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Synthesis of mono- and polyhydroxylated cyclobutane nucleoside analogs

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Abstract—Enantiomerically enriched cyclobutene compounds **13** and **24** are good precursors of several cyclobutane nucleoside analogs. The synthetic ways involve, in the key step, either hydroboration or dihydroxylation.

1. Introduction

Several nucleoside analogs have interesting biological activities and may act as antiviral or anticancer agents. Among them, oxetanocin **1**,[1] and its carbocyclic analogs **2** cyclobut-A and cyclobut-G,[2] are important examples of dihydroxylated four membered ring compounds of this family. Another carbocyclic analog, carbovir **3**,[3] and its prodrug abacavir **4**,[4] showed antiviral properties. In previous works, we prepared cyclobutene analogs of carbovir **5**,[5] then compounds **6**[6] with a methylene spacer between the carbocycle and the base. We then envisioned, using the carbon–carbon double bond of an intermediate of synthesis of compounds **6**, or a related product, to prepare dihydroxylated nucleoside analogs **A** and **B**, via an hydroboration step. On the other hand, a dihydroxylation step would lead to trihydroxylated products **C** and **D** (Fig. 1).

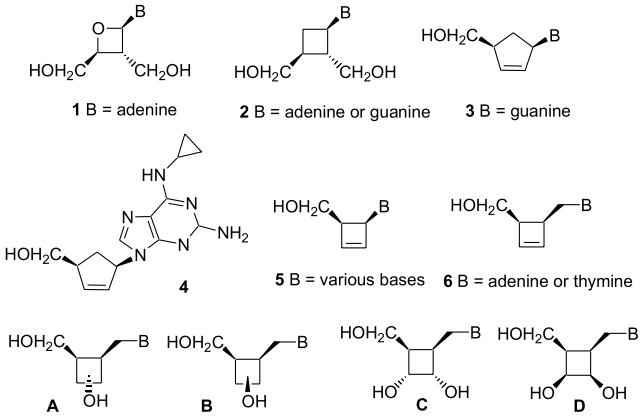

Figure 1.

2. Results and discussion

In a first approach in racemic series,[7] we carried out a Mitsunobu reaction with the benzylated compounds **8a** or **8b** and *N*-3-benzoylthymine (Scheme 1). However, an unexpected migration of the benzyloxy groups occurred and a mixture of the two regioisomers **9a** and **9b** was obtained. Fortunately, the migration did not occur starting from a

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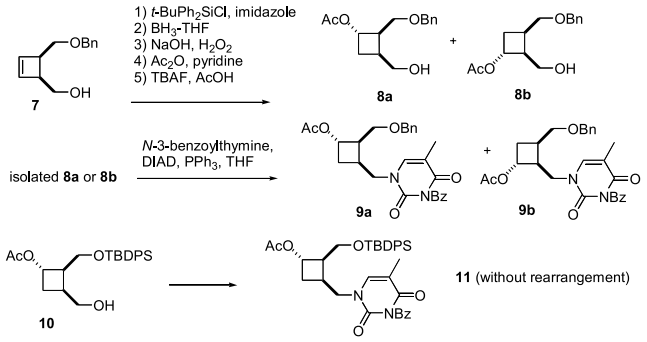


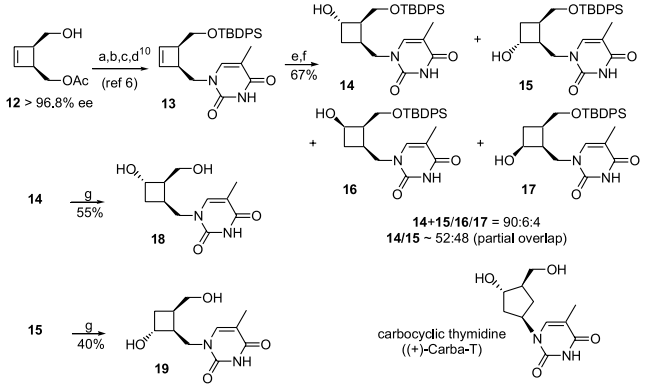
Scheme 1.

silylated compound **10**, which only led to the product of direct substitution **11**.

We then used this protecting group for the synthesis of the enantiomerically enriched compounds (Scheme 2). The starting material was the monoacetate **12**, which is available in high enantiomeric excess by an enzymatic acylation.[8] In this approach, the base coupling was envisioned before the addition step.

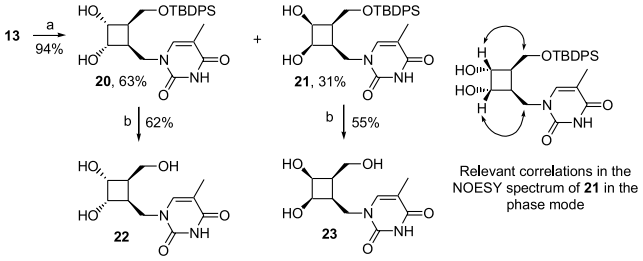
Scheme 2.

Compound **13**, previously described,[6] was subjected to hydroboration, which provided a mixture of the four expected products **14**–**17** (Scheme 3). These compounds were identified by NMR experiments including HMBC spectra to assign position of secondary OH groups.[7] Deprotection of **14** and **15** by a treatment with HF–pyridine provided the target molecules **18** and **19**, respectively. Compound **18** is a cyclobutane analog of carbocyclic thymidine, (+)-Carba-T,[9] which proved to be effective against HSV-1 and HSV-2, whereas the (−)-isomer was inactive.



