Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 5782–5787
Tetrahedron

Synthesis of new nucleoside analogues comprising a methylenecyclobutane unit

Sophie Danappe,[a] Ashutosh Pal,[a] Christian Alexandre,[a,*] Anne-Marie Aubertin,[b] Nathalie Bourgougnon[c] and François Huet[a,*]

[a]*Laboratoire de Synthèse Organique, UMR CNRS 6011, Faculté des Sciences, Université du Maine, Avenue Olivier Messiaen, F-72085 Le Mans Cedex 9, France*
[b]*Institut de Virologie, INSERM U 544, Faculté de Médecine, Université Louis Pasteur, 3 Rue Koeberlé, F-67000 Strasbourg, France*
[c]*Laboratoire de Biologie et Chimie Moléculaires, Centre de recherche et d'enseignement Yves Coppens, Campus de Tohannic, BP 573, F-56017 Vannes, France*

Received 7 February 2005; revised 1 April 2005; accepted 14 April 2005

Available online 11 May 2005

Abstract—Synthesis of eight nucleoside analogues **3–10** with a methylene cyclobutane unit is described. Wittig or Peterson reactions with protected 2-hydroxycyclobutanones **12** and **13** gave *E*- and *Z*-derivatives, respectively. After functional modifications the heterocyclic moieties were introduced via a Mitsunobu reaction either on the lateral chain or on the cycle. When adenine was used in this reaction only the *N*-9 substitution products were obtained. Removal of the protecting groups provided the target products.

1. Introduction

Nucleoside analogues are at the center of current interest because they display a wide range of biological activities especially as antiviral and antitumor agents.[1] Several analogues have been prepared and evaluated in order to obtain compounds with better properties particularly towards enzymatic cleavage. Products with good activity were found among a large number of structures,[2–6] and it is difficult to predict which compounds will be sufficiently active and selective against viral enzymes. Structures of these analogues could be close of nucleosides as the HIV drug 3′-azido-2′,3′-dideoxythymidine (AZT) or very different as the acyclic analogues gancyclovir. Among these products, several compounds with a methylenecyclobutane unit **1** and **2** (Fig. 1) were described by Zemlicka.[5] A moderated effect of **1** against EBV was established but was not separated from cytotoxicity. The methylenecyclobutane system is a rigid linker between the hydroxymethyl group and base residue so that a modification of this system could lead to more active compounds. And thus we examined different geometries in this series, keeping the same distance between the two active parts but with different positions of double bond and cyclobutane.

Figure 1.

In the course of our research program towards nucleoside analogues, we have already synthesized some carbocyclic compounds with double bonds in endocyclic[7a,b,d,e] or exocyclic[7c] position and acyclic dienic[8a] and methylenic[8b] compounds. We then planned to synthesize products related to **1** and **2** but not bearing the base in the vinylic position. We thus selected compounds **3–10** (Fig. 2) as targets and we describe here a short route to these compounds from 2-hydroxycyclobutanone **11**.

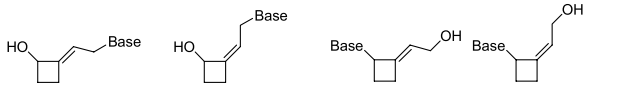


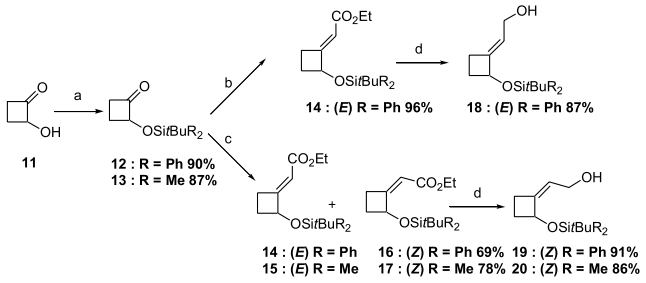
Figure 2.

Keywords: Nucleoside analogues; Methylenecyclobutane; Mistsunobu conditions.
* Corresponding authors. Tel.: +33 2 4383 3338; fax: +33 2 4383 3902 (F.H.); tel.: +33 2 4383 3096; fax: +33 2 4383 3902 (C.A.); e-mail addresses: calexan@univ-lemans.fr; fhuet@univ-lemans.fr

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.023

2. Results and discussion

The starting material for the synthesis of *Z*- and *E*-methylenecyclobutane analogues was 2-hydroxycyclobutanone **11**[9] (Scheme 1). This ketol was first protected as silyl ether. The resulting compounds **12** and **13**[10] were treated by two different methods. The first one was the Wittig reaction with ethoxycarbonylmethylene phosphorane, which led to *E*-isomers **14** as sole product. The other one was the Peterson reaction with ethyl trimethylsilylacetate in basic medium, which led to a mixture of *E*- and *Z*-isomers **14** and **16** (ratio 1/12) or **15** and **17** (ratio 1/18).



Scheme 1. Reagents and conditions: (a) tBuR$_2$SiCl, imidazole, DMF, rt, 20 h; (b) $Ph_3P{=}CHCOOEt$, C_6H_6, rt, 72 h; (c) LDA, $(Me)_3SiCH_2COOEt$, THF −78 °C, 1 h; (d) DIBALH, CH_2Cl_2, toluene −60 °C, 2 h.

These compounds were separated by column chromatography. The NOE experiments were used to distinguish the two isomers. Thus, *Z* isomer **14** showed NOE enhancement of the olefinic signal after irradiation of the H_2, similar effect was absent in *E* isomer **16**. Reduction of esters with DIBALH gave, respectively, alcohol **18** from ester **14** and alcohol **20** from ester **17**. With these key compounds in our hands, two different methods were used to obtain the target products either **3**–**6** or **7**–**10** (Fig. 3).

