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# Preparation of Novel Difluorocyclopropane Nucleosides

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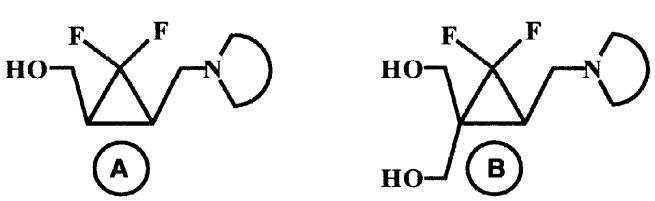
**Abstract**

Novel difluorinated cyclopropane nucleoside analogues possessing both two vicinal hydroxymethyl groups and a methylene spacer between the base and the ring were synthesized starting from 1,3-dibenzyloxy-2-propanol. After oxidation, olefination, reduction and acetylation the target molecules were obtained by difluoro-cyclopropanation, deacetylation and Mitsunobu reactions followed by two consecutive deprotection steps. 

*Keywords: Cyclopropanes; Nucleosides; Antivirals*

## Introduction

A large number of cyclopentanoid or cyclobutanoid carbocyclic nucleoside analogues has been synthesized as potential chemotherapeutic agents [1-4]. More recently, cyclopropane derived nucleosides have been in the focus of interest [5-10]; thus, analogues possessing an additional spacer or an unsaturated group [11, 12] between the cyclopropane unit and the heterocycle as well as compounds with an (in)direct attachment of the heterocycle but with two geminal or vicinal hydroxymethyl units at the cyclopropane skeleton [13-17] have shown promising antiviral activity. Although the incorporation of one or two fluorine substituents is known to be of advantage both for an improved activity, higher bioavailability as well as for causing a retarded metabolism of several drugs, only very recently, the first successful synthesis of several difluoro-cyclopropyl homo-nucleosides of type **A** has been reported [18]. The general principle used for the synthesis of compounds of type **A** could be used for the straightforward synthesis of compounds of type **B**.

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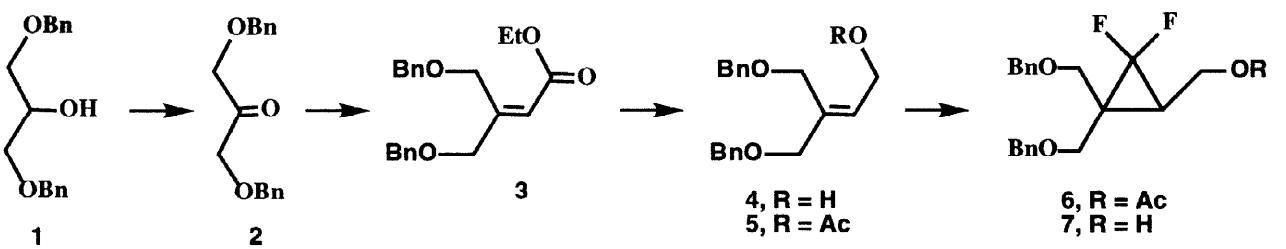
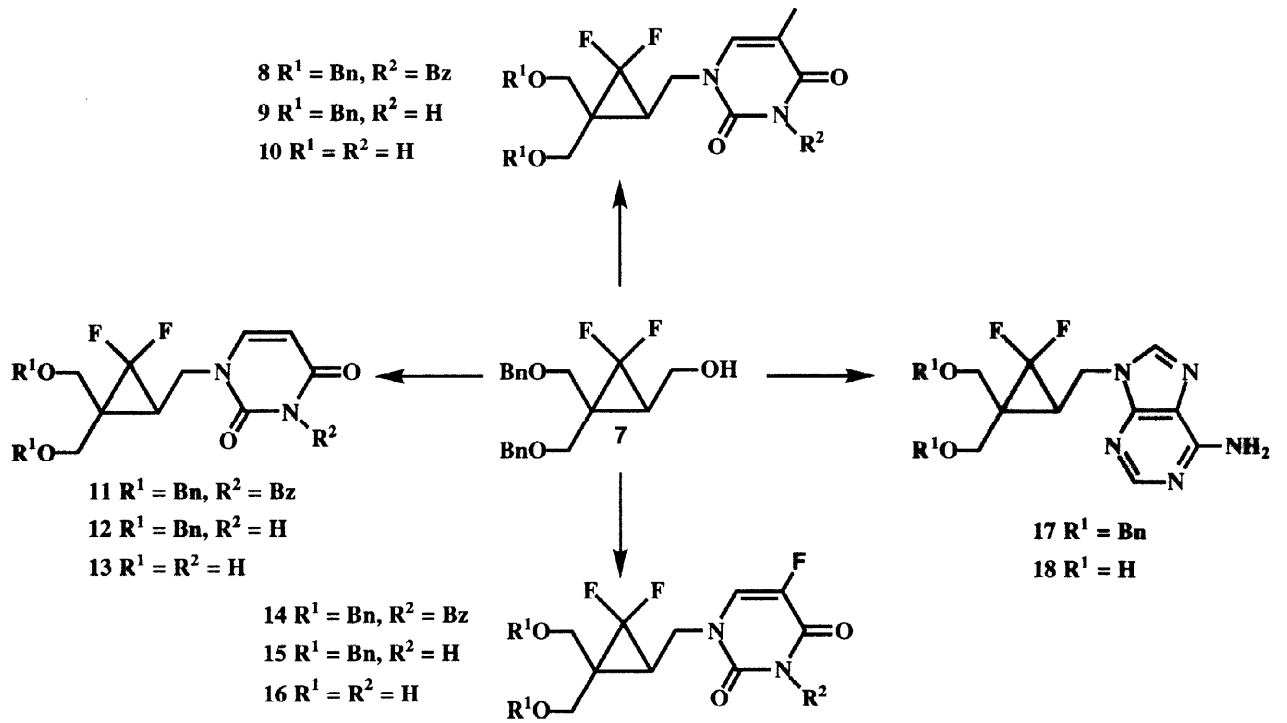
## Results and Discussion

