Synthesis of 1,2-Disubstituted Carbocyclic Nucleoside Analogues of Cytidine

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The synthesis of new 1,2-disubstituted, five- or six-ring-carbocyclic nucleoside analogues of cytidine, compounds **1** and **2a**–**d**, are described. These compounds were obtained by aminolysis, starting from the corresponding uracil derivative, *via* nucleophilic displacement of a triazolyl (*Scheme 1*) or a (2,4,6-triisopropylphenyl)sulfonyl (TPS) group (*Scheme 2*) at 4-position of the pyrimidine ring.

Introduction. – Nucleoside analogues have attracted great interest due to their potential activities as enzyme inhibitors, which has resulted in several antitumor or antiviral agents [1][2]. Modification of conventional nucleosides has led to a large variety of structures that can produce nucleoside classes for very specific enzyme targets [3]. In the sugar portion, the removal of the 2′- and 3′-OH groups has led to inhibitors of reverse transcriptase, an attractive enzyme target in anti-HIV chemotherapy [4][5]. Similarly, replacement of the sugar ring-O-atom by a CH_2 unit results in carbocyclic nucleoside analogues, resistant to cleavage by phosphorylases or hydrolases, that often display enhanced bioactivity [6]. Nucleosides with modified heterocyclic bases, in particular pyrimidine-modified nucleosides, have been less extensively studied. Nevertheless, research in this area has led to many new compounds with potent activities [7]. A selection of known nucleoside analogues, incorporating several of the above structural features, are shown in the *Figure*.

As part of our study on the therapeutic potential of five- and six-membered, 1,2-disubstituted carbocyclic nucleosides [8–11], we herein describe the synthesis of two types of such analogues. Carbocyclic nucleosides have been extensively studied [6][12–14], but little effort has been directed so far towards the synthesis of *six-membered* carbocyclic analogues [10][11][15], despite the fact that some of these compounds have shown potent antiviral activities [16]. In contrast, cyclopentane rings are present in very interesting carbocyclic nucleosides [17][18].

Results and Discussion. – Our goal was to elaborate an efficient synthesis of the racemic cytidine-nucleoside analogues **1** and **2** (*Schemes 1* and *2*, resp.) from the corresponding uracil derivatives, which involved compounds **3**–**9**. A crucial step was uracil activation at C(4), and introduction of an NH_2 group by displacement of a suitable leaving group.

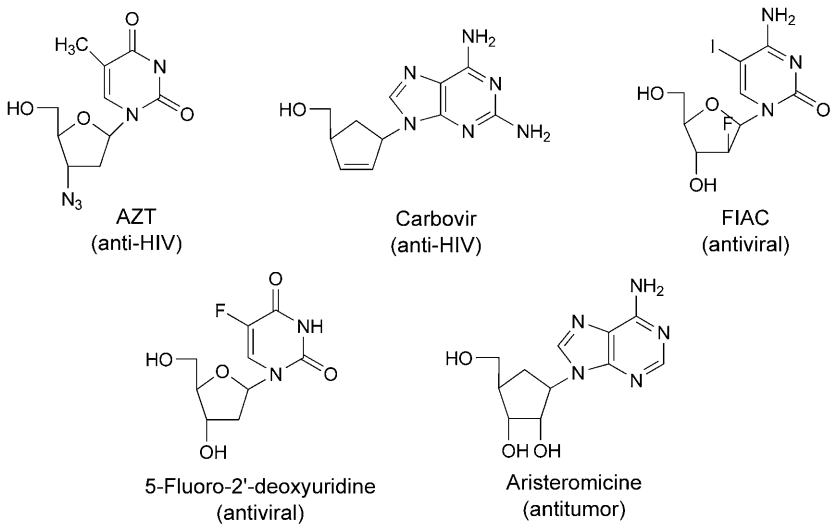
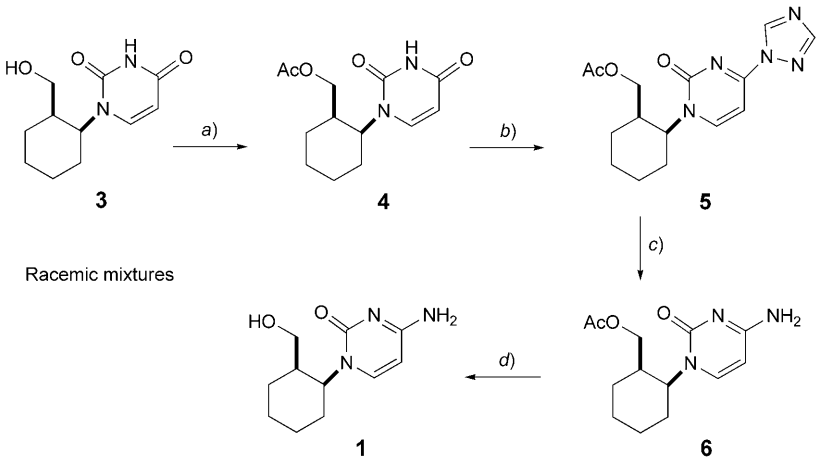


Figure. *A selection of biologically active nucleoside analogues*

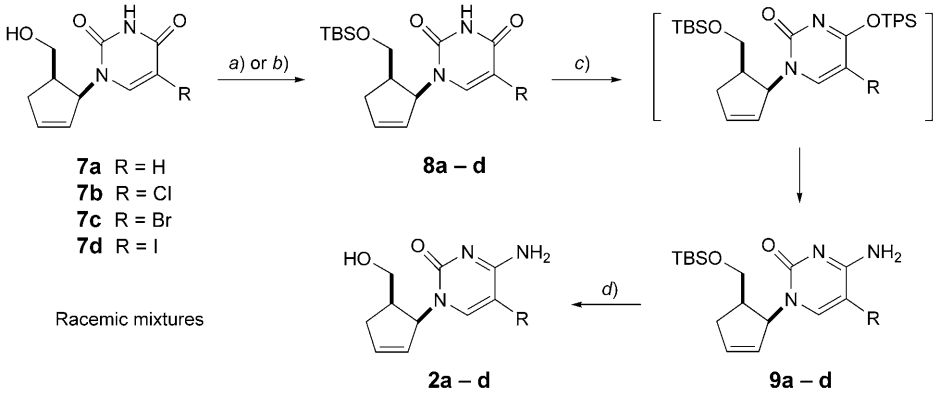
Scheme 1



a) Ac_2O, anh. pyridine, 4°; 70%. *b*) 1*H*-1,2,4-triazol, anh. pyridine, 4-chlorophenyl dichlorophosphate, r.t., 3 d; 60%. *c*) NH_4OH, 1,4-dioxane, r.t.; 80%. *d*) aq. NaOH, r.t.; 71%.