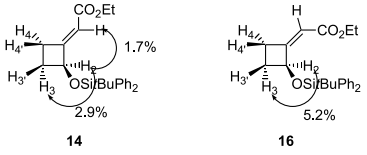
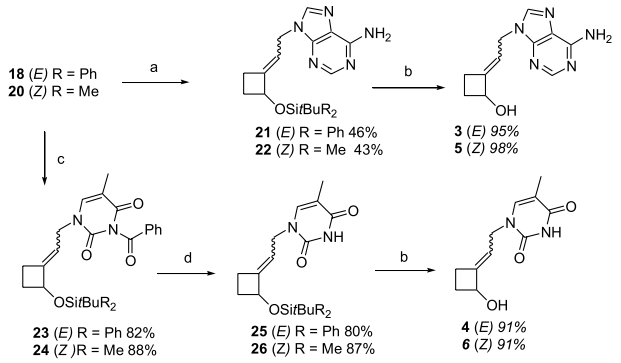


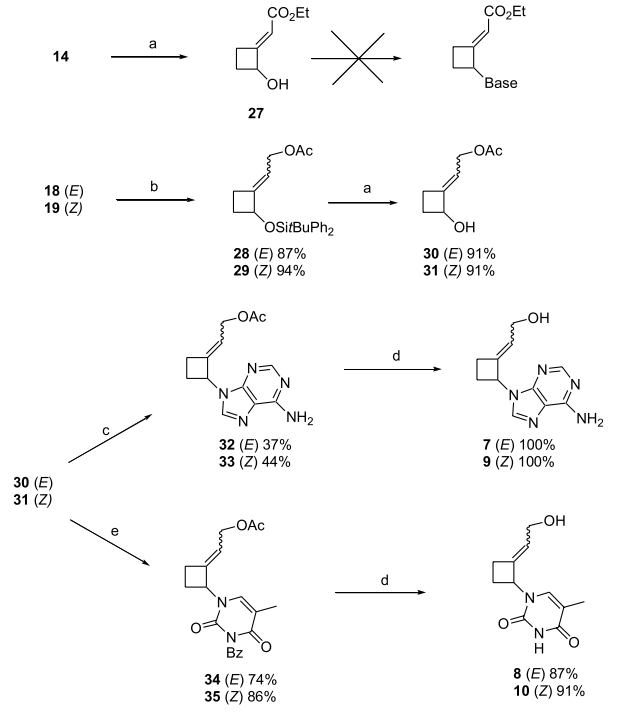
Figure 3. NOE enhancements of **14** and **16**.

To access the series **3**–**6** (Scheme 2) with the nucleic base in allylic position, direct substitutions with protected thymine and free adenine were performed, in Mitsunobu conditions, separately from alcohols **18** (*E*) or **20** (*Z*). The reactions were carried out with triphenylphosphine and DIAD in THF and led to good results. It is worth mentioning that reaction with adenine only led to the *N*-9 substitution products. We could not detect any other isomer by NMR analysis of the crude products. These assignments were proved by $^1H/^{13}C$ HMBC NMR spectra. In the adenine series the target products **3** and **5** were obtained after desilylation with TBAF. For the thymine analogs **4** and **6**, an additional mild treatment with NH_3/MeOH was necessary to remove the benzoyl group. In every case the final product was obtained as single isomer.

For obtaining compounds **7**–**10** (Scheme 3) with base directly linked to the cycle, we first tried to introduce the



Scheme 2. Reagents and conditions: (a) Adenine, DIAD, Ph_3P, THF, rt, 7 days; (b) $(n\text{Bu})_4NF$, THF, rt, 2.5 h; (c) *N*3-benzoyl thymine, DIAD, Ph_3P, THF, rt, 7 days; (d) sat NH_3/MeOH, rt, 48 h.



Scheme 3. Reagents and conditions: (a) $(n\text{Bu})_4NF$, THF, rt, 2.5 h; (b) Ac_2O, pyridine, rt, 14 h; (c) Adenine, DIAD, Ph_3P, THF, rt, 7 days; (d) sat NH_3/MeOH, rt, 15 h; (e) *N*3-benzoyl thymine, DIAD, Ph_3P, THF, rt, 7 days.

nucleic base by substitution in Mitsunobu conditions with alcohol **27** resulting from removal of the silyl group on **14**. Unfortunately, in these conditions, benzoyl thymine led to several products including the expected product in low yield and another one resulting from Michael addition to the conjugated double bond. As to adenine, it did not react. We thought that these difficulties could be avoided by using compounds **30** and **31**. Both of these products were prepared from alcohols **18** and **19** by acetylation providing compounds **28** and **29**, followed by desilylation. These very volatile compounds can only be obtained in good yield if suitable precautions were taken for solvent evaporation stage. The subsequent Mitsunobu reactions provided compounds **32** to **35** and cleavage of acetyl group only (from **32** and **33**) or of acetyl and benzoyl groups (from **34**

and **35**) with NH_3/MeOH gave the target molecules in satisfying overall yields.

Compounds **3** to **10** were tested against HIV-1 and HSV-1, none of them had a significant antiviral activity.

3. Experimental

3.1. General

NMR spectra were recorded at 400 and 100 MHz for ^1H and ^{13}C, respectively. IR spectra were recorded with a FT infrared spectrophotometer. Melting points are uncorrected. Elemental analyses were performed by the service of microanalyses, CNRS ICSN, Gif sur Yvette. High-resolution mass measurements were performed at the CRMPO (Rennes). The column chromatographies were run on silica gel Gerudan SI 60, 230–400 mesh, under 1–2 bars.

3.1.1. 2-{(*tert*-Butyldiphenylsilyl)oxycyclobutanone} 12. To a solution of alcohol **11** (1.50 g, 17.5 mmol) in DMF (4 mL) were added imidazole (1.43 g, 21 mmol) and *tertio*-butylchlorodiphenylsilane (5.4 mL, 21 mmol). The resulting mixture was stirred 20 h at rt. Water (15 mL) was added and the aqueous layer was extracted with diethyl ether. The combinated organic layers were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **12** (5.1 g, 90%) as a colorless oil. IR (film, cm^{-1}): 1793, 1170, 1113, 704. ^1H NMR ($CDCl_3$) δ: 1.08 (9H, s), 1.92 (1H, m), 2.19 (1H, m), 2.61 (2H, m), 4.82 (1H, dtt, $J=8.1$, 1.7 Hz), 7.40 (6H, m), 7.68 (2H, m), 7.77 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 19.3, 22.4, 26.7, 38.4, 82.3, 127.91, 127.93, 130.1, 132.8, 133.4, 135.6, 135.7, 206.6. Anal. Calcd for $C_{20}H_{24}SiO_2$: C, 74.03; H, 7.45. Found C, 73.77; H, 7.54.

