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Synthesis of Difluorocyclopropyl Carbocyclic Homo-nucleosides

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Abstract: Racemic difluorinated carbocyclic homo-nucleoside analogues are easily accessible from (*Z*)-4-(benzyloxy)-2-butenyl acetate by difluorocyclopropanation using sodium chlorodifluoro acetate in diglyme at 190°C followed by Mitsunobu reactions.

A large number of nucleoside analogues has been synthesized as potential chemotherapeutic agents. Among them, several carbocyclic nucleosides are particularly interesting since they exhibit potent anti-HIV activities and are considered as alternatives to drugs as ddI, ddC and AZT. The side effects and toxicity of the latter compounds limit their usefulness as antiretroviral agents.[1, 2] As a part of our drug discovery program for AIDS and other viral diseases we became interested in the synthesis and biological evaluation of cyclopropyl carbocyclic nucleosides.[3, 4] Previously the incorporation of one or two fluorine substituents has been shown to be of advantage both for an improved activity, higher bioavailability and retarded metabolism of several drugs.[5] Thus, herein we report the first synthesis of difluorocyclopropyl homo-nucleoside analogues [6] in a very efficient way.

Thus, the easily available (*Z*)-4-(benzyloxy)-2-butenyl acetate (**1**)[7] was subjected to a difluorocyclopropanation using sodium difluoro acetate in diglyme at 190°C [8] to afford **2**. **2** is characterized in its ^{19}F NMR spectrum by the presence of two signals at δ = -126.82 and -152.61 ppm showing each a $^{2}J_{F,F}$ = 162.7 Hz; the quaternary carbon bearing the two fluorine substituents is found in the ^{13}C NMR spectrum at δ = 114.13 ppm. Smooth Zemplen deacetylation of **2** with catalytic amounts of sodium methoxide in methanol gave the key intermediate **3**. Treatment of **3** with triphenylphosphine (TPP) diethyl azodicarboxylate (DEAD) and 6-chloro-purine under Mitsunobu conditions [9] afforded **4** [10] that was subjected to an ammonolysis to afford **5** in 77% yield.[11] A more direct preparation of **5** was achieved by a Mitsunobu reaction of **3** with adenine. Finally, **5** was debenzylated with *Pearlman*'s catalyst using cyclohexene as a hydrogen donor to afford the adenine analogue **6** in 74% yield. **6** shows in the ^{19}F NMR spectrum two signals at δ = -124.38 and -151.45 ppm; the signal for the CH_2-N-moiety is found in the ^{13}C NMR spectrum at δ = 36.53 ppm and shows a $^{3}J_{C,F}$ = 4.98 Hz. The NH_2-group of the heterocycle is observed in the ^{1}H NMR spectrum at δ = 5.59 ppm as a broad signal.

By a similar strategy a thymine analogue was prepared using again **3** as a starting material. Thus, reaction of **3** with N^3-benzoyl-thymine [12], DEAD and TPP in dry 1,4-dioxane [13] for 16 h at ambient

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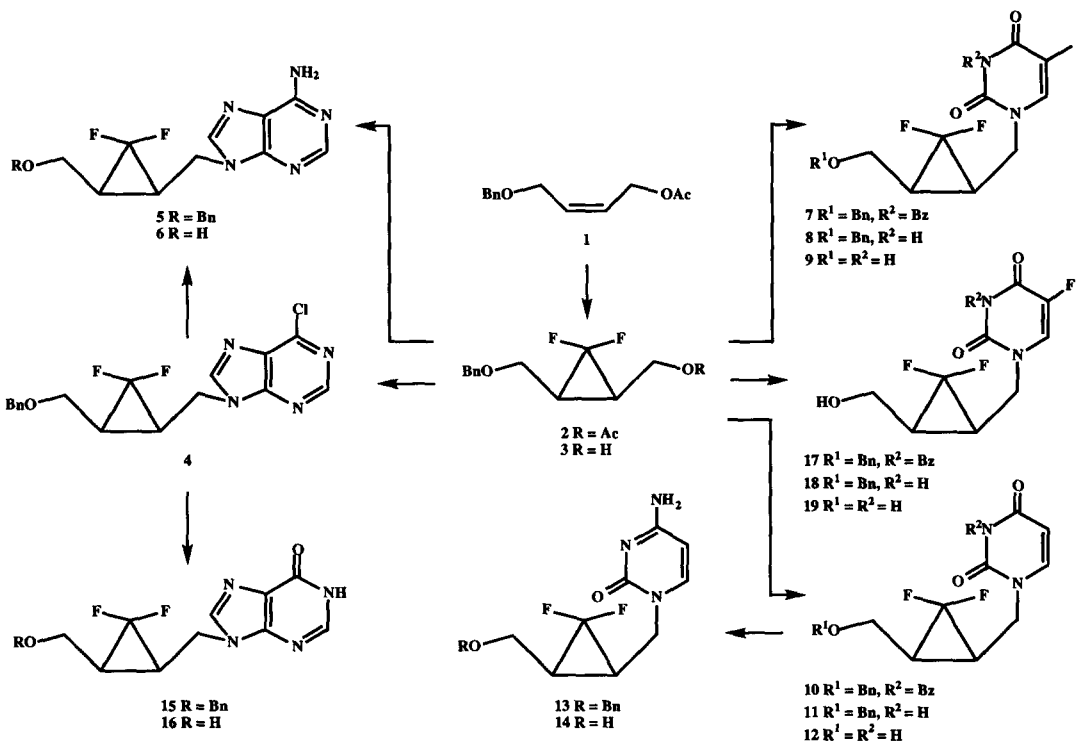
temperature gave 68% of oily **7** that was debenzoylated with 1 N NaOH to afford **8** whose debenzylation yielded 71% of the thymine analogue **9** as a white solid.



Mitsunobu reaction of **3** with N^3-benzoyl-uracil [14] gave **10** that was debenzoylated to afford **11** whose debenzylation gave the uracil analogue **12**. To access a cytosine analogue the uracil derivative **11** was allowed to react with 1,2,3-triazole and $POCl_3$/triethylamine [15] to afford **13** whose deprotection finally gave the desired cytosine analogue **14** albeit in a somewhat low yield.

Treatment of **4** with trifluoroacetic acid gave **15** that upon debenzylation resulted in the smooth formation of the hypoxanthine derivative **16**.[16] Finally, a 5-fluoro-uracil analogue was prepared by the reaction of **3** with N^3-benzoyl-5-fluoro-uracil [17], DEAD, TPP to give 73% of the fully protected derivative **17** whose debenzoylation with ammonium hydroxide yielded **18** that was debenzylated to afford **19**. **19** is characterized in its ^{19}F NMR spectrum by the presence of three signals at δ = -126.38, -152.60 and -169.67 ppm the latter of which can be assigned to the fluoro substituent at the 5'-position of the heterocycle.

Since preliminary screening of the compounds revealed some cytotoxic activity the synthesis of enantiomerically pure samples by a chemoenzymatic process is presently investigated in our laboratories.[18]

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Experimental Part

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 LCQ 7000 (electrospray, voltage 4.5 kV, under nitrogen) instrument; 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).

(±)-(1 *SR*, 3 *RS*)-[3-Benzyloxymethyl-2,2-difluorocyclopropyl]-methyl acetate [(±)-2] A solution of (*Z*)-4-(benzyloxy)-2-butenyl acetate (**1**) (3.3 g, 15 mmol) in dry diglyme (5 *ml*) was heated to 190 °C. A solution of sodium chloro-difluoro acetate (25 g, 164 mmol) in dry diglyme (43 *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 allowed to cool to room temperature, poured into ice water and the aqueous solution was extracted with hexane (4 x 100 *ml*). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The remaining brown oil was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:5) to afford **2** (3.33 g, 83%) as a colorless oil contaminated with some starting material which was easily separated in the next reaction step; an analytical sample was prepared by deacetylation (*vide infra*), chromatography (ethyl acetate 1:2) and re-acetylation (pyridine/acetic anhydride); R_F (ethyl acetate/hexane 1:4) 0.41; UV (methanol): λ_{max} = 266 nm (log ε = 3.57); IR (film): ν 3370*w*, 3035*w*, 2965*w*, 2870*m*, 1955*w*, 1740*s*, 1600*w*, 1090*s*, 1035*s*; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (*m*, 5 H, phenyl), 4.54 and 4.48 (AB system, J_{AB} = 11.7, 2 H, CH_2-phenyl), 4.31-4.11 (*m*, 2 H, CH_2-O-Ac), 3.69-3.59 (*m*, 2 H, CH_2-O-Bn), 2.13-2.03 (*m*, 2 H, cyclopropyl), 2.04 (*s*, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.82 (*s*, CO), 138.83 (*s*, C_q phenyl), 129.56 (*d*, C_{ortho} phenyl), 128.93 (*d*, C_{meta} phenyl), 128.81 (*d*, C_{para} phenyl), 114.13 (*dd*, $^1J_{C,F}$ = 283.7, 290.68, CF_2), 73.91 (*t*, CH_2-phenyl), 63.73 (*dt*, $^3J_{C,F}$ = 32.2, CH_2-O-Bn), 58.77 (*dt*, $^3J_{C,F}$ = 5.0, CH_2-O-Ac), 26.07 (*dt*, $^2J_{C,F}$ = 10.0, C(1)), 24.71 (*dt*, $^2J_{C,F}$ = 21.1, C(3)), 21.60 (*q*, CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ -126.82 (*ddd*, $^2J_{F,F}$ = 162.65, $^3J_{H,F}$ = 10.8, $^3J_{H,F}$ = 11.0, F), -152.61 (*d*, $^2J_{F,F}$ = 162.65, F'); MS (e.i., 70 eV): 270 (1%), 227 (1%), 210 (1%), 190 (1%), 180 (1%), 163 (1%), 144 (6%), 119 (1%), 105 (13%), 91 (100%), 65 (17%), 43 (56%); HRMS calcd. for $C_{14}H_{16}O_3F_2$: 270.1067; found: 270.1068; Anal. calcd. for $C_{14}H_{16}O_3F_2$ (270.28): C, 62.22; H, 5.97; found: C, 62.51; H, 6.04.