Protection of the OH group of the starting material **3** [10] led to the acetate **4**, which was treated with 4-chlorophenyl dichlorophosphate and 1*H*-1,2,4-triazol in anhydrous pyridine at room temperature to afford the triazolyl-activated derivative **5** in 60% yield after 3 d [19]. Subsequent reaction of **5** with aqueous ammonia in 1,4-dioxane yielded the cytidine derivative **6** in 80% yield, which was deprotected with 0.5M aqueous NaOH solution to the target compound **1** in 71% yield (*Scheme 1*).

Scheme 2



a) ^{t}Bu(Me$_2$)SiCl (TBSCl), 1*H*-imidazole, DMF, r.t.; 76% (**8a**), 71% (**8b**), 68% (**8c**). *b*) ^{t}Bu(Me$_2$)SiOSO$_2$CF$_3$ (TBSTf), 2,6-lutidine, CH$_2$Cl$_2$, r.t.; 72% (**8d**). *c*) 1. (2,4,6-Triisopropylphenyl)sulfonyl chloride (TPSCl), 4-(dimethylamino)pyridine (DMAP), Et$_3$N, MeCN, r.t.; 2. aq. NH$_4$OH, r.t.; 89% (**9a**), 78% (**9b**), 82% (**9c**), 78% (**9d**). *d*) Bu$_4$NF (TBAF), THF, r.t.; 63% (**2a**), quant. (**2b**,**c**), 69% (**2d**).

For the synthesis of **2** (*Scheme 2*), the (2,4,6-triisopropylphenyl)sulfonyl (TPS) group was chosen as a leaving group [20]. First, the OH group of the uracil derivatives **7** [9] was protected as the *tert*-butyl(dimethyl)silyl (TBS) ether by exposure to ^{t}Bu(Me$_2$)SiCl and 1*H*-imidazol in anhydrous DMF, which gave good results in the case of **8a**–**c**. However, the low yield (17%) of the iodine derivative **8d** prompted us to use the corresponding trifluoromethanesulfonate (TBSTf). Next, treatment of **8** with TPSCl in the presence of 4-(dimethylamino)pyridine (DMAP) and Et$_3$N in MeCN, followed by aminolysis, afforded the protected cytidine derivatives **9** in yields of 78–89%. Finally, the TBS group was removed with 1M tetrabutylammonium fluoride (TBAF) in THF at room temperature to furnish the target compounds **2** in good-to-excellent yields.

The structures of the cytidine analogues **1** and **2** were deduced by ^{1}H- and ^{13}C-NMR spectroscopy, and by MS analysis. In the ^{1}H-NMR spectra, the imide-type NH resonance, characteristic of the uracil nucleus, had disappeared. Instead, two *singlet*s due to the cytosine NH$_2$ group were observed at δ(H) 7.06 and 6.96 for **1**, or at 7.69 and 7.08 in the case of, *e.g.*, **2a** (see *Exper. Part*).

In summary, we have worked out two strategies for the preparation of 1,2-disubstituted carbocyclic nucleoside analogues of cytidine. The first one (*Scheme 1*) involved the transformation of an uracil to a cytosine moiety through an activated triazole derivative, a process that, unfortunately, was fairly time-consuming (reaction time: 3 d) and not very economic since the triazole **5** had to be purified before the following aminolysis. In the second approach (*Scheme 2*), based on a TPS derivative, the reaction was much faster and allowed us to carry out the aminolysis *in situ*, affording the cytidine analogues in higher overall yield. Thus, we are currently in the process of applying the second methodology to the synthesis of a larger series of new carbocyclic cytosine analogues for biological evaluation.

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Experimental Part

General. Column chromatography (CC): *Merck* silica gel *60* (230–400 mesh). TLC: *Merck* precoated silica gel *60* F_{254} (0.25-mm thick). Melting points (m.p.) were determined in open capillary tubes on a *Gallenkamp* apparatus. IR Spectra: *Perkin-Elmer 1640 FTIR* spectrometer, in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker ARX-400* instrument; at 400 and 100 MHz, resp.; δ in ppm, J in Hz. Complete signal assignments were performed by NOE, DEPT, HMQC, and HMBC experiments. EI-MS: *Hewlett-Packard 5988A* mass spectrometer; in *m*/*z* (rel. %). Elemental analyses: *Perkin-Elmer 240B* elemental analyzer.

*(±)-*cis*-1-[2-(Acetoxymethyl)cyclohexyl]uracil* (**4**). Ac_2O (0.74 ml) was added to a soln. of **3** (349 mg, 1.56 mmol) in anh. pyridine (8.24 ml) under Ar. The mixture was stirred at 4° overnight, the solvent was evaporated under vacuum, and the residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 98:2). Yield: 290 mg (70%). M.p. 176–178°. IR (KBr): 3204, 3068, 3023, 1739, 1670, 1648, 1551, 1239, 1222, 1013. ^1H-NMR ($CDCl_3$): 9.16 (br. *s*, NH); 7.20 (*d*, J=8.1, H–C(6)); 5.68 (*d*, J=8.1, H–C(5)); 4.57 (*m*, CHN); 4.12 (*d*, J=6.8, OCH_2); 2.62 (*m*, OCH_2CH); 1.96 (*s*, Ac); 1.53–1.85 (*m*, 1 CH_2). ^{13}C-NMR ($CDCl_3$): 172.1; 163.8 (C(4)); 151.9 (C(2)); 141.8 (C(6)); 101.6 (C(5)); 62.8 (OCH_2); 57.3 (C(1′)); 36.0; 28.4; 26.3; 26.1; 21.3; 20.9. EI-MS: 266 (5, M^+), 206 (10, $[M-AcOH]^+$), 113 (11, $[M-C_9H_{16}O_2]^+$); 95 (18), 58 (100). Anal. calc. for $C_{13}H_{18}N_2O_4$ (266.29): C 58.63, H 6.81, N 10.52; found: C 58.49, H 7.05, N 10.30.