3.1.2. 2-{(*tert*-Butyldimethylsilyl)oxycyclobutanone} 13.[10] With the same procedure as above from **11** (1.17 g, 14 mmol), imidazole (1.295 g, 19 mmol) and *tertio*-butylchlorodimethylsilane (1.38 g, 19 mmol) in DMF (3 mL), **13** (2.36 g, 87%) was obtained as a colorless oil. ^1H NMR ($CDCl_3$) δ: 0.10 (3H, s), 0.12 (3H, s), 0.91 (9H, s), 1.86 (1H, m), 2.37 (1H, m), 3.72 (2H, m), 4.88 (1H, m). ^{13}C NMR ($CDCl_3$) δ: −4.7, −4.5, 18.5, 22.5, 25.8, 26.0, 38.5, 82.2, 207.3.

3.1.3. (*E*)-2-{(*tert*-Butyldiphenylsilyl)oxycyclobutylidene}ethyl acetate 14. To a solution of ketone **12** (0.953 g, 2.94 mmol) in benzene (6 mL) was added carbethoxymethylene triphenylphosphorane (1.637 g, 4.70 mmol). The resulting mixture was stirred for 3 days at rt. The solvent was removed under reduced pressure and the residue was diluted with petroleum ether. After filtration the solid was washed with petroleum ether and the filtrate was evaporated under reduced pressure. The resulting oil was purified by column chromatography on silica gel to give **14** (1.109 g, 96%) as a colorless oil. IR (film, cm^{-1}): 1716, 1685, 704. ^1H NMR ($CDCl_3$) δ: 1.07 (9H, s); 1.28 (3H, d, $J=7.4$ Hz), 1.99 (2H, m), 2.40 (1H, m), 2.95 (1H, m), 4.18 (2H, m), 4.75 (1H, m), 5.87 (1H, m), 7.40 (6H, m), 7.65 (3H, m). ^{13}C NMR ($CDCl_3$) δ: 13.9, 18.7, 24.8, 26.3, 29.4, 59.4, 71.4, 109.8, 127.2, 129.4, 132.8, 133.1, 135.1, 166.1, 167.3. Anal. Calcd for $C_{24}H_{30}SiO_3$: C, 73.05; H, 7.66. Found C, 73.49; H, 7.74.

3.1.4. (*Z*)-2-{(*tert*-Butyldiphenylsilyl)oxycyclobutylidene}ethyl acetate 16. To a solution of diisopropylamine (0.21 mL, 1.5 mmol) in THF (0.5 mL) at 0 °C was added a 1.6 M solution of BuLi in hexane (0.98 mL). The resulting mixture was stirred 30 min at 0 °C before cooling at −78 °C. At this temperature ethyl trimethylsilylacetate (0.275 mL, 1.5 mmol) was added. After 45 min a solution of ketone **12** (0.487 g, 1.5 mmol) in THF (2 mL) was added slowly. After 1 h the reaction mixture was allowed to warm to rt, and hydrolyzed with a 3 M solution of HCl (2 mL). The aqueous layer was extracted with dichloromethane and the organic layer was dried and concentrated under reduced pressure. The crude product (mixture *Z*/*E* 12/1) was purified by column chromatography on silica gel to give isomer *Z* **16** (0.377 g, 69%) as a colorless oil. IR (film, cm^{-1}): 1724, 1687, 1190, 1112, 703. ^1H NMR ($CDCl_3$) δ: 1.05 (9H, s), 1.20 (3H, t, $J=6.9$ Hz), 1.82 (2H, m), 2.26 (1H, m), 2.50 (1H, m), 3.96 (1H, dq, $J=14.4$, 6.9 Hz), 4.16 (1H, dq, $J=14.4$, 6.9 Hz), 5.17 (1H, m), 5.63 (1H, m), 7.38 (6H, m), 7.74 (4H, m). ^{13}C NMR($CDCl_3$) δ: 14.3, 19.2, 25.3, 16.9, 59.9, 72.5, 114.0, 127.5, 127.6, 129.5, 129.6, 133.8, 134.4, 135.7, 135.9, 163.5, 165.5. Anal. Calcd for $C_{24}H_{30}SiO_3$: C, 73.05; H, 7.66. Found C, 73.04; H, 7.68.

3.1.5. (*Z*)-2-{(*tert*-Butyldimetylsilyl)oxycyclobutylidene}ethyl acetate 17. With the same procedure as above from **13** (1 g, 5 mmol), (*Z*) ester **17** (1.05 g, 78%) was obtained as a colorless oil. IR (film, cm^{-1}: 1726, 1686, 1192, 1083. ^1H NMR ($CDCl_3$) δ: 0.09 (3H, s), 0.13 (3H, s), 0.87 (9H, s), 1.24 (3H, t, $J=7.5$ Hz), 1.99 (1H, m), 2.35 (1H, m), 2.41 (1H, m), 2.62 (1H, m), 4.07 (1H, m), 4.17 (1H, m), 5.05 (1H, m), 5.61 (1H, m). ^{13}C NMR ($CDCl_3$) δ: −5.3, −4.9, 2.3, 14.4, 18.2, 25.1, 26.1, 29.8, 59.8, 71.5, 114.3, 165.1. Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found C, 62.41, H, 9.64.

3.1.6. (*E*)-2-{(*tert*-Butyldiphenylsilyl)oxycyclobutylidene}ethanol 18. To a stirred solution of the ester **14** (1.3 g, 3.34 mmol) in dry dichloromethane (185 mL) at −60 °C was added dropwise a 1 M solution of DIBALH in toluene (16.85 mL). The mixture was stirred for 2 h at this temperature. A solution of 10% citric acid (150 mL) was added at −20 °C, the aqueous layer was extracted with toluene (2×50 mL) then the combinated organic layers were dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **18** (1.01 g, 87%) as a colorless oil. IR (film, cm^{-1}): 3378, 1428, 1112, 703. ^1H NMR ($CDCl_3$) δ: 1.07 (s, 9H), 1.60 (1H, br s), 1.99 (3H, m), 2.45 (1H, m) 4.10 (2H, m), 4.70 (1H, m), 5.64 (1H, m), 7.39 (6H, m), 7.67 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 18.7, 21.2, 26.3, 29.8, 59.1, 71.1, 117.3, 127.2, 129.2, 133.5, 135.1, 147.9. Anal. Calcd for $C_{22}H_{28}SiO_2$: C, 74.95; H, 8.01. Found C, 74.64; H, 7.98.