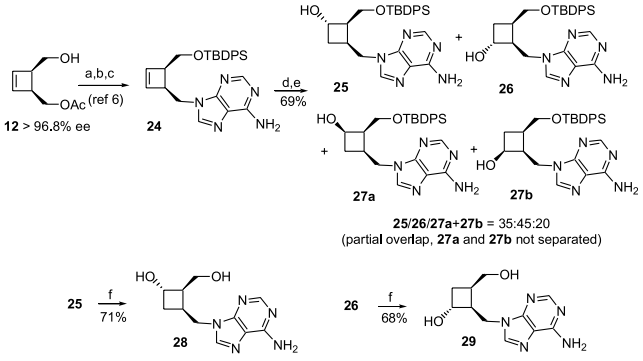
Scheme 3. (a) *t*BuPh$_2$SiCl/imidazole/DMF; (b) NH$_3$/MeOH; (c) PPh$_3$/DEAD/*N*-3-benzoylthymine; (d) NaOH[10]; (e) BH$_3$·THF; (f) H$_2$O$_2$/NaOH; (g) HF–pyridine.

Dihydroxylation of cyclobutene compound **13** by reaction with *N*-methylmorpholine *N*-oxide in the presence of osmium tetroxide as catalyst[11] yielded a mixture of compounds **20** and **21**, which were separated (Scheme 4). Isomer **20** was assigned thanks to the NOESY spectrum in the phase mode showing correlations between ^{1}H near of OH and ^{1}H of the vicinal CH$_2$. Desilylation of **20** and **21** gave the two trihydroxylated nucleosides, **22** and **23**, respectively.



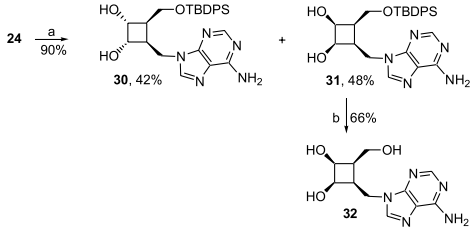
Scheme 4. (a) OsO$_4$, NMO, THF/H$_2$O; (b) HF–pyridine.

Hydroboration of compound **24**[6] provided a mixture of **25**, **26**, **27a** and **27b** (Scheme 5). The *trans*-isomers **25** and **26** were separated and equally identified thanks to NMR experiments, whereas the *cis*-isomers **27a** and **27b** could not be separated. Finally, desilylation of **25** and **26** provided nucleosides **28** and **29**, respectively.



Scheme 5. (a) *t*BuPh$_2$SiCl/imidazole/DMF; (b) NH$_3$/MeOH; (c) PPh$_3$/DEAD/adenine/THF; (d) BH$_3$·THF; (e) H$_2$O$_2$/NaOH; (f) HF–pyridine.

Dihydroxylation of **24** yielded a mixture of **30** and **31** (Scheme 6). Compound **31** was desilylated to lead to another trihydroxylated nucleoside **32**. In contrast, the same reaction failed from **30** probably due to its insolubility in CH$_2$Cl$_2$.



Scheme 6. (a) OsO$_4$, NMO, THF/H$_2$O; (b) HF–pyridine.

Several of these new products were subjected to biological evaluation. Compounds **19**, **22**, **23**, **28**–**30** and **32** did not show significant activity against HSV-1 and HIV-1. Compounds **19** and **22** showed neither cytotoxicity (KB cells) nor significant inhibition of acetylcholine esterase.

3. Conclusion

In conclusion, we prepared four dihydroxylated (**18**, **19**, **28**, **29**), and three trihydroxylated (**22**, **23**, **32**) new cyclobutane nucleosides as well as eight monohydroxylated (**14**–**17**, **25**, **26**, **27a** + **27b**) and four dihydroxylated (**20**, **21**, **30**, **31**) monosilylated precursors. We think that, it should be worth incorporating several of them in oligonucleotidic short sequences to test the biological properties. This following part of our research program is in progress.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC 400 spectrometer at 400 and 100.6 MHz, for ^{1}H and ^{13}C, respectively. All melting points are uncorrected. Elemental analyses were performed by the service of microanalyses, CNRS, ICSN, Gif sur Yvette. High resolution mass spectra were recorded on a ZabSpec TOF Micromass spectrometer at the CRMPO, Rennes. Infrared spectra were measured with a FT infrared spectrometer Genesis Matteson instrument.