*(±)-*cis*-1-[2-(Acetoxymethyl)cyclohexyl]-4-(1,2,4-triazol-1-yl)-1*H*-pyrimidin-2-one* (**5**). To a cooled (0°) soln. of **4** (210 mg, 0.79 mmol) and 1*H*-1,2,4-triazol (675 mg, 9.8 mmol) in anh. pyridine (5 ml), 4-chlorophenyl dichlorophosphate (0.53 ml, 3.24 mmol) was added dropwise. The mixture was stirred at r.t. for 3 d, the solvent was evaporated in vacuum, and the residue was dissolved in CH_2Cl_2 (10 ml) and washed with H_2O (4×25 ml). The org. layer was dried (Na_2SO_4), evaporated under vacuum, and the residue was purified by CC (SiO_2; hexane/AcOEt 7:3). Yield: 150 mg (60%). M.p. 44°. ^1H-NMR ($CDCl_3$): 9.29 (*s*, =C(H)N); 8.13 (*s*, =C(H)N); 7.84 (*d*, J=7.2, H–C(6)); 7.03 (*d*, J=7.2, H–C(5)); 4.85 (*m*, CHN); 4.11 (*m*, OCH_2); 2.85 (*m*, OCH_2CH); 1.99 (*s*, Ac); 1.25–2.05 (*m*, 1 CH_2). EI-MS: 316 (4, $[M-1]^+$), 257 (20, $[M-C_2H_3O_2]^+$); 244 (25, $[M-C_3H_4O_2]^+$); 214 (16), 164 (100), 137 (13), 94 (35, $[M-C_{11}H_{17}N_3O_2]^+$), 79 (23). Anal. calc. for $C_{15}H_{19}N_5O_3$ (317.34): C 56.77, H 6.03, N 22.07; found: C 56.63, H 6.18, N 22.15.

*(±)-*cis*-1-[2-(Acetoxymethyl)cyclohexyl]cytosine* (**6**). A soln. of **5** (90 mg, 0.28 mmol) in 25% NH_4OH (1 ml) and 1,4-dioxane (3 ml) was stirred overnight at r.t. The solvent was evaporated in vacuum, and the residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 97:3). Yield: 60 mg (80%). M.p. 205°. ^1H-NMR ($CDCl_3$): 7.26 (*d*, J=7.4, H–C(6)); 5.65 (*d*, J=7.4, H–C(5)); 5.42 (*s*, NH_2); 4.72 (*m*, CHN); 4.03 (*m*, OCH_2); 2.70 (*m*, OCH_2CH); 1.94 (*s*, Ac); 1.53–1.84 (*m*, 1 CH_2). Anal. calc. for $C_{13}H_{19}N_3O_3$ (265.31): C 58.85, H 7.22, N 15.84; found: C 58.73, H 7.15, N 15.92.

*(±)-*cis*-1-[2-(Hydroxymethyl)cyclohexyl]cytosine* (**1**). A solution of **6** (50 mg, 0.23 mmol) in 0.5M aq. NaOH soln. (1 ml) was stirred for 10 min at r.t., and then neutralized with 0.5M aq. HCl. The solvent was evaporated under vacuum (azeotropic mixture with EtOH/toluene), and the residue was dissolved in H_2O and extracted with AcOEt. The combined org. layers were dried, and evaporated to afford the title compound. Yield: 30 mg (71%). M.p. 217–218°. IR (KBr): 3375, 2898, 2795, 1648, 1284, 1170, 1023, 773. ^1H-NMR ((D$_6$)DMSO): 7.44 (*d*, J=7.3, H–C(6)); 7.06 (br. *s*, 1 H of NH_2); 6.96 (br. *s*, 1 H of NH_2); 5.60 (*d*, J=7.3, H–C(5)); 4.38 (*m*, OH); 4.32 (*t*, J=5.2, CHN); 3.47 (*m*, 1 H of OCH_2); 3.16 (*m*, 1 H of OCH_2); 2.10 (*m*, OCH_2CH); 1.38, 1.90 (2*m*, 1 CH_2). ^{13}C-NMR ((D$_6$)DMSO): 165.5 (C(4)); 156.0 (C(2)); 143.6 (C(6)); 92.7 (C(5)); 57.6 (C(1′)); 56.7 (C(7′)); 38.8; 26.5; 26.2; 25.8; 20.0. EI-MS: 223 (13, M^+), 222 (15, $[M-1]^+$), 192 (26, $[M-CH_2OH]^+$), 136 (8), 112 (100, $[M-C_4H_5N_3O_2]^+$), 69 (22), 58 (35). Anal. calc. for $C_{11}H_{17}N_3O_2$ (223.27): C 59.17, H 7.67, N 18.82; found: 59.24, H 7.73, N 18.93.

General Procedure (*GP 1*) *for the Preparation of Compounds* **8a**–**c**. A soln. of *tert*-butyl(dimethyl)-silyl chloride (TBSCl; 87 mg, 0.576 mmol) in anh. DMF (1.5 ml) was slowly added to a soln. of the corresponding uracil analogue **7** (0.48 mmol) and 1*H*-imidazol (78 mg, 1.15 mmol) in DMF (1.5 ml). The

mixture was stirred at r.t. for 4 h, diluted with Et_2O (5 ml), and washed with H_2O (3×5ml). The org. layer was dried (Na_2SO_4) and concentrated under vacuum, and the residue was purified by CC (SiO_2; hexane/AcOEt 2:1 (**8b**,**c**) or 3:1 (**8b**).

(±)-cis-*1-[2-({[(*tert-*Butyl)(dimethyl)silyl]oxy}methyl)cyclopent-4-en-1-yl]uracil* (**8a**). Prepared according to *GP 1*. Yield: 76%. M.p. 152–154°. ^{1}H-NMR ($CDCl_3$): 9.16 (br. *s*, NH); 7.06 (*d*, *J* = 8.1, H–C(6)); 6.22 (*m*, H–C(4′)); 5.68 (*m*, H–C(1′)); 5.61 (*m*, H–C(5′)); 5.57 (*d*, *J* = 8.1, H–C(5)); 3.50 (*m*, OCH_2); 2.76 (*m*, H–C(2′)); 2.54–2.48 (*m*, H–C(3′)); 2.36–2.28 (*m*, H–C(3′)); 0.80 (*s*, *t*-Bu); −0.03, −0.04 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 163.6 (C(4)); 151.4 (C(2)); 142.7 (C(6)); 138.3 (C(4′)); 127.7 (C(5′)); 100.7 (C(5)); 62.1 (C(1′)); 61.9 (OCH_2); 41.6 (C(2′)); 34.4 (C(3′)); 25.8 (Me_3C); 18.2 (Me_3C); −5.6 (Me_2Si). EI-MS: 323 (8, M^+), 307 (15, $[M-CH_4]^+$), 265 (34, $[M-C_4H_{10}]^+$), 188 (8, $[M-C_6H_{19}OSi]^+$), 187 (69, $[M-C_6H_{20}OSi]^+$), 170 (13, $[M-C_7H_{25}OSi]^+$), 169 (100, $[M-C_7H_{26}OSi]^+$), 99 (16), 79 (38, $[M-C_{10}H_{20}N_2O_3Si]^+$), 75 (19, $[M-C_{10}H_{24}N_2O_3Si]^+$), 73 (13, $[M-C_{10}H_{26}N_2O_3Si]^+$). Anal. calc. for $C_{16}H_{26}N_2O_3Si$ (322.47): C 59.59, H 8.13, N 8.69; found: C 59.71, H 8.23, N 8.75.

