracil (6)

A suspension of uracil (0.388 g, 3.46 mmol) was treated during 17 hours under reflux with hexamethyldisilazane (HMDS, 18 mL) and a catalytic amount of ammonium sulfate. After cooling to room temperature, the mixture was evaporated under reduced pressure, and the residue, obtained as a colorless oil, was diluted with anhydrous 1,2-dichloroethane (7 mL). To the resulting solution was added **4** (1.05 g, 2.41 mmol) in anhydrous 1,2-dichloroethane (13 mL), followed by addition of trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.93 mL, 4.82 mmol). The solution was stirred for 22 hours at room temperature under argon atmosphere, then diluted with chloroform (150 mL), washed with a saturated aqueous sodium hydrogen carbonate solution (150 mL), and with water (2 × 100 mL). The organic phase was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of diethyl ether (10–30%) in methylene chloride] to afford pure **9** (620 mg, 53%) as a pale yellow foam.

^{1}H-NMR (DMSO-d_6): δ 11.52 (s, 1H, NH), 8.0–7.4 (m, 6H, C_6H_5CO, H-6), 6.01 (d, 1H, H-1′, $J_{1'-2'} = 4.9$ Hz), 5.72 (d, 1H, H-3′, $J_{2'-3'} = 6.9$ Hz), 5.59 (m, 2H, H-5,H-3′), 4.45 (dd, 2H, H-6′, H-6″, J = 36.8 Hz, J = 11.5 Hz), 3.9–3.5 (dd, 2H, H-5, H-5′, J = 17.0 Hz, J = 117.9 Hz), 2.06 (s, 3H, CH_3CO_2),

2.03 (s, 3H, CH_3CO_2); MS (matrix GT): FAB > 0 *m/z* 975 $(2M+H)^+$, 488 $(M+H)^+$, 105 $(C_6H_5CO)^+$, 43 $(CH_3CO)^+$ FAB < 0 *m/z* 486 $(M-H)^-$, 121 $(C_6H_5CO_2)^-$, 111 $(B)^-$, 59 $(CH_3CO_2)^-$.

1-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)thymine (7)

Thymine was condensed with **4** (1.05 g, 2.41 mmol) under the same conditions as described for **6** to give **7** (517 mg) in 45% yield.

^{1}H-NMR (DMSO-d_6): δ 11.52 (s, 1H, NH), 8.0–7.3 (m, 6H, C_6H_5CO, H-6), 5.99 (d, 1H, H-1′, $J_{1'-2'} = 5.4$ Hz), 5.65 (d, 1H, H-3′, $J_{2'-3'} = 6.8$ Hz), 5.50 (pt, 1H, H-2′, $J_{2'-3'} = 6.7$, $= J_{1'-2'} = 5.5$ Hz), 4.40 (dd, 2H, H-6′, H-6″, J = 52.2 Hz, J = 11.5 Hz), 3.9–3.5 (dd, 2H, H-5, H-5′, J = 17.0 Hz, J = 121.9 Hz), 2.00 (s, 3H, CH_3CO_2), 1.98 (s, 3H, CH_3CO_2), 1.51 (s, 3H, CH_3); MS (matrix GT): FAB > 0 *m/z* 1003 $(2M+H)^+$, 502 $(M+H)^+$, 376 $(S)^+$, 127 $(BH_2)^+$, 105 $(C_6H_5CO)^+$, 43 $(CH_3CO)^+$ FAB < 0 *m/z* 500 $(M-H)^-$, 125 $(B)^-$, 121 $(C_6H_5CO_2)^-$, 59 $(CH_3CO_2)^-$.

1-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)-N^4-benzoylcytosine (8)

N^4-Benzoylcytosine was condensed with **4** (1.04 g, 2.39 mmol) under the same conditions as described for **6** to give **8** (670 mg) in 47% yield.