3.1.7. (*Z*)-2-{(*tert*-Butyldiphenylsilyl)oxycyclobutylidene}ethanol 19. With the same procedure as above from ester **16** (0.5 g, 1.27 mmol), **19** (0.405 g, 91%) was obtained as a colorless oil. IR (film, cm^{-1}): 3421, 1428, 1112, 704. ^1H NMR ($CDCl_3$) δ: 1.09 (9H, s), 1.62 (1H, m),

1.76 (1H, m), 2.04 (1H, m), 2.23 (1H, m), 2.94 (1H, br s), 4.20 (1H, dd, $J=13.1$, 4.3 Hz), 4.33 (1H, dd, $J=13.1$, 5.3 Hz), 4.95 (1H, m), 5.46 (1H, m), 7.40 (6H, m), 7.71 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 18.9, 23.0, 26.8, 29.5, 59.5, 72.4, 121.4, 127.6, 127.7, 129.8, 132.9, 133.6, 135.6, 135.7, 145.5. Anal. Calcd for $C_{22}H_{28}SiO_2 \cdot 0.2\ H_2O$: C, 74.19; H, 8.04. Found C, 74.19; H, 8.11.

3.1.8. (*Z*)-2-{(*tert*-Butyldimethylsilyl)oxycyclobutylidene}ethanol 20. With the same procedure as above from ester **17** (1.3 g, 4.82 mmol), **20** (0.94 g, 86%) was obtained as a colorless oil. IR (film, cm^{-1}): 3374, 1254, 1131. ^{1}H NMR ($CDCl_3$) δ: 0.08 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.88 (1H, m), 2.20 (2H, m), 2.33 (1H, m), 3.10 (1H, br s), 4.07 (1H, m), 4.15 (1H, m), 4.86 (1H, m), 5.42 (1H, m). ^{13}C NMR ($CDCl_3$) δ: −5.1, −4.7, 2.1, 17.9, 23.1, 25.7, 29.9, 59.7, 71.4, 121.6, 145.4. HRMS Calcd for $C_8H_{15}O_2Si$ [M−*t*Bu] 171.08413. Found 171.0843.

3.1.9. (*E*)-{2-[2-(*tert*-Butyldiphenyl-silanyloxy)-cyclobutylidene]-ethyl}-9*H*-purin-6-ylamine 21. To a solution of alcohol **18** (0.61 g, 1.73 mmol), triphenylphosphine (0.99 g) and adenine (0.495 g) in THF (10 mL), was added for 2.5 h a solution of DIAD (0.55 mL) in THF (10 mL). The mixture was stirred at rt for 1 week. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give **21** (0.374 g, 46%) as white needles, mp 174–175 °C. IR (film, cm^{-1}): 3301, 3147, 1670, 1601, 1144, 1109. ^{1}H NMR ($CDCl_3$) δ: 1.05 (9H,s), 1.99 (1H, m), 2.10 (2H, m), 2.44 (1H, m), 4.70 (2H, d, $J=7$ Hz), 4.74 (1H, m), 5.60 (1H, m), 5.81 (2H, br s), 7.36 (6H, m), 7.62 (4H, m), 7.76 (1H,s), 8.36 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 19.1, 21.6, 26.8, 29.9, 41.1, 71.5, 112.1, 119.6, 127.7, 129.8, 133.7, 135.5, 140.0, 150.0, 151.6, 153.0, 155.4. Anal. Calcd for $C_{27}H_{31}N_5SiO$: C, 69.05; H, 6.65, N, 14.91. Found C, 68.90; H, 6.64, N, 14.88.

3.1.10. (*Z*)-{2-[2-(*tert*-Butyldimethyl-silanyloxy)-cyclobutylidene]-ethyl}-9*H*-purin-6-ylamine 22. With the same procedure as above from ester **20** (0.47 g, 2.06 mmol), **22** (0.305 g, 43%) was obtained as white powder, mp 178.6–180 °C (methanol). IR (film, cm^{-1}): 3430, 3293, 3148, 1671, 1604, 1135. ^{1}H NMR ($CDCl_3$) δ: 0.11 (3H, s), 0.12 (3H, s), 0.89 (9H, s), 1.96 (1H, m), 2.26 (2H, m), 2.37 (1H, m), 4.92 (2H, d, $J=7$ Hz), 4.98 (1H, m), 6.20 (2H, br s), 8.01 (1H, s), 8.37 (1H, s). ^{13}C NMR($CDCl_3$) δ: −5.0, −4.5, 17.9, 23.2, 25.7, 29.9, 40.1, 71.4, 115.17, 119.5, 140.9, 149.8, 150.1, 152.8, 155.5. HRMS Calcd for $C_{17}H_{27}N_5OSi$ 345.1985. Found 345.1964.

3.1.11. (*E*)-2-[2-(6-Amino-purin-9-yl)-ethylidene]-cyclobutanol 3. To a solution of protected alcohol **21** (0.32 g, 0.68 mmol) in THF (5.5 mL) was added tetrabutylammonium fluoride (1 M, 1.3 mL) and the mixture was stirred for 2.5 h at rt. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give alcohol **3** (0.26 g, 95%). IR (film, cm^{-1}): 3272, 1678, 1605, 1577, 1298. ^{1}H NMR (DMSO-d_6) δ: 1.75 (1H, m), 2.22 (2H, m), 2.55 (1H, m), 4.57 (1H, m), 4.74 (2H, d, $J=7.0$ Hz), 5.47 (1H, m), 5.64 (1H, m), 7.30 (2H, br s), 8.21 (1H, s), 8.23 (1H, s). ^{13}C NMR (DMSO-d_6) δ: 21.2, 29.2, 40.6, 69.9, 112.7, 118.7, 140.5, 149.4, 151.3, 152.5, 156.0. HRMS Calcd for $C_{11}H_{13}ON_5$ 231.1120. Found 231.1133. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13, H, 5.66, N, 30.28. Found C, 56.66, H, 5.52, N, 30.12.