4.1.1. (+)-*N*1-[(1*S*,2*R*,3*S*)-2-(*tert*-Butyl-diphenyl-silyloxymethyl)-3-hydroxy-cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 14; (−)-*N*1-[(1*S*,2*R*,4*R*)-2-(*tert*-butyl-diphenyl-silyloxymethyl)-4-hydroxy-cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 15; (+)-*N*1-[(1*S*,2*R*,3*R*)-2-(*tert*-butyl-diphenyl-silyloxymethyl)-3-hydroxy-cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 16; (+)-*N*1-[(1*S*,2*R*,4*S*)-2-(*tert*-butyl-diphenyl-silyloxymethyl)-4-hydroxy-cyclobutyl]-methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 17. A 1 M solution of $BH_3\cdot THF$ (2.3 mL, 2.3 mmol) in dry THF (4.5 mL) was added dropwise at 0 °C under argon and with stirring to a solution of **13**[6] (0.800 g, 1.74 mmol), obtained from a sample of **12**[8] of >96.8% ee, in dry THF (3.5 mL). The reaction mixture was stirred for 3 h at room temperature then 3 M NaOH (770 μL, 2.3 mmol) and then 30–35% H_2O_2 (250 μL, ~2.3 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h at room temperature. Evaporation, extraction of the resulting aqueous phase with Et_2O (4×15 mL), washing of the combined organic phases with brine (20 mL), drying ($MgSO_4$), evaporation then column chromatography on silica gel (cyclohexane/EtOAc: 3:1→3:2) successively led to **17** (23 mg, 0.048 mmol, 4%), **16** (32 mg, 0.067 mmol, 6%), **14** (218 mg, 0.877 mmol), **14**+**15** (99 mg, 0.207 mmol) then **15** (184 mg, 0.384 mmol), yields of **14** and **15** ~30 and 27%, respectively. Data for **14**: white solid, mp 101.5–102.7 °C; $[\alpha]_D^{20}$ +116 (*c* 2.100, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.57 (br s, 1H), 7.68–7.63 (m, 4H), 7.45–7.37 (m, 6H), 6.91 (d, 1H, J=1.2 Hz), 4.32 (ddd, 1H, J=7.4, 7.4, 7.4 Hz), 4.02 (dd, 1H, J=13.8, 11.3 Hz), 3.84 (dd, 1H, J=11.3, 4.9 Hz), 3.78 (dd, 1H, J=11.3, 6.9 Hz), 3.75 (dd, 1H, J=13.8, 4.9 Hz), 3.65–3.61 (m, 1H), 2.68–2.58 (m, 1H), 2.57–2.50 (m, 1H), 2.13 (ddd, 1H, J=11.3, 7.4, 2.9 Hz), 1.92–1.82 (m, 4H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.4, 151.3, 140.2, 135.5 (4C), 133.2 (2C), 129.9 (2C), 127.8 (4C), 110.7, 66.7, 61.8, 49.0, 48.7, 32.7, 28.9, 27.0 (3C), 19.2, 12.3; IR (ν cm^{-1}) 3412 (br), 3195 (br), 3048, 2930–2856, 1677, 1469–1426, 1363, 1255, 1109, 1059, 822, 739–703. Anal. Calcd for $C_{27}H_{34}N_2O_4Si\cdot 0.4H_2O$: C, 66.75; H, 7.22; N, 5.77. Found: C, 66.56; H, 7.06; N, 5.64. Data for **15**: white solid, mp 62.1–64.3 °C; $[\alpha]_D^{20}$ −54 (*c* 1.895, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 10.1 (br s, 1H), 7.67–7.64 (m, 4H), 7.46–7.37 (m, 6H), 6.97 (m, 1H), 4.37 (ddd, 1H, J=7.9, 7.9, 7.9 Hz), 4.15 (dd, 1H, J=14.3, 9.8 Hz), 3.80 (dd, 1H, J=14.3, 4.4 Hz), 3.78 (dd, 1H, J=10.8, 7.4 Hz), 3.71 (dd, 1H, J=10.8, 4.4 Hz), 3.66–3.62 (m, 1H), 2.67–2.59 (m, 1H), 2.47–2.37 (m, 1H), 2.05–1.91 (m, 2H), 1.81 (d, 3H, J=1.2 Hz), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.8, 150.9, 140.1, 134.6 (4C), 132.1 (2C), 128.8 (2C), 126.8 (4C), 109.8, 69.1, 63.3, 48.3, 45.9, 30.8, 30.1, 25.9 (3C), 18.2, 11.2; IR (ν cm^{-1}) 3404 (br), 3208 (br), 3049, 2932–2857, 1682, 1361, 1259–1224, 1111, 1075, 823, 740–702; HRMS calcd for $C_{27}H_{34}N_2O_4SiNa$ $[M+Na]^+$: 501.2186. Found: 501.2194. Data for **16**: colorless oil; $[\alpha]_D^{20}$ +362 (*c* 2.105, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.09 (br s, 1H, N–H); 7.71–7.66 (m, 4H), 7.49–7.39 (m, 6H), 6.68 (d, 1H, J=1.2 Hz), 4.36–4.29 (m, 1H), 4.12 (dd, 1H, J=11.3, 5.9 Hz), 4.05 (dd, 1H, J=11.3, 5.4 Hz), 3.82 (dd, 1H, J=13.8, 5.9 Hz), 3.70 (dd, 1H, J=13.8, 9.3 Hz), 2.94 (d, 1H, J=7.4 Hz), 2.77–2.69 (m, 1H), 2.52–2.44 (m, 1H), 2.43–2.33 (m, 1H), 2.05–1.98 (m, 1H), 1.81 (d, 3H, J=1.2 Hz), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.2, 150.8, 140.3, 135.6 (4C), 132.4 (2C), 130.1 (2C), 127.8 (4C), 110.3, 65.5, 61.1, 49.7, 44.5, 36.9, 28.3, 27.0, (3C), 19.1, 12.3; IR (ν cm^{-1}) 3428, 3068–3048, 2929–2856, 1681, 1363, 1252–1223, 1109, 1074, 741–704; HRMS calcd for $C_{27}H_{34}N_2O_4NaSi$ $[M+Na]^+$: 501.2186. Found: 501.2186. Data for **17**: colorless oil; $[\alpha]_D^{20}$ +179 (*c* 1.390, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.08 (br s, 1H), 7.66 (dd, 4H, J=7.8, 1.5 Hz), 7.48–7.38 (m, 6H), 7.13 (d, 1H, J=1.2 Hz), 4.25–4.20 (m, 1H), 4.19 (dd, 1H, J=14.3, 11.3 Hz), 4.08 (m, 1H), 3.89 (dd, 1H, J=14.3, 3.0 Hz), 3.85 (dd, J=11.3, 6.9 Hz), 3.75 (dd, 1H, J=11.3, 3.9 Hz), 2.87–2.78 (m, 1H), 2.55–2.46 (m, 1H), 2.44–2.37 (m, 1H), 1.91 (d, 3H, J=1.2 Hz), 1.72 (ddd, 1H, J=12.8, 5.4, 4.2 Hz), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.2, 151.5, 141.2, 135.5 (4C), 132.8 (2C), 130.0 (2C), 127.8 (4C), 111.0, 66.7, 64.2, 44.5, 42.4, 34.9, 31.6, 26.9 (3C), 19.2, 12.3; IR (ν cm^{-1}) 3427, 3060, 2957–2857, 1673, 1368, 1243–1219, 1112, 1079, 737–702.