Our approach to the target compounds started from easily accessible 1,3-dibenzyloxy-2-propanol (**1**) [19] that was oxidized to the corresponding ketone **2** [20] with the 2,2,6,6,-tetramethyl-piperidin-1-oxyl radical (TEMPO). Although a broad variety of different oxidants have been tested, the TEMPO [21, 22] mediated synthesis of **2** has been found to be superior even to periodinane, *N*-bromo-succinimide-dimethylsulfoxide, perruthenate, pyridinium chlorochromate and pyridinium dichromate. Olefination [23] of **2** furnished the alkene **3** that upon treatment with diisobutyl aluminium hydride (DIBAH) at –40°C [23] resulted in the formation of alcohol **4** without affection of the double bond. Alcohol **4** was acetylated and the acetate **5** was subjected to a difluoro-cyclopropanation reaction using sodium chlorodifluoro acetate in diglyme at 190°C to afford the cyclopropane **6**. Compound **6** is characterized in its $^{19}F$ NMR spectrum by the presence of two signals at $\delta = -136.00$ and –147.36 ppm showing a $^{2}J_{F,F} = 164.5$ Hz. The quaternary carbon bearing the two diastereotopic fluorine substituents is found in the $^{13}C$ NMR spectrum at $\delta = 114.27$ ppm showing $^{1}J_{C,F(1)} = 286.7$ and $^{1}J_{C,F(2)} = 292.9$ Hz. Treatment of **6** with catalytic amounts of sodium methoxide in methanol gave very smoothly 92% of the key intermediate **7** that is characterized in its IR spectrum by the presence of a broad line at $\nu = 3662$ cm$^{-1}$ resulting from the presence of the hydroxy group; in addition, in the $^{1}H$ NMR spectrum a signal exchangeable with $D_2O$ is found at $\delta = 2.92$ ppm. The two dibenzyloxymethyl groups are diastereotopic showing two independent AB systems in the $^{1}H$ NMR spectrum at $\delta = 3.63$ and 3.88 ppm ($J_{A,B}$= 12.65 Hz, $CH_2O_{trans}$) and $\delta = 3.24$ and 3.63 ppm ($J_{A,B} = 10.55$ Hz, $CH_2O_{cis}$), respectively.




Treatment of **7** with triphenylphosphine (TPP), diethyl azodicarboxylate (DEAD) and N$^3$-benzoyl-thymine under Mitsunobu conditions [18, 24] afforded **8** whose debenzoylation with ammonium hydroxide for 12 h at room temperature gave **9** that was debenzylated with *Pearlman*'s catalyst using cyclohexene as a hydrogen donor to afford the thymine analogue **10** in 63% yield. **10** shows in the $^{19}F$ NMR spectrum two signals at $\delta = -130.71$ and $\delta = -140.97$ ppm with a $^{2}J_{F,F} = 160.8$ Hz; the signal for the $CH_2$-N moiety is found in the $^{13}C$ NMR spectrum at $\delta = 41.15$ ppm showing a $^{3}J_{C,F} = 4.0$ Hz. The assignment of all signals was performed by 2D homo- and heteronuclear COSY as well as 2D-NOESY experiments.

Similarly, the Mitsunobu reaction of **7** with N$^3$-benzoyl-uracil gave **11** in 84% yield. Consecutive deprotection as above afforded **12** and finally the uracil analogue **13**. Mitsunobu reaction of **7** with N$^3$-benzoyl-5-fluoro-uracil, TPP and DEAD gave 67% of **14** whose debenzoylation yielded 92% of **15** that was debenzylated to afforded the target compound **16**.




Compound **16** is characterized in its $^{19}F$ NMR spectrum by the presence of three signals at $\delta = -134.27$, $-144.44$ and $-167.49$ ppm the latter of which can be assigned to the fluoro substituent at the 5'-position of the heterocycle.

Finally, an adenine analogue was prepared by the same strategy starting from **7** that was subjected to a Mitsunobu reaction to afford **17** in 72% yield. Debenzylation of **17** under the usual conditions gave the adenine analogue **18**.

The synthesis of enantiomerically pure analogues, their (tri)-phosphates as well as their incorporation in DNA and RNA fragments is presently investigated in our laboratories.

## EXPERIMENTAL

*General methods*: [ref 18]; in addition, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or an a Finnigan MAT LCQ 7000 (electronspray, voltage 4.5 kV, under nitrogen) instrument; 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). Column chromatography was performed on silica gel 60 (FLUKA, 0.04 - 0.06 mm). Only substance **2** was purified on silica gel 60 (FLUKA, 0.06 - 0.2 mm).

*1,3-Dibenzyloxy-2-propanone* (**2**). A solution of **1** (14.2 g, 51.9 mmol), TEMPO (0.16 g, 1.04 mmol) in dichloromethane (34 *ml*) and a solution of KBr (1.21 g, 11.4 mmol)

in water (5.2 *ml*) were vigorously stirred and cooled to –10 °C. The pH of NaOCl (114 *ml*, 1 M in water, 114 mmol) was adjusted to 9.5 by dissolving $NaHCO_3$ (1.64 g) immediately before use. This NaOCl solution was added over 15 min, keeping the temperature of the reaction mixture between 10 and 15 °C. The mixture was stirred for 60 min. The orange colored organic phase was separated and the aqueous phase was extracted with dichloromethane (150 *ml*). The combined organic phases were washed with 10% aqueous HCl (300 *ml*) containing KI (4.0 g), 10% aqueous $Na_2S_2O_3$ (140 *ml*) and water (140 *ml*). The organic phase was dried ($MgSO_4$), the solvent was removed under reduced pressure and the remaining yellowish oil was subjected to column chromatography (silica gel 60 (0.06 - 0-2 mm), hexane/ethyl acetate 4:1) to afford **2** (11.8 g, 84%) as a white solid; mp 37 °C; $R_F$ (hexane/ethyl acetate 4:1) 0.25; UV (methanol): $\lambda_{max}$= 260 nm (log ε = 2.59); IR (KBr): ν 3462*m*, 3059*m*, 3033*m*, 2926*m*, 2872*s*, 1956*m*, 1818*m*, 1743*s*, 1602*m*, 1496*m*, 1469*m*, 1453*m*, 1422*s*, 1397*s*, 1356*m*, 1294*m*, 1236*m*, 1217*m*, 1139*s*, 1073*s*, 1017 *s* ; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37-7.24 (*m*, 10 H, phenyl), 4.56 (*s*, 4 H, $CH_2$-phenyl), 4.23 (*s*, 4 H, $CH_2$-O-Bn); $^{13}$C (100 MHz, $CDCl_3$): δ 205.58 (*s*, CO), 136.99 (*s*, $C_q$ phenyl), 128.39 (*d*, $C_{ortho}$ phenyl), 127.91 (*d*, $C_{meta}$ phenyl), 127.78 (*d*, $C_{para}$ phenyl), 73.36 (*t*, $CH_2$-phenyl (A)), 73.25 (*t*, $CH_2$-phenyl (B)); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 326.1 (12%) $[MHNaCH_3OH]^+$, 325.1 (65%) $[MNaCH_3OH]^+$, 294.1 (18%) $[MHNa]^+$, 293.0 (100%) $[MNa]^+$; Anal. calcd. for $C_{17}H_{18}O_3$ (270.32): C, 75.53; H, 6.71; found: C, 75.29; H, 6.86.

