Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9635–9639

TETRAHEDRON

Synthesis of new acyclonucleosides comprising unexpected regioisomers in the case of purines

Stéphane Guillarme,[a] Stéphanie Legoupy,[a] Nathalie Bourgougnon,[b] Anne-Marie Aubertin[c] and François Huet[a,*]

[a]*Laboratoire de Synthèse Organique, UMR CNRS 6011, Faculté des Sciences et Techniques, Université du Maine, Avenue Olivier Messiaen, F-72085 Le Mans Cedex 9, France*
[b]*Laboratoire de Biologie et Chimie Moléculaire, Centre de recherche et d'enseignement Yves Coppens, Campus de Tohannic, BP 573, F-56017 Vannes, France*
[c]*Faculté de Médecine, Institut de Virologie, INSERM U544, Université Louis Pasteur, 3 rue Koeberlé, F-67000 Strasbourg, France*

Received 30 May 2003; revised 2 September 2003; accepted 29 September 2003

Abstract—Acyclonucleosides **4** have been obtained by a short way starting from ethyl 2-hydroxymethyl acrylate **5**. The key intermediate was acetate **9**. Its reaction with free or protected nucleic bases gave either the expected compounds or unusual regioisomers.

1. Introduction

Nucleoside analogues are currently used as antiviral agents, for instance against human immunodeficiency virus (HIV), or hepatitis B (HBV) and herpes viruses. In several cases, acyclic nucleosides appeared as an useful class of compounds for antiviral chemotherapy.[1] Indeed, the remarkable activity of acyclonucleosides such as acyclovir **1**[2] and ganciclovir **2**[3] which are potent antiherpetic agents shows the interest of this class of compounds. In these cases, the biological activity is remarkable despite important modifications of the sugar moiety with respect to the natural products (Fig. 1).

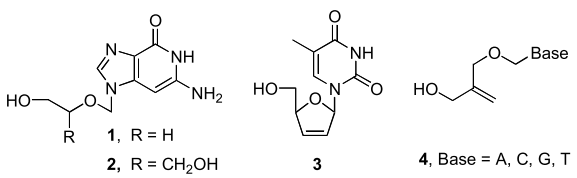


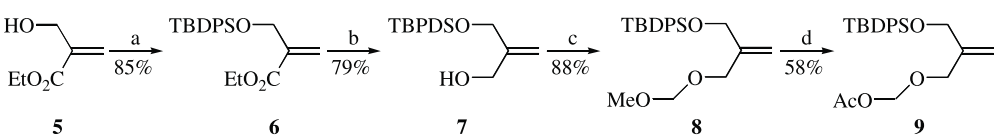
Figure 1.

Ongoing our interest in the synthesis of acyclic nucleosides[4] we considered the synthesis of new class of unsaturated acyclonucleosides **4**, which can be viewed as regioisomers of the 1′,2′-seconucleoside of d4T **3**, used in the treatment of AIDS[5] (Scheme 1).

2. Results and discussion

Starting from ethyl 2-hydroxymethyl acrylate **5**, adduct of Baylis–Hillman,[6] a two step synthesis led to alcohol **7** in 67% overall yield. However, first attempts to obtain directly the acetate **9** by reaction of alcohol **7** with methyl chloroacetate[7] in basic conditions gave no result. Therefore, we first prepared compound **8** following the method of Gras et al.[8] and it was obtained in 88% yield. Its treatment with acetic anhydride in the presence of sulfuric acid provided the required acetate **9** in 58% yield (Scheme 1).[9]