4.1.2. (+)-*N*1-[(1*S*,2*R*,3*S*)-2-Hydroxymethyl-3-hydroxy-cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 18. A solution of 65–70% HF–pyridine (9 μL) was added to a cooled solution (0 °C) of **14** (40 mg, 0.084 mmol) in CH_2Cl_2 (0.6 mL). The reaction mixture was stirred for one night at room temperature then a small amount of $NaHCO_3$ was added. After 30 min more of stirring, evaporation then column chromatography on silica gel (CH_2Cl_2/MeOH: 95:5) provided **18** (11 mg, 0.046 mmol, 55%) as a white solid, mp≤25 °C; $[\alpha]_D^{20}$ +529 (*c* 1.295, MeOH); ^{1}H NMR (CD_3OD) δ 7.45 (d, 1H, J=0.8 Hz), 4.16 (ddd, 1H, J=7.4, 7.4, 7.4 Hz), 3.93 (dd, 1H, J=13.6, 10.6 Hz), 3.88 (dd, 1H, J=13.6, 6.0 Hz), 3.72 (dd, 1H, J=11.0, 6.0 Hz), 3.67 (dd, 1H, J=11.0, 8.0 Hz), 2.70–2.60 (m, 1H), 2.53–2.45 (m, 1H), 2.11 (ddd, 1H, J=11.2, 7.4, 2.4 Hz), 1.86 (m, 4H); ^{13}C NMR (CD_3OD) δ 168.5, 154.9, 144.7, 112.7, 69.4, 62.4, 51.8, 51.1, 34.7, 31.2, 13.8; IR (ν cm^{-1}) 3402, 2935, 2500, 1681, 1375, 1257, 1084, 772; HRMS calcd for $C_{11}H_{16}N_2O_4Na$ $[M+Na]^+$: 263.1008. Found: 263.1002.

4.1.3. (+)-*N*1-[(1*S*,2*R*,4*R*)-2-Hydroxy-4-hydroxymethyl-cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 19. Desilylation of **15** (40 mg, 0.084 mmol) (see preparation of **18**) followed by column chromatography on silica gel (CH_2Cl_2/MeOH: 95:5) provided **19** (8 mg, 0.033 mmol, 40%) as a white solid, mp 186.3–187.0 °C; $[\alpha]_D^{20}$ +106 (*c* 0.960, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.53 (d, 1H, J=1.0 Hz), 4.92 (d, 1H, J=7.4 Hz), 4.61 (dd, 1H, J=5.3, 4.7 Hz), 3.99 (ddd, 1H, J=7.6, 7.6, 7.6 Hz), 3.78–3.71 (m, 2H), 3.57–3.41 (m, 2H), 2.47–2.39 (m, 1H), 2.20–2.12 (m, 1H), 1.88 (ddd, 1H, J=10.3, 7.6, 2.0 Hz), 1.74–1.66 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 168.4, 155.0, 141.7, 112.7, 68.2, 61.4, 46.7, 45.9, 32.5, 30.5, 12.2; IR (ν cm^{-1}) 3488, 3044–2940, 1670, 1464–1422, 1338, 1220, 1080, 756; HRMS calcd for $C_{11}H_{16}N_2O_4Na$ $[M+Na]^+$: 263.1008. Found: 263.1006.