*Ethyl 4-benzyloxy-3-benzyloxymethyl-2-butenoate* (**3**). According to ref [23] from **2** (7.73 g, 28.6 mmol), sodium hydride (1.14 g, used as received as a 60% dispersion in mineral oil, 28.6 mmol) and triethyl phosphonoacetate (6.41 g, 28.6 mmol) **3** (7.98 g, 82%) was obtained as a colorless liquid; $R_F$ (hexane/ethyl acetate 6:1) 0.32; UV (methanol): $\lambda_{max}$= 212 nm (log ε = 3.27); IR (film): ν 3694*w*, 3088*w*, 3064*m*, 3031*m*, 2980*m*, 2858*m*, 1952*w*, 1870*w*, 1713*s*, 1654*s*, 1605*w*, 1540*w*, 1496*m*, 1454*s*, 1376*s*, 1351*m*, 1312*s*, 1214*s*, 1146*s*, 1099*s*, 1028 *s*; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.40-7.26 (*m*, 10 H, phenyl), 6.17 (*t*, $^4J_{H,H}$ = 1.7, 1 H, CH vinyl), 4.72 (*t*, $^4J_{H,H}$ = 1.7, 2 H, $CH_2O_{cis}$), 4.59 (*s*, 2 H, $CH_2$-phenyl), 4.52 (*s*, 2 H, $CH_2$-phenyl), 4.31 ( *t*, $^4J_{H\text{-}H}$ = 1.0, 2 H, $CH_2O_{trans}$), 4.16 (*q*, $^3J_{H,H}$ = 7.0, 2 H, $CH_2$ ethyl), 1.30 (*t*, $^3J_{H,H}$ = 7.0, 3 H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 167.34 (*s*, CO), 156.05 (*s*, C vinyl), 139.27 (*s*, $C_q$ phenyl), 139.11 (*s*, $C_q$ phenyl), 129.57-128.77 (*m*, CH phenyl), 117.12 (*d*, CH vinyl), 74.00 (*t*, $CH_2$-phenyl), 73.95 (*t*, $CH_2$-phenyl), 71.17 (*t*, $CH_2O_{trans}$), 68.41 (*t*, $CH_2O_{cis}$), 61.06 (*t*, $CH_2$ ethyl), 15.20 (*q*, $CH_3$); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 364.1 (18%) $[MHNa]^+$, 363.2 (100%) $[MNa]^+$; Anal. calcd. for $C_{21}H_{24}O_4$ (340.41): C, 74.09; H, 7.10; found: C, 73.98; H, 6.86.

*4-Benzyloxy-3-benzyloxymethyl-2-butenol* (**4**). According to ref [23] from **3** (7.98 g, 23.4 mmol) and DIBAH (78 *ml*, 1.2 M in toluene, 93.6 mmol) **4** (5.71 g, 85%) was obtained as a colorless oil; $R_F$ (hexane/ethyl acetate 1:1) 0.31; UV (methanol): $\lambda_{max}$= 260 nm (log ε = 2.58); IR (film): ν 3411*m*, 3087*w*, 3063*w*, 3030*w*, 2858*m*, 1954*w*, 1605*w*, 1496*m*, 1453*m*, 1362*m*, 1310*w*, 1251*w*, 1205*w*, 1175*w*, 1097*s*, 1070*s*, 1027 *m*; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (*m*, 10 H, phenyl), 5.95 (*t*, $^3J_{H,H}$ = 6.5, 1 H, CH vinyl), 4.51 (*s*, 4 H, phenyl), 4.21 (*d*, $^3J_{H,H}$ = 6.8, 2 H, $CH_2$-OH), 4.12 (*s*, 2 H, $CH_2O_{cis}$), 4.05 (*s*, 2 H, $CH_2O_{trans}$), 2.05 (*brs*, 1 H, OH); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 139.37 (*s*, $C_q$ phenyl), 139.01 (*s*, $C_q$ phenyl), 137.28 (*s*, C vinyl), 132.31 (*d*, CH vinyl), 129.60-128.76 (*m*, CH phenyl), 73.75 (*t*, $CH_2$-phenyl), 73.65 (*t*, $CH_2$-phenyl), 73.30 (*t*, $CH_2O_{trans}$), 66.98 (*t*, $CH_2O_{cis}$), 59.67 (*t*, $CH_2$-OH);

HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 322.1 (18%) $[MHNa]^+$, 321.1 (100%) $[MNa]^+$; Anal. calcd. for $C_{19}H_{22}O_3$ (298.38): C, 76.48; H, 7.43; found: C, 76.31; H, 7.63.

*4-Benzyloxy-3-benzyloxymethyl-2-butenyl acetate* (**5**). To a 5 °C cold solution of **4** (5.71 g, 19.2 mmol) in dry pyridine (12 *ml*) acetic anhydride (2.4 g, 23.0 mmol) was slowly added, and the reaction mixture was stirred for 4 h at 25 °C. Then methanol (36 *ml*) was slowly added at room temperature, the solvents were evaporated under reduced pressure and residual pyridine was removed by repeated co-evaporation with toluene. Purification was achieved by column chromatography (silica gel, hexane/ethyl acetate 3:1) to afford **5** (5.49 g, 84%) as a colorless oil; $R_F$ (hexane/ethyl acetate 3:1) 0.33; UV (methanol): $\lambda_{max}$= 238 nm (log 3.43); IR (film): ν 3357*m*, 3064*m*, 3032*m*, 2862*m*, 1958*w*, 1739*s*, 1598*m*, 1584*m*, 1496*m*, 1454*s*, 1369*s*, 1312*m*, 1235*s*, 1071*s*, 1028 *s*; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.34-7.24 (*m*, 10 H, phenyl), 5.86 (*t*, $^3J_{H,H}$ = 6.8, 1 H, CH vinyl), 4.71 (*d*, $^3J_{H,H}$ = 6.8, 2 H, $CH_2O$ allyl), 4.52 (*s*, 2 H, $CH_2$-phenyl), 4.49 (*s*, 2 H, $CH_2$-phenyl), 4.13 (*s*, 2 H, $CH_2O_{cis}$), 4.08 (*d*, $^4J_{H,H}$ = 0.8, $CH_2O_{trans}$), 2.05 (*s*, 3 H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.83 (*s*, CO), 138.19 (*s*, $C_q$ phenyl), 138.05 (*s*, $C_q$ phenyl), 138.01 (*s*, C vinyl), 128.40-127.62 (*m*, CH phenyl), 125.04 (*d*, CH vinyl), 72.41 (*t*, $CH_2$-phenyl), 72.33 (*t*, $CH_2$-phenyl), 71.73 ( *t*, $CH_2O_{trans}$), 65.55 (*t*, $CH_2O_{cis}$), 60.27 (*t*, $CH_2O$ ethyl), 20.72 (*q*, $CH_3$); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 364.2 (20%) $[MHNa]^+$, 363.2 (100%) $[MNa]^+$; Anal. calcd. for $C_{21}H_{24}O_4$ (340.41): C, 74.09; H, 7.10; found: C, 73.95; H, 7.09.