^{1}H-NMR (DMSO-d_6): δ 11.37 (brs, 1H, NH), 8.19 (d, 1H, H-6, $J_{5-6} = 7.4$ Hz), 7.7–7.4 (m, 10H, $2C_6H_5CO$), 7.33 (d, 1H, H-5, $J_{5-6} = 7.4$ Hz), 6.06 (d, 1H, H-1′, $J_{1'-2'} = 3.7$ Hz), 5.84 (d, 1H, H-3′, $J_{2'-3'} = 7.1$ Hz), 5.70 (dd, 1H, H-2′, $J_{2'-3'} = 7.0$, $= J_{1'-2'} = 3.7$ Hz), 4.51 (dd, 2H, H-6′, H-6″, J = 23.0 Hz, J = 11.5 Hz), 4.0–3.6 (dd, 2H, H-5, H-5′, J = 13.5 Hz, J = 74.8 Hz), 2.08 (s, 6H, $2CH_3CO_2$); MS (matrix GT): FAB > 0 *m/z* 591 $(M+H)^+$, 376 $(S)^+$, 216 $(BH_2)^+$, 105 $(C_6H_5CO)^+$, 43 $(CH_3CO)^+$ FAB < 0 *m/z* 589 $(M-H)^-$, 214 $(B)^-$, 121 $(C_6H_5CO_2)^-$, 59 $(CH_3CO_2)^-$.

1-(4-*C*-Azidomethyl-β-D-ribofuranosyl)uracil (9)

A solution of **6** (620 mg, 1.27 mmol) in methanolic ammonia (previously saturated at −10°C) (32 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (60 ml) and water (60 ml). The aqueous layer was washed with ethyl acetate (2 × 60 mL) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: methanol (10%) in methylene chloride] to give pure **9** (330 mg, 87%) which was crystallized from absolute ethanol to afford white crystals.

m.p.: 202–203°C (dec.); UV (EtOH): $\lambda_{max} = 260$ nm ($\varepsilon = 11700$), $\lambda_{min} = 229$ nm ($\varepsilon = 3000$); ^{1}H-NMR (DMSO-d_6): δ 11.35 (s, 1H, NH), 8.06 (d, 1H,

H-6, $J_{6-5} = 8.3$ Hz), 5.90 (d, 1H, H-1′, $J_{1'-2'} = 7.7$ Hz), 5.69 (d, 1H, H-5, $J_{5-6} = 8.1$ Hz), 5.45 (d, 1H, OH-2′, $J_{2'\text{-OH}} = 6.4$ Hz), 5.40 (d, 1H, OH-3′, $J_{3'\text{-OH}} = 4.7$ Hz), 5.29 (t,1, OH-5′, $J_{5'\text{-OH}} = J_{5''\text{-OH}} = 5.1$ Hz), 4.23 (m, 1H, H-2′), 4.04 (pt, 1H, H-3′, J = 4.6 Hz, J = 5.0 Hz), 3.56–3.50 (m, 2H, H-5′, H-5″), 3.47–3.31 (m, 2H, H-6′, H-6″); MS (matrix GT): FAB > 0 *m/z* 300 $(M+H)^+$, 113 $(BH_2)^+$, FAB < 0 *m/z* 298 $(M-H)^-$, 111 (B^-); Anal. Calcd ($C_{10}H_{13}N_5O_6$): C 40.14, H 4.38, N 23.40. Found: C 39.77, H 4.40, N 23.20.

1-(4-*C*-Azidomethyl-β-D-ribofuranosyl)thymine (10)

Compound **7** (494 mg, 0.985 mmol) was treated with methanolic ammonia under the same conditions as described for the preparation of **9**. After the usual work-up, the residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (5%–7%) in methylene chloride] to give pure **10** (286 mg, 93%) which was crystallized from a methylene chloride/methanol mixture as white crystals.

m.p.: 184–185°C (dec.); UV (EtOH): $\lambda_{max} = 265$ nm ($\varepsilon = 7700$), $\lambda_{min} = 232$ nm ($\varepsilon = 2000$); ^{1}H-NMR (DMSO-d_6): δ 11.35 (s, 1H, NH), 7.89 (s, 1H, H-6), 5.89 (d, 1H, H-1′, $J_{1'-2'} = 7.8$ Hz), 5.40 (d, 1H, OH-2′, $J_{2'\text{-OH}} = 6.5$ Hz), 5.34 (d, 1H, OH-3′, $J_{3'\text{-OH}} = 4.6$ Hz), 5.29 (t,1, OH-5′, $J_{5'\text{-OH}} = J_{5''\text{-OH}} = 5.2$ Hz), 4.26 (m, 1H, H-2′), 4.04 (pt, 1H, H-3′, J = 4.6 Hz, J = 5.0 Hz), 3.57–3.48 (m, 2H, H-5′, H-5″), 3.39–3.34 (m, 2H, H-6′, H-6″), 1.79 (s, 1H, CH_3); MS (matrix GT): FAB > 0 *m/z* 627 $(2M+H)^+$, 314 $(M+H)^+$, 127 $(BH_2)^+$, FAB < 0 *m/z* 625 (2M+H)+, 312 $(M-H)^-$, 125 (B^-); Anal. Calcd ($C_{11}H_{15}N_5O_6$): C 42.17, H 4.83, N 22.36. Found: C 42.31, H 4.88, N 21.96.

