Synthesis of *trans*-Configurated Spacered Nucleoside Analogues Comprising a Difluorocyclopropane Moiety

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A novel class of *trans*-configurated difluorinated cyclopropanoic nucleoside analogues containing a methylene spacer between the cyclopropane ring and the heterocycle has been prepared. Some of these compounds showed weak anti-HIV activity in preliminary screenings.

Key words: Nucleoside Analogues, Cyclopropanes

Introduction

Fluorinated carbocyclic nucleoside analogues are regarded as most promising candidates for a successful therapy against viruses. During our own efforts towards the development of cyclopropanoic nucleoside analogues, we became interested in the synthesis of compounds showing a *trans* relationship between the hydroxymethyl moiety and the methylene spacered heterocycle.

Thus, a difluorinated, *trans* configurated and suitably substituted cyclopropane seemed to be the best suited starting material for such an approach. Geminal difluorinated cyclopropanes have previously been prepared by the addition of difluorocarbenes to nucleophilic olefins using either phenyl(trifluoromethyl)mercury [1 – 3] or bromodifluoromethylphosphonium bromide in the presence of cesium or potassium fluoride [4 – 6] or by the thermal decomposition of sodium chlorodifluoroacetate [7 – 10].

Results and Discussion

A suitable precursor has previously been synthesized by Taguchi *et al.* [10] by a sequence of reactions starting from [(*E*)-4-(benzyloxy)-2-butenyl]oxy(*tert*-butyl)dimethylsilane whose thermal reaction with sodium chlorodifluoroacetate yielded the corresponding difluorocyclopropane that was subsequently subjected to a de-silylation reaction. The yields of this approach were only moderate and thus another approach to a suitable starting material was called for.

Thus, commercially available (*E*)-1,4-dibromo-but-2-ene (**1**) was acetylated using anhydrous potassium acetate in glacial acetic acid [11] to afford **2.** Since the mono-deacetylation with potassium carbonate in methanol [12] failed to give excellent yields especially for large scale preparations, a different route had to be established. Chemoenzymatic routes have been used in the past very successfully for different hydrolyses reactions. Several lipases, esterases, amidases and proteases were screened on a small scale; among these the esterase from porcine liver (PLE) showed a high selectivity and an excellent reaction rate. Using pH-stat-conditions at pH = 7 the chemoenzymatic mono-deacetylation of **2** yielded 83% of the monoacetate (*E*)-4-hydroxy-2-butenyl acetate (**3**). Reaction of **3** with benzyl bromide / sodium hydride [13] gave the benzyl ether **4**. Reaction of **4** with sodium chlorodifluoroacetate in dry diglyme at 190 – 200 °C gave the racemic difluorocyclopropane **5** together with unreacted starting material **4**. The chromatographic separation of these two compounds failed under many different conditions. Thus, a different strategy had to be applied: Treatment of the mixture **4**/**5** under *Zemplén* conditions with a catalytic amount of sodium methoxide in methanol led to a deacetylation reaction affording a mixture of **6** and **7** that was easily separated by column chromatography. Re-acetylation of **6** gave **4**.

The *trans*-configurated difluorocyclopropane **6** is well characterized by its ^{19}F NMR spectrum. Whereas for the corresponding *cis*-analogue **8** the difference in the chemical shifts of the two fluorine substituents $|\Delta_{F-1,F-2}|$ = 25.4 ppm is rather large, for the trans-

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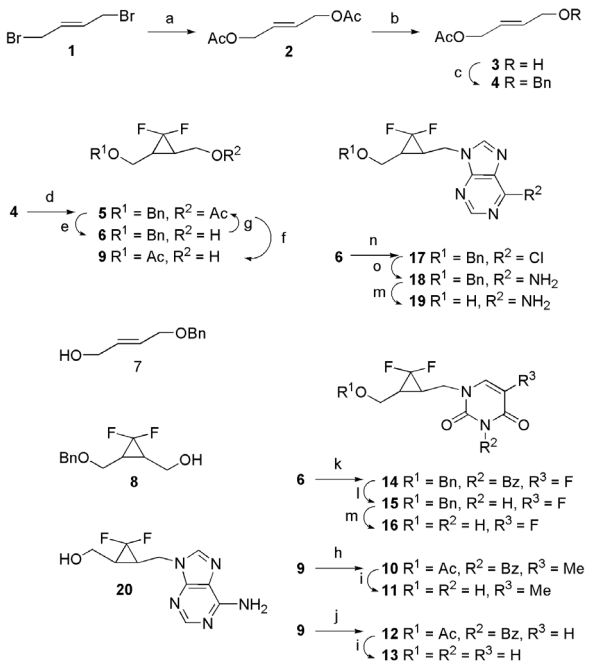


Scheme 1. Reactions: a) KOAc/Ac_2O; b) PLE, pH = 7.0; c) BnBr, NaH; d) ClF_2CCO_2Na, 190 – 200 °C, diglyme; e) NaOMe (cat.) in MeOH; f) H_2, Pd/C, MeOH; g) pyridine/Ac_2O; h) DEAD, TPP, N^3-benzoyl-thymine; i) KOH/MeOH; j) DEAD, TPP, N^3-benzoyl-uracil; k) DIAD, TPP, N^3-benzoyl-5-fluoro-uracil; l) NH_3, MeOH; m) Pearlman's catalyst, MeOH, cyclohexene; n) 6-chloro-purine, DEAD, TPP; o) NH_3, 75 °C, 3.6 Mpa.

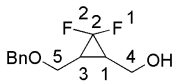
analogue **6** $|\delta_{F-1,F-2}|$ = 1.5 ppm is small. In the ^{13}C NMR spectrum of **6** the signal for the carbon bearing the geminal fluoro substituents is found as a doublet of doublet with $^1J_{C,F}$ = 286.7 and $^1J_{C,F}$ = 285.9 Hz. Characteristic NMR parameters for **8** and **6** are compiled in Table 1.

Hydrogenolysis of **5** using Pd/C in methanol afforded **9**. Reaction of **9** under *Mitsunobu* conditions [13] with 3-benzoyl-thymine, triphenylphosphane (TPP) and diethyl azodicarboxylate (DEAD) in dry 1,4-dioxane afforded 52% of the thymine analogue **10** whose treatment with potassium hydroxide in methanol gave 63% of **11**.

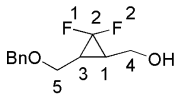
In an analogous manner from the reaction of **9** with TPP/DEAD/3-benzoyl-uracil **12** was obtained whose deprotection with potassium hydroxide in methanol afforded 62% of the target molecule **13** as a white solid.