3.1.12. (*Z*)-2-[2-(6-Amino-purin-9-yl)-ethylidene]-cyclobutanol 5. With the same procedure as above from protected alcohol **22** (0.15 g, 0.434 mmol), alcohol **5** was obtained (0.098 g, 98%) as a white powder, mp 196.8–197.5 °C (methanol). IR (film, cm^{-1}): 3427, 3290, 1688, 1614, 1576, 1159. ^{1}H NMR (DMSO-d_6) δ: 1.78 (1H, m), 2.20 (3H, m), 4.80 (1H, m), 4.89 (1H, m), 5.35 (1H, m), 6.09 (1H, d, $J=8$ Hz), 7.16 (2H, br s), 8.10 (1H, s), 8.15 (1H, s). ^{13}C NMR 22.9, 29.3, 39.8, 70.4, 115.3, 119.1, 140.7, 149.2, 150.8, 152.3, 156.2. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13, H, 5.66, N, 30.28. Found C, 57.02, H, 5.71, N, 30.11.

3.1.13. (*E*)-Benzoyl-1-{2-[2-(*tert*-butyldiphenyl-silanyloxy)-cyclobutylidene]-ethyl}-5-methyl-1*H*-pyrimidine-2,4-dione 23. With the same procedure as for **21** from alcohol **18** (0.45 g, 1.27 mmol) and *N*-3-benzoylpyrimidine (0.585 g, 2.55 mmol) **23** was obtained (0.591 g, 82%) as a white powder, mp 68.8–69.7 °C. IR (film, cm^{-1}): 1748, 1699, 1656, 1234, 1110. ^{1}H NMR ($CDCl_3$) δ: 1.07 (9H, s), 1.98 (3H, s), 2.12 (3H, m), 2.50 (1H, m), 4.25 (2H, m), 4.73 (1H, m), 5.40 (1H, m), 7.03 (1H, s), 7.40 (5H, m), 7.48 (4H, m), 7.63 (4H, m), 7.92 (2H, d, $J=7$ Hz). ^{13}C NMR($CDCl_3$) δ: 12.3, 15.1, 18.9, 21.6, 26.6, 29.7, 45.1, 71.3, 100.5, 111.6, 127.5, 128.9, 129.6, 130.3, 131.5, 133.5, 134.8, 135.4, 139.1, 149.7, 152.1, 162.9, 169.0.

3.1.14. (*Z*)-Benzoyl-1-{2-[2-(*tert*-butyldimethyl-silanyloxy)-cyclobutylidene]-ethyl}-5-methyl-1*H*-pyrimidine-2,4-dione 24. With the same procedure as for **23** from alcohol **20** (0.40 g, 1.75 mmol), **24** was obtained (0.678 g, 88%) as a white powder, mp 130–131.2 °C. IR (film, cm^{-1}): 1701, 1658, 1599, 1252. ^{1}H NMR ($CDCl_3$) δ: 0.16 (6H, s), 0.97 (9H, s), 1.97 (3H, s), 1.98 (1H, m), 2.30 (2H, m), 2.43 (1H, m), 4.25 (1H, dd, $J=13.8$, 9.8 Hz), 4.73 (1H, dd, $J=13.8$, 5.3 Hz), 4.96 (1H, m), 5.26 (1H, m), 7.50 (2H, dd, $J=7$, 7 Hz), 7.56 (1H, s), 7.63 (2H, t, $J=7.7$ Hz) 7.94 (2H, d, $J=7$ Hz). ^{13}C NMR ($CDCl_3$) δ −4.7, −4.2, 12.5, 18.2, 23.6, 26.0, 30.4, 44.0, 71.6, 110.5, 115.1, 129.3, 130.6, 132.0, 140.3, 150.2, 151.0, 163.5, 169.6.

3.1.15. (*E*)-1-{2-[2-(*tert*-Butyldiphenyl-silanyloxy)-cyclobutylidene]-ethyl}-5-methyl-1*H*-pyrimidine-2,4-dione 25. A solution of **23** (0.34 g, 0.60 mmol) in methanol saturated with ammonia (9.5 mL) was stirred for 48 h at rt. After removal of the volatile substances, the residue was purified by column chromatography on silica gel to give **25** (0.22 g, 80%) as a white powder, mp 58.8–59.8 °C. IR (film, cm^{-1}): 3170, 1680, 1112, 702. ^{1}H NMR ($CDCl_3$) δ: 1.08 (9H, s), 1.94 (3H, s), 1.98 (1H, m), 2.10 (2H, m), 2.48 (1H, m), 4.25 (2H, m), 4.72 (1H, m), 5.39 (1H, m), 6.96 (1H, s), 7.38 (6H, m), 7.68 (4H, m) 10.05 (1H, br s). ^{13}C NMR ($CDCl_3$) δ: 12.4, 19.1, 21.8, 26.7, 26.8, 29.9, 44.9, 71.5, 110.7, 112.3, 127.6, 127.8, 129.7, 129.8, 133.7, 133.8, 135.5, 139.6, 151.2, 151.5, 164.7. HRMS Calcd for $C_{27}H_{32}N_2O_3Si$ 460.2182. Found 460.2169.

3.1.16. (*Z*)-1-{2-[2-(*tert*-Butyldimethyl-silanyloxy)-cyclobutylidene]-ethyl}-5-methyl-1*H*-pyrimidine-2,4-dione 26. With the same procedure as above from protected alcohol **24** (0.33 g, 0.75 mmol), **26** was obtained (0.219 g,

87%) as a white powder, mp 134.8–135.9 °C (petroleum ether/ether 2/1). IR (film, cm^{-1}): 3464, 3414, 1695, 1681, 1640, 1134. ^1H NMR ($CDCl_3$) δ: 0.12 (6H, s), 0.91 (9H, s), 1.91 (3H, s), 1.92 (1H, m), 2.27 (2H, m), 2.39 (1H, m), 4.19 (1H, dd, $J=14.0$, 10.3 Hz), 4.73 (1H, dd, $J=14.0$, 4.3 Hz), 4.94 (1H, m), 5.25 (1H, m), 7.42 (1H, s), 9.75 (1H, br s). ^{13}C NMR($CDCl_3$) δ: −4.5, 12.3, 18.0, 23.3, 25.8, 30.2, 43.5, 71.4, 110.4, 115.5, 140.3, 150.1, 151.4, 164.7. HRMS Calcd for $C_{17}H_{28}O_3N_2Si$ 336.1869. Found 336.1849.