4.1.4. (−)-*N*1-[(1*S*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(*tert*-butyl-diphenyl-silyloxymethyl)-cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 20; (+)-*N*1-[(1*S*,2*R*,3*S*,4*R*)-2,3-dihydroxy-4-(*tert*-butyl-diphenyl-silyloxymethyl)-cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 21. 4-Methylmorpholine *N*-oxide (390 mg, 3.320 mmol) and a 4% aqueous solution of OsO_4 (140 μL, 5.6 mg, 0.022 mmol) were added to a solution of **13** (500 mg, 1.085 mmol) in a THF/H_2O (10:1) mixture (5 mL). The reaction mixture was stirred for 2 h at 30 °C. Cooling, treatment with a 20% aqueous solution of $NaHSO_3$ (3 mL), evaporation, dilution with brine (5 mL), extraction with EtOAc (5×15 mL), drying of the organic phases (Na_2SO_4), evaporation then column chromatography on silica gel (cyclohexane/EtOAc: 2:1→1:5) successively led to **21** (168 mg, 0.340 mmol, 31%), then to **20** (336 mg, 0.680 mmol, 63%). Data for **20**: white solid, mp 155.8–156.6 °C; $[\alpha]_D^{20}$ −8 (*c* 1.707, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.96 (br s), 7.66–7.63 (m, 4H), 7.46–7.37 (m, 6H), 6.89 (d, 1H, J=1.4 Hz), 4.39 (dd, 1H, J=6.4, 6.4 Hz), 4.31–4.29 (m, 1H), 4.20 (dd, 1H, J=14.3, 10.3 Hz), 4.19–4.18 (m, 1H), 3.81 (dd, 1H, J=10.8, 6.4 Hz), 3.73 (dd, 1H, J=10.8, 4.2 Hz), 3.71 (dd, 1H, J=14.3, 4.7 Hz), 3.28 (d, 1H, J=3.9 Hz), 2.87–2.79 (m, 1H), 2.40–2.35 (m, 1H), 1.81 (d, 3H, J=1.4 Hz), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 164.6, 151.8, 140.9, 135.6 (4C), 132.9, 132.7, 129.9 (2C), 127.9 (4C), 111.0, 70.2, 70.1, 61.9, 48.9, 44.5, 42.6, 26.9 (3C), 19.1, 12.3; IR (ν cm^{-1}) 3395, 3069, 2930, 2858, 1682, 1427, 1386, 1361, 1220, 1143, 1111, 1005, 908, 822, 735–702; HRMS calcd for $C_{27}H_{34}N_2O_5NaSi$ $[M+Na]^+$: 517.2134. Found: 517.2135. Data for **21**: white solid, mp 66.8 °C; $[\alpha]_D^{20}$ +415 (*c* 1.625, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.92 (br s), 7.69–7.65 (m, 4H), 7.48–7.38 (m, 6H), 7.11 (d, 1H, J=1.5 Hz), 4.39 (d, 1H, J=4.4 Hz), 4.34–4.29 (m, 1H), 4.26 (m, 1H), 4.07–3.99 (m, 3H), 3.83 (dd, 1H, J=14.3, 3.4 Hz), 3.05 (d, 1H, J=6.4 Hz), 2.84–2.75 (m, 1H), 2.51–2.44 (m, 1H), 1.91 (d, 3H, J=1.5 Hz), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.8, 151.3, 140.9, 135.5 (4C), 132.6, 132.5, 130.0 (2C), 127.9 (4C), 111.2, 69.6, 66.4, 61.6, 44.1, 43.5, 36.9, 26.9 (3C), 19.1, 12.3; IR (ν cm^{-1}) 3403, 3192, 3070–3048, 2930, 2893–2857, 1678, 1427, 1385, 1365, 1247, 1217, 1158, 1111, 1008, 909, 823, 734–703; HRMS calcd for $C_{27}H_{34}N_2O_5NaSi$ $[M+Na]^+$: 517.2134. Found: 517.2130. Anal. Calcd for $C_{27}H_{34}N_2O_5Si\cdot 0.6H_2O$: C, 64.16; H, 7.02; N, 5.54. Found: C, 64.07; H, 6.81; N, 5.46.

4.1.5. (+)-*N*1-[((1*S*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-hydroxymethyl)cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 22. Desilylation of **20** (11 mg, 0.063 mmol) (see preparation of **18**) followed by column chromatography on silica gel (EtOAc→EtOAc/MeOH: 8:2) provided **22** (11 mg, 0.043 mmol, 68%) as a white solid, mp 197.2–198.9 °C; $[\alpha]_D^{20}$ +266 (*c* 1.450, DMSO); ^{1}H NMR (DMSO-d_6) δ 11.15 (br s, 1H), 7.52 (d, 1H, J=1.0 Hz), 4.71 (d, 1H, J=4.0 Hz), 4.67 (d, 1H, J=5.9 Hz), 4.59–4.56 (m, 1H), 3.90–3.83 (m, 2H), 3.74 (d, 2H, J=8.4 Hz), 3.51–3.44 (m, 2H), 2.55–2.48 (m, 1H), 2.17–2.10 (m, 1H), 1.72 (d, 3H, J=1.0 Hz); ^{13}C NMR (DMSO-d_6) δ 164.3, 151.0, 141.7, 108.1, 69.5, 68.9, 59.2, 46.5, 43.3, 42.2, 12.0; IR (ν cm^{-1}) 3324, 3186, 2950, 1669, 1478, 1417, 1365, 1217, 1156, 1021, 874; HRMS calcd for $C_{11}H_{16}N_2O_5Na$ $[M+Na]^+$: 279.0957. Found: 279.0961.