*(±)-(1* RS*)-[2,2-Di(benzyloxymethyl)-3,3-difluorocyclopropyl]-methyl acetate* [(±)-**6**]. A solution of **5** (5.49 g, 16.1 mmol) in dry diglyme (6.5 *ml*) was heated to 190 °C. A solution of sodium chlorodifluoro acetate (26.83 g, 177.1 mmol) in dry diglyme (52 *ml*) was added at this temperature over a period of 60 minutes. After keeping the reaction at 190 °C for an additional 15 min, and cooling to room temperature, the reaction mixture was poured into ice water, the aqueous solution was extracted with hexane (4 x 100 *ml*), and the combined organic layers were washed with brine, dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The remaining oil was subjected to column chromatography (silica gel, hexane/ethyl acetate 6:1 ) to afford **6** (4.71 g, 75%) as a colorless oil contaminated with some starting material that was easily separated in the next reaction step; $R_F$ (hexane/ethyl acetate 6:1) 0.38; UV (methanol): $\lambda_{max}$ = 260 nm (log ε = 2.58); IR (film): ν 3089*m*, 3064*m*, 3031*s*, 2868*s*, 2359*w*, 1954*w*, 1875*w*, 1743*s*, 1604*w*, 1586*w*, 1479*s*, 1454*s*, 1386*s*, 1365*s*, 1231*s*, 1166*s*, 1095*s*, 1028 *s*; $^1$H NMR (200 MHz, $CDCl_3$): δ 7.38-7.24 (*m*, 10 H, phenyl), 4.52-4.48 (*m*, 4 H, $CH_2$-phenyl), 4.16-4.06 (*m*, 2 H, $CH_2$-O-Ac), 3.79 and 3.61 (AB system, $J_{AB}$=10.35, $^4J_{H,F}$ = 1.95, 2 H, $CH_2O_{cis}$), 3.79 and 3.48 (AB system, $J_{AB}$ = 10.35, $^4J_{H,F}$ = 1.95, 2 H, $CH_2O_{trans}$), 2.00 (*s*, 3 H, $CH_3$), 1.90 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 170.67 (*s*, CO), 137.98 (*s*, $C_q$ phenyl), 137.83 (*s*, $C_q$ phenyl), 128.36-127.53 (*m*, CH phenyl), 114.27 (*dd*, $^1J_{C,F}$ = 286.70, 292.86, $CF_2$), 73.11 (*t*, $CH_2$-phenyl), 72.71 (*t*, $CH_2$-phenyl), 67.71 (*dt*, $^3J_{C,F}$ = 5.4, $CH_2O_{trans}$), 63.35 (*dt*, $^3J_{C,F}$ = 5.4, $CH_2O_{cis}$), 58.04 (*dt*, $^3J_{C,F}$ = 5.4, $CH_2$-O-Ac), 33.81 (*t*, $^2J_{C,F}$ = 9.2, C(2)), 27.78 (*dt*, $^2J_{C,F}$ = 10.0, C(1)H), 20.71 (*q*, $CH_3$); $^{19}$F NMR (188 MHz, $CDCl_3$): δ –136.00 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.6, F), –147.36 (*d*, $^2J_{F,F}$ = 164.5, F'); HPLC-MS ( ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 414.1 (21%) $[MHNa]^+$, 413.1 (100%) $[MNa]^+$; Anal. calcd. for $C_{22}H_{24}F_2O_4$ (390.42): C, 67.78; H, 6.19; found: C, 67.48; H, 6.16.

*(±)-(1 RS)-[2,2-Di(benzyloxymethyl)-3,3-difluorocyclopropyl]-methanol* [(±)-**7**]. A solution of **6** (4.71 g, 13.8 mmol) in methanol (22 *ml*) was treated with catalytic amounts of sodium methoxide. After 30 min the reaction was complete and the reaction mixture was neutralized by the addition of 10 % aqueous hydrochloric acid. The solvent was evaporated, the residue was suspended in water (10 *ml*) and the suspension was extracted with ethyl acetate (4 x 40 *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, hexane/ethyl acetate 2:1) to afford **7** (4.37 g, 91 %) as a colorless oil; $R_F$ (hexane/ethyl acetate 2:1) 0.42; UV (methanol): $\lambda_{max}$ = 260 nm (log ε = 2.60); IR (film): ν 3462*m*, 3063*w*, 3031*m*, 2870*m*, 1586*w*, 1496*m*, 1475*m*, 1454*m*, 1417*m*, 1363*m*, 1265*m*, 1155*m*, 1093*m*, 1028 *m*; $^1$H NMR (400 MHz, $CDCl_3$): δ 7.40-7.29 (*m*, 10 H, phenyl), 4.56-4.44 (*m*, 4 H, $CH_2$-phenyl), 4.04-4.00 (*m*, 2 H, $CH_2$-OH), 3.88 and 3.63 (AB system, $J_{AB}$ = 12.65, 2 H, $CH_2O_{trans}$), 3.63 and 3.24 (AB system, $J_{AB}$ = 10.55, 2 H, $CH_2O_{cis}$), 2.92 (*brs*, 1 H, OH), 1.84-1.76 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 137.82 (*s*, $C_q$ phenyl), 136.80 (*s*, $C_q$ phenyl), 128.57-127.59 (*m*, CH phenyl), 114.18 (*dd*, $^1J_{C,F}$ = 288.2, 292.1, $CF_2$), 73.73 (*t*, $CH_2$-phenyl), 72.55 (*t*, $CH_2$-phenyl), 68.32 (*dt*, $^3J_{C,F}$ = 6.00, $CH_2O_{trans}$), 63.19 (*dt*, $^3J_{C,F}$ = 4.00, $CH_2O_{cis}$), 55.86 (*dt*, $^3J_{C,F}$ = 4.00, $CH_2$-OH), 34.13 (*t*, $^2J_{C,F}$ = 10.0, C(2)), 31.88 (*dt*, $^2J_{C,F}$ = 9.5, C(1)H); $^{19}$F NMR (188 MHz, $CDCl_3$): δ −134.00 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.6, F), −145.00 (*d*, $^2J_{F,F}$ = 164.5, F'); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 403.1 (6%), 372.1 (16%) $[MHNa]^+$, 371.2 (100%) $[MNa]^+$; Anal. calcd. for $C_{20}H_{22}F_2O_3$ (348.39): C, 68.95; H, 6.36; found: C, 68.71; H, 6.26.