1-(4-*C*-Azidomethyl-β-D-ribofuranosyl)cytosine, hydrochloride form (11)

Compound **8** (670 mg, 1.13 mmole mmol) was treated with methanolic ammonia (previously saturated at −10°C), (23 mL) at 100°C in a stainless-steel bomb for 3 hours, then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride (40 ml) and water (40 mL). The aqueous layer was washed with methylene chloride (2 × 40 mL) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: methylene chloride/methanol/ammonium hydroxide solution 75:20:5, v/v)]. The collected fractions were concentrated and diluted with absolute ethanol (6.3 mL). To the solution was added a 2N hydrochloric acid solution (1.5 mL) and the mixture was stirred before being concentrated under reduced pressure. The procedure was repeated twice to allow **11** (217 mg, 57%) to crystallize as a white solid from absolute ethanol.

m.p.: 213–215°C (dec.); UV (EtOH): λ_{max} = 277 nm (ε = 11900), λ_{min} = 229 nm (ε = 5300); ^{1}H-NMR (DMSO-d_6): δ 9.80 (s, 1H, NH_2), 8.70 (s, 1H, NH_2), 8.21 (1H, H-6, J_{6-5} = 7.8 Hz), 6.20 (1H, H-5, J_{6-5} = 7.8 Hz), 5.89 (d, 1H, H-1′, $J_{1'-2'}$ = 7.8 Hz), 5.8–5.0 (brs, 3H, OH-2′, OH-3′, OH-5′), 4.23 (pt, 1H, H-2′, J = 5.6 Hz, J = 6.2 Hz), 4.10 (d, 1H, H-3′, J = 5.1 Hz), 3.64–3.48 (m, 4H, H-5′, H-5″, H-6′, H-6″); MS (matrix GT): FAB > 0 *m/z* 627 $(2M+H)^+$, 314 $(M+H)^+$, 127 $(BH_2)^+$, FAB < 0 *m/z* 625 (2M+H)+, 312 $(M-H)^-$, 125 (B^-); Anal. Calcd ($C_{10}H_{15}ClN_6O_5$): C 35.88, H 4.52, N 25.11, Cl 10.59. Found: C 36.04, H 4.65, N 24.88, Cl 10.66.

9-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)adenine (12)

A solution of **4** (1.00 g, 2.30 mmol) in anhydrous acetonitrile (46 ml) was treated with adenine (379 mg, 2.80 mmol) and tin(IV) chloride ($SnCl_4$, 540 μl, 4.60 mmol) and stirred at room temperature overnight. The solution was concentrated under reduced pressure, diluted with chloroform (100 ml) and treated with a cold saturated aqueous solution of $NaHCO_3$ (100 ml). The mixture was filtered on celite, and the precipitate was washed with hot chloroform. The combined filtrates were washed with water (100 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (2–4%) in dichloromethane] to afford **12** (581 mg, 50%), which was crystallized from absolute ethanol to afford white crystals.

m.p.: 120–122°C (dec.); ^{1}H-NMR (DMSO-d_6): δ 8.31 (s, 1H, H-2), 8.1–7.3 (m, 6H, C_6H_5CO, H-8), 7.36 (brs, 2H, NH_2), 6.37 (d, 1H, H-1′, $J_{1'-2'}$ = 5.8 Hz), 6.27 (t, 1H, H-2′, $J_{1'-2'} = J_{2'-3'}$ = 6.0 Hz), 5.98 (d, 1H, H-3′, $J_{2'-3'}$ = 6.2 Hz), 4.67 (d, 1H, H-5′, J = 11.8 Hz), 4.45 (d, 1H, H-5″, J = 11.8 Hz), 3.94 (d, 1H, H-6′, J = 13.4 Hz), 3.67 (d, 1H, H-6″, J = 13.4 Hz), 2.14 (s, 3H, CH_3CO_2), 2.02 (s, 3H, CH_3CO_2); MS (matrix GT): FAB > 0 *m/z* 1021 $(2M+H)^+$, 511 $(M+H)^+$, 136 $(BH_2)^+$, 105 $(C_6H_5CO)^+$, 43 $(CH_3CO)^+$ FAB < 0 *m/z* 509 $(M-H)^-$, 134 $(B)^-$, 121 $(C_6H_5CO_2)^-$, 59 $(CH_3CO_2)^-$.