Although this approach allowed the synthesis of the thymine and the uracil analogues with fair to good

Table 1. Characteristic NMR data for compounds **8** (*cis*) and **6** (*trans*)



8



6

Nucleus	δ(ppm) **8**	δ (ppm) **6**	$\lvert\Delta(\delta_8 - \delta_6)\rvert$
C-1	28.35	28.79	0.44
C-2	113.78	114.23	0.45
C-3	24.83	26.44	1.61
C-4	55.58	59.06	3.48
C-5	62.58	65.97	3.39
F-1	−124.0	−138.90	14.9
F-2	−149.60	−140.53	9.07
$\lvert\Delta(\delta_{F-1} - \delta_{F-2})\rvert$	25.6	1.63	

yields, the same strategy seemed not to be suited for the synthesis of the adenine as well as for the 5-fluoro-uracil analogue due to functional group incompatibility. Thus, intermediate **6** was allowed to react with 3-benzoyl-5-fluoro-uracil under *Mitsunobu* conitions with TPP and diisopropyl azodicarboxylate (DIAD) to afford 73% of **14** whose treatment with a solution of dry ammonia in methanol gave 81% of debenzoylated **15**. Hydrogenolysis of **15** in the presence of Pearlman's catalyst and cyclohexene finally gave **16**.

Reaction of **6** with 6-chloro-purine/TPP/DEAD in 1,4-dioxane gave 73% of **17** whose ammonolysis (75 °C, 3.6 MPa) in an autoclave gave 71% of the corresponding 6-amino-purine **18**. Transfer-hydrogenolysis of **18** with cyclohexene and Pearlman's catalyst afforded 78% of the adenosine analogue **19**.

Again, ^{19}F NMR spectroscopy can be used quite efficiently to distinguish between *cis* and *trans* configurated difluorocyclopropanes as exemplified for the *cis*- and *trans*-adenosine analogues **19** and **20**, respectively. Thus, whereas for *cis*-**20** the signals of the two difluoro substituents are found at δ = −124.38 and δ = −151.45 ppm, for the *trans*-configurated **19** an AB-spin system is observed (δ = −136.92 and δ = −138.56 ppm, J_{AB} = 164.5 Hz).

Compounds **11**, **13**, **16** and **19** have been tested for *anti*-HIV activity but only weak to moderate activity was observed.

Experimental Section

General: Melting points are uncorrected (*Leica* hot stage microscope), optical rotations were obtained using a Perkin-Elmer 341 polarimeter (1 cm micro cell), NMR spectra (internal Me_4Si) were recorded using the Varian spectrometers

Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me_4Si for ^1H and ^{13}C NMR spectra, internal CCl_3F was used for ^{19}F NMR spectra, C' correspond to the atoms of the heterocycle), IR spectra (film or KBr pellet) on a Perkin-Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 instrument (electrospray, voltage 4.5 kV, sheath gas nitrogen); for elemental analysis a Foss-Heraeus Vario EL instrument was used; tlc was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium$^{(IV)}$) sulfate followed by gentle heating.

(E)-Butene-1,4-diol monoacetate (**3**)

In a pH-stat equipment a mixture of **2** (146.0 g, 0.85 mol) in water (2000 ml) was stirred at pH = 7 in the presence of PLE (Boehringer-Mannheim, 10×200 μl) for 5 days keeping the pH constant at 7.0 by the addition of 1 N sodium hydroxide (amount: 855 ml). The reaction mixture was extracted with ethyl acetate (7×400 ml), the combined organic phases were dried and the solvent evaporated. The crude product was purfied by chromatography (silica gel, hexane/ethyl acetate 4:1) to afford pure **3** (91.8 g, 83.1%) as a colorless liquid. – n_D = 1.4523. – R_F (ethyl acetate/hexane 1:4) 0.14. – IR (film): ν = 3410s, 3015w, 2945m, 2875m, 2360w, 1740s, 1450m, 1385s, 1365s, 1240s, 1090s, 1025s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (dtt, J = 15.6, 4.5, 1.2 Hz, 1 H, −CH=C), 5.80 (dtt, J = 15.6, 5.8, 1.2 Hz, −CH=C), 4.55 (m, 2 H, CH_2-OAc), 4.15 (dq, J = 5.0, 1.2 Hz, 2 H, CH_2O), 2.16 (br s, 1 H, OH), 2.05 (s, 3 H, CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.10 (s, CO), 134.82 (d, CH=C), 125.95 (d, CH=C), 65.29 (t, CH_2OH), 63.42 (t, CH_2-OAc), 21.75 (q, CH_3). – MS (EI, 70 eV): *m/z* (%) = 112 (1), 100 (1), 99 (1), 70 (35), 69 (12), 61 (12), 43 (100). – Analysis for $C_6H_{10}O_3$ (130.14): calcd. C 55.37, H 7.74; found C 55.21, H 7.82.

(E)-4-(benzyloxy)-2-butenyl acetate (**4**)

To a suspension of sodium hydride (24.0 g, 60%) in dry dioxane (350 ml) at 0 °C a solution of **3** (62 g, 0.476 mol) in dioxane (100 ml) was slowly added; stirring was continued at room temperature for 30 min until the evolution of hydrogen had ceased. The reaction mixture was cooled to 0 °C and benzyl bromide (86 g, 0.5 mol) was slowly added within 1 h. After stirring for 12 h at room temperature and usual work-up followed by chromatography (silica gel, hexane/ethyl acetate 8:1 → 3:2) **4** (91.72 g, 87.4%) was obtained as an oil. – n_D = 1.5083. – R_F (ethyl acetate/hexane 1:3) 0.40. – IR (film): ν = 3090w, 3065w, 3030w, 2940w, 2855m, 2360w, 2340w, 1740s, 1605w, 1495w, 1455m, 1380m, 1365s, 1235s, 1105s, 1025s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 5 H, phenyl), 5.87 (m, 2 H, CH=), 4.60 (d, J = 4.7 Hz, CH_2OAc), 4.52 (s, 2 H, CH_2-Ph), 4.02 (d, J = 4.7 Hz, CH_2OBn), 2.07 (s, 3 H, CH_3). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5 (s, CO), 138.03 (s, C_q-phenyl), 130.83 (d, CH=), 128.31 (d, phenyl), 127.62 (d, phenyl), 127.55 (d, CH=), 72.30 (t, CH_2-ph), 69.66 (t, OCH_2), 64.12 (t, CH_2-OAc), 20.78 (q, CH_3). – MS (EI, 70 eV): m/z (%) = 221 (6), 220 (13), 160 (6), 105 (46), 92 (20), 91 (100). – Analysis for $C_{13}H_{16}O_3$ (220.27): calcd. C 70.89, H 7.32; found C 70.85, H 7.38.

