Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Synthesis of New Nucleoside Analogues with a Methylenecyclobutane Unit

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Published online: 24 Nov 2006.

To cite this article: Sophie Danappe, Fabien Boeda, Christian Alexandre, Anne-Marie Aubertin, Nathalie Bourgougnon & François Huet (2006) Efficient Synthesis of New Nucleoside Analogues with a Methylenecyclobutane Unit, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:21, 3225-3239, DOI: 10.1080/00397910600908918

To link to this article: http://dx.doi.org/10.1080/00397910600908918

Synthetic Communications®, 36: 3225–3239, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600908918

Efficient Synthesis of New Nucleoside Analogues with a Methylenecyclobutane Unit

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Abstract: Synthesis of eight nucleoside analogues **4**–**11** with a methylenecyclobutane unit is described. Wittig reaction with 2-hydroxymethylcyclobutanone **12** gave a mixture of *Z* (**13**) and *E* (**14**) derivatives, which was separated before functional modifications. The heterocyclic moieties were introduced via a Mitsunobu reaction either on the saturated chain or on the unsaturated chain. When adenine was used in this reaction, only the *N*-9 substitution products were obtained. Removal of the protecting groups provided the target products.

Keywords: Mitsunobu reaction, nucleoside analogues, total synthesis, Wittig reaction

Received in Poland March 29, 2006
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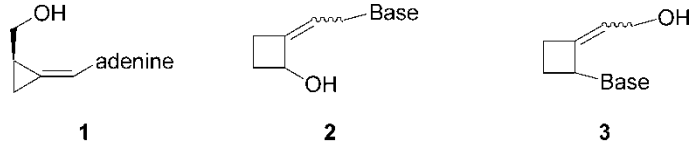
INTRODUCTION

Among nucleoside analogues synthesized in recent years, some displayed significant antiviral activity. The most important modifications concerned the sugar part of the nucleoside. In many cases, the oxygen in the furanose ring was substituted by a methylene group to stabilize the structure toward hydolysis.[1] A large number of solutions were proposed to link the two important groups that are necessary to confer antiviral activity, the heterocyclic base and the hydroxyl group. The spacers may be rigid as in thymallene[2] or adenallen[3] or flexible as in acyclovir.[4] Other compounds with various arrangements of a double bond and the cycle were also prepared. For example, the methylenecyclopropane derivative **1**[5] is an efficient anti-HIV agent. Our group has already synthesized methylenecyclobutane analogues **2** and **3**,[6] but none of them had significant antiviral activity (Fig. 1).

Another factor that may influence antiviral activity is the distance between the two functional groups. The structure modifications that were proposed covered increasing the length of the chain and modification of the flexibility of this one. This chain flexibility allowed the synthetic substance to improve interaction with enzymes.[7] In continuation of our efforts to synthesize nucleoside analogues, we explore the synthetic feasibility of analogues with a supplementary methylene group. In this article, synthesis of eight compounds, **4**–**11** with a methylenecyclobutane unit is described (Fig. 2).

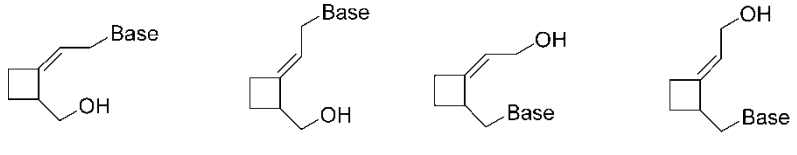
RESULTS AND DISCUSSION

For the synthesis of all compounds **4**–**11**, 2-hydroxymethylcyclobutanone **12**[8] was a convenient starting material (Scheme 1). Reaction of alcohol **12** with



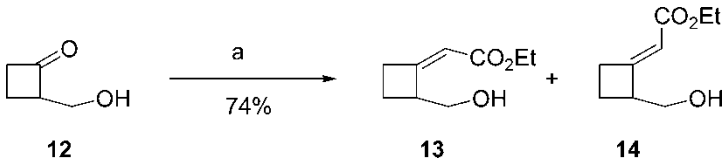
1 **2** **3**

Figure 1. Examples of nucleoside analogues.



4 Base = adenine
5 Base = thymine
6 Base = adenine
7 Base = thymine
8 Base = adenine
9 Base = thymine
10 Base = adenine
11 Base = thymine

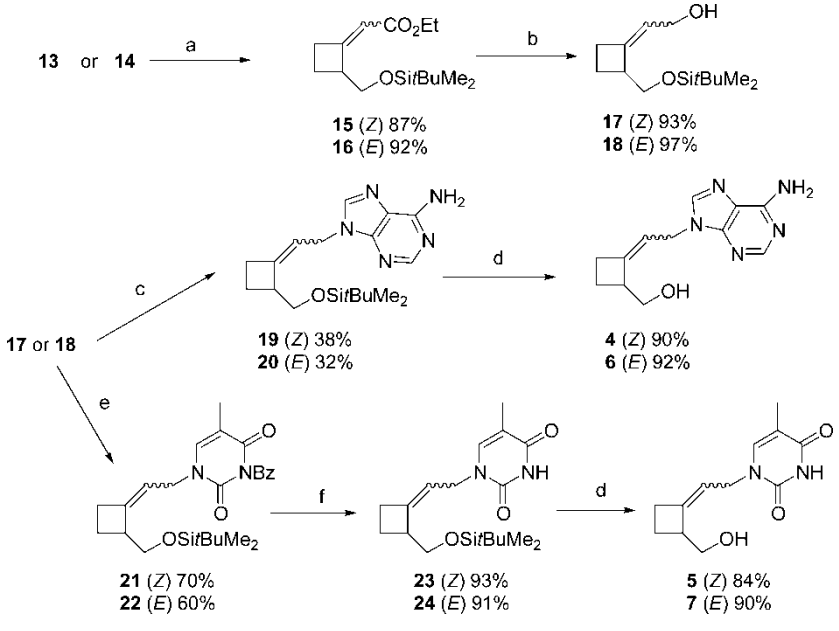
Figure 2. Target compounds.