9-(4-*C*-Azidomethyl-β-D-ribofuranosyl)adenine (13)

Compound **12** (575 mg, 1.13 mmol) was treated with methanolic ammonia and purified under the same conditions as described for **9** to give pure **13** (350 mg, 96%) which was crystallized from absolute ethanol to give white crystals.

m.p.: 120–122°C (dec.); UV (ethanol): λ_{max} = 258 nm (ε = 15600), λ_{min} = 226 nm (ε = 1800); ^{1}H-NMR (DMSO-d_6): δ 8.42 (s, 1H, H-2), 8.21 (s, 1H, H-8), 7.42 (s, 2H, NH_2), 5.98 (d, 1H, H-1′, $J_{1'-2'}$ = 7.8 Hz), 5.67 (pt, 1H, OH-5′, J = 4.7 Hz, J = 6.7 Hz), 5.56 (d, 1H, OH-2′, J = 6.7 Hz), 5.51 (d, 1H,

OH-3′, J = 4.3 Hz), 4.99 (dd, 1H, H-2′, J = 6.8 Hz, J = 12.3 Hz), 4.23 (dd, 1H, H-3′, J = 4.3 Hz, J = 4.7 Hz), 3.74–3.62 (m, 2H, H-5′, H-5″); MS (matrix GT): FAB > 0 *m/z* 645 $(2M+H)^+$, 323 $(M+H)^+$, 136 $(B+2H)^+$, FAB < 0 *m/z* 321 $(M-H)^-$, 134 $(B)^-$; Anal. Calcd ($C_{11}H_{14}N_8O_4.0.5\ H_2O$): C 39.88, H 4.56, N 33.82. Found: C 39.48, H 4.46, N 33.38.

9-(4-*C*-Azidomethyl-β-D-ribofuranosyl)-6-methylaminopurine (15)

To a solution of **4** (600 mg, 1.38 mmol) and 6-chloropurine (234 mg, 1.52 mmol) in dry acetonitrile (5.5 ml) was added at 0°C under argon DBU (0.62 ml, 4.15 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSTf, 1.06 mL, 5.48 mmol). The solution was stirred for 2 hrs at 60°C under argon atmosphere, then diluted with methylene chloride (100 mL), washed with a saturated aqueous sodium hydrogen carbonate solution (100 mL) and with water (100 mL). The organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude material **14** was treated with 40% methylamine in water (27.6 ml) and stirred at room temperature overnight. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride (50 ml) and water (50 ml). The aqueous layer was washed with methylene chloride (2 × 50 mL), and concentrated under reduced pressure. The residue was purified by chromatography on LiChroprep RP-18, using a stepwise gradient of acetonitrile (2–12%) in water and lyophilized to give **15** (355 mg, 76%, 2 steps) as a white powder.

^{1}H-NMR (DMSO-d_6): δ 8.35 (s, 1H, H-2), 8.24 (s, 1H, H-8), 7.84 (brs, 1H, NH), 5.92 (d, 1H, H-1′, $J_{1'-2'}$ = 7.8 Hz), 5.61 (brs, 1H, OH-5′), 5.49 (brs, 2H, OH-2′, OH-3′), 4.93 (dd, 1H, H-2′, J = 5.0 Hz, J = 7.7 Hz), 4.18 (d, 1H, H-3′, J = 4.9 Hz), 3.67–4.46 (m, 4H, 4H, H-5′, H-5″, H-6′, H-6″), 2.96 (brs, 1H, CH_3); MS (matrix GT): FAB > 0 *m/z* 337 $(M+H)^+$, 150 $(B+2H)^+$, FAB < 0 *m/z* 671 $(2M-H)^-$, 335 $(M-H)^-$, 1148 $(B)^-$.