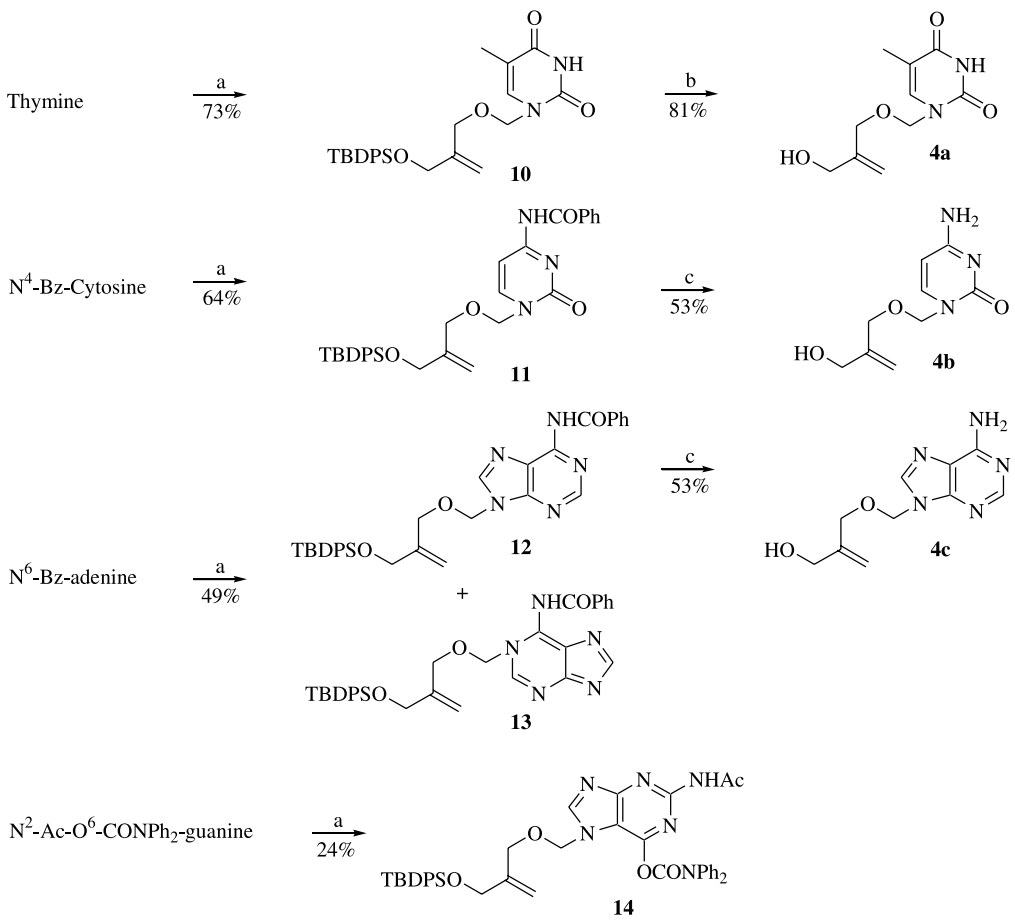
When **9** was subjected to the one-pot substitution by thymine and *N*-4-benzoylcytosine in Vorbrüggen et al.[10]



Scheme 1. (a) *t*BuPh$_2$SiCl, pyridine; (b) DIBAL–H, toluene, −70°C; (c) CH$_2$(OMe)$_2$, LiBr, APTS; (d) H$_2$SO$_4$, Ac$_2$O.

Keywords: nucleosides; purines; pyrimidines; regiochemistry.
* Corresponding author. Tel.: +33-2-43-83-33-38; fax: +33-2-43-83-39-02; e-mail: fhuet@univ-lemans.fr

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.093



Scheme 2. (a) (1) BSA, CH_3CN; (2) TMSOTf, **9**; (b) TBAF, THF; (c) (1) NH_3/MeOH, (2) TBAF, THF.

conditions modified by Dudycz et al.,[11] the expected products **10** and **11** were obtained in good yields (Scheme 2).

Regiochemistry for the nucleoside **10** was confirmed by HMBC experiments (Fig. 2). Condensation also worked with the protected purine bases but in lower yield. On the other hand unexpected isomers were isolated. With protected adenine, at 20°C, we were surprised to obtain a mixture of N-9 **12** and N-1 **13** alkylated products, in a 1:1 ratio, which could be separated by chromatography (Scheme 2). The reaction run at 85°C afforded the thermodynamically more stable regioisomer N-9 **12**. To assign N-9 and N-1 regiochemistries for isomers **12** and **13**, respectively, HMBC experiments have been carried out (Fig. 2). In purine derivatives, C-5 is the only quaternary C of the base moiety close to only one N. Therefore, its signal is always at higher field. The long-range couplings (^3J) between C-5 and H-8, but not with H-2, in the HMBC spectrum, easily led to assignment of these two protons. Afterwards the ^1J $^1H/^{13}C$ correlation led to the assignments of the corresponding carbons, C-2 and C-8. As C-6 was correlated only with H-2, and C-4 with H-2 and H-8, they also could be assessed. Finally, for **12**, correlation (^3J) between H-1′ and C-8 and C-4 proved the N-9 regiochemistry. For **13**, correlation (^3J) between H-1′ and C-6 and C-2 proved the N-1 regiochemistry. Obtaining the kinetic isomer N-1 **13**, which is quite unusual, could be explained by the mechanism proposed by Vorbrügen et al.[10b] Regioselectivity was surprising also for the protected guanine, which exclusively led, at 20°C, to the N-7 isomer **14** (Scheme 2) (Fig. 2). When alkylation reaction was performed at 85°C, the same result was obtained, and all attempts to isomerize[12] **14** to the corresponding N-9 isomer have been unsuccessful. This result was not expected, however, such a regioselectivity has already been observed by Goodnow et al.[13] Removal of the protecting groups afforded the acyclonucleosides **4a**, **4b** and **4c** in 81, 53 and 53% yield, respectively.