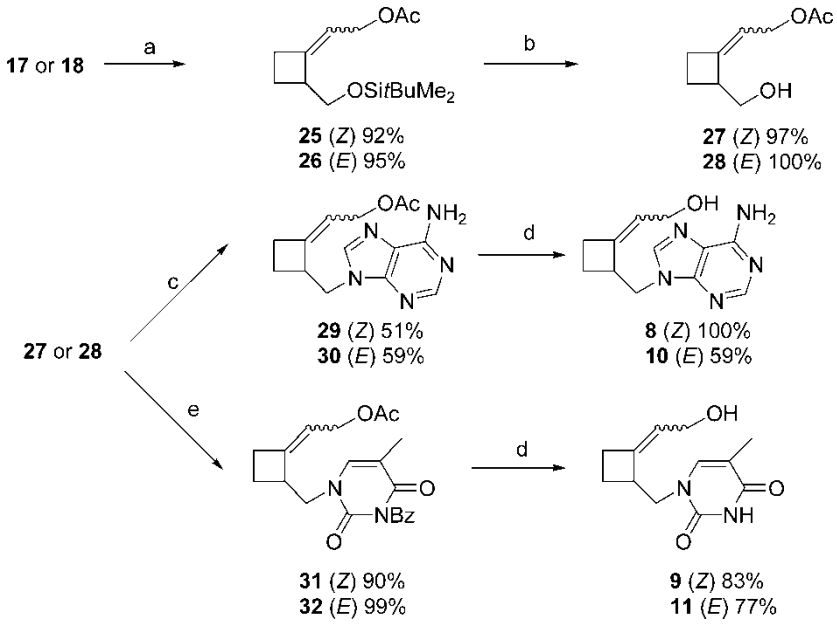
Scheme 1. Synthesis of methylenecyclobutane unit: $Ph_3P = CHCOOEt$, toluene, 80°C, 3 d.

carbethoxymethylene–triphenylphosphorane gave a mixture of isomers **13** (*Z*) and **14** (*E*) in 74% total yield (ratio *Z*/*E*, 1/1). The mixture was separated by column chromatography on silica gel to afford pure alcohols **13** and **14**. Configurations of double bonds were established by nuclear Overhauser effect (NOE) experiments.

These two products, **13** and **14**, were precursors for the series *Z* (**4**, **5**, **8**, and **9**) and *E* (**6**, **7**, **10**, and **11**) respectively. The sequence was the same in both cases (Scheme 2). Protection of alcohol **13** with t-butylchlorodimethylsilane gave ester **15**, which was reduced with diisobutylaluminium hydride (DIBAL-H)[9] to afford alcohol **17**. Under Mitsunobu conditions, **17** reacted



Scheme 2. Synthesis of the nucleoside analogues **4**–**7**: (a) $tBuMe_2SiCl$, imidazole, DMF, 20 h, rt; (b) DIBAL-H, CH_2Cl_2/toluene, − 60°C, 2 h; (c) adenine, Ph_3P, DIAD, THF, 7 d; (d) TBAF, THF 2.5 h, rt; (e) *N*-3-benzoylthymine, Ph_3P, DIAD, THF, 7 d; and (f) NH_3/MeOH, 48 h, rt.



Scheme 3. Synthesis of the nucleoside analogues **8**–**11**. (a) Ac_2O, pyridine, 14 h, rt; (b) TBAF, THF 2.5 h, rt; (c) adenine, Ph_3P, DIAD, THF, 7 d; (d) NH_3/MeOH, 14 h, rt; and (e) *N*-3-benzoylthymine, Ph_3P, DIAD, THF, 7 d.

with adenine to give **19**. It is worth mentioning that reaction with adenine only led to the *N*-9 substitution product, and it was the same in the three other cases of coupling with adenine. We could not detect any other isomer by NMR analysis of the crude product. This assignement was proved by $^{1}H/^{13}C$ heteronuclear multiple bond correlation (HMBC) NMR spectra. A final deprotection step with tetrabutylammonium fluoride (TBAF) led to nucleoside analogue **4**. This straightforward route yielded the target molecule in 16% yield from alcohol **12**.

Under the same conditions, **17** reacted with *N*-3-benzoyl thymine to give **21**, which, after two deprotection steps (removal of the benzoyl group with NH_3/MeOH and of the silyl group with tetrabutylammonium fluoride), afforded the nucleoside analogue **5** in 23% overall yield from **12**. Similarly, **18** was converted into the nucleoside analogues **6** in 15% overall yield from **12**, and **7** in 25% overall yield from **12**.

Alcohols **17** and **18** were also used to obtain the other nucleoside analogues in which positions of the base and the hydroxyl group were inverted (Scheme 3).

Acetylation of alcohol **17** gave acetate **25**, which was then deprotected to give alcohol **27**. Under the Mitsunobu condition, **27** reacted with adenine to afford acetate **29**. Deacetylation with NH_3/MeOH gave the nucleoside

analogue **8** in 21% overall yield from **12**. *N*-3-Benzoyl thymine and **27** reacted in the same conditions to give acetate **31**. Treatment of **31** with NH_3/MeOH simultaneously allowed deacetylation and debenzoylation to afford nucleoside analogue **9** in 31% overall yield from **12**. Similarly, alcohol **18** led to the nucleoside analogues **10** and **11** (27 and 37% overall yield from **12**).