*(±)-3-Benzoyl-1-[(1* RS*)-2,2-di(benzyloxymethyl)-3,3-difluorocyclopropylmethyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**8**]. To a mixture of **7** (0.85 g, 2.4 mmol), TPP (1.27 g, 4.8 mmol) and N$^3$-benzoylthymine (1.10 g, 4.8 mmol) in dry 1,4-dioxane (15 *ml*) a solution of DEAD (0.84 g, 4.8 mmol) in 1,4-dioxane (30 *ml*) was added dropwise at room temperature over a period of 2 h. The reaction mixture was stirred overnight, the solvent evaporated and the remaining yellowish oil purified by column chromatography (silica gel, hexane/ethyl acetate 1:1) to afford **8** (1.10 g, 82%) as a colorless gel 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 8:3); $R_F$ (hexane/ethyl acetate 1:1) 0.28; UV (methanol): $\lambda_{max}$= 255 nm (log ε = 4.23); IR (film): ν 3064*w*, 3030*w*, 2981*w*, 2928*w*, 2872*w*, 1799*w*, 1747*s*, 1701*s*, 1660*s*, 1598*m*, 1496*m*, 1438*s*, 1361*m*, 1243*s*, 1175*m*, 1097*s*, 1046*m*, 1028*m*, 1001 *m*; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.89 (*s*, 1 H, H-C(6')), 7.87-7.23 (*m*, 15 H, phenyl), 4.51-4.41 (*m*, 4 H, $CH_2$-phenyl), 4.00 (*d*, $^3J_{H,H}$ = 7.2, 2 H, $CH_2N$), 3.81 and 3.68 (AB system, $J_{AB}$ = −10.5, $^4J_{H,F}$ = 1.9, 2 H, $CH_2O_{cis}$), 3.76 and 3.44 (AB system, $J_{AB}$ = −10.16, $^4J_{H,F}$ = 2.73, 2 H, $CH_2O_{trans}$), 2.15-2.08 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (100 MHz, $CD_3OD$): δ 170.50 (*s*, CO (Bz)), 165.18 (*s*, C(2')), 151.48 (*s*, C(4')), 142.96 (*d*, C(6')), 139.54 (*s*, $C_q$ phenyl (Bn)), 139.38 (*s*, $C_q$ phenyl (Bn)), 136.43 (*s*, $C_q$ phenyl (Bz)), 133.11 (*d*, $C_{para}$ phenyl (Bz)), 131.57 (*d*, $C_{ortho}$ phenyl (Bz)), 130.50 (*d*, $C_{meta}$ phenyl (Bz)), 129.58-128.90 (*m*, CH phenyl (Bn)), 115.98 (*dd*, $^1J_{C,F}$ = 294.6, 286.5, $CF_2$), 111.43 (*d*, C(5')), 74.38 (*t*, $CH_2$-phenyl) 73.97 (*t*, $CH_2$-phenyl), 68.75 (*dt*, $^3J_{C,F}$ = 5.8, $CH_2O_{trans}$), 64.34 (*dt*, $^3J_{C,F}$ = 5.8, $CH_2O_{cis}$), 43.35 (*dt*, $^3J_{C,F}$ = 4.55, $CH_2N$), 35.61 (*t*, $^2J_{C,F}$ = 9.71, C(2)), 28.86 (*dt*, $^2J_{C,F}$ = 9.95, C(1)), 12.07 (*q*, $CH_3$); $^{19}$F NMR (188 MHz, $CD_3OD$): δ −133. 15 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.62, F), −144.05 (*d*, $^2J_{F,F}$ = 164.5); HPLC-MS (ESI,4.1 kV, 8 µl/min, $N_2$, methanol): 584.2 (35%)

[MHNa]$^+$, 583.2 (100%) [MNa]$^+$; HRMS calcd for $C_{32}H_{30}F_2N_2O_5$: 560.21225; found 560.21226.

*(±)-1-[(1* RS*)-2,2-Di(benzyloxymethyl)-3,3-difluorocyclopropylmethyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**9**]. A solution of **8** (1.10 g, 2.0 mmol) in methanol (25 *ml*) was treated with ammonium hydroxide (8 *ml*, 25%) for 12 h. The volatiles were evaporated and the remaining oil was subjected to column chromatography (silica gel, hexane/ethyl acetate 1:1) to give **9** (0.83 g, 91%) as a white solid; mp = 111-112 °C; $R_F$ (hexane/ethyl acetate 1:1) 0.18; UV (methanol): $\lambda_{max}$= 270 nm (log ε = 4.09); IR (KBr): ν 3453*s*, 3032*m*, 2865*m*, 1681*s*, 1475*s*, 1454*s*, 1388*m*, 1366*s*, 1251*s*, 1165*m*, 1092*s*, 1042*m*, 1027*m*, 1001 *m*; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.32 (*d*, $^4J_{H,H}$ = 1.2, 1 H, C(6')), 7.31-7.21 (*m*, 10 H, phenyl), 4.49-4.41 (*m*, 4 H, $CH_2$-phenyl), 4.00 and 3.89 (AB system, $J_{AB}$ = –14.8, $^3J_{H,H}$ = 7.8, 2 H, $CH_2N$), 3.84 and 3.68 (AB system, $J_{AB}$ = –10.4, $^4J_{H,F}$ = 2.7, 2 H, $CH_2O_{cis}$), 3.75 and 3.45 (AB system, $J_{AB}$ = –10.3, $^4J_{H,F}$ = 1.9, 2 H, $CH_2O_{trans}$), 2.08-2.02 (*m*, 1 H, cyclopropyl), 1.68 (*d*, $^4J_{H,H}$ = 1.2, 3 H, $CH_3$); $^{13}$C NMR (100 MHz, $CD_3OD$): δ 166.78 (*s*, C(2')), 152.98 (*s*, C(4')), 142.37 (*d*, C(6')), 139.59 (*s*, $C_q$ phenyl), 139.46 (*s*, $C_q$ phenyl), 129.57-128.85 (*m*, CH phenyl), 116.07 (*dd*, $^1J_{C,F}$ = 285.92, 294.21, $CF_2$), 111.55 (*s*, C(5')), 74.38 (*t*, $CH_2$-phenyl), 73.99 (*t*, $CH_2$-phenyl), 68.87 (*dt*, $^3J_{C,F}$ = 5.4, $CH_2O_{trans}$), 64.43 (*dt*, $^3J_{C,F}$ = 6.2, $CH_2O_{cis}$), 42.70 (*dt*, $^3J_{C,F}$ = 5.0, $CH_2N$), 35.58 (*t*, $^2J_{C,F}$ = 9.5, C(2)), 29.02 (*dt*, $^2J_{C,F}$ = 10.4, C(1)), 11.96 (*q*, $CH_3$); $^{19}$F NMR (188 MHz, $CD_3OD$): δ –133.30 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.62, F), –144.14 (*d*, $^2J_{F,F}$ = 164.5, F'); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol/TFA (0.1%)): 480.1 (25%) [MHNa]$^+$, 479.2 (100%) [MNa]$^+$; HRMS calcd. for $C_{25}H_{26}F_2N_2O_4$: 456.1860; found: 456.1860.