(±)-cis-*1-[2-({[(*tert-*Butyl)(dimethyl)silyl]oxy}methyl)cyclopent-4-en-1-yl]-5-chlorouracil* (**8b**). Prepared according to *GP 1*. Yield: 71%. M.p. 138–141°. ^{1}H-NMR ($CDCl_3$): 8.38 (br. *s*, NH); 7.29 (*s*, H–C(6)); 6.32 (*m*, H–C(4′)); 5.67 (*m*, H–C(1′)); 5.64 (*m*, H–C(5′)); 3.64 (*dd*, *J* = 11.0, 3.7, 1 H of OCH_2); 3.55 (*dd*, *J* = 11.0, 6.0, 1 H of OCH_2); 2.78 (*m*, H–C(2′)); 2.56–2.50 (*m*, 1 H of CH_2(3′)); 2.46–2.38 (*m*, 1 H of CH_2(3′)); 0.83 (*s*, *t*-Bu); −0.01, −0.03 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 159.1 (C(4)); 150.6 (C(2)); 140.0 (C(6)); 139.4 (C(4′)); 127.3 (C(5′)); 107.2 (C(5)); 63.1 (C(1′)); 61.7 (OCH_2); 41.5 (C(2′)); 34.0 (C(3′)); 25.8 (Me_3C); 18.3 (Me_3C); −5.6, −5.7 (Me_2Si). EI-MS: 359 (4, $[M+2]^+$), 357 (11, M^+), 301 (5, $[M+2-C_4H_{10}]^+$), 299 (12, $[M-C_4H_{10}]^+$), 223 (9, $[M+2-C_6H_{20}OSi]^+$), 221 (28, $[M-C_6H_{20}OSi]^+$), 204 (10, $[M-C_6H_{17}ClSi]^+$), 203 (78, $[M-C_6H_{18}ClSi]^+$), 133 (6), 89 (12), 79 (100, $[M-C_{10}H_{18}ClN_2O_3Si]^+$), 75 (56, $[M-C_{10}H_{22}ClN_2O_3Si]^+$), 73 (34, $[M-C_{10}H_{24}ClN_2O_3Si]^+$), 63 (5, $[M-C_{11}H_{22}ClN_2O_3Si]^+$). Anal. calc. for $C_{16}H_{25}ClN_2O_3Si$ (356.92): C 53.84, H 7.06, N 7.85; found: C 53.70, H 7.24, N 7.69.

(±)-cis-*5-Bromo-1-[2-({[(*tert-*butyl)(dimethyl)silyl]oxy}methyl)cyclopent-4-en-1-yl]uracil* (**8c**). Prepared according to *GP 1*. Yield: 68%. M.p. 137–139°. ^{1}H-NMR ($CDCl_3$): 8.34 (br. *s*, NH); 7.39 (*s*, H–C(6)); 6.32 (*m*, H–C(4′)); 5.71–5.62 (*m*, H–C(1′), H–C(5′)); 3.65 (*dd*, *J* = 11.0, 3.7, 1 H of OCH_2); 3.55 (*dd*, *J* = 11.0, 6.0, 1 H of OCH_2); 2.78 (*m*, H–C(2′)); 2.56–2.50 (*m*, H–C(3′)); 2.45–2.38 (*m*, H–C(3′)); 0.84 (*s*, *t*-Bu); −0.01, −0.02 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 159.1 (C(4)); 150.7 (C(2)); 142.5 (C(6)); 139.4 (C(4′)); 127.3 (C(5′)); 94.9 (C(5)); 63.2 (C(1′)); 61.7 (OCH_2); 41.5 (C(2′)); 34.1 (C(3′)); 25.9 (Me_3C); 18.3 (Me_3C); −5.5, −5.6 (Me_2Si). EI-MS: 268 (5, $[M+2-C_6H_{19}OSi]^+$), 267 (42, $[M+2-C_6H_{20}OSi]^+$), 266 (5, $[M-C_6H_{19}OSi]^+$), 265 (41, $[M-C_6H_{20}OSi]^+$), 250 (7, $[M+2-C_7H_{25}OSi]^+$), 249 (59, $[M+2-C_7H_{26}OSi]^+$), 248 (7, $[M-C_7H_{25}OSi]^+$), 247 (57, $[M-C_7H_{26}OSi]^+$), 179 (6, $[M+2-C_{12}H_{22}NOSi]^+$), 177 (6, $[M-C_{12}H_{22}NOSi]^+$), 89 (12), 80 (7, $[M-C_{10}H_{17}BrN_2O_3Si]^+$), 79 (100, $[M-C_{10}H_{18}BrN_2O_3Si]^+$), 78 (7, $[M-C_{10}H_{19}BrN_2O_3Si]^+$), 77 (10, $[M-C_{10}H_{20}BrN_2O_3Si]^+$), 75 (53, $[M-C_{10}H_{22}BrN_2O_3Si]^+$), 73 (32, $[M-C_{10}H_{24}BrN_2O_3Si]^+$), 66 (5, $[M-C_{11}H_{19}BrN_2O_3Si]^+$). Anal. calc. for $C_{16}H_{25}BrN_2O_3Si$ (401.37): C 47.88, H 6.28, N 6.98; found: C 47.75, H 6.17, N 7.01.