Compounds **4** to **11** were tested against HIV-1 and HSV-1; none of them had a significant antiviral activity.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AC 400 spectrometer at 400 and 100.6 MHz, respectively. All melting points are uncorrected. Elemental analyses were performed by the service of microanalyses, National Center of Scientific Research, Institute of Chemistry of Natural Substances, Gif sur Yvette. High-resolution mass spectra (HRMS) were recorded on a Varian Mat 311 or ZabSpec TOF micromass spectrometer at the Regional Center of Physical measurements of Ouest, Rennes. Infrared spectra were measured with a FT infrared spectrometer Genesis Matteson instrument.

3-(2-Hydroxymethyl-cyclobutylidene)-Acetic Acid Ethyl Ester (13) and (14)

Carbethoxymethylene triphenylphosphorane (6.548 g, 18.8 mmol) was added to a solution of ketone **12** (1.2 g, 12 mmol) in toluene (6 mL). The resulting mixture was stirred for 3 d at 80°C. 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 to give a mixture of **13** and **14**. The resulting oil was purified by column chromatography on silica gel to give **13** and **14** [(*Z*) **13** Rf = 0.31, (*E*) **14** Rf = 0.21, ethyl acetate/toluene 2:8] in a 1/1 ratio (global yield: 1.517 g, 74%).

Isomer (*Z*) **13** obtained as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.2$ Hz, 3H), 1.73 (m, 1H), 2.25 (m, 1H), 2.72 (m, 1H), 2.88 (m, 1H), 3.62 (m, 1H), 3.84 (2H, m), 4.17 (m, 3H), 5.72 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 14.0$, 20.4, 30.1, 48.0, 60.2, 65.0, 113.7, 167.2, 167.8 ppm. IR (ν cm^{-1}): 3435, 1716, 1673, 1194. Isomer (*E*) **14** obtained as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.2$ Hz, 3H), 1.93 (m, 1H), 2.22 (m, 1H), 3.07 (m, 2H), 3.29 (m, 1H), 3.70 (dd, $J = 10.8$, 6.4 Hz, 1H), 3.78 (dd, $J = 10.8$, 6.4 Hz, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 5.73 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 14.2$, 20.6, 31.0, 46.5, 59.7, 63.9, 112.5, 166.5, 167.7 ppm. IR (ν cm^{-1}): 3450, 1713, 1673, 1191. Anal. calcd. for $C_9H_{14}O_3$, 0.15 H_2O: C, 62.52; H, 8.34. Found: C, 62.49; H, 8.37.

(*Z*)-3-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-acetic Acid Ethyl Ester (15)

Imidazole (192 mg, 2.83 mmol) and tertio-butylchlorodimethylsilane (409 mg, 2.71 mmol) were added to a solution of alcohol **13** (384 mg, 2.26 mmol) in DMF (2 mL). The resulting mixture was stirred for 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 **15** (562 mg, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$ (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.27 (t, $J = 7.2$ Hz, 3H), 2.08 (m, 1H), 2.17 (m, 1H), 2.62 (m, 1H), 2.84 (m, 1H), 3.53 (m, 1H), 3.90 (m, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 5.61 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$, 14.3, 18.3, 20.6, 30.5, 25.9, 47.9, 59.5, 63.2, 113.6, 165.9, 167.8 ppm. IR (ν cm^{-1}): 1718, 1676, 1189, 1090, 838. Anal. calcd. for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.31; H, 10.03.

(*E*)-3-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-acetic Acid Ethyl Ester (16)

With the same procedure as before from alcohol **14** (1.645 g, 9.66 mmol), **16** was obtained as a colorless oil (2.521 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$ (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.83 (m, 1H), 2.17 (m, 1H), 3.03 (m, 2H), 3.22 (m, 1H), 3.67 (dd, $J = 11.3$, 6.9 Hz, 1H), 3.70 (dd, $J = 11.3$, 6.4 Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 5.70 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$, 14.3, 18.2, 20.7, 31.0, 25.8, 46.6, 59.5, 64.7, 112.5, 166.5, 168.2 ppm. IR (ν cm^{-1}): 1716, 1676, 1189, 1084, 838. Anal. calcd. for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.31; H, 10.03.

(*Z*)-2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethanol (17)

A 1 M solution of DIBAL-H in toluene (26 mL) was added dropwise to a stirred solution of ester **15** (2.513 g, 8.83 mmol) in dry dichloromethane (185 mL) at -60°C. 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), and 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** (1.987 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.10$ (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.53 (m, 1H), 2.14 (m, 1H), 2.57 (m, 1H), 2.72 (m, 1H), 3.13 (br s, 1H), 3.29 (m, 1H), 3.67 (dd, $J = 9.8$,

9.3 Hz, 1H), 3.77 (dd, $J = 9.8$, 5.4 Hz, 1H), 4.06 (m, 2H), 5.44 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.5$, 18.4, 19.8, 28.7, 25.9, 44.4, 59.9, 66.1, 122.0, 143.4 ppm. IR (ν cm^{-1}): 3367, 1255, 1089, 843. Anal. calcd. for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.41, H, 11.01.