*(±)-1-[(1* RS*)-2,2-Difluoro-3,3-di(hydroxymethyl)-cyclopropylmethyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (= [±]-1-(2,2-difluoro-3,3-di(hydroxymethyl)-cyclopropylmethyl) thymine)* [(±)-**10**]. To a solution of **9** (0.83 g, 1.8 mmol) in methanol (26 *ml*) cyclohexene (*21 ml*) and *Pearlman's* catalyst (2.90 g, 20%) were added and the reaction mixture was heated under reflux for 6 h. After filtration and evaporation of all volatiles the remaining residue was subjected to column chromatography (silica gel, hexane/ethyl acetate 1:4) to give **10** (0.31 g, 63%) as a white solid; mp: 215-217°C; $R_F$ (hexane/ethyl acetate 1:4) 0.30; UV (methanol): $\lambda_{max}$= 270 nm (log ε = 4.06); IR (KBr): ν 3484*s*, 3031*m*, 2959*m*, 2893*m*, 2873*m*, 2580*m*, 2248*w*, 1681*s*, 1470*s*, 1383*m*, 1352*m*, 1302*m*, 1271*m*, 1249*m*, 1220*m*, 1184*m*, 1171*m*, 1152*m*, 1117*m*, 1054*m*, 1034 *s*; $^1$H NMR (500 MHz, DMSO): δ 11.24 (*s*, 1 H, NH), 7.46 (*d*, $^4J_{H,H}$ = 1.04, 1 H, H-C(6')), 4.87 (*q*, $^3J_{H,H}$ = 5.7, 2 H, OH), 3.96 (*m*, $^2J_{H,H}$ = –13.1, $^4J_{H,F}$ = 3.1, 1 H, $CH_2N$), 3.78-3.73 (*m*, 1 H, $CH_2N$), 3.78-3.73 (*m*, 1 H, $CH_2O_{cis}$), 3.58-3.55 (*m*, 1 H, $CH_2O_{cis}$), 3.58-3.55 (*m*, 1 H, $CH_2O_{trans}$), 3.43 (*m*, $^2J_{H,H}$ = –11.3, $^3J_{H,H}$ = 5.4, 1 H, $CH_2O_{trans}$), 1.99-1.93 (*m*, 1 H, cyclopropyl), 1.74 (*d*, $^4J_{H,H}$ = 1.04, 3 H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO): δ 164.11 (*d*, C(2')), 150.75 (4')), 140.72 (*d*, C(6')), 115.91 (*dd*, $^1J_{C,F}$ = 286.2, 294.1, $CF_2$), 108.67 (*s*, C(5')), 58.58 (*dt*, $^3J_{C,F}$ = 5.9, $CH_2OH_{trans}$), 54.02 (*dt*, $^3J_{C,F}$ = 7.0, $CH_2OH_{cis}$), 41.15 (*dt*, $^3J_{C,F}$ = 4.0, $CH_2N$), 36.84 (*t*, $^2J_{C,F}$ = 8.5, C(2)), 26.97 (*dt*, $^2J_{C,F}$ = 9.5, C(1)), 11.91 (*q*, $CH_3$); $^{19}$F NMR (188 MHz, DMSO-$d_6$): δ –130.71 (*dd*, $^2J_{F,F}$ = 160.8, $^3J_{H,F}$ = 14.5, F), –140.97 (*d*, $^2J_{F,F}$ = 160.8, F'); Anal. calcd. for $C_{11}H_{14}F_2N_2O_4$ (276.238): C, 47.83; H, 5.11; N, 10.14; found: C, 47.56; H, 4.97; N, 10.04.

*(±)-3-Benzoyl-1-[(1* RS*)-2,2-di(benzyloxymethyl)-3,3-difluorocyclopropylmethyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**11**]. The reaction was performed under the conditions as described for **8** using **7** (0.85 g, 2.4 mmol), TPP (1.27 g, 4.8 mmol), $N^3$-benzoyluracil (1.04 g, 4.8 mmol), 1,4-dioxane (15 *ml)* and DEAD (0.84 g, 4.8 mmol) in 1,4-dioxane (30 *ml*). After evaporation of the solvents and purification by column chromatography (silica gel, hexane/ethyl acetate 1:1) **11** (1.10 g, 84%) was obtained as a colorless gel 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); $R_F$ (hexane/ethyl acetate 1:1) 0.28; UV (methanol): $\lambda_{max}$= 255 nm (log ε = 4.27); IR (KBr): ν 3031*w*, 2918*w*, 2869*w*, 1749*s*, 1706*s*, 1666*s*, 1598*w*, 1440*m*, 1363*m*, 1240*m*, 1175*m*, 1094 *m*; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.88 (*d*, $^3J_{H,H}$ = 8.2, 1 H, H-C(6')), 7.89-7.24 (*m*, 15 H, phenyl), 5.63 (*d*, $^3J_{H,H}$ = 8.0, 1 H, C(5')), 4.51-4.41 (*m*, 4 H, $CH_2$-phenyl), 4.07-3.96 (*m*, 2 H, $CH_2N$), 3.86 and 3.66 (AB system, $J_{AB}$ = –10.5, $^4J_{H,F}$ = 1.95, 2 H, $CH_2O_{cis}$), 3.76 and 3.42 (AB system, $J_{AB}$ = –10.55, $^4J_{H,F}$ = 2.53, 2 H, $CH_2O_{trans}$), 2.15-2.08 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (100 MHz, $CD_3OD$): δ 170.32 (*s*, CO (Bz)), 164.70 (*s*, C(2')), 151.48 (*s*, C(4')), 147.22 (*d*, C(6')), 139.54 (*s*, $C_q$ phenyl (Bn)), 139.32 (*s*, $C_q$ phenyl (Bn)), 136.48 (*s*, $C_q$ phenyl (Bz)), 133.03 (*d*, $C_{para}$ phenyl (Bz)), 131.57 (*d*, $C_{ortho}$ phenyl (Bz)), 130.52 (*d*, $C_{meta}$ phenyl (Bz)), 129.62-128.92 (*m*, CH phenyl (Bn)), 115.98 (*dd*, $^1J_{C,F}$ = 284.0, 296.1, $CF_2$), 102.36 (*d*, C(5')), 74.44 (*t*, $CH_2$-phenyl), 73.97 (*t*, $CH_2$-phenyl), 68.75 (*dt*, $^3J_{C,F}$ = 4.9, $CH_2O_{trans}$), 64.25 (*dt*, $^3J_{C,F}$ = 5.8, $CH_2O_{cis}$), 43.87 (*dt*, $^3J_{C,F}$ = 4.9, $CH_2N$), 35.50 (*t*, $^2J_{C,F}$ = 9.74, C(2)), 28.71 (*dt*, $^2J_{C,F}$ = 9.9, C(1)); $^{19}$F NMR (188 MHz, $CD_3OD$): δ –133.17 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.62, F), –144.05 (*d*, $^2J_{F,F}$ = 164.5, F'); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 570.2 (35%) $[MHNa]^+$, 569.2 (100%) $[MNa]^+$; Anal. calcd. for $C_{31}H_{28}F_2N_2O_5$ (546.567): C, 68.12; H, 5.16; N, 5.13; found: C, 68.04; H, 5.02; N, 5.27.