(±)-(1 *SR*, 3 *RS*)-3-Benzyloxymethyl-2,2-difluorocyclopropyl-methanol [(±)-3] A solution of **2** (3.33 g, 12.3 mmol) in methanol (7 *ml*) was treated with catalytic amounts of sodium methoxide. After 30 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 was suspended in water (10 *ml*). The 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 1:3) to afford **3** (2.4 g, 70 % yield from **1**) as a colorless oil; R_F (ethyl acetate/hexane 1:2) 0.29; UV (methanol): λ_{max} = 266 nm (log ε = 5.06); IR (film): ν 3430*s*, 3090*w*, 3065*m*, 3035*m*, 2880*s*, 1960*w*, 1880*w*, 1815*w*, 1735*w*, 1605*w*, 1585*w*, 1480*s*, 1420*m*, 1365*s*, 1285*s*, 1250*s*, 1185*s*, 1075*s*, 1030*s*, 1000*s*; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (*m*, 5 H, phenyl), 4.53 (AB system, J_{AB} = 11.59, 2 H, CH_2-phenyl), 3.87 (*m*, $^2J_{H,H}$ = -10.85, $^3J_{H,H(C3)}$ = 4.54, 1 H, CH_2-OH), 3.83 (*m*, $^2J_{H,H}$ = -11.38, $^3J_{H,H(C3)}$ = 4.1, 1 H, CH_2-OBn), 3.60 (*m*, $^2J_{H,H}$ = -10.85, $^3J_{H,H(C1)}$ = 6.37, 1 H, CH_2-OH), 3.58 (*m*, $^2J_{H,H}$ = -11.38, $^3J_{H,H}$ = 6.47, 1 H, CH_2-OBn), 2.85 (*d*, 1 H, OH), 2.08 (*m*, $^3J_{H(C3),H(C1)}$ = 11.59, 1 H, H-C(1)), 2.06 (*m*, $^3J_{H(C3),H(C1)}$ = 11.59, 1 H, H-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.78 (*s*, C_q phenyl), 128.60

(*d*, C_{ortho} phenyl), 128.17 (*d*, C_{meta} phenyl), 127.95 (*d*, C_{para} phenyl), 113.78 (*dd*, $^1J_{C,F}$ = 289.40, 284.0, CF_2), 73.35 (*t*, $^1J_{C,H}$ = 141.82, CH_2-phenyl), 62.58 (*dt*, $^3J_{C,F}$ = 3.73, CH_2-OBn), 55.58 (*dt*, $^3J_{C,F}$ = 3.73, $^1J_{C,H}$ = 145.50, CH_2OH), 28.35 (*dt*, $^2J_{C,F}$ = 9.95, $^1J_{C,H}$ = 356.76, C(1)), 24.83 (*dt*, $^2J_{C,F}$ = 9.95, $^1J_{C,H}$ = 364.21, C(3)); ^{19}F NMR (470 MHz, $CDCl_3$): δ -124.35 (*ddd*, $^2J_{F,F}$ = 162.58, $^3J_{F,H}$ = 13.80, $^3J_{F,H}$ = 14.05, F), -149.79 (*dd*, $^2J_{F,F}$ = 162.58, $^3J_{F,H}$ = 1.47, F'); MS (e.i., 70 eV): 228 (2.9%), 107 (100%), 102 (22.9%), 91 (50%), 77 (14.3%), 65 (16.4%); Anal. calcd. for $C_{12}H_{14}F_2O_2$ (228.24): C, 63.15, H, 6.18; found: C, 63.15; H, 6.27.

(±)-[(1 *SR*, 3 *RS*)-(3-Benzyloxymethyl-2,2-difluorocyclopropyl)-methyl]-6-chloro-9*H*-purine [(±)-4] To a mixture of **3** (0.41 g, 1.8 mmol), triphenylphosphine (0.95 g, 3.6 mmol) and 6-chloropurine (0.56 g, 3.6 mmol) in dry 1,4-dioxane (8 *ml*) a solution of DEAD (0.57 *ml*, 3.6 mmol) in 1,4-dioxane (30 *ml*) was added dropwise at room temperature over a period of 2.5 hours. The reaction mixture was stirred overnight, the solvent was evaporated and the remaining yellowish oil was purified by column chromatography (silica gel, ethyl acetate/hexane 1:1) to afford **4** (0.44 g, 67 %) as an oil contaminated with some impurities that were easily removed after the next reaction step; an analytical sample was obtained by column chromatography (silica gel RP-18, methanol/water 7:3); R_F (ethyl acetate/hexane 1:1) 0.24; UV (methanol): λ_{max} = 267 nm (log ε = 3.99); IR (film): ν 3450*w*, 3031*w*, 2865*w*, 1735*w*, 1595*m*, 1560*m*, 1500*w*, 1475*m*, 1440*w*, 1405*m*, 1370*w*, 1335*m*, 1275*w*, 1255*w*, 1210*m*, 1185*w*, 1145*w*, 1075*m*, 1030*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (*s*, 1 H, H-C(4')), 8.18 (*s*, 1 H, H-C(8')), 7.35-7.25 (*m*, 5 H, phenyl), 4.57-4.30 (*m*, 4 H, CH_2-phenyl and CH_2-N), 3.86-3.61 (*m*, 2 H, CH_2-O-Bn), 2.34-2.12 (*m*, 2 H, cyclopropyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.17 (*s*, C(6')), 151.88 (*s*, C(2')), 151.34 (*s*, C(4')), 145.00 (*s*,C(8')), 137.11 (*s*, C_q phenyl), 131.67 (*d*, C_{ortho} phenyl), 128.26 (*d*, C_{meta} phenyl), 127.93 (*d*, C_{para} phenyl), 113.99 (*s*, C(5')), 112.49 (*dd*, $^1J_{C,F}$ = 293.20, 282.43, CF_2), 73.22 (*t*, CH_2-phenyl), 62.03 (*dt*, $^3J_{C,F}$ = 4.12, CH_2-OBn), 37.92 (*dt*, $^3J_{C,F}$ = 6.22, CH_2-N), 25.26 (*dt*, $^2J_{C,F}$ = 10.06, C(3)), 24.28 (*dt*, $^2J_{C,F}$ = 11.06, C(1)); ^{19}F NMR (188 MHz, $CDCl_3$): δ -126.69 (*ddd*, $^2J_{F,F}$ = 168.1, $^3J_{F,H}$ = 10.8 , $^3J_{F,H}$ = 11.0, F), -151.75 (*d*, $^2J_{F,F}$ = 168.1, F'); MS (e.i., 80 eV): 367 (0.6%), 365 (1.8%), 258 (10.3%), 238 (31.6%), 181 (7.1%), 155 (9.6%), 104 (17.7%), 91 (100%), 71 (43.3%); HRMS calcd. for $C_{17}H_{15}ON_4F_2Cl$: 364.0902; found: 364.0904; Anal. calcd. for $C_{17}H_{15}ON_4F_2Cl$ (364.79): C, 55.98; H, 4.14; N, 15.36; found: C, 55.79; H, 4.29; N, 15.42.

(±)-9-[(1 *SR*, 3 *RS*)-(3-Benzyloxymethyl-2,2-difluoro-cyclopropyl)-methyl]-9*H*-6-purinamine [(±)-5]

a) From **4**: Treatment of compound **4** (0.11 g, 0.3 mmol) with liquid ammonia (10 *ml*) in an autoclave at 75 °C and 40 bar for 18 hours resulted after evaporation of the volatiles and column chromatography (silica gel, ethyl acetate/prop-2-OH 3:1) in the formation of **5** (80 mg, 77%).

b) From **3**: A more direct preparation of **5** was achieved by a Mitsunobu reaction as described for **4** using **3** (0.92 g, 4.03 mmol), triphenylphosphine (2.11 g, 8.06 mmol), adenine (1.09 g, 8.06 mmol) suspended in 1,4-dioxane (18 *ml*) and DEAD (1.27 *ml*, 8.06 mmol) dissolved in 1,4-dioxane (20 *ml*). The solvent was evaporated and the residue was purified by column chromatography (silica gel, ethyl acetate/prop-2-OH 3:1) to afford **5** (0.61 g, 43%).