(±)-cis-*1-[2-({[(*tert-*Butyl)(dimethyl)silyl]oxy}methyl)cyclopent-4-en-1-yl]-5-iodouracil* (**8d**). 2,6-Lutidine (0.61 ml, 5.207 mmol) and TBSTf (0.63 ml, 2.47 mmol) was added to a suspension of **7d** (600 mg, 1.80 mmol) in CH_2Cl_2 (15 ml). The mixture was stirred at r.t. for 7 min. Then, sat. aq. $NaHCO_3$ soln. (15 ml) was added, and the mixture was extracted with CH_2Cl_2 (4×15 ml). The org. layer was dried (Na_2SO_4) and evaporated under vacuum, and the residue was chromatographed (SiO_2; hexane/AcOEt 3:1). Yield: 577 mg (72%). M.p. 126–128°. ^{1}H-NMR ($CDCl_3$): 8.43 (br. *s*, NH); 7.48 (*s*, H–C(6)); 6.32 (*m*, H–C(4′)); 5.65 (*m*, H–C(1′), H–C(5′)); 3.64 (*dd*, *J* = 11.0, 4.0, 1 H of OCH_2); 3.54 (*dd*, *J* = 11.0, 6.2, 1 H of OCH_2); 2.78 (*m*, H–C(2′)); 2.56 –2.50 (*m*, 1 H of CH_2(3′)); 2.45–2.38 (*m*, 1 H of CH_2(3′)); 0.85 (*s*, *t*-Bu); 0.00, −0.01 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 160.1 (C(4)); 151.4 (C(2)); 147.9 (C(6)); 139.7 (C(4′)); 127.8 (C(5′)); 66.7 (C(5)); 63.5 (C(1′)); 62.2 (OCH_2); 42.0 (C(2′)); 34.5 (C(3′)); 26.3 (Me_3C); 18.8 (Me_3C), −5.0, −5.1 (Me_2Si). EI-MS: 392 (7, $[M-C_4H_8]^+$), 391 (29, $[M-C_4H_9]^+$), 314 (11, $[M-C_6H_{18}OSi]$), 313 (92, $[M-C_6H_{19}OSi]^+$), 296 (11, $[M-C_7H_{24}OSi]^+$), 295 (100,

$[M-C_7H_{25}OSi]^+$), 225 (13), 131 (9), 89 (9), 79 (694, $[M-C_{10}H_{18}IN_2O_3Si]^+$), 75 (19, $[M-C_{10}H_{22}IN_2O_3Si]^+$), 73 (23, $[M-C_{10}H_{24}IN_2O_3Si]^+$), 69 (24). Anal. calc. for $C_{16}H_{25}IN_2O_3Si$ (448.37): C 42.86, H 5.62, N 6.25; found: C 42.63, H 5.44, N 6.12.

General Procedure (*GP 2*) *for the Preparation of Compounds* **9**. A soln. of **8** (0.31 mmol), DMAP (0.62 mmol), TPSCl (0.62 mmol), and Et_3N (0.62 mmol) in MeCN was stirred at r.t. for 5 h. Then, 25% NH_4OH soln. (13 ml) was added, and the mixture was stirred for 3 h. The solvent was evaporated to dryness, and the resulting residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 97:3 (**9a**,**b**), 94:4 (**9c**), or 95:5 (**9d**).

(±)-cis-*1-[2-({[(*tert-*Butyl)(dimethyl)silyl]oxy}methyl)cyclopent-4-en-1-yl]cytosine* (**9a**). Prepared according to *GP 2*. Yield: 89%. M.p. 152–154°. ^{1}H-NMR ((D_6)DMSO): 7.10 (*d*, *J* = 7.3, H–C(6)); 7.01 (br. *s*, 1 H of NH_2); 6.90 (*s*, 1 H of NH_2); 6.14 (*m*, H–C(4′)); 5.63 (*m*, H–C(5′)); 5.57 (*d*, *J* = 7.3, H–C(5)); 5.51 (*m*, H–C(1′)); 3.37 (*dd*, *J* = 10.2, 5.6, 1 H of OCH_2); 3.21 (*dd*, *J* = 10.2, 6.8, 1 H of OCH_2); 2.59 (*m*, H–C(2′)); 2.43 (*m*, 1 H of CH_2(3′)); 2.29–2.23 (*m*, 1 H of CH_2(3′)); 0.76 (*s*, *t*-Bu); −0.11, −0.13 (2*s*, Me_2Si). ^{13}C-NMR ((D_6)DMSO): 165.1 (C(4)); 155.7 (C(2)); 143.3 (C(6)); 136.5 (C(4′)); 128.9 (C(5′)); 92.7 (C(5)); 61.8 (OCH_2); 61.5 (C(1′)); 41.3 (C(2′)); 34.5 (C(3′)); 25.7 (*Me*$_3$C); 17.8 (Me_3*C*); −5.2, −5.3 (Me_2Si). EI-MS: 321 (7, M^+), 265 (8, $[M-C_4H_8]^+$), 264 (40, $[M-C_4H_9]^+$), 210 (7), 186 (48, $[M-C_6H_{19}OSi]^+$), 176 (14, $[M-C_7H_{17}OSi]^+$), 169 (13, $[M-C_7H_{24}OSi]^+$), 168 (100, $[M-C_7H_{25}OSi]^+$), 153 (5, $[M-C_7H_{26}NOSi]^+$), 112 (8), 79 (19, $[M-C_{10}H_{20}N_3O_2Si]^+$), 75 (17, $[M-C_{10}H_{24}N_3O_2Si]^+$), 74 (12, $[M-C_{10}H_{25}N_3O_2Si]^+$), 73 (15, $[M-C_{10}H_{26}N_3O_2Si]^+$), 69 (9). Anal. calc. for $C_{16}H_{27}N_3O_2Si$ (321.49): C 59.78, H 8.47, N 13.07; found: C 59.63, H 8.32, N 13.12.

(±)-cis-*1-[2-({[(*tert-*Butyl)(dimethyl)silyl]oxy}methyl)cyclopent-4-en-1-yl]-5-chlorocytosine* (**9b**). Prepared according to *GP 2*. Yield 78%. M.p. 225–227°. ^{1}H-NMR ($CDCl_3$): 7.35 (*s*, H–C(6)); 6.27 (*m*, H–C(4′)); 5.82 (*s*, 1 H of NH_2); 5.78 (*m*, H–C(1′)); 5.62 (*m*, H–C(5′)); 5.52 (*s*, 1 H of NH_2); 3.57 (*m*, OCH_2); 2.82 (*m*, H–C(2′)); 2.51 (*m*, CH_2(3′)); 0.82 (*s*, *t*-Bu); −0.03, −0.08 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 161.5 (C(4)); 155.8 (C(2)); 142.0 (C(6)); 138.4 (C(4′)); 128.1 (C(5′)); 98.5 (C(5)); 64.0 (C(1′)); 61.8 (OCH_2); 41.2 (C(2′)); 34.3 (C(3′)); 25.8 (*Me*$_3$C); 18.3 (Me_3*C*); −5.6, −5.7 (Me_2Si). EI-MS: 358 (4, $[M+2]^+$), 357 (6, $[M+1]^+$), 356 (10, M^+), 355 (9, $[M-1]^+$), 300 (19, $[M+2-C_4H_{11}]^+$), 298 (46, $[M-C_4H_{11}]^+$), 222 (10, $[M+2-C_6H_{20}OSi]^+$), 220 (28, $[M-C_6H_{20}OSi]^+$), 204 (21, $[M+2-C_7H_{26}OSi]^+$), 203 (8), 202 (60, $[M-C_7H_{26}OSi]^+$), 89 (11), 79 (100, $[M-C_{10}H_{19}ClN_3O_2Si]^+$), 78 (10, $[M-C_{10}H_{20}ClN_3O_2Si]^+$), 77 (12, $[M-C_{10}H_{21}ClN_3O_2Si]^+$), 76 (8, $[M-C_{10}H_{22}ClN_3O_2Si]^+$), 75 (65, $[M-C_{10}H_{23}ClN_3O_2Si]^+$), 74 (38, $[M-C_{10}H_{24}ClN_3O_2Si]^+$), 73 (55, $[M-C_{10}H_{25}ClN_3O_2Si]^+$), 66 (7, $[M-C_{11}H_{20}ClN_3O_2Si]^+$). Anal. calc. for $C_{16}H_{26}ClN_3O_2Si$ (355.93): C 53.99, H 7.36, N 11.81; found: 53.82, H 7.24, N 12.00.