9-(2,3-Di-*O*-acetyl-4-*C*-azidomethyl-5-*O*-benzoyl-β-D-ribofuranosyl)-2-amino-6-chloropurine (16)

A suspension of 2-amino-6-chloropurine (1.52 g, 8.96 mmol) was treated with HMDS (45 mL) and a catalytic amount of ammonium sulfate during 17 hours under reflux. After cooling to room temperature, the mixture was evaporated under reduced pressure, and the residue, obtained as a yellow solid, was diluted with dry toluene (15 mL). To the resulting solution was added **4** (3.0 g, 6.89 mmol) in dry toluene (15 mL), followed by addition of TMSOTf (2.26 mL, 11.7 mmol). The solution was refluxed for 1 hours under argon atmosphere, then diluted with ethyl acetate (200 mL), washed with a saturated aqueous sodium hydrogen carbonate solution (100 mL), and with water (2 × 100 mL). The organic phase was dried over sodium

sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography [eluent: stepwise gradient of ethyl acetate (15–20%) in methylene chloride] to afford pure **16** (1.56 g, 42%) as a beige foam.

^{1}H-NMR (DMSO-d_6): δ 8.36 (s, 1H, H-8), 8.0–7.4 (m, 5H, C_6H_5CO), 7.04 (brs, 2H, NH_2), 6.30 (d, 1H, H-1′, $J_{1'-2'} = 6.0$ Hz), 6.10 (t, 1H, H-2′, $J_{1'-2'} = J_{2'-3'} = 6.1$ Hz), 6.02 (d, 1H, H-3′, $J_{2'-3'} = 6.2$ Hz), 4.63 dd (2H, H-5′, H-5″, J = 11.6 Hz, J = 46, 4 Hz), 3.82 (dd, 2H, H-6′, H-6″, J = 61.5 Hz), 2.18 (s, 3H, CH_3CO_2), 2.05 (s, 3H, CH_3CO_2); MS (matrix GT): FAB > 0 *m/z* 545 $(M+H)^+$, 376 $(S)^+$, 170 $(BH_2)^+$, 105 $(C_6H_5CO)^+$, 43 $(CH_3CO)^+$ FAB < 0 *m/z* 543 $(M-H)^-$, 168 $(B)^-$, 121 $(C_6H_5CO_2)^-$, 59 $(CH_3CO_2)^-$.

9-(4-*C*-Azidomethyl-β-D-ribofuranosyl)guanine (17)

To a solution of **16** (810 mg, 1.49 mmol) in dry methanol (30 mL) was added 2-mercaptoethanol (0.418 mL, 5.96 mmol) and sodium methoxide (322 mg, 5.96 mmol). The reaction mixture was stirred at reflux overnight under argon atmosphere, neutralized with Dowex 50 W × 2 resin (H^+ form) and concentrated under reduced pressure. The residue was partitioned between methylene chloride (70 mL) and water (50 mL). The aqueous layer was washed with methylene chloride (50 mL), with ethyl acetate (50 mL), filtered and evaporated to dryness. The crude residue was purified by chromatography on LiChroprep RP-18 [eluent: stepwise gradient of acetonitrile (0–7%) in water] to afford pure **17** (155 mg, 31%). Crystallization from water gave **17** as a crystalline solid.

m.p.: 242–243°C (dec.); UV (ethanol): $\lambda_{max} = 252$ nm ($\varepsilon = 14600$), $\lambda_{shoulder} = 268$ nm ($\varepsilon = 10200$), $\lambda_{min} = 221$ nm ($\varepsilon = 3000$); ^{1}H-NMR (DMSO-d_6): δ 10.64 (s, 1H, NH), 8.22 (s, 1H, H-8), 6.47 (sl, 2H, NH_2), 5.75 (d, 1H, H-1′, $J_{1'-2'} = 7.9$ Hz), 5.47 (d, 1H, OH, OH-2′, $J_{OH-2'} = 6.7$ Hz), 5.37 (d, 1H, OH-3′, $J_{OH-3'} = 4.3$ Hz), 5.23 (t, 1H, OH, OH-5′, $J_{OH-5'} = J_{OH-5''} = 5.4$ Hz), 4.69 (dd, 1H, H-2′, J = 7.1 Hz, J = 12.3 Hz), 4.12 (t, 1H, H-3′, $J_{3'-2'} = J_{3'-OH'} = 4.5$ Hz), 3.58–3.50 (m, 4H, H-5′, H-5″, H-6′, H-6″); MS (matrix GT): FAB > 0 *m/z* 677 $(2M+H)^+$, 339 $(M+H)^+$, 152 $(BH_2)^+$, FAB < 0 *m/z* 337 $(M-H)^-$, 150 $(B)^-$; Anal. Calcd ($C_{11}H_{14}N_8O_5.1.5\ H_2O$): C 36.16, H 4.69, N 30.68. Found: C 36.87, H 5.20, N 30.66.