4.1.6. (+)-*N*1-[((1*S*,2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-hydroxymethyl)cyclobutyl]methyl-5-methyl-1*H*,3*H*-pyrimidine-2,4-dione, 23. Desilylation of **21** (56 mg, 0113 mmol) (see preparation of **18**) followed by column chromatography on silica gel (CH_2Cl_2/MeOH: 95:5→9:1) provided **23** (16 mg, 0.033 mmol, 40%) as a white solid, mp 53.7–54.1 °C; $[\alpha]_D^{20}$ +824 (*c* 2.850, MeOH); ^{1}H NMR (CD_3OD) δ 7.53 (d, 1H, J=1.0 Hz), 4.31–4.27 (m, 1H), 4.25–4.22 (m, 1H), 4.10–3.95 (m, 2H), 3.91–3.88 (m, 2H), 2.67–2.59 (m, 2H), 1.85 (d, 3H, J=1.0 Hz); ^{13}C NMR (CD_3OD) δ 167.1, 153.4, 144.2, 110.9, 71.1, 68.8, 59.6, 45.6, 44.3, 38.5, 12.4; IR (ν cm^{-1}) 3381, 3226, 2938, 1671, 1423, 1335, 1222, 1149; HRMS calcd for $C_{11}H_{16}N_2O_5Na$ $[M+Na]^+$: 279.0957. Found: 279.0957.

4.1.7. (+)-*N*9-[(1*S*,2*R*,3*S*)-2-(*tert*-Butyl-diphenyl-silyloxymethyl)-3-hydroxy-cyclobutyl]methyl-9*H*-purin-6-amine, 25; (−)-*N*9-[(1*S*,2*R*,4*R*)-2-(*tert*-butyl-diphenyl-silyloxymethyl)-4-hydroxy-cyclobutyl]methyl-9*H*-purin-6-amine, 26 and *cis*-isomers, 27a and 27b. Hydroboration of **24** (750.9 mg, 1.6 mmol) (see preparation of **14**–**17**) followed by column chromatography on silica gel (EtOAc) successively provided a mixture of **27a** and **27b** (65.5 mg, 0.134 mmol), a mixture of **27a**, **27b** and **25** (72.1 mg, 0.148 mmol), **25** (176.8 mg, 0.362 mg), a mixture of **25** and **26** (21.9 mg, 0.045 mmol) then **26** (201.6 mg, 0.413 mmol), yields of **27a**+**27b**, **25**, **26** ~14, 24 and 31%, respectively. Data for **25**: white solid, mp 93.5–95.3 °C; $[\alpha]_D^{20}$ +218 (*c* 2.025, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1H), 7.75 (s, 1H), 7.68–7.65 (m, 4H), 7.47–7.38 (m, 6H), 5.63 (br s, 2H), 4.45–4.39 (m, 2H), 4.29 (dd, 1H, J=13.8, 10.8 Hz), 3.88 (dd, 1H, J=11.2, 5.2 Hz), 3.83 (dd, 1H, J=11.2, 6.4 Hz), 2.94–2.84 (m, 1H), 2.58–2.51 (m, 1H), 2.13 (ddd, 1H, J=11.7, 8.4, 2.9 Hz), 1.90 (ddd, 1H, J=11.7, 8.7, 7.4 Hz), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.4, 152.8, 150.1, 140.1, 135.6 (2C), 135.5 (2C), 133.4, 133.2, 129.9 (2C), 127.8 (4C), 119.4, 66.8, 61.8, 60.4, 48.8, 45.3, 33.3, 26.9 (3C), 19.2; IR (ν cm^{-1}) 3330–3185, 2930–2857, 1709–1597, 1472–1415, 1361, 1220, 1106, 1059, 823, 740–698; HRMS calcd for $C_{27}H_{34}N_5O_2Si$ $[M+H]^+$: 488.2482. Found: 488.2453. Data for **26**: white solid, mp 75.5–76.7 °C; $[\alpha]_D^{20}$ −19 (*c* 1.705, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.28 (s, 1H), 7.70–7.67 (m, 4H), 7.65 (s, 1H), 7.48–7.38 (m, 6H), 5.85 (br s, 2H), 4.51 (ddd, 1H, J=8.0, 8.0, 8.0 Hz), 4.47 (dd, 1H, J=14.3, 4.4 Hz), 4.37 (dd, 1H, J=14.3, 9.5 Hz), 3.86 (dd, 1H, J=10.8, 6.9 Hz), 3.81 (dd, 1H, J=10.8, 4.9 Hz), 2.83–2.75 (m, 1H), 2.55–2.47 (m, 1H), 2.15 (ddd,

1H, $J=11.3$, 8.0, 2.5 Hz), 1.90 (ddd, 1H, $J=11.3$, 9.8, 8.0 Hz), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.4, 152.6, 149.7, 140.3, 135.7–135.6 (4C), 133.3–133.2 (2C), 129.9 (2C), 127.8 (4C), 119.3, 69.7, 64.2, 47.5, 44.7, 31.5, 31.2, 27.0 (3C) 19.2; IR (ν cm^{-1}) 3329, 2932–2858, 1709–1599, 1473–1417, 1361, 1221, 1105, 1074, 823, 741–701; HRMS calcd for $C_{27}H_{34}N_5O_2Si$ $[M+H]^+$: 488.2482. Found: 488.2470.