Data for **5**: white solid, mp: 149-150 °C; R_F (ethyl acetate/methanol 4:1) 0.48; UV (methanol): λ_{max} = 263 nm (log ε = 4.16); IR (KBr): ν 3355*s*, 3155*m*, 2925*m*, 2865*w*, 1650*s*, 1605*s*, 1575*m*, 1475*s*, 1420*m*, 1370*m*, 1330*m*, 1310*m*, 1245*s*, 1195*m*, 1165*m*, 1115*m*, 1075*m*, 1030*m*, 1005*m*; ^{1}H NMR (400 MHz, CD_3OD): δ 8.35 (*s*, 1 H, H-C(2')), 7.84 (*s*, 1 H, H-C(8')), 7.36-7.25 (*m*, 5 H, phenyl), 4.49 (AB system, J_{AB} = 11.99, 2 H, CH_2-phenyl), 4.46 (*m*, $^2J_{H,H}$ = -6.73, $^3J_{H,H}$ = 5.46, 1 H, CH_2-N), 4.19 (*m*, $^2J_{H,H}$ = -6.73, $^3J_{H,H}$ = 14.95, 1 H, CH_2-N), 3.79 (*m*, $^2J_{H,H}$ = -11.06, $^3J_{H,H}$ = 6.66, 1 H, CH_2-OBn), 3.64 (*m*, $^2J_{H,H}$ = -11.06, $^3J_{H,H}$ = 8.76, 1 H, CH_2-OBn), 2.28 (*m*, $^3J_{H,H}$ = 7.32, 1 H, H-C(1)), 2.13 (*m*, $^3J_{H,H}$ = 7.32, 1 H, H-C(3)); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.74 (*s*, C(6')), 153.04 (*d*, $^1J_{C,H}$ = 201.66, C(2')), 149.94 (*s*, C(4')), 140.00 (*d*, $^1J_{C,H}$ = 210.92, C(8')), 137.22 (*s*, C_q phenyl), 128.50 (*d*, C_{ortho} phenyl), 127.97 (*d*, C_{meta} phenyl), 127.77 (*d*, C_{para}

phenyl), 119.52 (*s*, C(5')), 112.67 (*dd*, $^1J_{CF}$=282.2, CF_2), 73.05 (*t*, $^1J_{C,H}$ = 139.81, CH_2-phenyl), 62.21 (*dt*, $^3J_{C,F}$ = 4.99, $^1J_{C,H}$ = 146.42, CH_2-OBn), 37.25 (*dt*, $^3J_{C,F}$ = 5.99, $^1J_{C,H}$ = 140.56, CH_2-N), 25.18 (*dt*, $^2J_{C,F}$ = 9.98, $^1J_{C,H}$ = 164.27, C(3)), 24.65 (*dt*, $^2J_{C,F}$ = 10.9, $^1J_{C,H}$ = 163.31, C(1)); ^{19}F NMR (188 MHz, $CDCl_3$): δ -126.91 (*ddd*, $^2J_{F,F}$ = 168.1, $^3J_{F,H}$ = 10.82, $^3J_{F,H}$ = 11.0, F), -152.14 (*dt*, $^2J_{F,F}$ = 168.1, F'); MS (e.i., 70 eV): 345 (1.4%), 325 (1.4%), 296 (12.7%), 239 (14.2%), 219 (100%), 224 (12.7%), 204 (9.2%), 148 (12.7%), 135 (32.6%), 108 (7.1%), 99 (11.3%), 91 (67.4%); HRMS calcd. for $C_{17}H_{17}F_2N_5O$: 345.1401; found: 345.1401.

(±)-(1 *RS*, 3 *SR*)-3-[(6-Amino-9*H*-9-purinylmethyl)]-2,2-difluorocyclopropyl-methanol [= 9-(3-hydroxymethyl-2,2-difluoro-cyclopropylmethyl) adenine] [(±)-6] To a solution of **5** (0.7 g, 2 mmol) in methanol (35 *ml*) were added cyclohexene (30 *ml*) and *Pearlman's* catalyst (0.31 g, 20 %) and the reaction mixture was heated under reflux for 12 hours. After filtration and evaporation of the volatiles the resulting crude product was subjected to column chromatography (silica gel RP-18, methanol/water 6:4 → 7:3) to afford **6** (0.38 g, 74 %) as a white solid; mp: 218-220 °C; R_F (ethyl acetate/methanol 1:1) 0.43; UV (methanol): λ_{max} = 262.67 nm (log ε = 4.15); IR (KBr): ν 3400*m*, 3115*m*, 2930*m*, 2465*m*, 2305*m*, 1715*m*, 1675*m*, 1615*s*, 1570*s*, 1545*m*, 1475*s*, 1420*s*, 1370*m*, 1340*m*, 1305*s*, 1265*m*, 1235*s*, 1195*m*, 1105*m*, 1055*m*, 1010*m*; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (*s*, 1 H, H-C(2')), 7.85 (*s*, 1 H, H-C(8')), 5.59 (*br s*, 2 H, NH_2, exchangeable with D_2O), 5.12 (*s*, 1 H, OH, exchangeable with D_2O), 4.49 (*m*, $^2J_{H,H}$ = -14.96, $^3J_{H,H}$ = 7.74, 1 H, CH_2-N), 4.43 (*m*, $^2J_{H,H}$ = -14.96, $^3J_{H,H}$ = 7.55, 1 H, CH_2-N), 3.91 (*m*, $^2J_{H,H}$ = -12.14, $^3J_{H,H}$ = 7.18, 1 H, CH_2-OBn), 3.77 (*m*, $^2J_{H,H}$ = -12.12, 1 H, CH_2-OBn), 2.39 (*m*, $^3J_{H,H}$ = 11.69, 1 H, H-C(1)), 2.15 (*m*, $^3J_{H,H}$ = 11.69, 1 H, H-C(3)); ^{13}C NMR (125 MHz, DMSO-d_6): δ 155.97 (*s*, C(6')), 152.49 (*d*, $^1J_{C,H}$ = 201.66, C(2')), 149.33 (*s*, C(4')), 140.46 (*d*, $^1J_{C,H}$ = 210.92, C(8')), 118.63 (s, C(5')), 114.16 (*dd*, $^1J_{C,F}$ = 290.23, 282.24, CF_2), 53.63 (*dt*, $^3J_{C,F}$ = 4.98, CH_2-OH), 36.53 (*dt*, $^3J_{C,F}$ = 4.98, CH_2-N), 27.17 (*dt*, $^2J_{C,F}$ = 8.98, C(3)), 23.96 (*dt*, $^2J_{C,F}$ = 9.97, C(1)); ^{19}F NMR (188 MHz, CD_3OD): δ -124.38 (*ddd*, $^2J_{F,F}$ = 168.1, $^3J_{F,H}$ = 10.7, $^3J_{F,H}$ = 11.1, F), -151.45 (*d*, $^2J_{F,F}$ = 164.5, F'); MS (e.i., 70 eV): 255 (8.3%), 235 (13.3%), 206 (71.6%), 149 (35%), 135 (100%), 108 (45%); HRMS calcd. for $C_{10}H_{11}N_5OF_2$: 255.0931; found 255.0931.

(±)-3-Benzoyl-1-[(1 *SR*, 3 *RS*)-3-benzyloxymethyl-2,2-difluorocyclopropylmethyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione [(±)-7] The reaction was performed under the conditions as described for **4** using **3** (0.34 g, 1.47 mmol), triphenylphosphine (0.77 g, 2.96 mmol), N^3-benzoylthymine (0.68 g, 2.96 mmol), 1,4-dioxane (8 *ml*) and DEAD (0.46 ml, 2.96 mmol) in 1,4-dioxane (15 *ml*). After evaporation of the solvents purification by column chromatography (silica gel, ethyl acetate/hexane 1:4 → 1:2) gave **7** (0.43g, 68%) as an oil; R_F (ethyl acetate/hexane 1:2): 0.12; UV (methanol): λ_{max1} = 280 nm (log ε = 3.88), λ_{max2} = 255 nm (log ε = 4.19); IR (film): ν 3305*w*, 3065*w*, 3030*w*, 2980*w*, 2930*w*, 2870*w*, 2140*w*, 1970*w*, 1800*w*, 1750*s*, 1700*s*, 1660*s*, 1600*m*, 1580*w*, 1475*m*, 1440*s*, 1385*m*, 1360*m*, 1330*m*, 1315*m*, 1250*s*, 1195*m*, 1180*m*, 1090*m*, 1075*m*, 1030*m*, 1000*m*; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94-7.27 (*m*, 10 H, phenyl), 7.16 (*s*, 1 H, H-C(6')), 4.53 (AB system, J_{AB} = 11.61, 2 H, CH_2-phenyl), 4.19-4.11 (*m*, 1 H, CH_2-OBn), 3.80-3.61 (*m*, 3 H, CH_2-OBn and CH_2-N), 2.20-2.11 (*m*, 2 H, cyclopropyl), 1.27 (*s*, 3 H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.83 (*s*, CO benzoyl), 162.94 (*s*, C(2')), 149.75 (*s*, C(4')), 139.59 (*d*, C(6')), 137.15 (*s*, C_q phenyl (Bn)), 134.93 (*s*, C_q phenyl (Bz)), 131.53 (*d*, C_{para} phenyl (Bz)), 130.35 (*d*, C_{ortho} phenyl (Bz)), 129.04 (*d*, C_{meta} phenyl (Bz)), 128.52 (*d*, C_{ortho} phenyl (Bn)), 128.02 (*d*, C_{meta} phenyl (Bn)), 127.77 (*d*, C_{para} phenyl (Bn)), 113.83 (*dd*, $^1J_{C,F}$ = 292.21, 281.25, CF_2), 111.08 (*s*, C(5')), 73.03 (*t*, CH_2-phenyl), 62.32 (*dt*, $^3J_{C,F}$ = 6.16, CH_2-OBn), 42.25 (*dt*, $^3J_{C,F}$ = 5.39, CH_2-N), 25.08 (*dt*, $^2J_{C,F}$ = 10.01, C(3)), 23.70 (*dt*, $^3J_{C,F}$ = 10.02, C(1)), 12.19 (*q*, CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ -126.48 (*ddd*, $^2J_{F,F}$ = 164.62, $^3J_{F,H}$ = 10.91, $^3J_{F,H}$ = 10.94, F), -150.81 (*d*, $^2J_{F,F}$ = 164.62, F'); MS (ESI): 441 (M+1, 2 %), 463 (M+Na, 38 %), 479 (M+K, 14 %), 271 (100 %); HRMS calcd. for $C_{24}H_{22}O_4N_2F_2$: 440.1548, found: 440.1548.