(±)-(1 SR, 3 SR)-trans-[3-Benzyloxymethyl-2,2-difluorocyclopropyl]methylacetate ((±)-**5**)

A solution of **4** (3.6 g, 16.4 mmol) in dry diglyme (5 ml) was heated to 190 °C. A solution of sodium chlorodifluoroacetate (27.3 g, 179 mmol) in dry diglyme (47 ml) was added at this temperature over a period of 60 minutes. After keeping the reaction at 190 °C for an additional 15 minutes it was cooled to room temperature, poured into ice water and the aqueous solution was extracted with hexane (4×100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), the solvents evaporated under reduced pressure and the remaining brown oil was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:8) to afford **5** (2.97 g, 67%) as a colorless oil contaminated with some starting material that was easily separated in the next reaction step; an analytical pure sample of compound **5** was prepared by deacetylation (*vide infra*), chromatography (silica gel, ethyl acetate/hexane 1:2 → 1:1 and re-acetylation (pyridine, acetic anhydride). – R_F (ethyl acetate/hexane 1:8) 0.18. – IR (film): ν = 3030w, 2865m, 1745s, 1670w, 1485s, 1455s, 1390s, 1370s, 1325m, 1230s, 1195s, 1100s, 1025s cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35 – 7.24 (m, 5 H, phenyl), 4.35 and 4.47 (AB system, J_{AB} = 11.9 Hz, 2 H, CH_2-phenyl), 4.25 – 4.02 (m, 2 H, CH_2-OAc), 3.65 (dd, $^3J_{H,H}$ = 5.7, 5.1 Hz, 2 H, CH_2-OBn), 2.03 (s, 3 H, CH_3), 1.86 – 1.73 (m, $^3J_{H,H}$ = 5.7, 5.1 Hz, 2 H, 1-H, 3-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.82 (s, C=O), 137.88 (s, C_q-phenyl), 128.50 (d, C_{ortho}-phenyl), 127.84 (d, C_{meta}-phenyl), 127.67 (d, C_{para}-phenyl), 113.78 (dd, $^1J_{C,F}$ = 286.7, 286.7 Hz, CF_2), 72.62 (t, CH_2-phenyl), 65.75 (t, CH_2-OBn), 60.53 (dt, $^3J_{C,F}$ = 2.4 Hz, CH_2-OAc), 26.85 (virt dt, $^2J_{C,F}$ = 10.5 Hz, C-3), 25.39 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-1), 20.80 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −139.92 (virt t, $^3J_{F,H}$ = 7.3 Hz, 2 F). – MS (EI, 70 eV): *m/z* (%) = 270 (1), 227 (1), 209 (1), 180 (1), 163 (1), 160 (2), 144 (7), 107 (7), 105 (8), 92 (10), 91 (100), 65 (14), 43 (53). – Analysis for $C_{14}H_{16}O_3F_2$ (270.28): calcd. C 62.21, H 5.97; found C 61.82, H 6.16.

(±)-(1 SR, 3 SR)-[3-Benzyloxymethyl-2,2-difluorocyclopropyl]methanol ((±)-**6**)

A solution of **5** (2.97 g, 11.0 mmol) in methanol (7 ml) was treated with catalytic amounts of sodium methoxide.

After 90 minutes the reaction was complete and the reaction mixture was neutralized by the addition of 10% aqueous hydrochloric acid. The solvent was evaporated and the residue suspended in water (10 ml). The resulting suspension was extracted with ethyl acetate (4 × 50 ml), the combined organic layers were washed with brine, dried ($MgSO_4$), and the solvents were evaporated. The remaining crude oil was purified by column chromatography (silica gel, ethyl acetate/hexane 1:2 → 1:1) to afford **6** (2.16 g, 58% yield from **4**) as a colorless oil. – R_F (ethyl acetate/hexane 1:1) 0.40. – UV/vis (methanol): λ_{max} (lg ε) = 263 nm (2.21). – IR (film): ν = 3400s, 3065w, 3030m, 2875s, 1485s, 1455s, 1365s, 1320w, 1265s, 1185s, 1095s, 1015s cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40 – 7.24 (m, 5 H, H-phenyl), 4.55 and 4.48 (AB system, J_{AB} = 11.9 Hz, 2 H, CH_2-phenyl), 3.67 – 3.60 (m, 2 H, CH_2-OH), 3.59 – 3.48 (m, 2 H, CH_2-OBn), 2.30 (br s, 1 H, OH), 1.82 – 1.59 (m, 2 H, 1-H, 3-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.67 (s, C_q-phenyl), 128.46 (d, C_{ortho}-phenyl), 127.86 (d, C_{meta}-phenyl), 127.76 (d, C_{para}-phenyl), 114.23 (dd, $^1J_{C,F}$ = 286.7, 285.9 Hz, CF_2), 72.72 (t, CH_2-phenyl), 65.97 (dt, $^3J_{C,F}$ = 3.9 Hz, CH_2-OBn), 59.06 (dt, $^3J_{C,F}$ = 5.4 Hz, CH_2-OH), 28.79 (virt dt, $^2J_{C,F}$ = 10.0 Hz, C-1), 26.44 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −138.90 and −140.53 (AB system, J_{AB} = 165.6 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 228 (6), 107 (14), 91 (100), 79 (4), 65 (5). – Analysis for $C_{12}H_{14}O_2F_2$ (228.24): calcd. C 63.14, H 6.13; found C 62.60, H 6.09.