9-(4-*C*-Azidomethyl-β-D-ribofuranosyl)-2-amino-6-cyclopropylaminopurine (18)

A solution of **16** (750 mg, 1.37 mmol) in methanolic ammonia (previously saturated at −10°C) (28 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography [eluent: stepwise gradient of methanol (5–6%) in dichloromethane] to afford the

intermediate 9-(4-*C*-azidomethyl-β-D-ribofuranosyl)2-amino-6-chloropurine as a white solid (355 mg, 0.995 mmol). This intermediate was treated with cyclopropylamine (0.482 ml, 6.97 mmol) in dry ethanol (20 ml) at reflux overnight. The solvents were evaporated under reduced pressure and the residue was purified by chromatography on LiChroprep RP-18, using a stepwise gradient of acetonitrile (0–15%) in water and lyophilized to give **18** (330 mg, 64%, 2 steps) as a white powder.

^{1}H-NMR (DMSO-d_6): δ 8.57 (s, 1H, H-8), 8.19 (s, 1H, NH), 5.82 (sl, 2H, NH_2), 5.77 (d, 1H, H-1′, $J_{1'\text{-}2'} = 7.9$ Hz), 5.62 (brs, 1H, OH-5′), 5.43 (brs, 1H, OH-2′), 5.37 (brs, 1H, OH-3′), 4.79 (dd, 1H, H-2′, J = 5.0 Hz, J = 7.7 Hz), 4.12 (d, 1H, H-3′, J = 4.9 Hz), 3.61–3.33 (m, 4H, H-5′, H-5″, H-6′, H-6″), 3.05 (brs, 1H, CH), 0.69–0.57 (m, 2H, CH_2-CH_2); MS (matrix GT): FAB > 0 *m/z* 755 $(2M+H)^+$, 378 $(M+H)^+$, 191 $(BH_2)^+$, FAB < 0 *m/z* 753 $(2M\text{-}H)^-$, 376 $(M\text{-}H)^-$, 189 $(B)^-$.