(±)-1-[(1 *SR*, 3 *RS*)-3-Benzyloxymethyl-2,2-difluorocyclopropylmethyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione [(±)-8] A solution of **7** (0.34 g, 0.78 mmol) in 1,4-dioxane (10 *ml*) was treated with sodium hydroxide (N, 10 *ml*) for 12h. The volatiles were evaporated and the remaining oil was

subjected to column chromatography (silica gel, ethyl acetate/hexane 4:1) to give **8** (0.22 g, 84 %) as a white solid mp: 162-163 °C; R_F (ethyl acetate/hexane 5:1) 0.39; UV (methanol): λ_{max} = 271 nm (log ε = 3.98); IR (KBr): ν 3445*m*, 3165*w*, 3035*m*, 2930*w*, 2875*w*, 1700*s*, 1665*s*, 1475*m*, 1380*m*, 1365*m*, 1275*m*, 1250*m*, 1230*w*, 1200*m*, 1175*w*, 1090*m*, 1030*w*; ^{1}H NMR (500 MHz, $CDCl_3$): 8.11 (*br s*, 1 H, NH), 7.37-7.23 (*m*, 5 H, phenyl), 7.01 (*s*, 1 H, H-C(6')), 4.50 (AB system, J_{AB} = 11.67, 2 H, CH_2-phenyl), 4.12 (*m*, $^2J_{H,H}$ = -12.37, $^3J_{H,H}$ = 6.97, 1 H, CH_2-OBn), 3.77 (*m*, $^2J_{H,H}$ = -12.37, $^3J_{H,H}$ = 7.62, 1 H, CH_2-OBn), 3.60 (*m*, $^2J_{H,H}$ = -8.77, $^3J_{H,H}$ = 10.53, 1 H, CH_2-N), 3.57 (*m*, $^2J_{H,H}$ = -8.77, $^3J_{H,H}$ = 9.76, 1 H, CH_2-N), 2.12 (*m*, $^3J_{H(C3),H(C1)}$ = 13.28, 1 H, H-C(3)), 2.07 (*m*, $^3J_{H(C3),H(C1)}$ = 13.28, 1 H, H-C(1)), 1.24 (*s*, 3 H, CH_3); ^{13}C NMR (100 MHz, d_6-DMSO): δ 164.348 (*s*, C(2')), 151.032 (*s*, C(4')), 140.917 (*d*, C(6')), 138,21 (*s*, C_q phenyl), 128.52, 128.00, 127.77 (each *d*, phenyl), 114.59 (*t*, $^1J_{C,F}$ = 285.66, CF_2), 108.96 (*s*, C(5')), 71.91 (*t*, $^1J_{C,H}$ = 139.51, CH_2-phenyl), 62.41 (*dt*, $^3J_{C,F}$ = 4.28, $^1J_{C,H}$ = 140.92, CH_2-OBn), 42.14 (*dt*, $^3J_{C,F}$ = 3.73, $^1J_{C,H}$ = 145.50, CH_2-N), 25.82 (*dt*, $^2J_{C,F}$ = 10.35, $^1J_{C,H}$ = 161.94, C(3)), 24.59 (*dt*, $^2J_{C,F}$ = 10.02, $^1J_{C,H}$ = 161.78, C(1)), 11.82 (*q*, CH_3); ^{19}F NMR (470 MHz, CD_3OD): δ -126.71 (*ddd*, $^2J_{F,F}$ = 164.23, $^3J_{F,H}$ = 13.27, F), -152.12 (*dd*, $^2J_{F,F}$ = 164.23, $^3J_{F,H}$ = 1.47, F'); MS (e.i., 70 eV): 336 (6.4%), 230 (73.7%), 210 (69.5%), 172 (9.6%), 151 (27.7%), 139 (15.9%), 126 (22.3%), 96 (17.7), 91 (100%); HRMS calcd. for $C_{17}H_{18}N_2O_3F_2$: 336.1285, found 336.1287.

(±)-1-[(1 *SR*, 3 *RS*)-2,2-Difluoro-3-hydroxymethyl-cyclopropylmethyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (= 1-(2,2-difluoro-3-hydroxymethyl-cyclopropylmethyl) thymine) [(±)-9] To a solution of **8** (0.86 g, 2.56 mmol) in methanol (35 *ml*) were added cyclohexene (28 *ml*) and *Pearlman's* catalyst (1.97 g, 20 %) and the reaction mixture was heated under reflux for 6 hours. After filtration and evaporation of all volatiles the remaining residue was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:1 → ethyl acetate/methanol 3:1) to give **9** (0.45 g, 71 %) as a white solid; mp: 183-185 °C; R_F (ethyl acetate/methanol 4:1) 0.54; UV (methanol): λ_{max} = 271 nm, (log ε = 3.87); IR (KBr): ν 3460*s*, 3185*s*, 3040*s*, 2925*m*, 2815*m*, 2550*m*, 1690*s*, 1645*s*, 1455*s*, 1417*m*, 1385*m*, 1355*s*, 1265*s*, 1250*s*, 1225*s*, 1195*s*, 1155*m*, 1125*m*, 1105*m*, 1050*s*, 1005*m*; ^{1}H NMR (500 MHz, d_6-DMSO): δ 11.24 (*br s*, 1 H, NH), 7.48 (*s*, 1 H, H-C(6')), 4.88 (*s*, 1 H, C-OH), 3.93 (*m*, $^2J_{H,H}$ = -14.11, $^3J_{H,H}$ = 7.09, 1 H, CH_2-N), 3.74 (*m*, $^2J_{H,H}$ = -14.70, $^3J_{H,H}$ = 7.73, 1 H, CH_2-OH), 3.64 (*m*, $^2J_{H,H}$ = -14.11, $^3J_{H,H}$ = 7.78, 1 H, CH_2-N), 3.55 (*m*, $^2J_{H,H}$ = -14.70, $^3J_{H,H}$ = 7.61, 1 H, CH_2-OH), 2.18 (*m*, $^3J_{H,H}$ = 11.84, 1 H, H-C(1)), 2.03 (*m*, $^3J_{H,H}$ = 11.84, 1 H, H-C(3)), 1.75 (*s*, 3 H, CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ 165.59 (*s*, C(2')), 151.70 (*s*, C(4')), 141.33 (*d*, C(6')), 113.8 (*dd*, $^1J_{C,F}$ = 291.07, 280.39, CF_2), 110.383 (*s*, C(5')), 54.47 (*dt*, $^3J_{C,F}$ = 6.03, CH_2-OH), 41.63 (*dt*, $^3J_{C,F}$ = 5.91, CH_2-N), 27.39 (*dt*, $^2J_{C,F}$ = 9.93, C(3)), 23.90 (*dt*, $^2J_{C,F}$ = 9.93, C(1)), 11.03 (*q*, CH_3); ^{19}F NMR (188 MHz, CD_3OD): δ -124.14 (*ddd*, $^2J_{F,F}$ = 164.5, $^3J_{F,H}$ = 10.82, $^3J_{F,H}$ = 11.06, F), -150.63 (*dt*, $^2J_{F,F}$ = 164.5, F'); MS (e.i., 70 eV): 246 (49%), 229 (85%), 215 (75%), 196 (17%), 172 (32%), 149 (38%), 139 (46%), 126 (86%), 91 (25%), 83 (31%), 96 (100%); HRMS calcd. for $C_{10}H_{12}O_3N_2F_2$: 246.0799; found: 246.0799.

(±)-3-Benzoyl-1-[(1 *SR*, 3 *RS*)-3-benzyloxymethyl-2,2-difluorocyclopropylmethyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione [(±)-10] The reaction was performed under the conditions as described for **4** using **3** (0,41 g, 1.80 mmol), triphenylphosphine (0.95 g, 3.60 mmol), N^3-benzoyluracil (0.78 g, 3.60 mmol), 1,4-dioxane (7 *ml*) and DEAD (0.57 *ml*, 3.60 mmol) in 1,4-dioxane (20 *ml*). After evaporation of the solvents and purification by column chromatography (silica gel, ethyl acetate/hexane 1:1) **10** (0.56 g, 71%) was obtained as an oil contaminated with some impurities that were easily separated in the next reaction step; an analytical sample was obtained by column chromatography (silica gel RP-18, methanol/water 8:3); R_F (ethyl acetate/hexane 1:1) 0.28; UV (methanol): λ = 255.2 nm (log ε = 3.28); IR (film): ν 3245*w*, 3090*w*, 3035*w*, 2870*w*, 1750*s*, 1705*s*, 1665*s*, 1600*m*, 1390*m*, 1560*w*, 1530*w*, 1475*m*, 1440*s*, 1365*m*, 1245*s*, 1210*m*, 1180*m*, 1075*m*, 1030*m*, 1000*m*; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91 (*d*, $^3J_{H,H}$ = 1.17, 1 H, H-C(6')), 7.66-7.27 (*m*, 10 H, phenyl), 5.63 (*d*, $^3J_{H,H}$ = 8.01, 1 H, H-C(5')), 4.48 (AB system, J_{AB} = 11.6, 2 H, CH_2-phenyl), 4.08 (*m*, 1 H, CH_2-N), 3.81-3.51 (*m*, 3 H, CH_2-OBn and CH_2-N), 2.14-2.02 (*m*, 2 H, cyclopropyl);

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.79 (*s*, CO benzoyl), 162.33 (*s*, C(2')), 149.84 (*s*, C(4')), 143.96 (*d*, C(6')), 137.25 (*s*, C_q phenyl (Bn)), 135.14 (*s*, C_q phenyl (Bz)), 131.49 (*d*, C_{para} phenyl (Bz)), 130.44 (*d*, C_{ortho} phenyl (Bz)), 129.25 (*d*, C_{meta} phenyl (Bz)), 128.53 (*d*, C_{ortho} phenyl (Bn)), 128.20 (*d*, C_{meta} phenyl (Bn)), 127.90 (*d*, C_{para} phenyl (Bn)), 112.79 (*dd*, $^1J_{C,F}$ = 293.60, 281.43, CF_2), 102.27 (*s*, C(5')), 73.03 (*t*, CH_2-phenyl), 62.08 (*dt*, $^3J_{C,F}$ = 4.14, CH_2-OBn), 42.53 (*dt*, $^3J_{C,F}$ = 5.80, CH_2-N), 25.02 (*dt*, $^2J_{C,F}$ = 10.36, C(3)), 23.68 (*dt*, $^2J_{C,F}$ = 10.36, C(1)); ^{19}F NMR (188 MHz, $CDCl_3$): δ -126.4 (*ddd*, $^2J_{F,F}$ = 166.31, $^3J_{F,H}$ = 10.96, $^3J_{F,H}$ = 11.04, F), -150.83 (*d*, $^2J_{F,F}$ = 166.31, F'); MS (e.i., 70 eV): 426 (3.5%), 321 (6.4%), 215 (67.2%), 196 (11%), 125 (7.4%), 105 (86%), 91 (100%), 77 (62%); HRMS calcd. for $C_{23}H_{20}O_4N_2F_2$: 426.1390; found: 426.1389.