(±)-cis-*5-Bromo-1-[2-({[(*tert-*butyl)(dimethyl)silyl]oxy}methyl)cyclopent-4-en-1-yl]cytosine* (**9c**). Prepared according to *GP 2*. Yield: 82%. M.p. 214–216°. ^{1}H-NMR ($CDCl_3$): 7.62 (br. *s*, 1 H of NH_2); 7.39 (*s*, H–C(6)); 6.25 (*m*, H–C(4′)); 5.74 (*m*, H–C(1′)); 5.61 (*m*, H–C(5′)); 5.53 (br. *s*, 1 H of NH_2); 3.55 (*m*, OCH_2); 2.81 (*m*, H–C(2′)); 2.50 (*m*, CH_2(3′)); 0.81 (*s*, *t*-Bu); −0.03, −0.07 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 162.0 (C(4)); 155.9 (C(2)); 144.5 (C(6)); 138.4 (C(4′)); 128.1 (C(5′)); 85.7 (C(5)); 64.0 (C(1′)); 61.8 (OCH_2); 41.2 (C(2′)); 34.3 (C(3′)); 25.9 (*Me*$_3$C); 18.3 (Me_3*C*); −5.6 (Me_2Si). EI-MS: 401 (3, $[M+1]^+$), 399 (3, $[M-1]^+$), 344 (18, $[M+1-C_4H_9]^+$), 342 (17, $[M-1-C_4H_9]^+$), 267 (6, $[M+1-C_6H_{18}OSi]^+$), 266 (45, $[M+1-C_6H_{19}OSi]^+$), 265 (6, $[M-1-C_6H_{18}OSi]^+$), 264 (43, $[M-1-C_6H_{19}OSi]^+$), 256 (7, $[M+1-C_7H_{17}OSi]^+$), 254 (8, $[M-1-C_7H_{17}OSi]^+$), 249 (13, $[M+1-C_7H_{24}OSi]^+$), 248 (100, $[M+1-C_7H_{25}OSi]^+$), 247 (13, $[M-1-C_7H_{24}OSi]^+$), 246 (100, $[M-1-C_7H_{25}OSi]^+$), 210 (7), 192 (5, $[M+1-C_{12}H_{21}OSi]^+$), 190 (5, $[M-1-C_{12}H_{21}OSi]^+$), 153 (5), 89 (9), 79 (58, $[M-C_{10}H_{19}BrN_3O_2Si]^+$), 77 (7, $[M-C_{10}H_{21}BrN_3O_2Si]^+$), 75 (36, $[M-C_{10}H_{23}BrN_3O_2Si]^+$), 74 (20, $[M-C_{10}H_{24}BrN_3O_2Si]^+$), 73 (29, $[M-C_{10}H_{25}BrN_3O_2Si]^+$). Anal. calc. for $C_{16}H_{26}BrN_3O_2Si$ (400.39): C 48.00, H 6.55, N 10.49; found: C 48.13, H 6.65, N 10.32.

(±)-cis-*1-[2-({[(*tert-*Butyl)(dimethyl)silyl]oxy}methyl)cyclopent-4-en-1-yl]-5-iodocytosine* (**9d**). Prepared according to *GP 2*. Yield: 78%. M.p. 192–194°. ^{1}H-NMR ($CDCl_3$): 7.50 (*s*, H–C(6)); 7.02 (br. *s*, 1 H of NH_2); 6.28 (*m*, H–C(4′)); 5.76 (*m*, H–C(1′)); 5.64 (*m*, H–C(5′)); 5.38 (br. *s*, 1 H of NH_2); 3.58 (*m*, OCH_2); 2.84 (*m*, H–C(2′)); 2.52 (*m*, CH_2(3′)); 0.85 (*s*, *t*-Bu); 0.00, −0.04 (2*s*, Me_2Si). ^{13}C-NMR ($CDCl_3$): 163.7 (C(4)); 156.5 (C(2)); 150.3 (C(6)); 138.9 (C(4′)); 128.5 (C(5′)); 64.0 (C(1′)); 62.3 (OCH_2); 54.8 (C(5)); 41.7 (C(2′)); 34.7 (C(3′)); 26.4 (*Me*$_3$C); 18.8 (Me_3*C*); −5.1 (Me_2Si). EI-MS: 447

(4, M^+), 391 (5, $[M-C_4H_8]^+$), 390 (27, $[M-C_4H_9]^+$), 313 (8, $[M-C_6H_{18}OSi]^+$), 312 (67, $[M-C_6H_{19}OSi]^+$), 302 (9, $[M-C_7H_{17}OSi]^+$), 295 (11, $[M-C_7H_{24}OSi]^+$), 294 (100, $[M-C_7H_{25}OSi]^+$), 238 (5, $[M-C_{12}H_{21}OSi]^+$), 210 (8), 167 (6, $[M-C_7H_{25}IOSi]^+$), 153 (8), 131 (5), 100 (8), 99 (8), 93 (7), 87 (9), 76 (57, $[M-C_{10}H_{22}IN_3O_2Si]^+$), 71 (37), 70 (21), 69 (36), 65 (10). Anal. calc. for $C_{16}H_{26}IN_3O_2Si$ (447.39): C 42.95, H 5.86, N 9.39; found: C 42.76, H 5.67, N 9. 41.