3.1.17. (*E*)-1-[2-(2-Hydroxy-cyclobutylidene)-ethyl]-5-methyl-1*H*-pyrimidine-2,4-dione 4. With the same procedure as for **3** from protected alcohol **25** (0.17 g, 0.369 mmol), alcohol **4** was obtained (0.074 g, 91%) as a white powder, mp 137.6–138.4 °C (methanol/ether 1/4). IR (film, cm^{-1}): 3406, 1696, 1673, 1117. ^1H NMR (CD_3OD) δ: 1.72 (1H, m), 1.77 (3H, s), 2.19 (2H, m), 2.45 (1H, m), 4.18 (2H, d, $J=7.5$ Hz), 4.49 (1H, m), 5.36 (1H, m), 7.28 (1H, s). ^{13}C NMR (CD_3OD) δ: 14.0, 24.3, 32.1, 48.1, 73.4, 113.1, 115.8, 144.5, 154.2, 154.7, 168.8. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 59.45, H, 6.35, N, 12.61. Found C, 59.01, H, 6.30, N, 12.22. HRMS Calcd for $C_{11}H_{14}O_3N_2Si$ 222.1004. Found 222.0094.

3.1.18. (*Z*)-1-[2-(2-Hydroxy-cyclobutylidene)-ethyl]-5-methyl-1*H*-pyrimidine-2,4-dione 6. With the same procedure as for **3** from protected alcohol **26** (0.16 g, 0.48 mmol), alcohol **6** was obtained (0.096 g, 91%) as a white powder, mp 129–130 °C (methanol/ether 1/4). IR (film, cm^{-1}): 3452, 1680, 1640, 1104. ^1H NMR (CD_3OD) δ: 1.88 (3H, s), 1.90 (1H, m), 2.30 (2H, m), 2.40 (1H, m), 4.39 (1H, dd, $J=14.2$, 8.3 Hz), 4.48 (1H, dd, $J=14.2$, 7.0 Hz), 4.85 (2H, br s), 5.26 (1H, m), 7.50 (1H, s). ^{13}C NMR (CD_3OD) δ: 14.0, 25.7, 31.8, 47.8, 73.5, 113.0, 118.5, 144.5, 144.6, 153.8, 154.7, 168.7. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 59.45, H, 6.35, N, 12.61. Found C, 59.39, H, 6.41, N, 12.69.

3.1.19. (*E*)-Acetic acid 2-[2-(*tert*-butyldiphenyl-silanyl-oxy)-cyclobutylidene]-ethyl ester 28. To a solution of alcohol **18** (0.252 g, 0.71 mmol) in pyridine (10 mL) at 0 °C acetic anhydride (0.3 mL, 3.18 mmol) was added slowly. After 10 min at this temperature the mixture was stirred for one night at rt. Dichloromethane (15 mL) was added and the organic layer was washed with water, the aqueous layer was extracted with dichloromethane (2×20 mL) and the combinated organic layers were dried ($MgSO_4$) then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **28** (0.245 g, 87%) as a colorless oil. IR (film, cm^{-1}): 1744, 1237, 1117, 704. ^1H NMR ($CDCl_3$) δ: 1.07 (9H, s), 2.03 (3H, m), 2.07 (3H, s), 2.48 (1H, m), 4.51 (2H, m), 4.69 (1H, m), 5.58 (1H, m), 7.39 (6H, m), 7.67 (4H, m). ^{13}C NMR 19.1, 21.0, 21.7, 26.8, 30.0, 61.1, 71.5, 112.8, 127.5, 127.6, 129.6, 133.7, 134.0, 135.5, 150.9, 170.9. Anal. Calcd for $C_{24}H_{30}O_3Si$: C, 73.05, H, 7.66. Found C, 72.96, H, 7.76.

3.1.20. (*Z*)-Acetic acid 2-[2-(*tert*-butyldiphenyl-silanyl-oxy)-cyclobutylidene]-ethyl ester 29. With the same procedure as above from alcohol **19** (1.473 g, 4.18 mmol), pyridine (30 mL) and acetic anhydride (1 mL, 10.6 mmol), **29** (1.548 g, 94%) was obtained as a colorless oil. IR (film, cm^{-1}): 1742, 1233, 1114, 705. ^1H NMR ($CDCl_3$) δ: 1.07 (9H, s), 1.80 (2H, m), 2.06 (3H, s), 2.09 (1H, m), 2.28 (1H, m), 4.80 (2H, dd, $J=1.4$, 0.8 Hz), 4.91 (1H, m), 5.35 (1H, m), 7.38 (6H, m), 7.68 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 18.9, 21.0, 23.2, 26.8, 29.5, 61.0, 72.1, 115.7, 127.5, 127.7, 129.6, 133.4, 134.0, 135.7, 135.8, 149.9, 170.9. Anal. Calcd for $C_{24}H_{30}O_3Si\cdot0.2\ H_2O$: C, 72.39, H, 7.70. Found C, 72.15, H, 7.53.

3.1.21. (*E*)-Acetic acid 2-(2-hydroxy-cyclobutylidene)-ethyl ester 30. With the same procedure as for alcohol **3** from acetate **28** (0.177 g, 0.45 mmol), alcohol **30** was obtained as a colorless oil (0.64 g, 91%). IR (film, cm^{-1}): 3399, 1744, 1251. ^1H NMR ($CDCl_3$) δ: 1.85 (1H, m), 2.06 (3H, s), 2.28 (1H, m), 2.37 (1H, m), 2.57 (1H, m), 4.53 (2H, m), 4.69 (1H, m), 5.60 (1H, m). ^{13}C NMR ($CDCl_3$) δ: 20.9, 21.7, 30.0, 60.9, 70.9, 113.4, 151.4, 171.0. HRMS: calcd for $C_6H_{10}O$ [M−C_2H_2O] 114.06808, found 114.0688.