(±)-[(1 *SR*, 3 *RS*)-3-Benzyloxymethyl-2,2-difluorocyclopropylmethyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione [(±)-11] A solution of **10** (0.56 g, 1.3 mmol) in methanol (20 *ml*) was treated with ammonium hydroxide (6 *ml*) for 2 hours. The volatiles were evaporated and the remaining oil was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:1) to give **11** (0.4 g, 95%) as a white solid; mp: 93-94 °C; R_F (ethyl acetate/hexane 4:1) 0.33; UV (methanol): λ_{max} = 266 nm (log ε = 3.92); IR (KBr): ν 3370*s*, 3175*m*, 3095*m*, 3045*m*, 2880*w*, 2815*w*, 1960*w*, 1695*s*, 1665*s*, 1625*m*, 1580*m*, 1470*m*, 1430*m*, 1395*m*, 1370*m*, 1285*w*, 1255*m*, 1215*w*, 1185*m*, 1145*w*, 1090*m*, 1075*m*, 1030*w*, 1005*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.1 (*br s*, 1 H, NH), 7.51-7.27 (*m*, 5 H, phenyl), 7.19 (*d*, $^3J_{H,H}$ = 7.93, 1 H, H-C(6')), 5.57 (*d*, $^3J_{H,H}$=8.93, 1 H, H-C(5')), 4.48 (AB system, J_{AB} = 11.27, 2 H, CH_2-phenyl), 4.11 (*m*, $^2J_{H,H}$ = -14.68, $^3J_{H,H}$ = 3.25, 1 H, CH2-N), 3.77 (*m*, $^2J_{H,H}$ = -10.8, $^3J_{H,H}$ = 4.62, 1 H, CH_2-OBn), 3.63 (*m*, $^2J_{H,H}$ = -14.68, $^3J_{H,H}$ = 5.87, 1 H, CH_2-N), 3.58 (*m*, $^2J_{H,H}$ = -10.8, $^3J_{H,H}$ = 6.96, 1 H, CH_2-OBn), 2.11509/2.1136 (*m*, $^3J_{H(C3),H(C1)}$ = 2.39, 2 H, cyclopropyl); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.19 (*s*, C(2')), 151.10 (*s*, C(4')), 144.14 (*d*, $^1J_{C,H}$ = 179.8, C(6')), 137.20 (*s*, C_q phenyl), 128.65, 128.63, 127.43 (each *d*, phenyl), 112.87 (*dd*, $^1J_{C,F}$ = 282.33, CF_2), 102.55 (*d*, $^1J_{C,H}$ = 174.4, C(5')), 73.03 (*t*, $^1J_{C,H}$ = 174.4, CH_2-phenyl), 62.15 (*dt*, $^3J_{C,F}$ = 4.22, $^1J_{C,H}$ = 142.06, CH_2-OBn), 42.23 (*dt*, $^3J_{C,F}$ = 5.39, $^1J_{C,H}$ = 144.32, CH_2-N), 24.96 (*dt*, $^2J_{C,F}$ = 10.36, $^1J_{C,H}$ = 165.2, C(3)), 23.82 (*dt*, $^2J_{C,F}$ = 10.36, $^1J_{C,H}$ = 165.2, C(1)); ^{19}F NMR (470 MHz, $CDCl_3$): δ -126.52 (*ddd*, $^2J_{F,F}$ = 164.66, $^3J_{F,H}$ = 12.87, $^3J_{F,H}$ = 13.02, F), -151.02 (*dd*, $^2J_{F,F}$ = 164.66, $^3J_{F,H}$ = 1.43, F'); MS (e.i., 70 eV): 321 (3.3%), 216 (51.6%), 196 (35%), 91 (100%); HRMS calcd. for $C_{16}H_{16}N_2O_3F_2$: 322.1129; found: 322.1130.

(±)-[(1 *SR*, 3 *RS*)-2,2-Difluoro-3-hydroxymethyl-cyclopropylmethyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione (= (±)-1-(2,2-difluoro-3-hydroxymethyl-cyclopropylmethyl) uracil) [(±)-12] To a solution of **11** (0.52 g, 1.61 mmol) in methanol (20 *ml*) were added cyclohexene (18.5 *ml*) and *Pearlman's* catalyst (1.24 g, 20 %) and the reaction mixture was heated at reflux for 4.5 hours. After filtration and evaporation of all volatiles the remaining residue was subjected to column chromatography (silica gel, ethyl acetate/methanol 3:1) to give **12** (0.11 g, 29 %) as a white solid; mp: 168-169 °C; R_F (ethyl acetate/prop-2-OH 10:1) 0.33; UV (methanol): λ_{max} = 266 nm (log ε = 4.07); IR (KBr): 3480*s*, 3165*s*, 3040*s*, 2940*m*, 2895*m*, 2800*m*, 1715*s*, 1660*s*, 1470*s*, 1420*m*, 1395*s*, 1360*s*, 1325*m*, 12.85*m*, 1255*s*, 1235*s*, 1170*s*, 1130*m*, 1110*m*, 1080*m*, 1050*s*; ^{1}H NMR (500 MHz, CD_3OD): δ 7.58 (*d*, $^3J_{H,H}$ = 7.87, 1 H, H-C(6')), 5.66 (*d*, $^3J_{H,H}$ = 7.87, 1 H H-C(5')), 4.14 (*m*, $^2J_{H,H}$ = -14.34, $^3J_{H,H}$ = 6.97, 1 H, CH_2-N), 3.84 (*m*, $^2J_{H,H}$ = -11.86, $^3J_{H,H}$ = 8.05, 1 H, CH_2-OH), 3.82 (*m*, $^2J_{H,H}$ = -14.34, $^3J_{H,H}$ = 8.56, 1 H, CH_2-N), 3.71 (*m*, $^2J_{H,H}$ = -11.86, $^3J_{H,H}$ = 8.03, 1 H, CH_2-OH), 2.19 (*m*, $^3J_{H,H}$ = 11.79, 1 H, H-C(1)), 2.06 (*m*, $^3J_{H,H}$ = 11.79, 1 H, H-C(3)); ^{13}C NMR (100 MHz, CD_3OD): δ 166.84 (*s*, C(2')), 152.94 (*s*, C(4')), 146.95 (*d*, $^1J_{C,H}$ = 182.52, C(6')), 115.10 (*dd*, $^1J_{C,F}$ = 291.4, CF_2), 102.71 (*d*, $^1J_{C,H}$ = 178.51, C(5')), 55.63 (*dt*, $^3J_{C,F}$ = 5.63, $^1J_{C,H}$ = 140.65, CH_2OH), 43.14 (*dt*, $^3J_{C,F}$ = 5.83, $^1J_{C,H}$ = 143.55, CH_2-N), 28.53 (*dt*, $^2J_{C,F}$ = 10.36, $^1J_{C,H}$ = 159.64, C(3)), 24.92 (*dt*, $^2J_{C,F}$ = 10.76, $^1J_{C,H}$ = 159.64, C(1)); ^{19}F NMR (470 MHz, CD_3OD): δ -126.9 (*ddd*, $^2J_{F,F}$ = 164.93, $^3J_{F,H}$ = 13.22, $^3J_{F,H}$ = 13.28, F), -153.12 (*dd*, $^2J_{F,F}$ = 164.93, $^3J_{F,H}$ = 1.45, F'); MS (e.i., 70 eV): 232 (21.3%), 215(100%), 201 (31.9%), 182 (39.7%), 158 (33.3%), 138 (53.2%), 125 (51.8%), 112 (35.8%), 95 (22.3%), 90 (25.5%), 82 (97.8%), 77 (20.5%), 69 (29.8%), 53 (23.8%); HRMS calcd. for $C_9H_{10}N_2O_3F_2$: 232.0659; found: 232.0659.