General Procedure (*GP 3*) *for the Preparation of Compounds* **2**. A solution of **9** (0.078 mmol) in THF (3ml) was treated with a 1M soln. of TBAF (0.086 mmol) in THF, and stirred for 4 h at r.t. The solvent was evaporated, and the resulting residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 9:1 (**2a**) or 95:5 (**2b**–**d**)).

(±)-cis-*1-[2-(Hydroxymethyl)cyclopent-4-en-1-yl]cytosine* (**2a**). Prepared according to *GP 3*. Yield: 63%. M.p. 225–228°. ^{1}H-NMR ((D$_6$)DMSO): 7.12 (*d*, *J* = 7.3, H–C(6)); 7.06 (br. *s*, 1 H of NH_2); 6.96 (br. *s*, 1 H of NH_2); 6.20 (*m*, H–C(4′)); 5.66 (*m*, H–C(5′)); 5.63 (*d*, *J* = 7.3, H–C(5)); 5.51 (*m*, H–C(1′)); 4.38 (*m*, OH); 3.15 (*dd*, *J* = 10.4, 5.5, 1 H of OCH_2); 2.97 (*dd*, *J* = 10.4, 7.9, 1 H of OCH_2); 2.56 (*m*, H–C(2′)); 2.45–2.40 (*m*, 1 H of CH_2(3′)); 2.23–2.17 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR ((D$_6$)DMSO): 165.3 (C(4)); 156.4 (C(2)); 142.9 (C(6)); 137.1 (C(4′)); 128.8 (C(5′)); 92.9 (C(5)); 61.3 (C(1′)); 60.4 (OCH_2); 42.3 (C(2′)); 34.9 (C(3′)). EI-MS: 208 (5, $[M+1]^+$), 207 (35, M^+), 177 (15, $[M+1-MeO]^+$), 176 (100, $[M-MeO]^+$), 133 (10), 112 (73, $[M-C_6H_7O]^+$), 111 (12, $[M-C_6H_8O]^+$), 108 (9, $[M-C_6H_{11}O]^+$), 79 (11, $[M-C_4H_6N_3O_2]^+$), 69 (10, $[M-C_8H_{12}NO]^+$), 67 (13, $[M-C_5H_6N_3O_2]^+$), 66 (10, $[M-C_5H_7N_3O_2]^+$), 65 (6, $[M-C_5H_8N_3O_2]^+$). Anal. calc. for $C_{10}H_{13}N_3O_2$ (207.23): C 57.96, H 6.32, N 20.28; found: C 57.84, H 6.25, N 20.17.

(±)-cis-*1-[2-(Hydroxymethyl)cyclopent-4-en-1-yl]-5-chlorocytosine* (**2b**). Prepared according to *GP 3*. Yield: quant. M.p. 258–260°. ^{1}H-NMR ((D$_6$)DMSO): 7.69 (br. *s*, 1 H of NH_2); 7.28 (*s*, H–C(6)); 7.08 (br. *s*, 1 H of NH_2); 6.22 (*m*, H–C(4′)); 5.69 (*m*, H–C(5′)); 5.49 (*m*, H–C(1′)); 4.40 (*m*, OH); 3.20 (*m*, 1 H of OCH_2); 3.04 (*m*, 1 H of OCH_2); 2.59 (*m*, H–C(2′)); 2.46–2.40 (*m*, 1 H of H–C(3′)); 2.33–2.26 (*m*, 1 H of H–C(3′)). ^{13}C-NMR ((D$_6$)DMSO): 161.1 (C(4)); 154.8 (C(2)); 140.9 (C(6)); 137.7 (C(4′)); 128.3 (C(5′); 98.0 (C(5)); 62.6 (C(1′)); 60.1 (OCH_2); 41.6 (C(2′)); 34.6 (C(3′)). EI-MS: 244 (4, $[M+2]^+$), 242 (16, M^+), 241 (49, $[M-1]^+$), 213 (5, $[M+2-MeO]^+$), 212 (30, $[M+2-CH_4O]^+$), 211 (12, $[M-MeO]^+$), 210 (91, $[M-CH_4O]^+$), 148 (32, $[M+2-C_6H_8O]^+$), 146 (100, $[M-C_6H_8O]^+$), 145 (33), 142 (34), 110 (34, $[M-C_6H_8ClO]^+$), 108 (10, $[M-C_6H_{10}ClO]^+$), 96 (9, $[M-C_4H_4ClN_3O]^+$), 95 (13, $[M-C_4H_5ClN_3O]^+$), 79 (11, $[M-C_4H_5ClN_3O_2]^+$), 67 (19, $[M-C_5H_5ClN_3O_2]^+$), 66 (13, $[M-C_5H_6ClN_3O_2]^+$), 65 (7, $[M-C_5H_7ClN_3O_2]^+$). Anal. calc. for $C_{10}H_{12}ClN_3O_2$ (241.67): C 49.70, H 5.00, N 17.39; found: C 49.58, H 5.13, N 17.46.

(±)-cis-*5-Bromo-1-[2-(hydroxymethyl)cyclopent-4-en-1-yl]cytosine* (**2c**). Prepared according to *GP 3*. Yield: quant. M.p. 229–231°. ^{1}H-NMR ((D$_6$)DMSO): 7.71 (br. *s*, 1 H of NH_2); 7.33 (*s*, H–C(6)); 6.86 (*s*, 1 H of NH_2); 6.23 (*m*, H–C(4′)); 5.69 (*m*, H–C(5′)); 5.49 (*m*, H–C(1′)); 4.40 (*m*, OH); 3.20 (*m*, 1 H of OCH_2); 3.04 (*m*, 1 H of OCH_2); 2.59 (*m*, H–C(2′)); 2.42 (*m*, 1 H of H–C(3′)); 2.32–2.26 (*m*, 1 H of H–C(3′)). ^{13}C-NMR ((D$_6$)DMSO): 161.6 (C(4)); 154.8 (C(2)); 143.5 (C(6)); 137.7 (C(4′)); 128.4 (C(5′); 85.1 (C(5)); 62.6 (C(1′)); 60.1 (OCH_2); 41.6 (C(2′)); 34.6 (C(3′)). EI-MS: 287 (35, $[M+1]^+$), 285 (33, $[M-1]^+$), 256 (99, $[M+1-MeO]^+$), 254 (100, $[M-1-MeO]^+$), 192 (89, $[M+1-C_6H_7O]^+$), 191 (23, $[M+1-C_6H_8O]^+$), 190 (92, $[M-1-C_6H_7O]^+$), 189 (21, $[M-1-C_6H_8O]^+$), 142 (65), 110 (59, $[M-C_6H_8BrO]^+$), 96 (20, $[M-C_4H_4BrN_3O]^+$), 95 (32, $[M-C_4H_5BrN_3O]^+$), 83 (25), 79 (61, $[M-C_4H_5BrN_3O_2]^+$), 78 (58, $[M-C_4H_6BrN_3O_2]^+$), 77 (33, $[M-C_4H_7BrN_3O_2]^+$), 69(41), 67 (71, $[M-C_5H_5BrN_3O_2]^+$), 66 (66, $[M-C_5H_6BrN_3O_2]^+$), 65 (38, $[M-C_5H_7BrN_3O_2]^+$), 63 (69, $[M-C_5H_9BrN_3O_2]^+$). Anal. calc. for $C_{10}H_{12}BrN_3O_2$ (286.13): C 41.98, H 4.23, N 14.69; found: C 41.85, H 4,32, N 14.53.