*(±)-[(1* RS*)-2,2-Di(benzyloxymethyl)-3,3-difluorocyclopropylmethyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**12**]. A solution of **11** (1.10 g, 2 mmol) in methanol (25 *ml*) was treated with ammonium hydroxide (8 *ml*, 25%) for 8 h. The volatiles were evaporated and the remaining oil was subjected to column chromatography (silica gel, hexane/ethyl acetate 1:3) to give **12** (0.92 g, 91%) as a white solid; mp: 98-100°C; $R_F$ (hexane/ethyl acetate 1:3) 0.32; UV (methanol): $\lambda_{max}$= 266 nm (log ε = 4.00); IR (KBr): ν 3181*m*, 3060*m*, 3033*m*, 2860*m*, 2805*m*, 1693*s*, 1586*s*, 1495*m*, 1479*s*, 1462*s*, 1410*m*, 1396*m*, 1369*s*, 1356*s*, 1311*m*, 1295*m*, 1257*s*, 1213*m*, 1181*s*, 1160*m*, 1087*s*, 1029*m*, 1009 *s*; $^1$H NMR (400MHz, $CD_3OD$): δ 7.50 (*d*, $^3J_{H,H}$ = 7.8, 1 H, H-C(6')), 7.33-7.22 (*m*, 10 H, phenyl), 5.47 (*d*, $^3J_{H,H}$ = 7.8, 1 H, H-C(5')), 4.51-4.40 (*m*, 4 H, $CH_2$-phenyl), 4.05 and 3.89 (*m*, $J_{AB}$ = –14.6, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 2.5, 2 H, $CH_2N$), 3.84 and 3.66 (AB system, $J_{AB}$ = –10.3, $^4J_{H,H}$ = 2.3, 2 H, $CH_2O_{cis}$), 3.77 and 3.42 (AB system, $J_{AB}$ = –10.3, $^4J_{H,H}$ = 2.7, 2 H, $CH_2O_{trans}$), 2.09-2.01 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (100 MHz, $CD_3OD$): δ 166.70 (*s*, C(2')), 152.82 (*s*, C(4')), 146.79 (*d*, C(4')), 139.52 (*s*, $C_q$ phenyl), 139.36 (*s*, $C_q$ phenyl), 129.58-128.87 (*m*, CH phenyl), 116.06 (*dd*, $^1J_{C,F}$ = 285.5, 294.2, $CF_2$, 102.47 (*d*, C(5')), 74.29 (*t*, $CH_2$-phenyl), 73.88 (*t*, $CH_2$-phenyl), 68.75 (*dt*, $^3J_{C,F}$ = 5.8, $CH_2O_{trans}$), 64.13 (*dt*, $^3J_{C,F}$ = 6.2, $CH_2O_{cis}$), 43.06 (*dt*, $^3J_{C,F}$ = 5.0, $CH_2N$), 35.53 (*t*, $^2J_{C,F}$ = 9.5, C(2)), 28.79 (*dt*, $^2J_{C,F}$ = 10.4, C(1)); $^{19}$F NMR (188 MHz, $CD_3OD$): δ –133.32 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.6, F), –144.14 (*d*, $^2J_{F,F}$ = 164.5, F'); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol/TFA (0.1%)): 466.1 (21%)

[MHNa]$^+$, 465.2 (100%) [MNa]$^+$; Anal. calcd. for $C_{24}H_{24}F_2N_2O_4$ (442.460): C, 65.15; H, 5.47; N, 6.33; found: C, 65.11; H, 5.68; N, 6.51.

*(±)-[(1 RS)-2,2-Difluoro-3,3-di(hydroxymethyl)-cyclopropylmethyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione (= (±)-1-(2,2-difluoro-3,3-(di(hydroxymethyl)-cyclopropylmethyl) uracil)* [(±)-**13**]. To a solution of **12** (668 mg, 1.5 mmol) in methanol (28 *ml*) cyclohexene (14 *ml*) and *Pearlman's* catalyst (1.6 g, 20 %) were added and the reaction mixture was heated under reflux for 4.5 h. After filtration and evaporation of all volatiles the remaining residue was subjected to column chromatography (silica gel, ethyl acetate/methanol 40:1) to give **13** (0.23 g, 58%) as a white solid; mp: 153-154 °C; $R_F$ (ethyl acetate/methanol 40:1) 0.32; UV (methanol): $\lambda_{max}$= 266 nm (log ε = 3.98); IR (KBr): ν 3442*s*, 3182*m*, 3050*m*, 2941*m*, 2889*m*, 1711*s*, 1650*s*, 1468*s*, 1393*s*, 1361*s*, 1286*m*, 1264*m*, 1241*s*, 1210*m*, 1182*m*, 1150*m*, 1117*m*, 1055*s*, 1044 *s*; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.60 (*d*, $^3J_{H,H}$ = 7.8, 1 H, H-C(6')), 5.66 (*d*, $^3J_{H,H}$ = 7.8, 1 H, H-C(5')), 4.16 (*m*, $^2J_{H,H}$ = –14.5, $^3J_{H,H}$ = 6.7, 1 H, $CH_2N$), 3.98 and 3.76 (AB system, $J_{AB}$ = –11.92, $^4J_{H,F}$ = 1.95, 2 H, $CH_2O_{trans}$), 3.88 (*m*, $^2J_{H,H}$ = –14.6, $^3J_{H,H}$ = 7.82, 1 H, $CH_2N$), 3.82 and 3.60 (AB system, $J_{AB}$ = –11.7, $^4J_{H,F}$ =1.95, 2 H, $CH_2O_{cis}$), 2.02-1.95 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (100 MHz, $CD_3OD$): δ 166.83 (*s*, C(2')), 152.94 (*s*, C(4')), 147.00 (*d*, C(6')), 116.63 (*dd*, $^1J_{C,F}$ = 285.1, 294.6, $CF_2$), 102.69 (*d*, C(5')), 61.02 (*dt*, $^3J_{C,F}$ = 6.2, $CH_2$-$OH_{trans}$), 56.15 (*dt*, $^3J_{C,F}$ = 5.04, $CH_2$-$OH_{cis}$), 43.46 (*dt*, $^3J_{C,F}$ = 5.0, $CH_2N$), 38.26 (*t*, $^2J_{C,F}$ = 9.53, C(2)), 28.80 (*dt*, $^2J_{C,F}$ = 9.95, C(1)); $^{19}$F NMR (188 MHz,$CD_3OD$): δ –134.37 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.6, F), –144.57 (*d*, $^2J_{F,F}$ = 164.5); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol/TFA (0.1%)): 286.0 (8%) [MHNa]$^+$, 285.0 (100%) [MNa]$^+$; HRMS calcd. for $C_{10}H_{12}F_2N_2O_4$: 262.0765; found: 262.0765.