(±)-4-Amino-1-[(1 *SR*, 3 *RS*)-3-benzyloxymethyl-2,2-difluorocyclopropylmethyl]-1,2,3,4-tetrahydro-2-pyrimidinone [(±)-13] To a suspension of 1,2,4-triazole (1.63 g, 23.6 mmol) in acetonitrile (13 *ml*) $POCl_3$ (0.45 *ml*, 5 mmol) was added at 0 °C. After stirring for 5 min triethylamine (3.75 *ml*) was added and stirring at 0°C was continued for an additional 1.5 hours. A solution of **11** (0.4 g, 1.24 mmol) in acetonitrile (6 *ml*) was added at 0 °C. The temperature was kept at 0 °C for 30 minutes, then the reaction mixture was allowed to warm to room temperature and was stirred for 5 hours. The filtrate was diluted with ethyl acetate (50 *ml*) and the organic layer was washed successively with a saturated aqueous solution of $NaHCO_3$ (10 *ml*). The volatiles were evaporated and the remaining oil was dissolved in 1,4-dioxane (6 *ml*) and an aqueous solution of NH_4OH (5 *ml*, 25%) was added. After stirring overnight the ammonia was evaporated under reduced pressure and the residue was subjected to column chromatography (silica gel, ethyl acetate/methanol 3:1) to afford **13** (0.12 g, 30%) as a white solid; mp: 241-243 °C; R_F (ethyl acetate/prop-2-OH 3:1) 0.29; UV (methanol): λ_{max} = 275 nm (log ε = 3.86); IR (KBr): ν 3345*s*, 3120*m*, 2915*w*, 2865*w*, 2360*w*, 1660*s*, 1625*s*, 1525*w*, 1480*m*, 1385*m*, 1280*m*, 1220*w*, 1205*w*, 1180*w*, 1115*w*, 1070*m*, 1025*w*, 1010*w*; ^{1}H NMR (400 MHz, CD_3OD): δ 7.42 (*d*, $^3J_{H,H}$ = 7.59, 1 H, H-C(6')), 7.30-7.26 (*m*, 5 H, phenyl), 5.74 (*d*, $^3J_{H,H}$ =7.19, 1 H, H-C(5')), 4.51 (AB system, J_{AB} = 11.60, 2 H, CH_2-phenyl), 4.07 (*m*, $^2J_{H,H}$ = -14.21, $^3J_{H,H}$ = 13.73, 1 H, CH_2-N), 3.77 (*m*, $^2J_{H,H}$ = -14.21, $^3J_{H,H}$ = 8.07, 1 H, CH_2-N), 3.74 (*m*, $^2J_{H,H}$ = -11.79, $^3J_{H,H}$ = 7.10, 1 H, CH_2-OBn), 3.67-3.61 (*m*, $^2J_{H,H}$ = -11.79, $^3J_{H,H}$ = 8.50, 1 H, CH_2-OBn), 2.24 (*m*, $^3J_{H,H}$ = 11.90, 1 H, H-C(1)), 2.12 (*m*, $^3J_{H,H}$ = 11.90, 1 H, H-C(3)); ^{13}C NMR (100 MHz, CD_3OD): δ 168.19 (*s*, C(4')), 159.10 (*s*, C(2')), 147.25 (*d*, $^1J_{C,H}$ = 181.15, C(6')), 139.45 (*s*, C_q phenyl), 129.60, 129.15, 128.99 (each *d*, phenyl), 115.18 (*dd*, $^1J_{C,F}$ = 291.14, 281.58, CF_2), 96.02 (*d*, $^1J_{C,H}$ = 174.51 C(5')), 73.91 (*t*, $^1J_{C,H}$ = 143.39, CH_2-phenyl), 63.74 (*dt*, $^3J_{C,F}$ = 4.93, $^1J_{C,H}$ = 145.06, CH_2-OBn), 44.37 (*dt*, $^3J_{C,F}$ = 4.92, $^1J_{C,H}$ = 143.36, CH_2-N), 26.27 (*dt*, $^2J_{C,F}$ = 10.76, $^1J_{C,H}$ = 164.13, C(3)), 25.18 (*dt*, $^2J_{C,F}$ = 10.76, $^1J_{C,H}$ = 164.13, C(1)); ^{19}F NMR (188 MHz, CD_3OD): δ -124.07 (*ddd*, $^2J_{F,F}$ = 160.82, $^3J_{F,H}$ = 14.62, $^3J_{F,H}$ = 14.65, F), -149.75 (*d*, $^2J_{F,F}$ = 160.82, F'); MS (e.i., 70 eV): 322 (5.3%), 272 (3.2%), 230 (3.7%), 215 (61%), 200 (28.7%), 195 (100%), 164 (5.7%), 136 (24.1%), 125 (17%), 111 (40,8%), 91 (51.1%); HRMS calcd. for $C_{16}H_{17}O_2N_3F_2$: 231.0189; found: 321.1289.

(±)-4-Amino-1-[(1 *SR*, 3 *RS*)-2,2-difluoro-3-hydroxymethyl-cyclopropylmethyl]-1,2,3,4-tetrahydro-2-pyrimidinone (=1-(2,2-difluoro-3-hydroxymethyl-cyclopropylmethyl) cytosine) [(±)-14] For deprotection a solution of the benzyl ether **13** (0.31 g, 0.96 mmol) in methanol (15 *ml*) was treated with cyclohexene (12 *ml*) and *Pearlman's* catalyst (0.74 g, 20%) under reflux for 10 hours. The catalyst was filtered off and all volatiles were removed under reduced pressure. The remaining oil was subjected to column chromatography (silica gel RP-18, methanol/water 7:3) to afford **14** (0.02 g, 10%) as a white solid; mp: 199-202 °C; R_F (ethyl acetate/prop-2-OH 3:1) 0.13; UV (methanol): λ_{max} = 275 nm (log ε = 3.86); IR (KBr): ν 3380*s*, 2825*m*, 1655*s*, 1610*s*, 1525*m*, 1480*s*, 1435*m*, 1385*s*, 1285*m*, 1250*m*, 1205*m*, 1180*m*, 1125*m*, 1045*m*, 1005*m*; ^{1}H NMR (500 MHz, CD_3OD): δ 7.58 (*d*, $^3J_{H,H}$ = 6.99, 1 H, H-C(6')), 5.87 (*d*, $^3J_{H,H}$ = 6.99, 1 H, H-C(5')), 4.17 (*m*, $^2J_{H,H}$ = -14.47, $^3J_{H,H}$ = 6.92, 1 H, CH_2-N), 3.83 (*m*, $^2J_{H,H}$ = -12.19, $^3J_{H,H}$ = 7.48, 1 H, CH_2-OH), 3.79 (*m*, $^2J_{H,H}$ = -14.47, $^3J_{H,H}$ = 7.85, 1 H, CH_2-N), 3.72 (*m*, $^2J_{H,H}$ = -12.19, $^3J_{H,H}$ = 8.16, 1 H, CH_2-OH, 2,21 (*m*, $^3J_{H,H}$ = 11.78, 1 H, H-C(1)), 2.04 (*m*, $^3J_{H,H}$ = 11.78, 1 H, H-C(3)); ^{13}C NMR (100 MHz, CD_3OD): δ 168.17 (*s*, C(4')), 159.19 (*s*, C(2')), 147.32 (*d*, $^1J_{C,H}$ = 179.35, C(6')), 115.239 (*dd*, $^1J_{C,F}$ = 291.49, 280.82, CF_2), 96.20 (*d*, $^1J_{C,H}$ = 174.62, C(5')), 55.65 (*dt*, $^3J_{C,F}$ = 6.03, $^1J_{C,H}$ = 143.71, CH_2-OH), 44.46 (*dt*, $^3J_{C,F}$ = 5.93, $^1J_{C,H}$ = 143.01, CH_2-N), 28.54 (*dt*, $^2J_{C,F}$ = 10.15, $^1J_{C,H}$ = 163.62, C(3)), 25.18 (*dt*, $^2J_{C,F}$ = 10.66, $^1J_{C,H}$ = 163.74, C(1)); ^{19}F NMR (188 MHz, CD_3OD): δ -124.10 (*dt*, $^2J_{F,F}$ = 164.48, $^3J_{F,H}$ = 14.62, F), -150.87 (*d*, $^2J_{F,F}$ = 164.48, F'); MS (ESI): 232.1 (M+1, 100 %), 254.1 (M+Na, 95 %); HRMS calcd. for $C_9H_{11}O_2N_3F_2$: 231.0189; found: 231.0189.

(±)-9-[(1 *SR*, 3 *RS*)-3-Benzyloxymethyl-2,2-difluoro-cyclopropylmethyl]-6,9-dihydro-1*H*-6-purinone [(±)-15] Compound **4** (0.4 g, 1.09 mmol) was stirred with trifluoroacetic acid (80%,17 *ml*) at room temperature for 19 hours, then the volatiles were evaporated under reduced pressure and co-evaporated with

toluene (15 *ml*). The residue was dissolved in methanol (23 *ml*) and treated with NH_4OH (2.8 *ml*, 25 %) for 2 hours at room temperature. Evaporation of the volatiles afforded the crude product, which was purified by column chromatography (silica gel, ethyl acetate → ethyl acetate/methanol 4:1) to afford **15** (0.38 g, 99%) as a greasy oil; R_F (ethyl acetate/methanol 3:1) 0.61; UV (methanol): λ_{max} = 252 nm (log ε = 3.99); IR (KBr): ν 3245*s*, 3055*m*, 2865*m*, 1700*s*, 1590*m*, 1555*m*, 1520*m*, 1475*m*, 1415*m*, 1385*s*, 1340*m*, 1285*m*, 1215*s*, 1190*m*, 1090*m*, 1030*m*; ^{1}H NMR (500 MHz, CD_3OD): δ 8.08 (*s*, 1 H, H-C(2')), 8.02 (*s*, 1 H, C(8')), 7.34-7.18 (*m*, 5 H, phenyl), 4.50 (AB system, J_{AB} = 11.99, 2 H, CH_2-phenyl), 4.45 (*m*, $^2J_{H,H}$ = -14.74, $^3J_{H,H}$ = 7.05, 1 H, CH_2-N), 4.21 (*m*, $^2J_{H,H}$ = -14.74, $^3J_{H,H}$ = 8.33, 1 H, CH_2-N), 3.81 (*m*, $^2J_{H,H}$ = -11.10, $^3J_{H,H}$ = 6.68, 1 H, CH_2-OBn), 3.64 (*m*, $^2J_{H,H}$ = -11.10, $^3J_{H,H}$ = 8.89, 1 H, CH_2-OBn), 2.27 (*m*, $^3J_{H,H}$ = 12.15, 1 H, H-C(1)), 2.15 (*m*, $^3J_{H,H}$ = 12.15, 1 H, H-C(3)); ^{13}C NMR (100 MHz, CD_3OD): δ 158.68 (*s*, C(6')), 149,92 (*s*, C(4')), 146.37 (*d*, $^1J_{C,H}$ = 207.2, C(2')), 141.44 (*d*, $^1J_{C,H}$ = 214.24, C(8')), 138.82 (*s*, C_q phenyl), 129.11, 128.50, 128.47 (each *d*, phenyl), 124.79 (*s*, C(5')), 113.69 (*dd*, $^1J_{C,F}$ = 291.28, 281.73, CF_2), 73.46 (*t*, $^1J_{C,H}$ = 142.12, CH_2-phenyl), 63.05 (*dt*, $^3J_{C,F}$ = 4.12, $^1J_{C,H}$ = 143.73, CH_2-OBn), 38.20 (*dt*, $^3J_{C,F}$ = 5.93, $^1J_{C,H}$ = 144.64, CH_2-N), 25.95 (*dt*, $^2J_{C,F}$ = 10.56, $^1J_{C,H}$ = 164.55, C(3)), 25.16 (*dt*, $^2J_{C,F}$ = 10.16, $^1J_{C,H}$ = 165.35, C(1)); ^{19}F NMR (188 MHz, CD_3OD): -124.31 (*ddd*, $^2J_{F,F}$ = 164.47, $^3J_{F,H}$ = 14.62, $^3J_{F,H}$ = 14.65, F), -150.21 (*d*, $^2J_{F,F}$ = 164.47, F'); MS (e.i., 70 eV): 345 (1.1%), 299 (1.1%), 277 (4.3%), 252 (5.7%), 240 (3.2%), 220 (2.1%), 207 (4.3%), 162 (15.6%); 122 (24.5%), 105 (92.5%), 91 (54.6%), 77 (100%); HRMS calcd. for $C_{17}H_{16}O_2N_4F_2$: 346.1241; found: 346.1241.