3.1.22. (*Z*)-Acetic acid 2-(2-hydroxy-cyclobutylidene)-ethyl ester 31. With the same procedure as for alcohol **3** from acetate **29** (1.53 g, 3.88 mmol), alcohol **31** was obtained as a colorless oil (0.549 g, 91%). IR (film, cm^{-1}) 3443, 1735, 1244^1H NMR ($CDCl_3$) δ: 1.83 (1H, m), 2.08 (3H, s), 2.30 (3H, m), 3.92 (1H, dd, $J=8.9$ Hz), 4.39 (1H, m), 4.82 (1H, m), 5.07 (1H, dd, $J=12.3$, 9.8 Hz), 5.26 (1H, m). ^{13}C NMR ($CDCl_3$) δ: 21.2, 23.3, 29.6, 61.3, 71.3, 115.7, 150.7, 171.9. HRMS Calcd for $C_6H_{10}O$ [M− C_2H_4O] 112.05243. Found 112.0515.

3.1.23. (*E*)-Acetic acid 2-[2-(6-amino-purin-9-yl)-cyclobutylidene]-ethyl ester 32. With the same procedure as for **21** from **30** (0.047 g, 0.3 mmol), alcohol **32** was obtained (0.03 g, 37%) as a white powder, mp 155–157 °C (methanol). IR (film, cm^{-1}): 1727, 1675, 1606, 1571, 1240. ^1H NMR ($CDCl_3$) δ: 2.06 (3H, s), 2.49 (1H, m), 2.74 (2H, m), 2.93 (1H, m), 4.56 (2H, m), 5.44 (1H, m), 5.71 (1H, m), 5.93 (2H, br s), 7.98 (1H, s), 8.36 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 20.6, 24.7, 27.7, 53.1, 60.4, 117.5, 119.4, 138.7, 145.1, 149.8, 152.9, 155.7, 170.7. Anal. Calcd for $C_{13}H_{15}N_5O_2$: C, 57.13, H, 5.53, N, 25.63. Found C, 57.14, H, 5.65, N, 25.11.

3.1.24. (*Z*)-Acetic acid 2-[2-(6-amino-purin-9-yl)-cyclobutylidene]-ethyl ester 33. With the same procedure as for **21** from **31** (0.384 g, 2.46 mmol), alcohol **33** was obtained (0.296 g, 44%) as a white powder, mp 155–157 °C (methanol). IR (film, cm^{-1}). ^1H NMR ($CDCl_3$) δ: 1.88 (3H, s), 2.47 (1H, m), 2.74 (2H, m), 2.90 (1H, m), 4.07 (1H, ddd, $J=12.8$, 7.4, 1.0 Hz), 4.21 (1H, ddd, $J=12.8$, 6.8, 1.5 Hz), 5.63 (1H, m), 5.81 (1H, m), 5.85 (1H, br s), 7.98 (1H, s), 8.38 (1H, s). ^{13}C NMR ($CDCl_3$) δ: 20.6, 26.3, 27.3, 53.0, 59.6, 119.7, 119.9, 139.0, 144.4, 149.5, 153.0, 155.9, 170.5. Anal. Calcd for $C_{13}H_{15}N_5O_2$: C, 57.13, H, 5.53, N, 25.63. Found C, 57.16, H, 5.56, N, 25.41.

3.1.25. (*E*)-2-[2-(6-Amino-purin-9-yl)-cyclobutylidene]-ethanol 7. A solution of **32** (0.112 g, 0.41 mmol) in methanol saturated with ammonia (9.5 mL) was stirred for 15 h at rt. After removal of the volatile substances, the residue was purified by column chromatography on silica gel to give **7** (0.095 g, 100%) as a white powder, mp 192 °C. IR (film, cm^{-1}): 3120, 1684, 1614, 1571. ^1H NMR (DMSO-d_6): δ: 2.57 (3H, m), 2.80 (1H, m), 3.90 (2H, m), 4.53 (1H, br s), 5.23 (1H, m), 5.56 (1H, m), 7.18 (2H, s), 8.15 (1H, s), 8.25 (1H, s). ^{13}C NMR (DMSO-d_6): 24.2, 26.0, 52.9, 57.3,

118.7, 122.3, 139.1, 140.9, 149.3, 152.3, 155.9. Anal. Calcd for $C_{11}H_{13}N_5O \cdot 0.1\ H_2O$: C, 56.69, H, 5.71, N, 30.05. Found C, 56.53, H, 5.73, N, 29.67.

3.1.26. (*Z*)-2-[2-(6-Amino-purin-9-yl)-cyclobutylidene]-ethanol 9. With the same procedure as above from acetate **33** (0.29 g, 1.06 mmol), alcohol **9** was obtained (0.245 g, 100%) as a white powder, mp 159.5–160.5 °C (methanol). IR (film, cm^{-1}): 3271, 3120, 1683, 1612, 1573, 1000. ^1H NMR (DMSO-d_6) δ: 2.52 (2H,m), 2.62 (1H, m), 2.77 (1H, m), 3.36 (1H, m), 3.45 (1H, m), 4.39 (1H, m), 5.42 (1H, m), 5.66 (1H, m), 7.17 (1H, s), 8.14 (1H, s), 8.22 (1H,s). ^{13}C NMR (DMSO-d_6): 25.4, 26.0, 52.3, 56.5, 118.7, 125.2, 139.3, 139.5, 149.0, 152.3, 155.9. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13, H, 6.67, N, 30.28. Found C, 56.81, H, 5.59, N, 30.23.

3.1.27. (*E*)-Acetic acid 2-[2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-cyclobutylidene]-ethyl ester 34. With the same procedure as for **21** from **31** (0.086 g, 0.55 mmol), alcohol **34** was obtained (0.151 g, 74%) as a white powder, mp 124–125 °C (methanol). IR (film, cm^{-1}): 1751, 1725, 1691, 1655, 1646, 1229. ^1H NMR ($CDCl_3$) δ: 1.97 (3H, s), 2.07 (3H, s), 2.21 (1H, m), 2.51 (1H, m), 2.60 (1H, m), 2.79 (1H, m), 4.51 (1H, ddd, $J=12.7$, 6.1, 1.5 Hz), 4.61 (1H, ddd, $J=12.7$, 7.4, 0.8 Hz), 5.45 (1H, m), 5.68 (1H, m), 7.30 (1H, s), 7.49 (2H, m), 7.64 (1H, m), 7.92 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 12.5, 20.8, 24.2, 26.2, 54.6, 60.4, 111.1, 117.9, 129.0, 130.3, 131.5, 134.9, 136.4, 144.4, 149.6, 162.6, 168.9, 170.7. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21, H, 5.47, N, 7.60. Found C, 65.33, H, 5.65, N, 7.41.