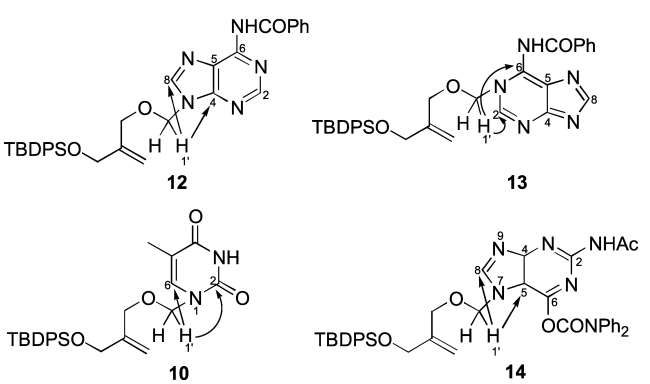


Figure 2. Relevant HMBC correlations.

In conclusion, three new acyclonucleosides were isolated in

6 steps. To the best of our knowledge, obtaining of a N-1 isomer, from reaction with adenine has never been reported. Biological tests showed that the compound **4a** did no have antitumor, anti-HIV and anti-herpes properties.

3. Experimental

3.1. General

All reagents were of commercial quality or purified if necessary and all solvents were distilled and dried by literature procedures.[14] All moisture-sensitive reactions were performed in oven-dried glassware and under inert atmosphere. All melting points were uncorrected. Infrared spectra were measured with a FT infrared spectrometer Genesis, Matteson Instruments. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC400 spectrometer at 400 and 100.6 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS which was used as an internal reference. Elemental analyses were carried out at the Service de Microanalyse, CNRS ICSN, Gif-sur-Yvette. High-resolution mass spectra were recorded on Varian MAT 311 and ZabSpec TOF Micromass spectrometers at the CRMPO, Rennes.

3.1.1. Ethyl 2-(*tert*-butyldiphenylsilyloxymethyl)-acrylate 6. A solution of ethyl 2-hydroxymethyl-acrylate **5**[6] (3.04 g, 23.38 mmol) and *tert*-butyldiphenylsilyl chloride (6.75 g, 25.54 mmol) in pyridine (30 mL) was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and then the residue was dissolved in CH_2Cl_2 (30 mL) and washed twice with water (15 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, cyclohexane/EtOAc: 95:5) of the crude product afforded **6** (7.21 g, 19.64 mmol, 85%) as a pale yellow oil: IR (neat, cm^{-1}) 3072, 3048, 1714, 1643, 1463, 1428, 1270; ^{1}H NMR ($CDCl_3$) δ: 7.62–7.40 (m, 10H, H arom), 6.32 (dt, 1H, =CH, J=2.0, 2.0 Hz), 6.10 (dt, 1H, =CH, J=2.0, 2.2 Hz), 4.42 (dd, 2H, CH_2–O, J=2.0, 2.2 Hz), 4.16 (q, 2H, CH_2–O, J=7.1 Hz), 1.25 (t, 3H, CH_3, J=7.1 Hz), 1.07 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 166.0 (C=O), 139.6 (quat C), 135.4 (quat C), 133.2 (CH), 129.7 (CH), 127.7 (CH), 123.7 (CH_2), 62.2 (CH_2–O), 60.5 (CH_2–O), 26.8 (CH_3), 19.3 (quat C), 14.1 (CH_3).