(±)-[(1 *SR*, 3 *RS*)-2,2-Difluoro-3-hydroxymethyl-cyclopropylmethyl]-6,9-dihydro-1H-6-purinone [(±)-16] A mixture of **15** (0.38 g, 1.1 mmol), cyclohexene (12.5 *ml*) and *Pearlman's* catalyst (0,85 g, 20%) in methanol (13 ml) was heated under reflux for 4 hours. The filtrate was concentrated *in vacuo* and the remaining residue was subjected to column chromatography (silica gel, ethyl acetate/methanol 4:1) to afford **16** (0.13g, 46%) as a white solid; mp: 270-271 °C; R_F (ethyl acetate/methanol 3:1) 0.31; UV (methanol): λ_{max} = 252 nm (log ε = 4.04); IR (KBr): 3390*s*, 3125*s*, 3050*s*, 2855*s*, 1675*s*, 1595*s*, 1550*s*, 1475*s*, 1415*s*, 1350*s*, 1290*s*, 1220*s*, 1175*s*, 1120*s*, 1050*s*; ^{1}H NMR (500 MHz, CD_3OD): δ 8.10 (*s*, 1 H, H-C(2')), 8.05 (*s*, 1 H, H-C(8')), 4.52 (*m*, $^2J_{H,H}$ = -14.88, $^3J_{H,H}$ = 7.60, 1 H, CH_2-N), 4.45 (*m*, $^2J_{H,H}$ = -14.88, $^3J_{H,H}$ = 8.04, 1 H, CH_2-N), 3.90 (*m*, $^2J_{H,H}$ = -12.27, $^3J_{H,H}$ = 7.28, 1 H, CH_2-OH), 3.75 (*m*, $^2J_{H,H}$ = -12.27, $^3J_{H,H}$ = 7.67, 1 H, CH_2-OH), 2.42 (*m*, $^3J_{H,H}$ = 12.04, 1 H, H-C(1)), 2.11 (*m*, $^3J_{H,H}$ = 12.04, 1 H, H-C(3)); ^{13}C NMR (100 MHz, CD_3OD): δ 159.18 (*s*, C(6')), 150.40 (*s*, C(4')), 146.90 (*d*, $^1J_{C,H}$ = 207.2, C(2')), 142.03 (*d*, $^1J_{C,H}$ = 213.84, C(8')), 125.35 (*s*, C(5')), 114.365 (*dd*, $^1J_{C,F}$ = 291.33, 281.38, CF_2), 55.54 (*dt*, $^3J_{C,F}$ = 5.43, $^1J_{C,H}$ = 137.89, CH_2-OH), 38.70 (*dt*, $^3J_{C,F}$ = 6.64, $^1J_{C,H}$ = 142.93, CH_2-N), 28.59 (*dt*, $^2J_{C,F}$ = 10.36, $^1J_{C,H}$ = 165.76, C(3)), 25.68 (*dt*, $^2J_{C,F}$ = 10.76, $^1J_{C,H}$ = 177.73, C(1)); ^{19}F NMR (470 MHz, CD_3OD): δ -127.00 (*ddd*, $^2J_{F,F}$ = 165.08, $^3J_{F,F}$ = 12.48, $^3J_{F,H}$ = 12.56, F), -154.01 (*dd*, $^2J_{F,F}$ = 165.08, $^3J_{F,H}$ = 1.48, F'); MS (e.i., 70 eV): 257 (21.2%), 240 (11%), 226 (6.4%), 207 (13.1%), 163 (7.1%), 150 (26.2%), 137 (100%), 110 (27.7%), 91 (24.1%), 77 (28.7%); HRMS calcd. for $C_{10}H_{10}O_2N_4F_2$: 256.0772; found: 256.0771.

(±)-3-Benzoyl-1-[(1 *SR*, 3 *RS*)-3-benzyloxymethyl-2,2-difluorocyclopropylmethyl]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione [(±)-17] The reaction was performed according to the Mitsunobu reaction as described for the preparation of compound **4** using **3** (0,54 g, 2.35 mmol) in 1,4-dioxane (3 *ml*), N^3-benzoyl-5-fluorouracil (1.1 g, 4.7 mmol), triphenylphosphine (1.23 g, 4.7 mmol) and DEAD (0.74 *ml*, 4.7 mmol) in 1,4-dioxane (20 *ml*). After stirring overnight the solvent was evaporated, the residue was purified by column chromatography (ethyl acetate/hexane 1:3) and **17** (0.76 g, 73%) was obtained as a colorless oil; R_F (ethyl acetate/hexane 1:1) 0.40; UV (methanol): λ_{max} = 256 nm (log ε = 4.30); IR (film): ν 3370*w*, 3070*w*, 2870*w*, 1755*s*, 1715*s*, 1670*s*, 1600*m*, 1475*m*, 1450*m*, 1365*m*, 1250*s*, 1180*m*, 1075*m*, 1030*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (*d*, $^3J_{H,H}$ = 8.43, 1 H, H-C(6')), 7.58-7.19 (*m*, 10 H, phenyl), 4.41 (AB system, J_{AB} = 11.78, 2 H, CH_2-phenyl), 3.93 (*m*, $^2J_{H,H}$ = -15.29, $^3J_{H,H}$ = 5.89, 1 H, CH_2-N), 3.69 (*m*, $^2J_{H,H}$ = -15.29, $^3J_{H,H}$ = 7.08, 1 H, CH_2-N), 3.68 (*m*, $^2J_{H,H}$ = -11.49, $^3J_{H,H}$ = 5.97, 1 H, CH_2-OBn), 3.49 (*m*, $^2J_{H,H}$ = -11.49, $^3J_{H,H}$ = 8.27, 1 H, CH_2-OBn), 2.06 (*m*, $^3J_{H,H}$ = 11.07, 1 H, H-C(1)), 2.01 (*m*, $^3J_{H,H}$ = 11.07, 1 H, H-C(3)); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 167.36 (*s*, O=C-phenyl), 156.22 (*d*, $^2J_{C,F}$ = 27.36, C(4')), 148.32 (*s*, C(2')), 139.86 (*d*, $^1J_{C,F}$ = 239.99, C(5')), 137.15 (*s*, C_q phenyl (Bn)), 135.43 (*s*, C_q phenyl (Bz)), 130.93 (*d*, C_{para} phenyl (Bz)), 130.41 (*d*, C_{ortho} phenyl (Bz)), 129.22 (*d*, C_{meta} phenyl (Bz)), 128.50 (*d*, C_{ortho} phenyl (Bn)), 128.45 (*dd*, $^2J_{C,F}$ = 33.56, C(6')), 128.00 (*d*, C_{meta} phenyl (Bn)), 127.78 (*d*, C_{para} phenyl (Bn)), 112.61 (*dd*, $^1J_{C,F}$ = 292.39, 280.72, CF_2), 72.91 (*t*, CH_2-phenyl), 61,91 (*dt*, $^3J_{C,F}$ = 4.12, CH_2-OBn), 42.48 (*dt*, $^3J_{C,F}$ = 5.43, CH_2-N), 24.99 (*dt*, $^2J_{C,F}$ = 10.36, C(3)), 23.36 (*dt*, $^2J_{C,F}$ = 10.36, C(1)); ^{19}F NMR (188 MHz, $CDCl_3$): δ -126.23 (*ddd*, $^2J_{F,F}$ = 164.44, $^3J_{F,H}$ = 10.84, $^3J_{F,H}$ = 10.96, F), -150.54 (*d*, $^2J_{F,F}$ = 164.44, F'), -166.15 (*s*, F-C(5')); MS (e.i., 70 eV): 444 (4.3%), 339 (16.4%), 318 (2.9%), 233 (57.1%), 214 (5.7%), 143 (6.4%), 105 (100%), 91 (68.6%), 77 (36.8%); HRMS calcd. for $C_{23}H_{19}O_4N_2F_3$: 444.1296; found: 444.1295.