(*E*)-2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethanol (18)

With the same procedure as before from ester **16** (2.496 g, 8.77 mmol), **18** was obtained as a colorless oil (2.054, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$ (s, 6H), 0.89 (s, 9H), 1.18 (t $J = 4.9$ Hz, 1H), 1.74 (m, 1H), 2.08 (m, 1H), 2.63 (m, 2H), 3.10 (m, 1H), 3.63 (dd, $J = 10.3$, 6.9 Hz, 1H), 3.68 (dd, J 10.3, 6.9 Hz, 1H), 4.03 (m, 2H), 5.45 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.3$, 18.3, 20.6, 26.5, 25.9, 45.5, 59.3, 65.6, 119.7, 146.0 ppm. IR (ν cm^{-1}): 3343, 1259, 1088, 841. Anal. calcd. for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.08; H, 10.93.

(*Z*)-9-{2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethyl}-9H-purin-6-ylamine (19)

A solution of DIAD (0.34 mL) in THF (8 mL) was added dropwise to a solution of alcohol **17** (250 mg, 1.03 mmol), triphenylphosphine (580 mg) and adenine (295 mg) in THF (8 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 **19** (140 mg, 38%) as a white solid. Mp: 159–161°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$ (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.69 (m, 1H), 2.14 (m, 1H), 2.60 (m, 1H), 2.73 (m, 1H), 3.32 (m, 1H), 3.78 (m, 2H), 4.74 (dd, $J = 14.5$, 7.4 Hz, 1H), 4.86 (dd, $J = 14.5$, 7.4 Hz, 1H), 5.44 (m, 1H), 5.76 (br s, 2H), 7.87 (s, 1H), 8.37 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.8$, 17.9, 19.0, 28.0, 25.4, 41.2, 65.1, 44.6, 115.3, 119.2, 148.1, 149.5, 155.1, 139.8, 152.3 ppm. IR (ν cm^{-1}): 1672, 1601, 1569, 1307, 1033. Anal. calcd. for $C_{18}H_{29}N_5OSi$: C, 60.13; H, 8.13. Found: C, 60.22; H, 8.28.

(*E*)-9-{2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethyl}-9H-purin-6-ylamine (20)

With the same procedure as before from alcohol **18** (250 mg, 1.03 mmol), **20** was obtained as a colorless oil (119 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$ (2s, 6H), 0.87 (s, 9H), 1.80 (m, 1H), 2.11 (m, 1H), 2.67 (m, 2H), 3.14 (m, 1H), 3.65 (dd, $J = 12.3$, 6.9 Hz, 1H), 3.67 (dd, $J = 12.3$, 6.4 Hz, 1H), 4.66 (d, $J = 7.4$ Hz, 2H), 5.53 (m, 1H), 5.73 (br s, 2H), 7.81 (s, 1H), 8.38 (s, 1H)

ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$, 18.3, 20.0, 26.6, 25.8, 41.1, 65.2, 45.4, 113.8, 119.7, 149.5, 150.0, 155.4, 140.1, 152.9 ppm. IR (ν cm^{-1}): 3125, 1673, 1603, 1572, 1083, 833. Anal. calcd. for $C_{18}H_{29}N_5OSi$: C, 60.13; H, 8.13; N, 19.48. Found: C, 60.12; H, 8.16; N, 19.41.

(*Z*)-{2-[2-(6-Amino-purin-9-yl)-ethylidene]-cyclobutyl}-methanol (4)

Tetrabutylammonium fluoride (1M, 0.57 mL) was added to a solution of the protected alcohol **19** (127 mg, 0.37 mmol) in THF (4 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 **4** (78 mg, 90%) as a white solid. Mp: 173–174°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.65$ (m, 1H), 2.02 (m, 1H), 2.48 (m, 1H), 2.63 (m, 1H), 3.27 (m, 1H), 3.62 (dd, $J = 6.9$, 5.4 Hz, 2H), 4.66 (dd, $J = 14.8$, 7.9 Hz, 1H), 4.74 (dd, $J = 14.8$, 7.4 Hz, 1H), 5.09 (t, $J = 5.4$ Hz, 1H), 5.35 (m, 1H), 7.21 (br s, 2H), 8.10 (s, 1H), 8.13 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 19.3$, 27.9, 41.2, 44.9, 63.3, 116.3, 118.8, 140.4, 146.9, 149.2, 152.3, 156.0 ppm. IR (ν cm^{-1}): 3118, 1687, 1607, 1576, 1302, 1062. Anal. calcd. for $C_{12}H_{15}N_5O$: C, 58.76, H, 6.16, N, 28.55. Found: C, 58.61, H; 6.28; N, 28.43.

(*E*)-{2-[2-(6-Amino-purin-9-yl)-ethylidene]-cyclobutyl}-methanol (6)

With the same procedure as before from the protected alcohol **20** (111 mg, 0.31 mmol), **6** was obtained as a white solid (70 mg, 92%). Mp: 190–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.68$ (m, 1H), 1.99 (m, 1H), 2.62 (m, 2H), 2.99 (m, 1H), 3.42 (m, 2H), 4.56 (t, $J = 5.4$ Hz, 1H), 4.58 (d, $J = 7.9$ Hz, 2H), 5.46 (m, 1H), 7.20 (br s, 2H), 8.10 (s, 1H), 8.13 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 20.1$, 26.1, 40.5, 45.3, 63.5, 114.7, 118.7, 140.5, 147.5, 149.3, 152.4, 155.9 ppm. IR (ν cm^{-1}): 3100, 1679, 1603, 1576, 1305, 1033. Anal. calcd. for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16. Found: C, 58.49; H, 6.27.