(±)-(1 SR, 3 SR)-[3-Acetoxymethyl-2,2-difluorocyclopropyl] methanol ((±)-**9**)

To a solution of **5** (0.49 g, 1.81 mmol) in methanol (30 ml) was added a catalytic amount of palladium on charcoal (10%). The resulting heterogeneous reaction mixture was subjected to a hydrogenation at 0.3 – 0.5 MPa in an autoclave. The reaction was observed by tlc. After completion of the reaction the catalyst was filtered off. After evaporation of all volatiles the title compound **9** (0.29 g, 89%) was obtained as a clear oil. – R_F (ethyl acetate/hexane 1:2) 0.20. – IR (film): ν = 3435m, 2960w, 2895w, 1740s, 1485s, 1390s, 1370s, 1325m, 1240s, 1190s, 1135m, 1040s, 1015s cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 4.21 – 4.16 (m, 1 H, H-CH'OAc), 4.04 (ddd, $^2J_{H,H}$ = −11.9 Hz, $^3J_{H,H}$ = 7.4 Hz, $^4J_{F,H}$ = 1.8 Hz, 1 H, H'-CHOAc), 3.69 (m, 2 H, CH_2-OH), 2.08 (br s, 1 H, OH), 2.05 (s, 3 H, CH_3), 1.81 – 1.74 (m, 2 H, cyclopr.). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.20 (s, C=O), 113.96 (dd, $^1J_{C,F}$ = 287.2, 287.2 Hz, CF_2), 60.44 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2-OH), 58.87 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2-OAc), 28.86 (virt dt, $^2J_{C,F}$ = 10.4 Hz, C-1), 25.13 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-3), 20.64 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −139.49 and −141.01 (AB system, J_{AB} = 164.5 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 163 (1), 149 (1), 100 (2), 91 (5), 90 (16), 77 (13), 64 (4), 51 (9), 43 (100). – Analysis for $C_7H_{10}O_3F_2$ (180.10): calcd. C 46.67, H 5.59; found C 46.66, H 5.61.

(±)-3-Benzoyl-1-[(1 SR, 3 R)-3-acetoxymethyl-2,2-difluorocyclopropylmethyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**10**)

The reaction was performed using the same conditions as described for **17** using **9** (0.28 g, 1.56 mmol), triphenylphosphane (0.8 g, 3.04 mmol), N^3-benzoylthymine (0.60 g, 2.61 mmol), 1,4-dioxane (7 ml) and DEAD (0.49 ml, 3.02 mmol) in 1,4-dioxane (20 ml). Evaporation of the solvents and purification by column chromatography (silica gel, ethyl acetate/hexane 1:2) gave **10** (0.50 g, 82%) as an oil. – R_F (ethyl acetate) 0.63. – UV/vis (MeOH): $\lambda_{max\,1}$ (lg ε) = 254 nm (4.26), $\lambda_{max\,2}$ (lg ε) = 283 nm, (3.91). – IR (film): ν = 3340w, 3070w, 2960w, 1750m, 1700m, 1650s, 1600s, 1485m, 1440m, 1365m, 1320m, 1245m, 1200m, 1180m, 1120w, 1040m, 1015m cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 7.94 – 7.89 (m, 2 H, H_{ortho}), 7.67 – 7.61 (m, 1 H, H_{para}), 7.53 – 7.27 (m, 2 H, H_{meta}), 7.10 (s, 1 H, 6'-H), 4.23 – 4.03 (m, 3 H, CH_2-OAC H-CH'N), 3.56 (dd, $^2J_{H,H}$ = −14.5 Hz, $^3J_{H,H}$ = 6.9 Hz, 1 H, H'-CHN), 2.09 – 1.84 (m, 7 H, 1-H, 3-H, 2×CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.68 (s, C=O (Ac)), 168.71 (s, C=O (Bz)), 162.87 (s, C-2'), 149.78 (s, C-4'), 139.47 (d, C-6'), 135.07 (s, C_q-phenyl), 131.44 (d, C_{para}-phenyl), 130.33 (d, C_{ortho}-phenyl), 129.12 (d, C_{meta}-phenyl), 113.29 (dd, $^1J_{C,F}$ = 289.0, 289.0 Hz, CF_2), 111.28 (s, C-5'), 59.82 (dt, $^3J_{C,F}$ = 4.6 Hz, CH_2-OAc), 45.52 (dt, $^3J_{C,F}$ = 3.8 Hz, CH_2-N), 26.21 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-3), 25.80 (virt dt, $^2J_{C,F}$ = 10.4 Hz, C-1), 20.56 (q, CH_3 (Ac)), 12.30 (q, 5'-CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −138.30 and −139.85 (AB system, J_{AB} = 164.4 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 392 (10), 364 (12), 333 (5), 322 (11), 305 (13), 277 (10), 262 (15), 183 (8), 105 (100), 77 (36). – Analysis for $C_{19}H_{18}N_2O_5F_2$ (440.15): calcd. C 57.16, H 5.02, N 6.76; found C 57.35, H 4.97, N 6.91.

(±)-1-[(1 SR, 3 SR)-2,2-Difluoro-3-hydroxymethyl-cyclopropylmethyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione [= 9-(3-hydroxymethyl-2,2-difluoro-cyclopropylmethyl)-thymine] ((±)-**11**)

A solution of **10** (0.44 g, 1.12 mmol) and potassium hydroxide (0.18 g, 3.2 mmol) in methanol (25 ml) was stirred at room temperature for 3 hours. After neutralization by hydrochloric acid (10%) all volatiles were removed *in vacuo* and the remaining oil was subjected to column chromatography (silica gel, ethyl acetate) to afford **11** (0.18 g, 63%) as a white solid. – M. p.: 157 – 161 °C. – R_F (ethyl acetate) 0.25. – UV/vis (methanol): λ_{max} (lg ε) = 271 nm, 3.92. – IR (KBr): ν = 3500m, 3165w, 3030m, 2830w, 1710s, 1665s, 1480m, 1420m, 1360m, 1315w, 1265m, 1240m, 1225m,

1200m, 1160m, 1130w, 1105w, 1045m cm^{-1}. – ^1H NMR (400 MHz, CD_3OD): δ = 7.41 (d, $^4J_{H,H}$ = 1.2 Hz, 1 H, 6'-H), 3.99 – 3.94 (m, 1 H, H-CH'N), 3.76 (dd, $^2J_{H,H}$ = −15.4 Hz, $^3J_{H,H}$ = 7.4, 1 H, H'-CHN), 3.59 (virt d, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2-OH), 1.98 – 1.89 (m, 2 H, 1-H, 3-H), 1.86 (d, $^4J_{H,H}$ = 1.2, 3 H, CH_3). – ^{13}C NMR (100 MHz, CD_3OD): δ = 167.03 (s, C-2'), 153.16 (s, C-4'), 142.74 (d, C-6'), 116.06 (dd, $^1J_{C,F}$ = 288.0, 285.5 Hz, CF_2), 111.62 (2, C-5'), 58.92 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2-OH), 46.15 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2-N), 30.67 (virt dt, $^2J_{C,F}$ = 10.2 Hz, C-3), 26.43 (virt dt, $^2J_{C,F}$ = 10.6 Hz, C-1), 12.13 (q, CH_3). – ^{19}F NMR (188 MHz, CD_3OD): δ = −135.95 and −138.41 (AB system, J_{AB} = 164.5 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 246 (58), 229 (71), 215 (100), 196 (16), 172 (27), 149 (33), 139 (40), 126 (42), 96 (62). – HRMS calcd. for $C_{10}H_{12}N_2O_3F_2$: 246.0816; found: 246.0816.