(±)-1-[(1 *SR*, 3 *RS*)-3-Benzyloxymethyl-2,2-difluorocyclopropylmethyl]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione [(±)-18] According to the procedure given for **11** compound **17** (0.52 g, 1.17 mmol) was dissolved in methanol (10 *ml*) and treated with NH_4OH (20 *ml*, 25 %) for an hour. Purification by column chromatography (ethyl acetate/hexane 1:3) afforded **18** (0.36 g, 90%) as a colorless oil; R_F (ethyl acetate/hexane 1:1) 0.28; UV (methanol): λ_{max} = 273 nm (log ε = 3.70); IR (film): ν 3185*w*, 3065*m*, 2870*w*, 1715*s*, 1475*m*, 1370*m*, 1285*m*, 1245*s*, 1205*m*, 1180*m*, 1090*m*, 1075*m*, 1030*m*; ^{1}H NMR (400 MHz, CD_3OD): δ 7.80 (*s*, 1 H, H-C(6')), 7.33-7.22 (*m*, phenyl), 4.51 (AB system, J_{AB} = 11.72, 2 H, CH_2-phenyl), 4.03 (*m*, 1 H, CH_2-N), 3.86-3.80 (*m*, 2 H, CH_2-N and CH_2-OBn), 3.79-3.67 (*m*, 1 H, CH_2-OBn), 2.35-2.19 (*m*, 2 H, cyclopropyl); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.21 (*d*, $^2J_{C,F}$ = 26.20, C(4')), 149.66 (*s*, C(2')), 140.5 (*d*, $^1J_{C,F}$ = 238.17, C(5')), 136.98 (*s*, C_q phenyl), 128.86 (*d*, $^2J_{C,F}$ = 36.99, C(6')), 128.57, 128.11, 127.85 (each *d*, phenyl), 112.65 (*dd*, $^1J_{C,F}$ = 292.88, 282.07, CF_2), 73.12 (*t*, CH_2-phenyl), 62.02 (*dt*, $^3J_{C,F}$ = 3.77, CH_2-OBn), 42.39 (*dt*, $^3J_{C,F}$ = 5.43, CH_2-N), 25.17 (*dt*, $^2J_{C,F}$ = 10.05, C(3)), 23.78 (*dt*, $^2J_{C,F}$ = 10.76, C(1)); ^{19}F NMR (188 MHz, $CDCl_3$): δ -126.37 (*ddd*, $^2J_{F,F}$ = 164.44, $^3J_{F,H}$ = 14.58, $^3J_{F,H}$ = 14.66, F), -150.58 (*d*, $^2J_{F,F}$ = 164.44, F'), -166.44 (*s*, F-C(5')); MS (e.i., 70 eV): 340 (6.4%), 234 (8.5%), 214 (9.5%), 176 (1.8%), 155 (3.5%), 143 (8.9%), 130 (8.2%), 107 (9.2%), 91 (100%), 85 (28.7%); HRMS calcd. for $C_{16}H_{15}O_3N_2F_3$: 340.1035; found: 340.1034.

(±)-[(1 *SR*, 3 *RS*)-2,2-Difluoro-3-hydroxymethyl-cyclopropylmethyl)-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione (= (±)-1-(2,2-difluoro-3-hydroxymethyl-cyclopropylmethyl)-5-fluorouracil) [(±)-19] Removal of the benzyl group was performed as described for **12** by treating **18** (0.29 g, 0.85 mmol) with cyclohexene (10 *ml*) and *Pearlman's* catalyst (0.66 g, 20%) in refluxing methanol (7 *ml*) for 4.5 hours. After column chromatography (silica gel, ethyl acetate/hexane 5:4) **19** (0.11 g, 56%) was obtained as a greasy oil; R_F (ethyl acetate/hexane 1:1) 0.18; UV (methanol): λ_{max} = 273 nm (log ε = 3.91); IR (KBr): ν 3455*m*, 3180*m*, 3120*m*, 3050*m*, 2820*w*, 2560*w*, 2305*w*, 1690*s*, 1660*s*, 1480*m*, 1465*m*, 1375*m*, 1350*m*, 1265*m*, 1240*s*, 1195*m*, 1170*m*, 1125*m*, 1110*m*, 1085*w*, 1035*m*, 1010*m*; ^{1}H NMR (500 MHz, CD_3OD): δ 7.82 (*d*, $^3J_{H,H}$ = 6.39, H-C(6')), 4.08 (*m*, $^2J_{H,H}$ = -14.87, $^3J_{H,H}$ = 7.23, 1 H, CH_2-N), 3.85 (*m*, $^2J_{H,H}$ = -12.17, $^3J_{H,H}$ = 7.10, 1 H, CH_2-OH); 3.83 (*m*, $^2J_{H,H}$ = -14.87, $^3J_{H,H}$ = 7.56, 1 H, CH_2-N), 3.70 (*m*, $^2J_{H,H}$ = -12.17, $^3J_{H,H}$ = 8.41, 1 H, CH_2-OH), 2.19 (*m*, $^3J_{H,H}$ = 11.61, 1 H, H-C(1)), 2.07 (*m*, $^3J_{H,H}$ = 11.61, 1 H, H-C(3)); ^{13}C NMR (100 MHz, CD_3OD): δ 159,86 (*d*, $^2J_{C,F}$ = 26.15, C(4')), 151.51 (*s*, C(2')), 141.84 (*d*, $^1J_{C,F}$ = 233.75, C(5')), 130.75 (*d*, $^2J_{C,F}$ = 33.4, $^1J_{C,H}$ = 163.85, C(6')), 114.98 (*dd*, $^1J_{C,F}$ = 291.74, 281.38, CF_2), 55.48 (*dt*, $^3J_{C,F}$ = 5.43, $^1J_{C,H}$ = 144.21, CH_2OH), 43.18 (*dt*, $^3J_{C,F}$ = 5.83, $^1J_{C,H}$ = 144.9, CH_2-N), 28.40 (*dt*, $^2J_{C,F}$ = 9.96, $^1J_{C,H}$ = 165.37, C(1)), 24.67 (*dt*, $^2J_{C,F}$ = 10.86, $^1J_{C,H}$ = 165.10, C(3)); ^{19}F NMR (470 MHz, CD_3OD): δ -126.38 (*dt*, $^2J_{F,F}$ = 164.61, $^3J_{F,H}$ = 12.5, $^3J_{F,H}$ = 12.7, F), -152.60 (*dd*, $^2J_{F,F}$ = 164.61, $^3J_{F,H}$ = 1.52, F'), -169.67 (*d*, $^3J_{F,H}$ = 6.11, F-C(5')); MS (e.i., 70 eV): 250 (23%), 233 (74%), 219 (60%), 200 (31%), 176 (23%), 153 (67%), 143 (61%), 130 (77%), 113 (19%), 100 (100%), 91 (42%), 87 (52%), 77 (69%), 71 (21%); HRMS calcd. for $C_9H_9N_2O_3F_3$: 250.0565; found: 250.0565.

References and Notes

Dedicated to Professor Dr. Werner Schroth on the ocassion of his 70th birthday. Ad multos annos!

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14 *N*-Benzoyl-uracil (3-benzoyl-1*H*-pyrimidine-2,4-dione) was obtained by benzoylation of uracil with benzoyl chloride/pyridine followed by the debenzoylation of the 2,5-di-*N*-benzoyl derivative with 0.25 M K_2CO_3 in dioxane/water and showed a mp 202-215°C (lit.: mp 148-149°C by Cruickshank, K.A.; Jiricny, J.; Reese, C. B. *Tetrahedron Lett.* **1984**, *25*, 681-684, 200-202°C by Novacek, A.; Hesoun, D.; Gut, J. *Coll. Czech. Chem. Commun.* **1965**, *30*, 1890-1899; 216°C by Pitha, P. *J. Org. Chem.* **1968**, *33*, 1341); selected analytical data: ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.62 (*br s*, 1 H, NH), 7.96 (*m*, 2 H, H_{ortho}), 7.84-7.58 (*m*, 4 H, H_{meta}, H_{para}, H-C(6)), 5.77 (*d*, $^3J_{H,H}$ = 7.73 Hz, 1 H, H-C(5)); ^{13}C NMR (50 MHz, DMSO-d_6): δ 169.98 (*s*, CO of Bz), 162.90 (*s*, C(2)), 150.03 (*s*, C(4)), 143.25 (*d*, C(6)), 135.36 (*s*, C_q of Bz), 131.31 (*d*, C_{para}), 130.16 (*d*, C_{ortho}), 129.46 (*d*, C_{meta}), 100.07 (*d*, C(5)); MS (e.i., 70 eV): 216 (7.8%), 188 (56.7%), 146 (5&), 105 (100%); HRMS calcd. for $C_{11}H_8O_3N_2$: 216.0534; found: 216.0535. It has previously been used in Mitsunobu reactions, *cf.* Altman, K.-H.; Schmit-Chiese, C.; Garcia-Echeverria, C. *Bioorg. Med. Chem. Lett.* **1977**, *7*, 1119-1122; Capaldi, D. C.; Eleuteri, A.; Chen, Q.; Schinanzi, R. F. *Nucleosides Nucleotides* **1997**, *16*, 403-416; Perez-Perez, M.-J.; Rozenski, J.; Busson, R.; Herdewijn *J. Org. Chem.* **1995**, *60*, 1531-1537.

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18 To obtain several compounds in an enantiomerically pure form a suitable HPLC system (Merck-Hitachi L7450/L7250/L7100/D7000 instrument; UV detection at 265 nm or 255 nm) had to be established and the Daicel Chiralcel OD-column (4.6 x 250 mm, 10μm, Daicel Chemical Industries, flow 0.8 *ml*/min, 19-20 kg/cm^2) using hexane/prop-2-OH mixtures as eluents were shown to give excellent results. We are indebted to *Dr. K. Mohr* and *Mrs. R. Ziehn* for their valuable assistance with these HPLC investigations.