3.1.2. 2-(*tert*-Butyldiphenylsilyloxymethyl)-prop-2-en-1-ol 7.[15] To a solution of **6** (6.0 g, 16.3 mmol) in anhydrous toluene (90 mL) under inert atmosphere at −70°C was added dropwise a solution 1 M of DiBAl–H in toluene (70 mL, 70 mmol). The solution was stirred 3 h and quenched with a solution 10% (300 mL) of citric acid. The solution was then allowed to warm to room temperature and the aqueous layer was extracted with EtOAc (4×75 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was purified by column chromatography (silica gel, cyclohexane/EtOAc 90:10→85:15) to give **7** (4.22 g, 12.88 mmol, 79%) as a colorless oil. IR (neat, cm^{-1}) 3361, 3072, 3048, 1112; ^{1}H NMR ($CDCl_3$) δ: 7.71–7.40 (m, 10H, H arom), 5.25 (m, 1H, =CH), 5.10 (m, 1H, =CH), 4.25 (s, 2H, CH_2–O), 4.16 (d, 2H, CH_2–O, J=5.6 Hz), 1.95 (t, 1H, OH, J=5.6 Hz), 1.06 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 147.1 (quat C), 135.5 (quat C), 132.2 (CH), 129.7 (CH), 127.7 (CH), 110.3 (CH_2), 65.5 (CH_2–O), 64.4 (CH_2–O), 26.8 (CH_3), 19.2 (quat C).

3.1.3. *tert*-Butyldiphenylsilyl 2-(methoxymethoxymethyl)-prop-2-enyl ether 8. A solution of **7** (4.0 g, 12.26 mmol), lithium bromide (266 mg, 3.06 mmol) and *p*-toluenesulfonic acid (234 mg, 1.23 mmol) in dimethoxymethane (35 mL) was stirred at room temperature for 18 h. Saturated aqueous NaCl was added (10 mL) and the aqueous phase was extracted with Et_2O (3×5 mL). The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 95:5) to afford **8** (3.99 g, 10.79 mmol, 88%) as a colorless oil: IR (neat, cm^{-1}) 3072, 3048, 2931, 2856, 1247, 1112; ^{1}H NMR ($CDCl_3$) δ: 7.62–7.47 (m, 10H, H arom), 5.31 (td, 1H, =CH, J=1.7, 2.0 Hz), 5.16 (m, 1H, =CH, J=2.0 Hz), 4.55 (s, 2H, CH_2–O), 4.22 (t, 2H, CH_2–O, J=1.7 Hz), 4.06 (s, 2H, CH_2–O), 3.34 (s, 3H, CH_3), 1.08 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 144.9 (quat C), 135.9 (quat C), 133.9 (CH), 130.9 (CH), 128.1 (CH), 122.4 (CH_2), 95.2 (CH_2–O), 68.3 (CH_2–O), 65.0 (CH_2–O), 55.1 (CH_3), 27.2 (CH_3), 19.7 (quat C); HRMS (EI) calcd for $C_{17}H_{19}O_2Si$ $[M-C_5H_{11}O]^+$: 283.1154. Found: 283.1158.

3.1.4. 2-(*tert*-Butyldiphenylsilyloxymethyl)-prop-2-enyl acetate 9. To a solution of **8** (3.9 g, 10.52 mmol) in Ac_2O (14 mL) at 0°C was added concentrated H_2SO_4 (233 μL, 4.5 mmol). The solution was stirred at 5°C for 18 h and poured at 0°C in saturated aqueous solution of $NaHCO_3$ (70 mL). Stirring continued at room temperature for 18 h. The solution was then extracted with CH_2Cl_2 (5×15 mL) and the organic phases were washed with water (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, cyclohexane/EtOAc 95:5) to lead to **9** (2.45 g, 6.14 mmol, 58%) as a colorless oil: IR (neat, cm^{-1}) 3072, 3048, 2931, 2857, 1747, 1228, 1114; ^{1}H NMR ($CDCl_3$) δ: 7.68–7.47 (m, 10H, H arom), 5.32 (td, 1H, =CH, J=1.2, 1.5 Hz), 5.21 (s, 2H, CH_2–O), 5.16 (td, 1H, =CH, J=1.2, 1.5 Hz), 4.20 (t, 2H, CH_2–O, J=1.2 Hz), 4.16 (s, 2H, CH_2–O), 2.04 (s, 3H, CH_3), 1.07 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 170.5 (C=O), 143.7 (quat C), 133.5 (quat C), 133.4 (CH), 129.6 (CH), 127.7 (CH), 112.7 (CH_2), 88.1 (CH_2–O), 70.5 (CH_2–O), 64.3 (CH_2–O), 26.5 (CH_3), 20.9 (CH_3), 19.2 (quat C); HRMS (EI) calcd for $C_{18}H_{19}O_3Si$ $[M-C_5H_{11}O]^+$: 311.1103. Found: 311.1116.