(±)-3-Benzoyl-1-[(1 SR, 3 R)-3-acetoxymethyl-2,2-difluorocyclopropylmethyl]-1,2,3,4-te trahydro-2,4-pyrimidinedione ((±)-**12**)

The reaction was performed under the conditions as described for **17** using **9** (0.37 g, 2.0 mmol), triphenylphosphane (1.50 g, 5.70 mmol), N^3-benzoyluracil (0.60 g, 2.78 mmol), 1,4-dioxane (10 ml) and DEAD (0.58 ml, 5.5 mmol) in 1,4-dioxane (17 ml). After evaporation of the solvents purification by column chromatography (silica gel, ethyl acetate/hexane 1:1) gave **12** (0.45 g, 59%) as an oil. – R_F (ethyl acetate/hexane 3:7) 0.26. – IR (film): ν = 3090w, 2965w, 1750s, 1705s, 1670s, 1600s, 1565m, 1485s, 1440s, 1385s, 1370s, 1320s, 1245s, 1140m, 1100m, 1045s, 1015s cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 7.90 (m, 2 H, H_{ortho}), 7.65 (m, 1 H, H_{para}), 7.48 (m, 2 H, H_{meta}), 7.24 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 6'-H), 5.81 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, 5'-H), 4.21 – 4.02 (m, 3 H, CH_2-OAC H-CH'N), 3.58 (dd, $^2J_{H,H}$ = −14.6 Hz, $^3J_{H,H}$ = 7.8, 1 H, H'-CHN), 2.03 (s, 3 H, CH_3), 2.09 – 1.84 (m, 2 H, 1-H, 3-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.77 (s, C=O (Ac)), 168.41 (s, C=O (Bz)), 162.09 (s, C-2'), 149.77 (s, C-4'), 143.48 (d, C-6'), 135.22 (s, Cq-phenyl), 131.33 (d, C_{para}-phenyl), 130.44 (d, C_{ortho}-phenyl), 129.25 (d, C_{meta}-phenyl), 113.50 (CF_2), 102.76 (d, C-5'), 59.83 (dt, $^3J_{C,F}$ = 3.9 Hz, CH_2-OAc), 45.97 (dt, $^3J_{C,F}$ = 4.6 Hz, CH_2-N), 26.35 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-3), 25.80 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-1), 20.67 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −138.32 and -139.91 (AB system, J_{AB} = −165.4 Hz, F_A and F_B); MS (EI, 70 eV): *m/z* (%) = 378 (18), 350 (21), 319 (13), 308 (8), 291 (24), 290 (12), 277 (10), 171 (8), 106 (22), 105 (100%). – Analysis for $C_{18}H_{16}N_2O_5F_2$ (444.13): calcd. C 57.15, H 4.23, N 7.40; found C 57.08, H 4.56; N 7.30.

*(±)-1-[(1 SR, 3 SR)-2,2-Difluoro-3-hydroxymethyl-cyclopropylmethyl]-1,2,3,4-te trahydro-2,4-pyrimidinedione [= 9-(3-hydroxymethyl-2,2-difluoro-cyclopropylmethyl)-uracil] ((±)-**13**)*

A solution of **12** (0.45 g, 1.19 mmol) and potassium hydroxide (0.47 g, 8.4 mmol) in methanol (20 ml) was stirred at room temperature overnight. After neutralization by diluted hydrochloric acid (10%) and filtration the filtrate was evaporated under reduced pressure and the remaining oil was subjected to column chromatography (silica gel, ethyl acetate → ethyl acetate/methanol 9:1) to afford **13** (0.17 g, 62%) as a white solid. – M. p.: 192 – 199 °C. – R_F (ethyl acetate) 0.20. – UV/vis (methanol): λ_{max} (lg ε) = 265 nm (3.96). – IR (KBr): ν = 3410s, 3155m, 3015s, 2970m, 2890m, 2825m, 2530s, 2270s, 1760m, 1680s, 1630s, 1480s, 1460s, 1430s, 1405m, 1375s, 1360s, 1315m, 1270s, 1255s, 1245s, 1205s, 1190m, 1175m, 1140m, 1115m, 1070w, 1040s, 1025m, 1000s cm^{-1}. – ^1H NMR (200 MHz, CD_3OD): δ = 7.56 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 6'-H), 5.66 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 5'-H), 4.11 – 3.97 (m, 1 H, H-CH'N), 3.83-3.66 (m, 1 H, H'-CHN), 3.61 – 3.58 (m, 2 H, CH_2-OH), 2.03 – 1.82 (m, 2 H, 1-H, 3-H). – ^{13}C NMR (100 MHz, CD_3OD): δ = 166.43 (s, C-2'), 152.55 (s, C-4'), 146.49 (d, C-6'), 115.54 (dd, $^1J_{C,F}$ = 287.9, 287.9 Hz, CF_2), 102.22 (d, C-5'), 58.43 (dt, $^3J_{C,F}$ = 4.9 Hz, CH_2-OH), 46.00 (dt, $^3J_{C,F}$ = 4.9 Hz, CH_2-N), 30.24 (virt dt, $^2J_{C,F}$ = 9.6 Hz, C-3), 25.90 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-1). – ^{19}F NMR (188 MHz, CD_3OD): δ = −136.12 and −138.55 (AB system, J_{AB} = 164.5 Hz, F_A and F_B). – HRMS calcd. for $C_9H_{10}N_2O_3F_2$: 232.0659; found: 232.0659. – Analysis for $C_9H_{10}N_2O_3F_2$ (232.18): calcd. C 46.56, H 4.34, N 12.07; found C 46.41, H 4.43, N 12.12.