(*Z*)-3-Benzoyl-1-{2-[2-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethyl}-5-methyl-1H-pyrimidine-2,4-dione (21)

With the same procedure as for **19**, from the protected alcohol **17** (250 mg, 1.03 mmol) and *N*3-benzoylthymine (502 mg, 2.18 mmol), **21** was obtained as a white solid (328 mg, 70%). Mp: 98°C (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.08$ (s, 6H), 0.91 (s, 9H), 1.64 (m, 1H), 1.99 (d, $J = 1.0$ Hz, 3H), 2.13 (m, 1H), 2.62 (m, 1H), 2.72 (m, 1H), 3.23 (m, 1H), 3.74 (m, 2H), 4.30 (dd,

$J = 14.5$, 7.3 Hz, 1H), 4.49 (dd, $J = 14.5$, 7.3 Hz, 1H), 5.26 (m, 1H), 7.22 (q, $J = 1.0$ Hz, 1H), 7.49 (m, 2H), 7.63 (m, 1H), 7.93 (m, 2H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$, 12.4, 18.4, 19.3, 28.5, 25.9, 45.1, 45.8, 65.7, 110.3, 115.6, 129.0, 130.4, 131.7, 134.8, 139.7, 149.2, 149.9, 163.2, 169.2 ppm. IR (ν cm^{-1}): 1744, 1687, 1645, 1086, 831. Anal. calcd. for $C_{25}H_{34}N_2O_4Si$: C, 66.05; H, 7.54; N, 6.16. Found: C, 65.93; H, 7.65; N, 6.11.

(*E*)-3-Benzoyl-1-{2-[2-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethyl}-5-methyl-1H-pyrimidine-2,4-dione (22)

With the same procedure as before from the protected alcohol **18** (250 mg, 1.03 mmol) and N3-benzoylthymine (502 mg, 2.18 mmol), **22** was obtained as a white solid (282 mg, 60%). Mp: 97–98°C (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$ (2, 6H), 0.90 (s, 9H), 1.80 (m, 1H), 1.95 (d, $J = 1.5$ Hz, 3H), 2.11 (m, 1H), 2.68 (m, 2H), 3.13 (m, 1H), 3.65 (dd, $J = 12.8$, 6.4 Hz, 1H), 3.67 (dd, $J = 12.8$. 6.4 Hz, 1H), 4.21 (d, $J = 6.9$ Hz, 2H), 5.34 (m, 1H), 7.08 (q, $J = 1.5$ Hz, 1H), 7.48 (m, 2H), 7.63 (m, 1H), 7.92 (m, 2H) ppm.^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$, 12.4, 18.2, 19.9, 26.7, 25.8, 45.4, 65.1, 45.4, 110.6, 113.6, 129.0, 130.3, 131.6, 134.8, 139.4, 149.8, 150.0, 163.1, 169.1 ppm. IR (ν cm^{-1}): 1744, 1690, 1641, 1087, 835. Anal. calcd. for $C_{25}H_{34}N_2O_4Si$: C, 66.05, H, 7.54; N, 6.16. Found: C, 65.66; H, 7.39; N, 6.08.

(*Z*)-1-{2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethyl}-5-methyl-1H-pyrimidine-2,4-dione (23)

A solution of **21** (289 mg, 0.64 mmol) in methanol saturated with ammonia (9.5 mL) was stirred for 14 h at rt. After removal of the volatile substances, the residue was purified by column chromatography on silica gel to give **25** (209 mg, 93%) as a white powder. Mp: 130–131°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.07$ (2s, 6H), 0.90 (s, 9H), 1.63 (m, 1H), 1.92 (d, $J = 1.0$ Hz, 3H), 2.12 (m, 1H), 2.60 (m, 1H), 2.71 (m, 1H), 3.23 (m, 1H), 3.71 (dd, $J = 10.3$, 8.4 Hz, 1H), 3.76 (dd, $J = 10.3$, 5.9 Hz, 1H), 4.27 (dd, $J = 14.3$, 6.9 Hz, 1H), 4.44 (dd, $J = 14.3$, 7.9 Hz, 1H), 5.23 (m, 1H), 7.11 (q, $J = 1.0$ Hz, 1H), 8.46 (br s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$, 12.3, 18.3, 19.3, 28.4, 25.9, 45.0, 45.5, 65.7, 110.3, 116.0, 139.9, 148.5, 151.1, 164.5 ppm. IR (ν cm^{-1}): 1675, 1639, 1079, 832. Anal. calcd. for $C_{18}H_{30}N_2O_3Si$: C, 61.68; H, 8.63. Found: C, 61.37; H, 8.61.

(*E*)-1-{2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethyl}-5-methyl-1H-pyrimidine-2,4-dione (24)

With the same procedure as before from the protected alcohol **22** (269 mg, 0.59 mmol), **24** was obtained as a white solid (188 mg, 91%). Mp:

152.8–153.4°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$ (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.80 (m, 1H), 1.92 (d, $J = 1.0$ Hz, 3H), 2.10 (m, 1H), 2.68 (m, 2H), 3.12 (m, 1H), 3.65 (m, 2H), 4.20 (d, $J = 6.9$ Hz, 2H), 5.31 (m, 1H), 6.96 (q, $J = 1.0$ Hz, 1H), 8.41 (br s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$, 12.3, 18.2, 19.9, 26.7, 25.8, 45.1, 65.2, 45.4, 110.6, 114.0, 139.6, 142.3, 151.0, 164.3 ppm. IR (ν cm^{-1}): 1679, 1651, 1361, 834. Anal. calcd. for $C_{18}H_{30}N_2O_3Si$: C, 61.68; H, 8.63; N, 7.99. Found: C, 61.61; H, 8.53; N, 7.81.