3.1.5. 1-[2′-(*tert*-Butyldiphenylsilyloxymethyl)-allyloxymethyl]-thymine 10. To a stirred suspension of thymine (73.7 mg, 0.584 mmol) in anhydrous CH_3CN (1.5 mL) under inert atmosphere was added BSA (297 mg, 1.46 mmol). The solution was stirred at room temperature until a clear solution was obtained. Then the mixture was cooled to 0°C and compound **9** (194 mg, 0.487 mmol) in solution in anhydrous CH_3CN (2 mL) and TMSOTf (113.6 mg, 0.511 mmol) were added. The reaction mixture was stirred at room temperature for 4 h. CH_2Cl_2 (2 mL) was added and then a saturated aqueous solution of $NaHCO_3$ until pH became basic. The organic solvents were removed under reduced pressure and aqueous phase was extracted

with EtOAc (3×3 mL). The organic layer was washed with water (2 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc 8:2) to afford **10** (164 mg, 0.353 mmol, 73%) as a colorless oil: IR (neat, cm^{-1}) 3206, 3070, 3048, 1681, 1112; ^1H NMR ($CDCl_3$) δ: 8.92 (broad s, 1H, NH), 7.68–7.63 (m, 4H, H arom), 7.45–7.32 (m, 6H, H arom), 7.03 (q, 1H, CH, J=1.2 Hz), 5.24 (td, 1H, =CH, J=1.5, 1.5 Hz), 5.18 (td, 1H, =CH, J=1.5, 1.5 Hz), 5.05 (s, 2H, CH_2–N), 4.18 (t, 2H, CH_2–O, J= 1.5 Hz), 4.07 (s, 2H, CH_2–O), 1.88 (d, 3H, CH_3, J=1.2 Hz), 1.05 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 163.9 (C=O), 151.0 (C=O), 143.4 (quat C), 138.9 (CH), 135.5 (quat C), 133.3 (CH), 129.7 (CH), 127.7 (CH), 113.2 (quat C), 111.6 (CH_2), 75.7 (CH_2–N), 69.9 (CH_2–O), 64.2 (CH_2–O), 26.7 (CH_3), 19.2 (quat C) 12.3 (CH_3); Anal calcd for $C_{26}H_{32}N_2O_4Si$: C, 67.21; H, 6.94; N, 6.03. Found: C, 67.57; H, 7.23; N, 5.77.

3.1.6. 1-[2′-(*tert*-Butyldiphenylsilyloxymethyl)-allyloxymethyl]-cytosine 11. *N*-4-Benzoylcytosine (215 mg, 1.0 mmol) and compound **9** (332 mg, 0.833 mmol) in anhydrous CH_3CN (7 mL) were stirred at room temperature for 20 h in the same experimental conditions as for **10**, to give **11** (296 mg, 0.535 mmol, 64%) as a colorless oil after column chromatography (silica gel, CH_2Cl_2/EtOAc 7:3→6:4): IR (neat, cm^{-1}) 3252, 3072, 1676, 1617, 1109; ^1H NMR ($CDCl_3$) δ: 8.91 (broad s, 1H, NH), 7.93 (d, 2H, H arom, J=7.1 Hz), 7.69–7.63 (m, 5H, H arom and CH), 7.58 (tt, 1H, H arom, J=1.2, 7.1 Hz), 7.51–7.46 (m, 2H, H arom), 7.42–7.35 (m, 7H, H arom and CH), 5.35 (td, 1H, =CH, J=1.2, 1.5 Hz), 5.22 (s, 2H, CH_2–N), 5.19 (td, 1H, =CH, J=1.2, 1.5 Hz), 4.19 (t, 2H, CH_2–O, J=1.2 Hz), 4.12 (s, 2H, CH_2–O), 1.06 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 162.9 (C=O, 2 signals overlap), 156.0 (quat C), 147.3 (CH), 143.4 (quat C), 135.5 (CH), 133.4 (CH), 133.2 (quat C, 2 signals overlap), 129.8 (CH), 129.0 (CH), 127.8 (CH), 127.7 (CH), 113.4 (CH_2), 96.5 (CH), 77.5 (CH_2–N), 70.7 (CH_2–O), 64.5 (CH_2–O), 27.0 (CH_3), 19.3 (quat C); Anal calcd for $C_{32}H_{35}N_3O_4Si$: C, 69.42; H, 6.37; N, 7.59. Found: C, 69.65; H, 6.17; N, 7.79.