REFERENCES

1. For reviews on *Flavivirus,* see: a) Leyssen, P.; De Clercq, E.; Neyts, J. Perspectives for the treatment of infections with *Flaviviridae*. *Clin. Microbiol. Rev.* **2000**, 13, 67–82. b) Ghosh, D.; Basu, A. Present perspectives on flaviviral chemotherapy. *Drug Discovery Today* **2008**, 13, 619–624. c) Malet, H.; Massé, N.; Selisko, B.; Romette, J.-L.; Alvarez, K.; Guillemot, J.-C.; Tolou, H.; Yap, T.L.; Vasudevan, S.G.; Lescar, J.; Canard, B. The flavivirus polymerase as a target for drug discovery. *Antiviral Res.* **2008**, 80, 23–35. d) Sampath, A.; Padmanabhan, R. Molecular targets for flavivirus drug discovery.*Antiviral Res.* **2009**, 81, 6–15.
2. a) www.who.int/mediacentre/factsheets (accessed February 16, 2009). b) www.cdc.gov/ncidod/diseases/hepatitis/c:fact (accessed February 16, 2009).
3. For two recent reviews on therapies in chronic hepatitis C, see: a) Zeuzem, S. Interferon-based therapy for chronic hepatitis C: Current and future perspectives. *Nature Clinical Practice Gastroenterology & Hepatology* **2008**, 5, 610–622. a) Soriano, V.; Peters, M.G.; Zeuzem, S. New therapies for hepatitis C virus infection. *Clin. Infect. Dis.* **2009**, 48, 313–320.
4. a) Kwong, A.D.; McNair, L.; Jacobson, I.; George, S. Recent progress in the development of selected hepatitis C virus NS3.4A protease and NS5B polymerase inhibitors. *Curr. Opin. Pharmacol.* **2008**, 8, 522–531. b) Liu-Young, G.; Kozal, M.J. Hepatitis C protease and polymerase inhibitors in development. *AIDS Patient Care and STDs* **2008**, 22, 449–457.
5. a) Sommadossi, J.-P.; La Colla, P. Methods and compositions for treating hepatitis C virus. Patent WO2001090121, 2001 (313 pages). b) Sommadossi, J.-P.; La Colla, P. Methods and compositions for treating flaviviruses and pestiviruses. Patent WO2001092282, 2001 (321 pages). c) Benzaria, S.; Bardiot, D.; Bouisset, T.; Counor, C.; Rabeson, C.; et al. 2′-*C*-methyl branched pyrimidine ribonucleoside analogues: potent inhibitors of RNA virus replication. *Antiviral Chem. Chemother.* **2007**, 18, 225–242.
6. a) Pierra, C.; Benzaria, S.; Amador, A.; Moussa, A.; Mathieu, S.; Storer, R.; Gosselin, G. NM283, an efficient prodrug of the potent anti-HCV agent 2′-*C*-methylcytidine. *Nucleosides, Nucleotides Nucleic Acids* **2005**, 24, 767–770. b) Pierra, C.; Amador, A.; Benzaria, S.; Cretton-Scott, E.; D'Amours, M.; Mao, J.; Mathieu, S.; Moussa, A.; Bridges, E.G.; Standring, D.N.; Sommadossi, J.-P.; Storer, R.; Gosselin, G. Synthesis and pharmacokinetics of valopicitabine (NM283), an efficient prodrug of the potent anti-HCV agent 2′-*C*-methylcytidine. *J. Med. Chem.* **2006**, 49, 6614–6620.
7. Godofsky, E.; Afdhal, N.; Rustgi, V.; Shick, L.; Duncan, L.; Zhou, X.-J.; Chao, G.; Fang, C.; Fielman, B.; Myers, M.; Brown, N. A phase I/II dose escalation trial assessing tolerance, pharmacokinetics, and antiviral activity of NM283, a novel antiviral treatment for hepatitis C. *Gastroenterology* **2004**, 126, A–681.
8. a) Rodriguez-Torres, M.; Lalezari, J.; Gane, E.J.; DeJesus, E.; Nelson, D. R.; et al. Potent antiviral response to the HCV nucleoside polymerase inhibitor R7128 for 28 days with Peg-INF and ribavirine:

subanalysis by race/ethnicity, weight and HCV genotype. The 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), San Francisco, California, USA, October 31-November 4, 2008, Abstract 1899. b) Gane, E.J.; Rodriguez-Torres, M.; Nelson, D.R.; Jacobson, I.M.; et al. Antiviral activity of the HCV nucleoside polymerase inhibitor R7128 in HCV genotype 2 and 3 prior non-responders: results of R7128 1500 mg BID with Peg-INF and ribavirine for 28 days. The 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), San Francisco, California, USA, October 31-November 4, 2008, Abstract LB10.