(*Z*)-1-[2-(2-Hydroxymethyl-cyclobutylidene)-ethyl]-5-methyl-1H-pyrimidine-2,4-dione (5)

With the same procedure as for **4**, from the protected alcohol **23** (200 mg, 0.57 mmol), **5** was obtained as a white solid (113 mg, 84%). Mp: 103–105°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.72$ (m, 1H), 1.86 (d, $J = 1.0$ Hz, 3H), 2.12 (m, 1H), 2.57 (m, 1H), 2.72 (m, 1H), 3.28 (m, 1H), 3.69 (dd, $J = 10.8$, 7.4 Hz, 1H), 3.74 (dd, $J = 10.8$, 6.4 Hz, 1H), 4.25 (dd, $J = 14.3$, 6.9 Hz, 1H), 4.37 (dd, $J = 14.3$, 7.4 Hz, 1H), 5.23 (7.47 (1H, q, $J = 1.0$ Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 12.2$, 20.6, 29.3, 46.2, 47.0, 65.3, 111.1, 117.2, 142.7, 148.9, 152.9, 166.8 ppm. IR (ν cm^{-1}): 3448, 3153, 1668, 1635, 1033. Anal. calcd. for $C_{12}H_{16}N_2O_3$, 0.2 H_2O: C, 60.09; H, 6.89; N, 11.68. Found: C, 60.11; H, 6.86; N, 11.66.

(*E*)-1-[2-(2-Hydroxymethyl-cyclobutylidene)-ethyl]-5-methyl-1H-pyrimidine-2,4-dione (7)

With the same procedure as before from the protected alcohol **24** (175 mg, 0.50 mmol), **7** was obtained as a white solid (106 mg, 90%). Mp: 118.7–119.1°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.86$ (m, 1H), 1.92 (d, $J = 1.0$ Hz, 3H), 2.15 (m, 1H), 2.23 (br s, 1H), 2.70 (m, 2H), 3.19 (m, 1H), 3.70 (m, 2H), 4.16 (dd, $J = 14.8$, 6.9 Hz, 1H), 4.25 (dd, $J = 14.8$. 7.4 Hz, 1H), 5.35 (m, 1H), 6.99 (q, $J = 1.0$ Hz, 1H), 9.53 (br s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 12.2$, 19.9, 26.7, 45.4, 64.3, 110.6, 114.3, 139.9, 148.4, 151.1, 164.5 ppm. IR (ν cm^{-1}): 3399, 3137, 1679, 1012. Anal. calcd. for $C_{12}H_{16}N_2O_3$, 0.1 H_2O: C, 60.54; H, 6.86; N, 11.77. Found: C, 60.44; H, 6.73; N, 11.75.

Acetic Acid (*Z*)-2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethyl Ester (25)

Acetic anhydride (1.75 mL, 18.4 mmol) was added slowly to a solution of alcohol **17** (1 g, 4.125 mmol) in pyridine (58 mL) at 0°C. After 10 min at this

temperature, the mixture was stirred for 1 night at rt. Dichloromethane (60 mL) was added, the organic layer was washed with water, the aqueous layer was extracted with dichloromethane (2 × 30 mL), and the combinated organic layers were dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford **25** (1.085 g, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H), 0.90 (s, 9H), 1.69 (m, 1H), 2.05 (s, 3H), 2.09 (m, 1H), 2.56 (m, 1H), 2.68 (m, 1H), 3.19 (m, 1H), 3.69 (d, $J = 6.9$ Hz, 2H), 4.46 (dd, $J = 12.3$, 6.4 Hz, 1H), 4.59 (dd, $J = 12.3$, 8.2 Hz, 1H), 5.34 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$. 18.3, 19.8, 28.6, 21.0, 25.9, 45.0, 61.7, 65.4, 116.3, 148.3, 170.9 ppm. IR (ν cm^{-1}): 1743, 1234, 1094, 838. Anal. calcd. for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.19; H, 10.01.

Acetic Acid (*E*)-2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-cyclobutylidene]-ethyl Ester (26)

With the same procedure as before from the protected alcohol **18** (1 g, 4.125 mmol), **26** was obtained as a colorless oil (1.113 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$ (s, 6H), 0.89 (s, 9H), 1.75 (m, 1H), 2.05 (s, 3H), 2.08 (m, 1H), 2.65 (m, 2H), 3.11 (m, 1H), 3.64 (dd, $J = 12.3$, 6.4 Hz, 1H), 3.67 (dd, $J = 12.3$, 6.9 Hz, 1H), 4.45 (d, $J = 7.4$ Hz, 2H), 5.39 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = -5.4$, 18.3, 20.3, 26.6, 20.9, 25.9, 45.5, 61.1, 65.4, 114.7, 149.0, 170.9 ppm. IR (ν cm^{-1}): 1745, 1231, 1092, 841. Anal. calcd. for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.18; H, 9.95.

Acetic Acid (*Z*)-2-(2-hydroxymethyl-cyclobutylidene)-ethyl Ester (27)

With the same procedure as for **4**, from the protected alcohol **25** (1.053 mg, 3.7 mmol), **27** was obtained as a colorless oil (612 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.77$ (m, 1H), 2.06 (s, 3H), 2.11 (m, 1H), 2.59 (m, 1H), 2.70 (m, 1H), 3.27 (m, 1H), 3.71 (dd, $J = 11.3$, 6.9 Hz, 1H), 3.80 (dd, $J = 11.3$, 5.9 Hz, 1H), 4.51 (dd, $J = 11.8$, 6.9 Hz, 1H), 4.58 (dd, $J = 11.8$, 8.4 Hz, 1H), 5.36 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 19.5$, 28.5, 21.0, 45.1, 61.7, 64.6, 116.6, 148.1, 171.2 ppm. IR (ν cm^{-1}): 3438, 1738, 1241. Anal. calcd. for $C_9H_{14}O_3$, 0.1 H_2O: C, 62.84; H, 8.32. Found: C, 62.52; H, 8.26.