3.1.7. 9-[2′-(*tert*-Butyldiphenylsilyloxymethyl)-allyloxymethyl]-*N*-benzoyl-adenine 12 and 1-[2′-(*tert*-butyldiphenylsilyloxymethyl)-allyloxymethyl]-*N*-benzoyladenine 13. *N*-6-Benzoyladenine (72.1 mg, 0.301 mmol) and compound **9** (100 mg, 0.251 mmol) in anhydrous CH_3CN (2.5 mL) were stirred at room temperature for 2 h 45 in the same experimental conditions as for **10**, to lead to a mixture of **12** (35.3 mg, 0.062 mmol, 24.5%) as a colorless oil and **13** (35.5 mg, 0.062 mmol, 24.5%) after column chromatography (silica gel, CH_2Cl_2/EtOAc 3:2→1:1).

Compound **12**. IR (neat, cm^{-1}) 3263, 3070, 1703, 1610, 1583; ^1H NMR ($CDCl_3$) δ: 9.21 (broad s, 1H, NH), 8.77 (s, 1H, CH), 8.05 (s, 1H, CH), 8.01 (d, 2H, H arom, J=7.4 Hz), 7.67–7.62 (m, 4H, H arom), 7.57 (tt, 1H, H arom, J=1.2, 7.4 Hz), 7.51–7.44 (m, 2H, H arom), 7.42–7.32 (m, 6H, H arom), 5.56 (s, 2H, CH_2–N), 5.34 (m, 1H, =CH, J= 1.2 Hz), 5.16 (m, 1H, =CH, J=1.2 Hz), 4.17 (m, 2H, CH_2–O), 4.08 (s, 2H, CH_2–O), 1.04 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 163.7 (C=O), 152.1 (CH), 151.4 (quat C), 148.6 (quat C), 142.1 (quat C), 142.0 (CH), 134.5 (CH), 132.6 (quat C), 131.7 (quat C), 128.7 (CH), 127.8 (CH), 126.9 (CH), 126.7 (CH), 126.6 (CH), 121.7 (quat C), 112.5 (CH_2), 70.7 (CH_2–N), 69.2 (CH_2–O), 63.2 (CH_2–O), 25.7 (CH_3), 18.2 (quat C); HRMS (EI) calcd for $C_{29}H_{26}N_5O_3Si$ $[M-C_4H_9]^+$: 520.1804. Found: 520.1830.

Compound **13**. IR (neat, cm^{-1}) 3224, 3069, 1634, 1595; ^1H NMR ($CDCl_3$) δ: 12.76 (broad s, 1H, NH), 8.34 (s, 1H, CH), 8.30–8.28 (m, 2H, H arom), 8.15 (s, 1H, CH), 7.66–7.62 (m, 4H, H arom), 7.54–7.50 (tt, 1H, H arom, J=1.2, 7.4 Hz), 7.45–7.33 (m, 8H, H arom), 5.84 (s, 2H, CH_2–N), 5.34 (dt, 1H, =CH, J=1.2, 1.5 Hz), 5.17 (m, 1H, =CH, J=1.2 Hz), 4.21 (s, 2H, CH_2–O), 4.19 (t, 2H, CH_2–O, J=1.2 Hz), 1.02 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 175.6 (C=O), 157.4 (quat C), 149.6 (quat C), 146.1 (CH), 143.3 (quat C), 141.7 (CH), 137.3 (quat C), 135.4 (CH), 133.2 (quat C), 132.2 (CH), 129.8 (CH), 129.7 (CH), 128.1 (CH), 127.6 (CH), 114.9 (quat C), 113.6 (CH_2), 76.6 (CH_2–N), 70.4 (CH_2–O), 64.2 (CH_2–O), 26.7 (CH_3), 19.1 (quat C); HRMS (EI) calcd for $C_{29}H_{26}N_5O_3Si$ $[M-C_4H_9]^+$: 520.1804. Found: 520.1780.