4.1.8. (+)-*N*9-[(1*S*,2*R*,3*S*)-2-Hydroxymethyl-3-hydroxycyclobutyl]methyl-9*H*-purin-6-amine, 28. Desilylation of **25** (36.8 mg, 0.076 mmol) (see preparation of **18**) followed by column chromatography on silica gel (EtOAc/MeOH: 5:1) provided **28** (13.3 mg, 0.053 mmol; 71%) as a white solid, mp 97.5–98.7 °C; $[\alpha]_D^{20}$ +461 (*c* 0.750, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H), 8.12 (s, 1H), 7.17 (br s, 2H), 5.04 (d, 1H, $J=5.9$ Hz), 4.59 (br s, 1H), 4.33 (dd, 1H, $J=13.8$, 5.4 Hz), 4.19 (dd, 1H, $J=13.8$, 11.3 Hz), 4.12–4.05 (m, 1H), 3.57–3.52 (m, 2H), 2.74–2.64 (m, 1H), 2.38–2.31 (m, 1H), 1.91 (ddd, 1H, $J=10.8$, 7.4, 2.5 Hz), 1.63 (ddd, 1H, $J=10.8$, 9.2, 8.2 Hz); ^{13}C NMR (DMSO-d_6) δ 155.4, 152.5, 150.1, 141.1, 119.5, 65.8, 52.2, 49.2, 44.4, 32.9, 29.1; IR (ν cm^{-1}) 3274, 2938, 1643, 1483–1420, 1365, 1217, 1081, 1007; HRMS calcd for $C_{11}H_{16}N_5O_2$ $[M+H]^+$: 250.1304. Found: 250.1304.

4.1.9. (−)-*N*9-[(1*S*,2*R*,4*R*)-2-Hydroxymethyl-3-hydroxycyclobutyl]methyl-9*H*-purin-6-amine, 29. Desilylation of **26** (51.8 mg, 0.106 mmol) (see preparation of **18**) followed by column chromatography on silica gel (EtOAc/MeOH: 9:1) provided **29** (17.9 mg, 0.072 mmol, 68%) as a white solid, mp 233.8–235.7 °C; $[\alpha]_D^{20}$ −122 (*c* 0.900, DMSO); ^{1}H NMR (DMSO-d_6) δ 8.36 (s, 1H), 8.09 (s, 1H), 7.26 (br s, 2H), 5.11 (br s, 1H), 4.87 (br s, 1H), 4.37 (dd, 1H, $J=14.0$, 7.8 Hz), 4.19 (dd, 1H, 14.0, 7.4 Hz), 4.04 (ddd, 1H, $J=7.4$, 7.4, 7.4 Hz), 3.55 (dd, 1H, $J=10.8$, 7.9 Hz), 3.45 (dd, 1H, $J=10.8$, 5.9 Hz), 2.64–2.57 (m, 1H), 2.17–2.09 (m, 1H), 1.86 (ddd, 1H, $J=9.8$, 7.4, 1.4 Hz), 1.63 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 155.9, 152.2, 149.5, 140.9, 118.7, 68.3, 61.3, 46.7, 42.5, 32.4, 30.5; IR (ν cm^{-1}) 3114, 2942, 1703, 1615, 1481–1422, 1371–1300, 1215, 1075, 1038; HRMS calcd for $C_{11}H_{16}N_5O_2$ $[M+H]^+$: 250.1304. Found: 250.1303.

4.1.10. (+)-*N*9-[(1*S*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(*tert*-butyl-diphenyl-silyloxymethyl)cyclobutyl]methyl-9*H*-purin-6-amine, 30; (+)-*N*9-[(1*S*,2*R*,3*S*,4*R*)-2,3-dihydroxy-4-(*tert*-butyl-diphenyl-silyloxymethyl)cyclobutyl]methyl-9*H*-purin-6-amine, 31. Dihydroxylation of **24** (512 mg, 1.090 mmol) (see preparation of **20**+**21**) followed by column chromatography on silica gel (EtOAc/MeOH, 99:1→90:10) successively led to **31** (263 mg, 0.522 mmol, 48%) then to **30** (231 mg, 0.459 mg, 42%). Data for **30**: white solid, mp 203.2–204.7 °C; $[\alpha]_D^{20}$ +62 (*c* 1.520, DMSO); ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H), 8.08 (s, 1H), 7.62 (dd, 4H, $J=7.4$, 1.5 Hz), 7.48–7.40 (m, 6H), 7.20 (br s, 2H), 4.88 (d, 1H, $J=5.4$ Hz), 4.81 (d, 1H, $J=6.4$ Hz), 4.37 (dd, $J=13.8$, 6.7 Hz), 4.31 (dd, 1H, $J=13.8$, 9.4 Hz), 4.07–3.98 (m, 2H), 3.84 (dd, 1H, $J=10.8$, 6.9 Hz), 3.79 (dd, 1H, $J=10.8$, 5.1 Hz), 2.87–2.80 (m, 1H), 2.40–2.33 (m, 1H), 1.00 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 156.0, 152.4, 149.7, 140.6, 135.2 (4C), 133.0 (2C), 129.9 (2C), 128.0 (4C), 118.9, 69.9, 68.7, 62.1, 43.5, 42.9, 42.6, 26.8, (3C) 18.9; IR (ν cm^{-1}) 3319, 2853, 1650–1600, 1361, 1258, 1150, 1088, 1042, 880, 739–701. Anal. Calcd for $C_{27}H_{33}N_5O_3Si\cdot 0.6H_2O$: C, 63.03; H, 6.70; N, 13.61. Found: C, 63.01; H, 6.63; N, 13.56. Data for **31**: white solid, mp 74.1–75.3 °C; $[\alpha]_D^{20}$ +200 (*c* 1.160, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.27 (s, 1H), 7.74 (s, 1H), 7.70–7.66 (m, 4H), 7.45–7.35 (m, 6H), 6.40 (br s, 2H), 4.60 (dd, 1H, $J=14.5$, 11.5 Hz), 4.31 (dd, 1H, $J=14.5$, 3.2 Hz), 4.32–4.27 (m, 2H), 4.23–4.20 (m, 1H), 4.10 (dd, 1H, $J=10.8$, 5.1 Hz), 2.91–2.83 (m, 1H), 2.49–2.42 (m, 1H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.8, 152.3, 149.2, 141.0, 135.5 (4C), 132.2 (2C), 129.8 (2C), 127.8 (4C), 119.5, 69.7, 66.0, 61.9, 44.4, 40.0, 38.5, 26.9 (3C), 19.1; IR (ν cm^{-1}) 3453, 2956–2864, 1650–1621, 1338–1328, 1256, 1169, 1095, 827, 744–707; HRMS calcd for $C_{27}H_{33}N_5O_3NaSi$ $[M+Na]^+$: 526.2250. Found: 526.2250.