(±)-cis-*1-[2-(Hydroxymethyl)cyclopent-4-en-1-yl]-5-iodocytosine* (**2d**). Prepared according to *GP 3*. Yield: 69%. M.p. 203–205°. ^{1}H-NMR ((D$_6$)-DMSO): 7.92 (br. *s*, 1 H of NH_2); 7.60 (*s*, H–C(6)); 6.72 (br. *s*, 1 H of NH_2); 6.47 (*m*, H–C(4′)); 5.94 (*m*, H–C(5′)); 5.72 (*m*, H–C(1′)); 4.64 (*m*, OH); 3.42 (*m*, 1 H of OCH_2); 3.25 (*m*, 1 H of OCH_2); 2.82 (*m*, H–C(2′)); 2.69 (*m*, 1 H of H–C(3′)); 2.54–2.48 (*m*, 1 H of H–C(3′)). ^{13}C-NMR ((D$_6$)DMSO): 164.0 (C(4)); 155.5 (C(2)); 149.2 (C(6)); 138.1 (C(4′)); 128.9 (C(5′)); 62.8 (C(1′)); 60.7 (OCH_2); 55.7 (C(5)); 42.1 (C(2′)); 35.2 (C(3′)). EI-MS: 333 (6, M^+), 303 (16, $[M-OCH_2]^+$), 302 (100, $[M-MeO]^+$), 293 (12), 281 (14), 243 (10), 238 (87, $[M-C_6H_7O]^+$), 237 (23, $[M-C_6H_8O]^+$), 231 (17), 219 (12), 205 (19), 204 (14), 193 (6), 181 (26), 169 (26), 131 (29), 119 (39), 111 (14), 110 (20,

$[M-C_6H_8IO]^+$), 93 (8), 76 (21, $[M-C_4H_8IN_3O_2]^+$), 65 (56, $[M-C_5H_7IN_3O_2]^+$), 62 (20, $[M-C_5H_{10}IN_3O_2]^+$), 61 (11, $[M-C_5H_{11}IN_3O_2]^+$). Anal. calc. for $C_{10}H_{12}IN_3O_2$ (333.13): C 36.05, H 3.63, N 12.61; found: C 36.17, H 3.49, N 12.70.

REFERENCES

[1] 'Nucleoside Analogs in Cancer Therapy', Eds. D. K. Cheson, M. J. Keating, W. Plunkett, Marcel Dekker, New York, 1997.
[2] 'Nucleosides and Nucleotides as Antitumor and Antiviral Agents', Eds. C. K. Chu, D. C. Baker, Plenum Press, New York, 1993.
[3] C. Simons, 'Nucleotide Mimetics: Their Chemistry and Biological Properties', Gordon & Breach, Amsterdam, 2001.
[4] A. Wog, I. Toth, *Curr. Med. Chem.* **2001**, *8*, 1123.
[5] R. Wang, S. Harada, H. Mitsuya, J. Zemlicka, *J. Med Chem*. **2003**, *46*, 4799.
[6] V. E. Marquez, in 'Advances in Antiviral Drug Design', Ed. E. De Clercq, JAI Press, Greenwich, 1996, Vol. 2, p. 89–146.
[7] E. De Clercq, R. T. Walker, *Prog. Med. Chem*. **1986**, *23*, 187; E. De Clercq, J. Balzarini, P. F. Torrence, M. P. Mertes, C. L. Schmidt, D. Shugar, P. J. Barr, A. S. Jones, G. Verhelst, R. T. Walker, *Mol. Pharmacol*. **1981**, *19*, 321; A. Holý, E. De Clercq, *Collect. Czech. Chem. C* **1980**, *45*, 2364; C. López, K. A. Watanabe, J. J. Fox, *Antimicrob. Agents Chemother*. **1980**, *17*, 303.
[8] P. Besada, M. J. González-Moa, C. Terán, L. Santana, E. Uriarte, *Synthesis* **2002**, 2245.
[9] M. J. González-Moa, P. Besada, M. Teijeira, C. Terán, E. Uriarte, *Synthesis* **2004**, 543.
[10] D. Viña, L. Santana, E. Uriarte, E. Quezada, L.Valencia, *Synthesis* **2004**, 2517.
[11] D.Viña, L. Santana, E. Uriarte, C. Terán, *Tetrahedron* **2005**, *61*, 473.
[12] P. Wang, L. A. Agrofoglio, M. G. Newton, C. K. Chu, *J. Org. Chem.* **1999**, *64*, 4173.
[13] M. T. Crimmins, B. W. King, W. J. Zuercher, A. L. Choy, *J. Org. Chem.* **2000**, *65*, 8499.
[14] O. R. Ludeck, C. Meier, *Synthesis* **2003**, 2101.
[15] H. P. Guan, M. B. Ksebati, E. R. Kern, J. Zemlincka, *J. Org. Chem.* **2000**, *65*, 5177; J. Wang, J. Morral, C. Hendrix, P. Herdewijn, *J. Org. Chem.* **2001**, *66*, 8478; J. Wang, D. Viña, R. Busson, P. Herdewijn, *J. Org. Chem.* **2003**, *68*, 4499.
[16] P. Herdewijn, E. De Clercq, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1591.
[17] R. Vince, M. Hua, *J. Med. Chem*. **1990**, *33*, 17.
[18] N. Katagiri, M. Nomura, H. Sato, C. Kaneko, K. Yusa, T. Tsuruo, *J. Med. Chem*. **1992**, *35*, 1882.
[19] W. L. Sung, *J. Chem. Soc., Chem. Commun*. **1981**, 1089.
[20] N. Bischofberger, *Tetrahedron Lett*. **1987**, *28*, 2821.

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