3.1.8. 7-[2′-(*tert*-Butyldiphenylsilyloxymethyl)-allyloxymethyl]-*N*-acetyl-*O*-(diphenylcarbamoyl)-guanine 14. *N*-2-Acetyl-*O*-6-(diphenylcarbamoyl)guanine[16] (87.0 mg, 0.223 mmol) and compound **9** (74.0 mg, 0.186 mmol) in anhydrous CH_3CN (1.8 mL) were stirred at room temperature for 12 h in the same experimental conditions as for **10**, to afford **14** (39.8 mg, 0.054 mmol, 24%) as a white solid after column chromatography (silica gel, CH_2Cl_2/EtOAc 1:1→2:3): mp 61–63°C; IR (KBr, cm^{-1}) 3246, 3069, 1745, 1634, 1568, 1493, 1450, 1116; ^1H NMR ($CDCl_3$) δ: 8.03 (broad s, 1H, NH), 7.98 (s, 1H, CH), 7.67–7.63 (m, 4H, H arom), 7.46–7.29 (m, 14H, H arom), 7.25–7.20 (m, 2H, H arom), 5.36 (m, 1H, =CH, J=1.2 Hz), 5.24 (s, 2H, CH_2–N), 5.05 (m, 1H, =CH, J=1.2 Hz), 4.13 (s, 2H, CH_2–O), 3.78 (s, 2H, CH_2–O), 2.64 (s, 3H, CH_3), 1.05 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 165.0 (C=O), 151.2 (quat C), 151.2 (quat C), 149.1 (C=O), 147.9 (CH), 142.3 (quat C), 140.9 (quat C), 135.1 (CH), 132.8 (quat C), 129.5 (CH), 128.9 (CH, several signals overlap), 127.4 (CH), 113.7 (CH_2), 111.1 (quat C), 74.5 (CH_2–N), 68.7 (CH_2–O), 63.7 (CH_2–O), 26.4 (CH_3), 24.8 (CH_3), 18.8 (quat C); HRMS (FAB) calcd for $C_{41}H_{43}N_6O_5Si$ $(M+H)^+$: 727.3064. Found: 727.3062.

3.1.9. 1-(2′-(Hydroxymethyl-allyloxymethyl)thymine 4a. To a solution of **10** (205 mg, 0.442 mmol) in THF (3 mL) was added a 1M a solution of TBAF (0.885 mL, 0.885 mmol) in THF. The reaction mixture was stirred at room temperature for 2 h and solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 99:1→96:4) to give **4a** (81.0 mg, 0.358 mmol, 81%) as a white powder: mp 94–95°C; IR (KBr, cm^{-1}) 3440, 3170, 3045, 1704, 1673, 1469, 1268; ^1H NMR (CD_3OD) δ: 7.49 (q, 1H, CH, J=1.2 Hz), 5.19 (m, 1H, =CH), 5.14 (m, 3H, =CH and CH_2–N), 4.11 (s, 2H, CH_2–O), 4.06 (s, 2H, CH_2–O), 1.87 (d, 3H, CH_3, J=1.2 Hz); ^{13}C NMR (CD_3OD) δ: 168.5 (C=O), 154.9 (C=O), 148.3 (quat C), 143.7 (quat C), 114.9 (CH_2), 113.6 (quat C), 79.3 (CH_2–N), 72.6 (CH_2–O), 65.4 (CH_2–O), 14.0 (CH_3); Anal calcd for $C_{10}H_{14}N_2O_4$,

$0.2H_2O$: C, 52.26; H, 6.31; N, 12.19. Found: C, 52.26; H, 6.31; N, 12.08.

3.1.10. 1-(2′-(Hydroxymethyl-allyloxymethyl)-cytosine 4b. To a solution of **11** (253 mg, 0.457 mmol) in MeOH (5 mL) was added, at 0°C, a saturated solution of NH_3 in MeOH (4 mL). The mixture was stirred at room temperature overnight and solvent was then removed under reduced pressure. The residue was dissolved in THF (3 mL) and a 1M solution of TBAF (0.761 mL, 0.761 mmol) in THF was added. The reaction mixture was stirred at room temperature for 2 h and the solvent was removed under reduced pressure. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2/MeOH 9:1) led to **4b** (51.5 mg, 0.244 mmol, 53%) as a white powder: mp 139–141°C; IR (KBr, cm^{-1}) 3331, 3134, 1659, 1630, 1484; ^1H NMR (CD_3OD) δ: 7.62 (d, 1H, CH, J=7.4 Hz), 5.88 (d, 1H, CH, J=7.4 Hz), 5.18 (s, 2H, CH_2–N), 5.17 (m, 1H, =CH), 5.13 (m, 1H, =CH), 4.12 (s, 2H, CH_2–O), 4.05 (s, 2H, CH_2–O); ^{13}C NMR (CD_3OD) δ: 169.6 (C=O), 160.5 (quat C), 148.0 (CH and quat C), 114.4 (CH_2), 97.8 (CH), 80.2 (CH_2–N), 72.2 (CH_2–O), 65.0 (CH_2–O); Anal calcd for $C_9H_{13}N_3O_3$, $0.6H_2O$: C, 48.69; H, 6.44; N, 18.92. Found: C, 48.41; H, 5.86; N, 18.69.