(±)-3-Benzoyl-1-[(1 SR, 3 SR)-3-benzyloxymethyl-2,2-difluorocyclopropylmethyl]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((*pm*)-**14**)

The reaction was performed according to the *Mitsunobu* reaction as described for the preparation of compound **17** using **6** (0.53 g, 2.33 mmol), triphenylphosphane (1.22 g, 4.66 mmol), N^3-benzoyl-5-fluorouracil (1.10 g, 4.66 mmol), 1,4-dioxane (4 ml) and DIAD (0.90 ml, 4.66 mmol) in 1,4-dioxane (20 ml). After stirring overnight the solvent was evaporated, the residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:2) and **14** (0.76 g, 73%) was obtained as a colorless oil. – R_F (ethyl acetate/hexane 1:2) 0.30. – UV/vis (methanol): $\lambda_{max\,1}$ (lg ε) = 259 nm (4.30), $\lambda_{max\,2}$ (lg ε) = 287 nm (3.97). – IR (film): ν = 3435w, 3095w, 2865w, 1755s, 1711m, 1665s, 1600w, 1475m, 1450m, 1410w, 1180m, 1105m, 1075w, 1010w cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 7.92 – 7.87 (m, 2 H, H_{ortho}-phenyl), 7.69 (m, 1 H, H_{para}-phenyl), 7.50 – 7.42 (m, 2 H, H_{meta}-phenyl), 7.37 - 7.26 (m, 6 H, H-phenyl, Bn), 6'-H), 4.53 and 4.47 (AB system, J_{AB} = −11.9 Hz, 2 H, CH_2-phenyl), 4.26 – 4.15 (m, 1 H, H-CH'N), 3.68 –

3.43 (m, 3 H, H'-CHN, CH_2-OBn), 1.96 – 1.76 (m, 2 H, 1-H, 3-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.18 (s, C=O (Bz)), 156.20 (d, $^2J_{C,F}$ = 26.9 Hz, C-4'), 148.56 (s, C-2'), 140.34 (d, $^1J_{C,F}$ = 241.6 Hz, C-5'), 137.55 (s, C_q-phenyl, Bn)), 135.55 (s, C_q-phenyl, Bz)), 131.07 (d, C_{para}-phenyl, Bz)), 130.66 (d, C_{ortho}-phenyl, Bz)), 129.36 (d, C_{meta}-phenyl, Bz)), 128.65 (d, C_{ortho}-phenyl, Bn)), 128.07 (d, C_{meta}-phenyl, Bn)), 127,86 (dd, $^2J_{C,F}$ = 33.6 Hz, C-6'), 127.73 (d, C_{para}-phenyl, Bn)), 113.55 (dd, $^1J_{C,F}$ = 290.9, 285.5 Hz, CF_2), 73.04 (t, CH_2-phenyl), 65.19 (dt, $^3J_{C,F}$ = 3.7 Hz, CH_2-OBn), 46.01 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2-N), 27.55 (virt dt, $^2J_{C,F}$ = 10.6 Hz, C-3), 25.05 (virt dt, $^2J_{C,F}$ = 11.0 Hz, C-1). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −137.65 and −139.60 (AB system, J_{AB} = 168.1 Hz, F_A and F_B), −165.16 (s, 5'-F); MS (EI, 70 eV): *m/z* (%) = 339 (69), 233 (31), 194 (5), 143 (5), 105 (100), 91 (19), 77 (21). – HRMS calcd. for $C_{23}H_{22}O_4N_2F_3$: 428.1548; found: 428.1548. – Analysis for $C_{23}H_{22}O_4N_2F_3$ (428.15): calcd. C 64.48, H 5.18, N 5.64; found C 64.41, H 5.13, N 5.37.

(±)-1-[(1 SR, 3 SR)-3-Benzyloxymethyl-2,2-difluorocyclopropylmethyl]-5-fluor o-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**15**)

A solution of **14** (0.70 g, 1.63 mmol) in methanol (27 ml) was treated with ammonium hydroxide (13 ml) for 3 hours. The volatiles were evaporated and the remaining oil was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:1) to give **15** (0.45 g, 81%) as a white solid. – M. p.: 114 – 116 °C. – R_F (ethyl acetate/hexane 1:1) 0.28. – UV/vis (methanol): λ_{max} (lg ε) = 276 nm (3.92). – IR (KBr): ν = 3400w, 3165w, 3070m, 2845m, 1690s, 1660s, 1475m, 1440w, 1415w, 1390m, 1370m, 1340m, 1315w, 1250s, 1240s, 1210m, 1180m, 1100m, 1075w, 1045m, 1030w, 1020w cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.73 (br s, 1 H, NH), 7.39 – 7.26 (m, 6 H, H-phenyl, Bn), H-C(6')), 4.53 and 4.46 (AB system, J_{AB} = −11.9 Hz, 2 H, CH_2-phenyl), 4.22 – 4.10 (m, 1 H, H-CH'N), 3.66 – 3.41 (m, 3 H, H'-CHN, CH_2-OBn), 1.91 – 1.77 (m, 2 H, 1-H, 3-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.39 (d, $^2J_{C,F}$ = 26.5 Hz, C-4'), 149.82 (s, C-2'), 140.72 (d, $^1J_{C,F}$ = 239.1 Hz, C-5'), 137.58 (s, C_q-phenyl, Bn)), 128.55 (d, C_{ortho}-phenyl, Bn)), 128.00 (dd, $^2J_{C,F}$ = 33.2 Hz, C-6'), 127.95 (d, C_{meta}-phenyl, Bn)), 127.66 (d, C_{para}-phenyl, Bn)), 113.62 (dd, $^1J_{C,F}$ = 290.5, 285.5 Hz, CF_2), 72.81 (t, CH_2-phenyl), 65.26 (dt, $^3J_{C,F}$ = 3.7 Hz, CH_2-OBn), 45.78 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2-N), 27.33 (virt dt, $^2J_{C,F}$ = 10.6 Hz, C-3), 24.89 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-1). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −137.84 and −139.78 (AB system, J_{AB} = 164.5 Hz, F_A and F_B), −166.26 (s, 5'-F). – MS (EI, 70 eV): *m/z* (%) = 340 (18), 234 (87), 214 (97), 143 (32), 130 (28), 107 (11), 100 (17), 91 (100), 85 (46). – HRMS calcd. for $C_{16}H_{15}O_3N_2F_3$: 340.1035; found: 340.1035. – Analysis for $C_{16}H_{15}O_3N_2F_3$ (340.10): calcd. C 56.47, H 4.44; N 8.23; found C 56.22, H 4.19, N 8.12.