3.1.28. (*Z*)-Acetic acid 2-[2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-cyclobutylidene]-ethyl ester 35. With the same procedure as for **21** from **31** (0.052 g, 0.33 mmol), alcohol **35** was obtained (0.104 g, 86%) as a white powder, mp 127–130 °C (methanol). IR (film, cm^{-1}): 1732, 1686, 1641, 1598, 1230. ^1H NMR ($CDCl_3$) δ: 1.99 (3H, s), 2.01 (3H, s), 2.21 (1H, m), 2.54 (1H, m), 2.64 (1H, m), 2.71 (1H, m), 4.41 (2H, m), 5.64 (1H, m), 5.77 (1H, m), 7.32 (1H, s), 7.51 (2H, m), 7.65 (1H, m), 7.95 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 12.4, 20.5, 25.5, 25.6, 54.6, 59.6, 111.1, 119.7, 129.0, 130.3, 131.4, 134.8, 136.6, 144.0, 149.3, 162.5, 168.8, 170.3. Anal. Calcd for $C_{20}H_{20}N_2O_5 \cdot 0.2\ H_2O$: C, 64.58, H, 5.53, N, 7.53. Found C, 64.52, H, 5.54, N, 7.81.

3.1.29. (*E*)-1-[2-(2-Hydroxy-ethylidene)-cyclobutyl]-5-methyl-1*H*-pyrimidine-2,4-dione 8. With the same procedure as for **25** from acetate **34** (0.163 g, 0.44 mmol), alcohol **8** was obtained (0.085 g, 87%) as a white powder, mp 133–139 °C (methanol). IR (film, cm^{-1}): 3422, 3022, 1673, 1636, 1265. ^1H NMR (CD_3OD) δ: 1.89 (3H, d, $J=$ 1 Hz), 2.24 (1H, m), 2.41 (1H, m), 2.56 (1H, m), 2.75 (1H, m), 4.06 (2H, m), 5.37 (1H, m), 5.61 (1H, m), 7.57, (1H, q, $J=1$ Hz). ^{13}C NMR(CD_3OD) δ: 12.4, 24.8, 26.8, 56.2, 59.1, 111.8, 123.2, 139.4, 143.4, 152.9, 166.5. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45, H, 6.35, N, 12.60. Found C, 59.21, H, 6.44, N, 12.28.

3.1.30. (*Z*)-1-[2-(2-Hydroxy-ethylidene)-cyclobutyl]-5-methyl-1*H*-pyrimidine-2,4-dione 10. With the same procedure as for **25** from acetate **35** (0.118 g, 0.32 mmol), alcohol **10** was obtained (0.065 g, 91%) as a white powder, mp 177 °C (methanol). IR (film, cm^{-1}) 3450, 3165, 1739, 1675, 1641, 1226. ^1H NMR (CD_3OD) δ: 1.89 (3H, d, $J=$ 1 Hz), 2.21 (1H, m), 2.44 (1H, m), 2.59 (1H, m), 2.69 (1H, m), 3.84 (2H, m), 5.54 (1H, m) 5.69 (1H, m), 7.54 (1H, q, $J=1$ Hz). ^{13}C NMR (CD_3OD) δ: 12.4, 26.3, 26.5, 56.1, 58.9, 111.9, 125.8, 139.6, 141.7, 152.5, 166.5. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45, H, 6.35, N, 12.60. Found C, 59.36, H, 6.42, N, 12.57.

Acknowledgements

We acknowledge Dr. Tran Thy Thu Thui for preliminary works.

References and notes

1. For reviews see for instance: Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768. Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571–623. Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611–10670. Herdewijn, P. *Drug Discov. Today* **1997**, *2*, 235–242. Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272. De Clercq, E. *Collect. Czech. Chem. Commun.* **1998**, *63*, 449–479. Agrofoglio, L. A.; Challand, S. R. In *Acycllic, carbocyclic and L-nucleosides*; Kluwer Academic: Dordrecht, 1998. Ichikawa, E.; Kato, K. *Synthesis* **2002**, 1–28. De Clercq, E.; Neyts, J. *Rev. Med. Virol.* **2004**, *14*, 289–300.
2. Qiu, Y.-L.; Ksebati, M. B.; Zemlicka, J. *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 31–37.
3. Panda, J.; Ghosh, S.; Ghosh, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3013–3016.
4. Guan, H.-P.; Ksebati, M. B.; Cheng, Y.-C.; Drach, J. C.; Kern, E. R.; Zemlicka, J. *J. Org. Chem.* **2000**, *65*, 1280–1290.
5. Guan, H.-P.; Ksebati, M. B.; J, C.; Kern, E. R.; Zemlicka, J. *J. Org. Chem.* **2000**, *65*, 5177–5184.
6. Demaison, C.; Hourioux, C.; Roingeard, P.; Agrofoglio, L. A. *Tetrahedron Lett.* **1998**, *39*, 9175–9178.
7. (a) Gourdel-Martin, M.-E.; Huet, F. *J. Org. Chem.* **1997**, *62*, 2166–2172. (b) Gourdel-Martin, M.-E.; Huet, F. *Nucleosides Nucleotides* **1999**, *18*, 645–648. (c) Gauvry, N.; Bhat, L.; Mévellec, L.; Zucco, M.; Huet, F. *Eur. J. Org. Chem.* **2000**, 2717–2722. (d) Gauvry, N.; Huet, F. *J. Org. Chem.* **2001**, *66*, 583–588. (e) Hubert, C.; Alexandre, C.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2002**, *58*, 3575–3578.
8. (a) Hubert, C.; Alexandre, C.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2003**, *59*, 3127–3130. (b) Guillarme, S.; Legoupy, S.; Bourgougnon, N.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2003**, *59*, 9635–9639.
9. Bloomfield, J. J.; Nelke, J. M. In *Organic syntheses*, *Collect. Vol. 6*; Wiley: New York, 1988; p 167.
10. Kazunori, T.; Akio, M. *Tetrahedron Lett.* **1992**, *33*, 4345–4348.