3.1.11. 9-(2′-(Hydroxymethyl-allyloxymethyl)-adenine 4c. Following the same procedure as for **4b**, **12** (99.7 mg, 0.173 mmol) afforded, after column chromatography (silica gel, CH_2Cl_2/MeOH 95:5), **4c** (21.6 mg, 0.092 mmol, 53%) as a white powder: mp 167–169°C; IR (KBr, cm^{-1}) 3302, 3086, 1680, 1607, 1107; ^1H NMR (CD_3OD) δ: 8.24 (s, 1H, CH), 8.23 (s, 1H, CH), 5.64 (s, 2H, CH_2–N), 5.14 (m, 1H, =CH), 5.10 (m, 1H, =CH), 4.12 (s, 2H, CH_2–O), 4.01 (s, 2H, CH_2–O); ^{13}C NMR (CD_3OD) δ: 158.7 (quat C), 155.5 (CH), 155.4 (quat C), 147.5 (quat C), 144.2 (CH), 121.2 (quat C), 114.5 (CH_2), 74.8 (CH_2–N), 72.3 (CH_2–O), 64.8 (CH_2–O); HRMS (EI) calcd for $C_{10}H_{13}N_5O_2$: 235.1069. Found: 235.1071.

Acknowledgements

We thank the local section of Sarthe of the Ligue Nationale contre le Cancer for a fellowship to S. G. and the NCI for the evaluation of the antitumor properties.

References

1. Agrofoglio, L. A.; Challand, S. R. *Acyclic, Carbocyclic and L-Nucleosides*. Kluwer Academic: Dordrecht, 1998; pp 18–173.
2. (a) Elion, G. B.; Furman, P. A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 5716–5720. (b) Schaeffer, H. J.; Beauchamp, L.; De Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature (London)* **1978**, *272*, 583.
3. (a) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. *J. Med. Chem.* **1983**, *26*, 759–761. (b) Meier, C.; Habel, C.; Haller-Meier, F.; Lomp, A.; Herderich, M.; Klöcking, R.; Meerbach, A.; Wultzler, P. *Antiviral Chem. Chemother.* **1998**, *9*, 389–402.
4. (a) Guillarme, S.; Legoupy, S.; Aubertin, A.-M.; Olicard, C.; Bourgougnon, N.; Huet, F. *Tetrahedron* **2003**, *59*, 2177–2184. (b) Hubert, C.; Alexandre, C.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2003**, *59*, 3127–3130.
5. (a) Balzarini, J.; Kang, G. J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162–167. (b) Barrish, J. C.; Zahler, R. Antiviral agents; *Ann. Rep. Med. Chem.* **1993**, *28*, 131–140.
6. Byun, H. S.; Reddy, K. C.; Bittman, R. *Tetrahedron Lett.* **1994**, *35*, 1371–1374.
7. Tendler, S. J. B.; Threagill, M. D.; Tisdale, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2617–2623, and references therein.
8. Gras, J.-L.; Kong Win Chang, Y.-Y.; Guerin, A. *Synthesis* **1985**, 74–75.
9. Beauchamp, L. M.; Tuttle, J. V.; Rodriguez, M. E.; Sznaidman, M. L. *J. Med. Chem.* **1996**, *39*, 949–956.
10. (a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234–1255. (b) Vorbrüggen, H.; Holfe, G. *Chem. Ber.* **1981**, *114*, 1256–1268. (c) Vorbrüggen, H.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1279–1286.
11. Dudycz, L.; Wright, G. E. *Nucleosides Nucleotides* **1984**, *3*, 33–44.
12. Robins, M. J.; Zou, R.; Guo, Z.; Wruk, S. F. *J. Org. Chem.* **1996**, *61*, 9207–9212.
13. Cheung, A. W.-H.; Sidduri, A.; Garofulo, L. M.; Goodnow, Jr. R. A. *Tetrahedron Lett.* **2000**, *41*, 3303–3307.
14. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed. Pergamon: Berlin, 1988.
15. Weigand, S.; Brueckner, R. *Synthesis* **1996**, 475–482.
16. Robins, M. J.; Zou, R.; Guo, Z.; Wnuk, S. F. *J. Org. Chem.* **1996**, *62*, 9207–9212, and references therein.