Acetic Acid (*E*)-2-(2-hydroxymethyl-cyclobutylidene)-ethyl Ester (28)

With the same procedure as before from the protected alcohol **26** (1.113 g, 3.9 mmol), **28** was obtained as a colorless oil (664 mg, 100%). ^{1}H NMR

(400 MHz, $CDCl_3$): $\delta = 1.53$ (t, $J = 5.9$ Hz, 1H), 1.84 (m, 1H), 2.06 (s, 3H), 2.13 (m, 1H), 2.70 (m, 2H), 3.18 (m, 1H), 3.70 (m, 2H), 4.47 (d, $J = 7.4$ Hz, 2H), 5.41 (m, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 20.0$, 26.7, 20.8, 45.3, 61.0, 64.4, 114.8, 148.3, 171.1 ppm. IR (ν cm^{-1}): 3428, 1739, 1238. Anal. calcd. for $C_9H_{14}O_3$, 0.1 H_2O: C, 62.84; H, 8.32. Found: C, 62.68; H, 8.29.

Acetic Acid (*Z*)-2-[2-(6-Amino-purin-9-ylmethyl)-cyclobutylidene]-ethyl Ester (29)

With the same procedure as for **19**, from acetate **27** (250 mg, 1.47 mmol), **29** was obtained as a white solid (215 mg, 51%). Mp: 142–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.78$ (m, 1H), 2.04 (s, 3H), 2.15 (m, 1H), 2.66 (m, 2H), 3.67 (m, 1H), 4.24 (d, $J = 7.4$ Hz, 2H), 4.38 (dd, $J = 14.3$, 7.9 Hz, 1H), 4.45 (dd, $J = 14.3$, 6.9 Hz, 1H), 5.42 (m, 1H), 5.81 (br s, 2H), 7.84 (s, 1H), 8.38 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 20.9$, 20.8, 28.3, 42.4, 46.4, 60.6, 118.0, 119.3, 140.4, 153.0, 145.8, 150.1, 155.7, 170.7 ppm. IR (ν cm^{-1}): 3105, 1736, 1674, 1601, 1573, 1229. Anal. calcd. for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96. Found: C, 58.44; H, 6.01.

Acetic acid (*E*)-2-[2-(6-Amino-purin-9-ylmethyl)-cyclobutylidene]-ethyl Ester (30)

With the same procedure as before from acetate **28** (251 mg, 1.47 mmol), **30** was obtained as a colorless oil (249 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.82$ (m, 1H), 2.05 (s, 3H), 2.17 (m, 1H), 2.72 (m, 2H), 3.58 (m, 1H), 4.28 (dd, $J = 13.8$, 7.9 Hz, 1H), 4.37 (dd, $J = 13.8$, 6.9 Hz, 1H), 4.44 (d, $J = 7.3$ Hz, 2H), 5.22 (m, 1H), 5.90 (br s, 2H), 7.81 (s, 1H), 8.37 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 20.8$, 21.4, 26.5, 42.6, 46.5, 60.6, 116.4, 119.4, 140.3, 152.9, 146.7, 150.0, 155.8, 170.8 ppm. IR (ν cm^{-1}): 3139, 1738, 1650, 1598, 1574, 1217, 1033. Anal. calcd. for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96. Found: C, 58.52; H, 6.03.

(*Z*)-2-[2-(6-Amino-purin-9-ylmethyl)-cyclobutylidene]-ethanol (8)

With the same procedure as before from acetate **29** (210 mg, 0.73 mmol), **8** was obtained as a white solid (179 mg, 100%). Mp: 173–175°C. ^{1}H NMR (400 MHz, DMSO-*d*6) $\delta = 1.70$ (m, 1H), 1.98 (m, 1H), 2.47 (m, 1H), 2.64 (m, 1H), 3.54 (m, 3H), 4.26 (dd, $J = 13.8$, 8.4 Hz, 1H), 4.34 (dd, $J = 13.8$, 6.4 Hz, 1H), 4.56 (t, $J = 5.4$ Hz, 1H), 5.28 (m, 1H), 7.23 (br s, 2H), 8.13 (s, 1H), 8.14 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, DMSO-*d*6) $\delta = 20.4$, 27.6, 42.1, 46.0, 57.2, 118.6, 123.9, 140.3, 140.9, 149.6, 152.4, 155.9 ppm.

IR (ν cm^{-1}): 3108, 1672, 1604, 1574, 1304, 1009. Anal. calcd. for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.61; H, 6.16; N, 28.31

(*E*)-2-[2-(6-Amino-purin-9-ylmethyl)-cyclobutylidene]-ethanol (10)

With the same procedure as before from acetate **30** (251 mg, 1.47 mmol), **10** was obtained as a colorless oil (249 mg, 59%). ^{1}H NMR (400 MHz, DMSO-*d*6) $\delta = 1.74$ (m, 1H), 1.96 (m, 1H), 2.57 (m, 2H), 3.48 (m, 1H), 3.79 (m, 2H), 4.18 (dd, $J = 13.8$, 8.4 Hz, 1H), 4.31 (dd, $J = 13.8$, 6.4 Hz, 1H), 4.49 (t, $J = 5.4$ Hz, 1H), 5.14 (m, 1H), 7.19 (br s, 2H), 8.127 (s, 1H), 8.132 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, DMSO-*d*6) $\delta = 21.3$, 26.1, 42.3, 46.0, 57.4, 118.7, 121.9, 140.9, 141.3, 149.6, 152.4, 155.9 ppm. IR (ν cm^{-1}): 3270, 3081, 1678, 1598, 1570, 1304, 1017. Anal. calcd. for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.98, H, 6.18; N, 28.29.