(±)-1-[(1 SR, 3 SR)-2,2-Difluoro-3-hydroxymethyl-cyclopropylmethyl]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione [= 9-(3-hydroxymethyl-2,2-difluoro-cyclopropylmethyl)fluorouracil] ((±)-**16**)

Removal of the benzyl group was performed by treating **15** (0.38 g, 1.11 mmol) with cyclohexene (17 ml) and Pearlman's catalyst (0.87 g, 20%) in refluxing methanol (19 ml) for 4 hours. After column chromatography (silica gel, ethyl acetate) **16** (0.1 g, 36%) was obtained as a white solid. – M. p.: 187 °C. – R_F (ethyl acetate) 0.44. – UV/vis (methanol): λ_{max} (lg ε) = 276 nm (3.95). – IR (KBr): ν = 3415w, 3025w, 2840w, 1695m, 1665w, 1470w, 1390w, 1375w, 1315w, 1265w, 1240w, 1170w, 1120w, 1040w cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 7.81 (d, $^3J_{F,H}$ = 6.2 Hz, 1 H, H-C(6')), 3.96 (dd*d*, $^2J_{H,H}$ = −14.7 Hz, $^3J_{H,H}$ = 7.8 Hz, $^4J_{F,H}$ = 2.2 Hz, 1 H, H-CH'N), 3.79 (dd*d*, $^2J_{H,H}$ = 14.7 Hz, $^3J_{H,H}$ = 7.1 Hz, $^4J_{F,H}$ = 1.0 Hz, 1 H, H'-CHN), 3.60 (dddd, $^2J_{H,H}$ = -12.1 Hz, $^3J_{H,H}$ = 7.6 Hz, $^4J_{F,H}$ = 1.3, 0.2 Hz, 1 H, H-CH'OH), 3.58 (dddd, $^2J_{H,H}$ = -12.1 Hz, $^3J_{H,H}$ = 7.2 Hz, $^4J_{F,H}$ = 2.7, 1.3 Hz, H'-CHOH), 1.96 (ddddd, $^3J_{F,H}$ = 14.1, 0.2 Hz, $^3J_{H,H}$ = 7.9, 7.1, 7.0 Hz, 1 H, 1-H), 1.94 (ddddd, $^3J_{F,H}$ = 14.6 Hz, 0.2 Hz, $^3J_{H,H}$ = 7.6, 7.2, 7.0 Hz, 1 H, 3-H). – ^{13}C NMR (100 MHz, CD_3OD): δ = 160.02 (d, $^2J_{C,F}$ = 26.2 Hz, C-4'), 151.70 (s, C-2'), 141.97 (d, $^1J_{C,F}$ = 233.8 Hz, C-5'), 130.80 (dd, $^2J_{C,F}$ = 33.9 Hz, C-6'), 115.97 (dd, $^1J_{C,F}$ = 288.4, 285.5 Hz, CF_2), 58.86 (dt, $^3J_{C,F}$ = 4.9 Hz, CH_2-OH), 46.56 (dt, $^3J_{C,F}$ = 5.4 Hz, CH_2-N), 30.76 (virt dt, $^2J_{C,F}$ = 10.2 Hz, C-3), 26.30 (virt dt, $^2J_{C,F}$ = 10.7 Hz, C-1). – ^{19}F NMR (188 MHz, CD_3OD): δ = −135.90 and −138.40 (AB system, J_{AB} = 164.5 Hz, F_A and F_B), −167.68 (s, 5'-F). – MS (EI, 70 eV): *m/z* (%) = 250 (26), 233 (40), 219 (100), 200 (33), 176 (20), 167 (2), 156 (24), 153 (36), 143 (50), 130 (54), 128 (11), 120 (9), 113 (11), 103 (11), 100 (61), 91 (19), 87 (24), 77 (24), 71 (7), 59 (6). – HRMS calcd. for $C_9H_9O_3N_2F_3$: 250.0565; found: 250.0565. – Analysis for $C_9H_9O_3N_2F_3$ (250.06): calcd. C 43.21, H 3.63, N 11.20; found C 43.01, H 3.41, N 11.02.

(±)-[(1 SR, 3 SR)-(3-Benzyloxymethyl-2,2-difluorocyclopropyl)-methyl]-6-chloro-9H-purine ((±)-**17**)

To a mixture of **6** (0.44 g, 1.93 mmol), triphenylphosphane (0.85 g, 3.24 mmol) and 6-chloropurine (0.45 g, 2.91 mmol) in dry 1,4-dioxane (20 ml) a solution of DEAD (0.53 ml, 3.22 mmol) in dioxane (10 ml) was added dropwise at room temperature over a period of 2 hours. The reaction mixture was stirred overnight, the solvent evaporated and the remaining yellowish oil purified by column chromatography (silica gel, ethyl acetate/hexane 2:3) to afford **17** (0.51 g, 73%) as an oil. – R_F (ethyl acetate) 0.30. – IR (film): ν = 3065w, 3030w, 2865w, 1725w, 1595s, 1565s, 1485s, 1455m, 1440m, 1425m, 1405s, 1365m, 1335s, 1260m, 1210s, 1180m, 1150m, 1095m, 1020m cm^{-1}. –

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (s, 1 H, 2'-H), 8.22 (s, 1 H, 8'-H), 7.31 – 7.15 (m, 5 H, H-phenyl), 4.48 – 4.29 (m, 4 H, CH_2-phenyl, CH_2-N), 3.58 (ddd, $^2J_{H,H}$ = −10.4, $^3J_{H,H}$ = 7.0, $^4J_{F,H}$ = 1.6, 1 H, H-CH'OBn), 3.46 – 3.41 (m, 1 H, H'-CHOBn), 2.06m – 1.93 (m, 2 H, H-1), 3-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.22 (s, C-6'), 152.85 (d, C-2'), 152.34 (s, C-4'), 145.78 (d, C-8'), 138.50 (s, C_q-phenyl), 129.58 (d, C_{ortho}-phenyl), 129.00 (d, C_{meta}-phenyl), 128.60 (d, C_{para}-phenyl), 115.00 (s, C-5'), 114.32 (dd, $^1J_{C,F}$ = 289.7, 286.3 Hz, CF_2), 73.84 (t, CH_2-phenyl), 66.07 (dt, $^3J_{C,F}$ = 3.3 Hz, CH_2-OBn), 42.28 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2-N), 28.85 (virt dt, $^2J_{C,F}$ = 10.6 Hz, C-3), 26.63 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-1). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −138.86 and −139.92 (AB system, J_{AB} = 164.5 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 364 (1), 277 (5), 258 (19), 238 (100), 223 (57), 203 (4), 181 (7), 167 (11), 155 (15), 91 (73). – HRMS calcd. for: $C_{17}H_{15}N_4OClF_2$: 364.0902; found: 364.0902. – Analysis for $C_{17}H_{15}N_4OClF_2$ (364.78): calcd. C 55.97, H 4.14, N 15.36; found C 55.83, H 4.27, N 15.43.