4.1.11. (+)-*N*9-[(1*S*,2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-hydroxymethylcyclobutyl]methyl-9*H*-purin-6-amine, 32. Desilylation of **31** (59.3 mg, 0.117 mmol) (see preparation of **18**) followed by column chromatography on silica gel (EtOAc/MeOH: 6:1) provided **32** (20.7 mg, 0.078 mmol, 66%) as a white solid, mp 188.6–191.3 °C; $[\alpha]_D^{20}$ +438 (*c* 1.415, DMSO); ^{1}H NMR (CD_3OD) δ 8.19 (s, 1H), 8.16 (s, 1H), 4.61 (dd, 1H, $J=14.3$, 10.8 Hz), 4.45 (dd, 1H, $J=14.3$, 4.7 Hz), 4.34–4.31 (m, 1H), 4.24–4.20 (m, 1H), 4.02–3.89 (m, 2H), 2.82–2.75 (m, 1H) 2.71–2.65 (m, 1H); ^{13}C NMR (CD_3OD) δ 159.0, 155.2, 152.2, 145.1, 121.7, 72.4, 70.5, 61.2, 45.7, 42.7, 41.2; IR (ν cm^{-1}) 3152, 2936, 1737, 1642–1601, 1478, 1365, 1230–1217, 1155, 1019; HRMS calcd for $C_{11}H_{15}N_5O_3Na$ $[M+Na]^+$: 288.1073. Found: 288.1071.

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References and notes

1. Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623–1625. Nakamura, H.; Hasegawa, S.; Shimada, N.; Fujii, A.; Takita, T.; Iitaka, Y. *J. Antibiot.* **1986**, *39*, 1626–1629. Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077–1078.
2. Hayashi, S.; Norbeck, D. W.; Rosenbrook, W.; Fine, R. L.; Matsukura, M.; Plattner, J. J.; Broder, S. B.; Mitsuya, H. *Antimicrob. Agents Chemother.* **1990**, *34*, 287–294.
3. Coates, J. A. V.; Inggall, H. J.; Pearson, B. A.; Penn, C. R.; Storer, R.; Williamson, C.; Cameron, J. M. *Antiviral Res.* **1991**, *15*, 161–168.
4. Hugues, W.; McDowell, J. A.; Shenep, J.; Flynn, P.; Kline, M. W.; Yogev, R.; Symonds, W.; Lou, H.; Hetherington, S. *Antimicrob. Agents Chemother.* **1999**, *43*, 609–615.
5. Gourdel, M.-E.; Huet, F. *J. Org. Chem.* **1997**, *62*, 2166–2172. Gourdel-Martin, M.-E.; Huet, F. *Nucleosides Nucleotides* **1999**, *18*, 645–648.

6. Hubert, C.; Alexandre, C.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2002**, *58*, 3775–3778.
7. Marsac, Y.; Nourry, A.; Legoupy, S.; Pipelier, M.; Dubreuil, D.; Huet, F. *Tetrahedron Lett.* **2004**, *45*, 6461–6463.
8. Pichon, C.; Hubert, C.; Alexandre, C.; Huet, F. *Tetrahedron: Asymmetry* **2000**, *11*, 2429–2434.
9. Béres, J.; Sági, G.; Tömöskozi, L.; Gruber, L.; Baitz-Gács, E.; Ötvös, L.; De Clercq, E. *J. Med. Chem.* **1990**, *33*, 1353–1360.
10. We observed, in the course of this work, that using 25% NH_4OH (25 mL for 5.16 mmol of benzoyl derivative in MeOH solution (65 mL)) led to an increase of the yield with respect to reaction with NaOH. Compound **13** was thus, obtained in 93% (in 48 h at room temperature) instead of 85% (in 72 h at room temperature).
11. Wengel, J.; Svendsen, M. L.; Jørgensen, P. N.; Nielson, C. *Nucleosides Nucleotides* **1995**, *14*, 1465–1479.