Acetic Acid (*Z*)-2-[2-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-cyclobutylidene]-ethyl Ester (31)

With the same procedure as for **21**, from alcohol **27** (152 mg, 0.89 mmol) and N3-benzoylthymine (411 mg, 1.78 mmol), **31** was obtained as an oil (306 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.77$ (m, 1H), 1.96 (d, $J = 1.0$ Hz, 3H), 2.05 (s, 3H), 2.20 (m, 1H), 2.64 (m, 1H), 2.82 (m, 1H), 3.49 (m, 1H), 3.93 (dd, $J = 13.8$, 6.9 Hz, 1H), 3.99 (dd, $J = 13.8$, 8.9 Hz, 1H), 4.39 (dd, $J = 12.3$, 7.4 Hz, 1H), 4.48 (dd, $J = 12.3$, 7.4 Hz, 1H), 5.42 (m, 1H), 7.14 (q, $J = 1.0$ Hz, 1H), 7.49 (t, $J = 7.9$ Hz, 2H), 7.64 (tt, $J = 1.5$, 7.4 Hz, 1H), 7.93 (dd, $J = 1.5$, 7.9 Hz, 2H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 12.3$, 20.9, 20.7, 28.6, 41.6, 51.1, 60.8, 110.5, 117.8, 129.1, 130.4, 131.6, 134.9, 140.2, 145.6, 150.0, 163.0, 168.9, 170.7 ppm. IR (ν cm^{-1}): 1739, 1695, 1645, 1598, 1435, 1225. HRMS: calcd. for $C_{21}H_{22}N_2O_5$ $[M]^+$: 382.15287. Found: 382.1534.

Acetic Acid (*E*)-2-[2-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-cyclobutylidene]-ethyl Ester (32)

With the same procedure as before from alcohol **28** (239 mg, 1.4 mmol), **32** was obtained as an oil (532 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.81$ (m, 1H), 1.96 (d, $J = 1.0$ Hz, 3H), 2.05 (s, 3H), 2.22 (m, 1H), 2.75 (m, 2H), 3.39 (m, 1H), 3.85 (dd, $J = 13.8$, 6.9 Hz, 1H), 3.90 (dd, $J = 13.8$, 7.9 Hz, 1H), 4.46 (d, $J = 6.9$ Hz, 2H), 5.33 (m, 1H), 7.10 (q, $J = 1.0$ Hz, 1H), 7.50 (t, $J = 7.9$ Hz, 2H), 7.65 (tt, $J = 1.5$, 7.9 Hz, 1H), 7.91 (dd, $J = 1.5$, 8.4 Hz, 2H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 12.3$, 20.9, 21.4, 26.7, 42.0, 51.2, 60.7, 110.2, 116.5, 129.1, 30.3, 131.6, 135.9,

140.4, 146.6, 149.9, 163.0, 168.9, 70.8 ppm. IR (ν cm^{-1}): 1738, 1695, 1645, 1598, 1224. HRMS: calcd. for $C_{21}H_{22}N_2O_5$ $[M]^+$: 382.15287. Found: 382.1532.

(*Z*)-1-[2-(2-Hydroxy-ethylidene)-cyclobutylmethyl]-5-methyl-1H-pyrimidine-2,4-dione (9)

With the same procedure as for **23**, from acetate **31** (300 mg, 0.78 mmol), **9** was obtained as a white solid (56 mg, 83%). Mp: 74.5–75.5°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.72$ (m, 1H), 1.91 (d, $J = 1.0$ Hz, 3H), 2.19 (m, 1H), 2.48 (m, 1H), 2.60 (m, 1H), 2.78 (m, 1H), 3.44 (m, 1H), 3.85 (dd, $J = 6.9$, 13.8 Hz, 1H), 3.96 (m, 2H), 3.99 (dd, $J = 7.9$, 13.8 Hz, 1H), 5.44 (m, 1H), 7.07 (q, $J = 1.0$ Hz, 1H), 9.66 (br s, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 12.1$, 20.9, 28.4, 41.6, 51.4, 59.0, 110.4, 122.6, 140.9, 142.3, 151.5, 164.6 ppm. IR (ν cm^{-1}): 3465, 3018, 1668. HRMS: calcd. for $C_{21}H_{22}N_2O_5$ $[M\text{-}H_2O]^+$: 218.10553. Found: 218.1044.

(*E*)-1-[2-(2-Hydroxy-ethylidene)-cyclobutylmethyl]-5-methyl-1H-pyrimidine-2,4-dione (11)

With the same procedure as before, from acetate **32** (516 mg, 1.35 mmol), **11** was obtained as a white solid (246 mg, 77%). Mp: 65–67°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.81$ (m, 1H), 1.86 (d, $J = 1.0$ Hz, 3H), 2.13 (m, 1H), 2.72 (m, 2H), 3.36 (m, 1H), 3.86 (dd, $J = 7.9$, 0.98 Hz, 2H), 3.95 (d, $J = 6.9$ Hz, 2H), 5.31 (m, 1H), 7.46 (q, $J = 1.0$ Hz, 1H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 12.2$, 22.4, 27.2, 43.3, 52.2, 59.2, 110.7, 122.2, 143.6, 144.8, 153.1, 166.8 ppm. IR (ν cm^{-1}): 1667. Anal. calcd. for $C_{12}H_{16}N_2O_3$, 0.1 H_2O: C, 60.54; H,. 6.86; N, 11.77. Found: C, 60.19; H, 6.61; N, 11.68.

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