9. a) Pockros, P.J.; Nelson, D.; Godofsky, E.; Rodriguez-Torres, M.; Everson, G.T.; et al. R1626 plus Peginterferon alfa-2a provides potent suppression of hepatitis C virus RNA and significant antiviral synergy in combination with ribavirin. *Hepatology* **2008**, 48, 385–397. b) Roberts, S.K.; Cooksley, G.; Dore, G.J.; Robson, R.; Shaw, D.; et al. Hepatology **2008**, 48, 398–406. c) Toniutto, P.; Fabris, C.; Bitetto, D.; Fumolo, E.; Fornasiere, E.; Pirisi, M. R-1626, a specific oral NS5B polymerase inhibitor of hepatitis C virus. *IDRUGS* **2008**, 11, 738–749.
10. Clark, J.L.; Hollecker, L.; Mason, J.C.; Stuyver, L.J.; Tharnish, P.M.; et al. Design, synthesis, and antiviral activity of 2′-deoxy-2′-fluoro-2′-*C*-methylcytidine, a potent inhibitor of hepatitis C virus replication. *J. Med. Chem.* **2005**, 48, 5504–5508.
11. a) Klumpp, K.; Lévêque, V.; Le Pogam, S.; Ma, H.; Jiang, W.-R.; et al. The novel nucleoside analog R1479 (4′-azidocytidine) is a potent inhibitor of NS5B-dependant RNA synthesis and hepatitis C virus replication in cell culture. *J. Biol. Chem.* **2006**, 281, 3793–3799. b) Smith, D.B.; Martin, J.A.; Klumpp, K.; Baker, S. J.; Blomgren, P.A.; et al. Design, synthesis, and antiviral properties of 4′-substituted ribonucleosides as inhibitors of hepatitis C virus replication: the discovery of R1479. *Bioorg. Med. Chem. Lett.* **2007**, 17, 2570–2576.
12. a) Gosselin, G.; Imbach, J.-L.; Sommadossi, J.-P. Methods and compositions for treating hepatitis C virus using 4′-modified nucleosides. Patent WO2003026589, 2003 (173 pages). b) Griffon, J.-F.; Dukhan, D.; Pierra, C.; Benzaria, S.; Loi, A.G.; et al. 4′-*C*-Methyl-β-D-ribofuranosyl purine and pyrimidine nucleosides revisited. *Nucleosides, Nucleotides Nucleic Acids* **2003**, 22, 707–709.
13. Baker, B.R. Stereochemistry of nucleoside synthesis, in *The Ciba Foundation Symposium on the Chemistry and Biology of the Purines*, eds. G.E. Wolstenholme and C.M. O'Connor, Churchill, London, 1957, pp. 120–130.
14. Gunic, E.; Girardet, J.-L.; Pietrzkowski, Z.; Esler, C.; Wang, G. Synthesis and cytotoxicity of 4′-*C*- and 5′-*C*-substituted toyocamycins. *Bioorg. Med. Chem.* **2001**, 9, 163–170.
15. a) Schaffer, R.; Isbell, H.S. Structure of 5-aldo-1,2-*O*-isopropylidene-D-xylo-pentofuranose. *J. Am. Chem. Soc.* **1957**, 79, 3864–3866. b) Schaffer, R. Branched-chain higher sugars. III. A 4-*C*-(hydroxymethyl)-pentose. *J. Am. Chem. Soc.* **1959**, 81, 5452–5454. c) Leonard, N.J.; Carraway, K.L. 5-Amino-5-deoxyribose derivatives. Synthesis and use in the preparation of reversed nucleosides. *J. Heterocyc. Chem.* **1966**, 3, 485–489. d) Jones, G.H.; Moffatt, J.G. Oxidation of carbohydrates by the sulfoxide-carbodiimide and related methods. Oxidation with dicyclohexylcarbodiimide-DMSO, diisopropylcarbodiimide-DMSO, acetic anhydride-DMSO, and phosphorus pentaoxide-DMSO (dimethyl sulfoxide). *Methods in Carbohydrate Chemistry* **1972**, 6, 315–322. e) Youssefyeh, R.D.; Verheyden, J.P.H.; Moffatt, J.G. 4′-Substituted nucleosides. 4. Synthesis of some 4′-hydroxymethyl nucleosides. *J. Org. Chem.* **1979**, 44, 1301–1309. f) Jones, G.H.; Taniguchi, M.; Tegg, D.; Moffatt, J.G. 4′-Substituted nucleosides. 5. Hydroxymethylation of nucleoside 5′-aldehydes. *J. Org. Chem.* **1979**, 44, 1309–1317.
16. a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. Nucleoside syntheses. XXII. Nucleoside synthesis with trimethylsilyl triflate and perchlorate as catalysts. *Chemische Berichte* **1981**, 114, 1234–1255. b) Vorbrüggen, H.; Hoefle, G. Nucleoside syntheses. XXIII. On the mechanism of nucleoside synthesis. *Chemische Berichte* **1981**, 114, 1256–1268.
17. Saneyoshi, M.; Satoh, E. Synthetic nucleosides and nucleotides. XIII. Stannic chloride catalyzed ribosylation of several 6-substituted purines. *Chem. Pharma. Bull.* **1979**, 27, 2518–2521.
18. Chu, C.K.; Ma, L.; Olgen, S.; Pierra, C.; Du, J.; et al. Synthesis and antiviral activity of oxaselenolane nucleosides. *J. Med. Chem.* **2000**, 43, 3906–3912.