(±)-[(1 SR, 3 SR)-3-[(6-Amino-9H-9-purinylmethyl)-2,2-difluorocyclopropyl]methanol [= 9-(3-hydroxymethyl-2,2-difluoro-cyclopropylmethyladenine] ((±) – **19**)

To a solution of **18** (0.45 g, 1.3 mmol) in methanol (50 ml) were added cyclohexene (40 ml) and Pearlman' catalyst (0.34 g, 20%) and the reaction mixture was heated under reflux for 26 hours. After filtration and evaporation of the volatiles the resulting crude product was subjected to column chromatography (silica gel, ethyl acetate/methanol 19:1) to afford **19** (0.26 g, 78%) as a white solid. – M. p. 205 – 214 °C. – R_F (ethyl acetate/methanol 19:1) 0.30. – UV/vis (methanol): λ_{max} (lg ε) = 263 (4.13). – IR (KBr): ν = 3345m, 3100m, 1670m, 1600m, 1575w, 1480w, 1415w, 1305w, 1250m, 1195w, 1045w, 1010w cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 8.24 (s, 1 H, 2'-H), 8.19 (s, 1 H, 8'-H), 4.41 (ddd, $^2J_{H,H}$ = −15.0 Hz, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.6 Hz, 1 H, H-CH'N), 4.38 (ddd, $^2J_{H,H}$ = −15.0 Hz, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.6 Hz, 1 H, H'-CHN), 3.58 (dddd, $^2J_{H,H}$ = −12.0 Hz, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.6, 0.8 Hz, 1 H, H-CH'OH), 3.56 (dddd, $^2J_{H,H}$ = −12.0 Hz, $^3J_{H,H}$ = 6.8 Hz, $^4J_{F,H}$ = 2.9, 1.4 Hz, 1 H, H'-CHOH), 2.13 (ddddd, $^4J_{F,H}$ = 13.9, 0.2 Hz, $^3J_{H,H}$ = 7.8, 7.7, 6.7 Hz, 1 H, 3-H), 2.01 (ddddd, $^3J_{F,H}$ = 14.8, 0.1 Hz, $^3J_{H,H}$ = 7.8, 6.8, 6.7 Hz, 1 H, 1-H). – ^{13}C NMR (100 MHz, CD_3OD): δ = 156.87 (s, C-6'), 153.05 (d, C-2'), 150.86 (s, C-4'), 142.79 (d, C-8'), 120.13 (s, C-5'), 115.82 (dd, $^1J_{C,F}$ = 288.0, 285.9 Hz, CF_2), 58.79 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2-OH), 41.78 (dt, $^3J_{C,F}$ = 5.4 Hz, CH_2-N), 31.03 (virt dt, $^2J_{C,F}$ = 10.2 Hz, C-3), 26.97 (virt dt, $^2J_{C,F}$ = 10.6 Hz, C-1). – ^{19}F NMR (188 MHz, CD_3OD): δ = −136.92 and −138.56 (AB system, J_{AB} = 164.5 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 255 (16), 199 (100), 183 (63), 149 (49), 77 (74). – HRMS calcd. for: $C_{10}H_{11}N_5OF_2$: 255.0931; found: 255.0931. – Analysis for $C_{10}H_{11}N_5OF_2$ (255.09): calcd. C 47.06; H 4.34, N 27.44; found C 47.23, H 4.11, N 27.20.

(±)-9-[(1 SR, 3 SR)-(3-Benzyloxymethyl-2,2-difluoro-cyclopropyl)methyl]-9H-6-purinamine ((±)-**21**)

Treatment of compound **17** (0.78 g, 2.14 mmol) with an excess of liquid ammonia in an autoclave at 75 °C and 40 bar resulted after evaporation of the volatiles and column chromatography (silica gel, ethyl acetate) in the formation of **18** (0.52 g, 71%) that was isolated as a white solid. – M. p. 148 – 149 °C. – R_F (ethyl acetate) 0.10. – UV/vis (methanol): λ_{max} (lg ε) = 263 nm (4.22). – IR (KBr): ν = 3295m, 3122m, 2860w, 1670m, 1600m, 1480m, 1415m, 1360w, 1310m, 1245m, 1210m, 1170w, 1115m, 1075m, 1020w cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 8.21 (s, 1 H, 2'-H), 8.17 (s, 1 H, 8'-H), 7.29 – 7.10 (m , 5 H, H-phenyl), 4.49 (dd, $^2J_{H,H}$ = −14.7 Hz, $^3J_{H,H}$ = 6.2 Hz, 1 H, H-CH'N), 4.33 – 4.12 (m, 3 H, H'-CHN, CH_2-phenyl), 3.60 (dd, $^2J_{H,H}$ = −10.7 Hz, $^3J_{H,H}$ = 6.8 Hz, H-CH'OBn), 3.47 – 3.41 (m, 1 H, H'-CHOBn), 2.24 – 2.10 (m, 2 H, 1-H, 3-H). – ^{13}C NMR (100 MHz, CD_3OD): δ = 157.07 (s, C-6'), 153.63 (d, C-2'), 150.45 (s, C-4'), 142.03 (d, C-8'), 138.92 (s, C_q-phenyl), 129.04 (d, C_{ortho}-phenyl), 128.34 (d, C_{meta}-phenyl), 128.17 (d, C_{para}-phenyl), 119.74 (s, C-5'), 115.21 (dd, $^1J_{C,F}$ = 287.2, 286.7 Hz, CF_2), 72.95 (t, CH_2-phenyl), 66.10 (t, CH_2-OBn), 41.18 (t, CH_2-N), 28.32 (virt dt, $^2J_{C,F}$ = 10.4 Hz, C-3), 27.11 (virt dt, $^2J_{C,F}$ = 10.8 Hz, C-1). – ^{19}F NMR (188 MHz, CD_3OD): δ = −136.62 and −137.37 (AB system, J_{AB} = 164.5 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 345 (2), 296 (2), 254 (2), 239 (11), 224 (6), 219 (100), 204 (8), 192 (3), 148 (9), 135 (25), 108 (4), 91 (28). – Analysis for $C_{17}H_{17}N_5OF_2$ (345.14): calcd. C 59.10, H 4.93, N 20.29; found C 59.34, H 4.85, N 20.00.

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