*(±)-3-Benzoyl-1-[(1 RS)-2,2-di(benzyloxymethyl)-3,3-difluorocyclopropylmethyl]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**14**]. The reaction was performed as described for the preparation of compound **8** using **7** (1.04 g, 3 mmol) in 1,4-dioxane (18 *ml*), $N^3$-benzoyl-5-fluorouracil (1.40 g, 6 mmol), TPP (1.58 g, 6 mmol) and DEAD (1.04 g, 6mmol) in 1,4-dioxane (27 *ml*). After stirring overnight the solvent was evaporated, the residue was purified by column chromatography (silica gel, hexane/ethyl acetate 3:1) and **14** (1.13 g, 67%) was obtained as a yellowish 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 8:3); $R_F$ (hexane/ethyl acetate 3:1) 0.11; UV (methanol): $\lambda_{max}$= 256 nm (log ε = 4.29); IR (film): ν 3066*m*, 3031*m*, 2871*m*, 1753*s*, 1714*s*, 1668*s*, 1599*m*, 1495*m*, 1449*s*, 1365*s*, 1245*s*, 1170*s*, 1094*s*, 1045*m*, 1028 *m*; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.99 (*d*, $^3J_{H,F}$ = 6.4, 1 H, H-C(6')), 7.90-7.23 (*m*, 10 H, phenyl), 4.51-4.46 (*m*, 4 H, $CH_2$-phenyl), 3.99 (*d*, $^3J_{H,H}$ = 7.4, 2 H, $CH_2N$), 3.85 and 3.65 (AB system, $J_{AB}$ = –10.4, $^4J_{H,F}$ = 2.1, 2 H, $CH_2O_{cis}$), 3.76 and 3.41 (AB system, $J_{AB}$ = –10.1, $^4J_{H,F}$ = 2.5, 2 H, $CH_2O_{trans}$), 2.16-2.09 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (100 MHz, $CD_3OD$): δ 169.00 (*s*, CO(Bz)), 158.25 (*d*, $^2J_{C,F}$ = 7.35, C(4')), 150.09 (*s*, C(2')), 141.27 (*d*, $^1J_{C,F}$ = 235.4, CF'), 139.48 (*s*, $C_q$ phenyl (Bn)), 139.21 (*s*, $C_q$ phenyl (Bn)), 136.74 (*s*, $C_q$ phenyl (Bz)), 131.72 (*d*, $C_{para}$ phenyl (Bz)), 130.60 (*d*, $C_q$ phenyl (Bz)), 129.63 (*d*, $C_q$ phenyl (Bz)), 129.59-128.79 (*m*, C phenyl (Bn), C(6')), 115.79 (*dd*, $^1J_{C,F}$ = 286.0, 294.6, $CF_2$), 74.48 (*t*, $CH_2$-phenyl (Bn)), 74.00 (*t*, $CH_2$-phenyl (Bn)), 68.71 (*dt*, $^3J_{C,F}$ = 5.8, $CH_2O_{trans}$), 64.27 (*dt*, $^3J_{C,F}$ =5.2, $CH_2O_{cis}$), 43.87 (*dt*, $^3J_{C,F}$ = 5.0 , $CH_2N$), 35.67 (*t*, $^2J_{C,F}$ = 9.5, C(2)), 28.54 (*dt*, $^2J_{C,F}$ = 10.6,

C(1)); $^{19}$F NMR (188 MHz, $CD_3OD$): δ –133.06 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 11.0, F), –143.71 (*d*, $^2J_{F,F}$ = 164.5, F'), –166.18 (*d*, $^3J_{H,F}$ = 7.3, F-C(5')); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 588.3 (35%) $[MHNa]^+$, 587.3 (100%) $[MNa]^+$; Anal. calcd. for $C_{31}H_{27}F_3N_2O_5$ (564.566): C, 65.95; H, 4.82; N, 4.96; found: C, 65.78; H, 4.69; N, 5.09.

*(±)-1-[(1* RS*)-2,2-Di(benzyloxymethyl)-3,3-difluorocyclopropylmethyl]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**15**]. According to the procedure given for **9** compound **14** (0.76 g, 1.3 mmol) was dissolved in methanol (10 *ml*) and treated with $NH_4OH$ (40 *ml*, 25%) for 4 h. Purification by column chromatography (silica gel, hexane/ethyl acetate 1:1) afforded **15** (0.55 g, 92%) as a yellowish oil; $R_F$ (hexane/ethyl acetate 1:1) 0.26; UV (methanol): $\lambda_{max}$= 272 nm (log ε = 3.87); IR (KBr): ν 3434*m*, 3031*m*, 2848*m*, 1700*s*, 1661*s*, 1481*m*, 1454*m*, 1394*m*, 1368*w*, 1315*w*, 1254*m*, 1241*m*, 1165*m*, 1095*m*, 1028*w*, 1001 *w*; $^1$H NMR (200 MHz, $CD_3OD$): δ 7.76 (*d*, $^3J_{H,F}$ = 6.2, 1 H, H-C(6')), 7.35-7.21 (*m*, 10 H, phenyl), 4.54-4.39 (*m*, 4 H, $CH_2$-phenyl), 4.07 and 4.00 (AB, $J_{AB}$ = –14.8, $^3J_{H,H}$ = 7.9, $^4J_{H,F}$ = 2.3, 2 H, $CH_2N$), 3.92-3.76 and 3.66 (*m*, $J_{AB}$ = –10.5, 2 H, $CH_2O_{cis}$, 3.92-3.76 and 3.42 (*m*, $J_{AB}$ = –10.3, $^4J_{H,F}$ = 1.9, 2 H, $CH_2O_{trans}$), 2.15-2.00 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (50 MHz, $CD_3OD$): δ 159.41 (*d*, C(4')), 151.33 (*s*, C(2')), 141.66 (*d*, $^1J_{C,F}$ = 231.2, C(5')), 139.18 (*s*, $C_q$ phenyl), 130.55 (*d*, $^2J_{C,F}$ = 33.1, C(6')), 129.49-128.82 (*m*, CH phenyl), 115.89 (*dd*, $^1J_{C,F}$ = 285.2, 293.6, $CF_2$), 74.34 (*t*, $CH_2$-phenyl), 73.92 (*t*, $CH_2$-phenyl), 68.75 (*dt*, $^3J_{C,F}$ = 6.2, $CH_2O_{trans}$), 64.17 (*dt*, $^3J_{C,F}$ = 5.4, $CH_2O_{cis}$), 43.13 (*dt*, $^3J_{C,F}$ = 5.4, $CH_2N$), 35.62 (*t*, $^2J_{C,F}$ = 9.5, C(2)), 28.70 (*dt*, $^2J_{C,F}$ = 10.4, C(1)); $^{19}$F NMR (188 MHz, $CD_3OD$): δ –133.19 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.5, F), –143.95 (*d*, $^2J_{F,F}$ = 164.4, F'), –167.23 (*d*, $^3J_{H,F}$ = 7.3, F-C(5')); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 469.3 $[MHLiH]^+$ (3.9%), 468.2 $[MHLi]^+$ (26.5%), 467.2 $[MLi]^+$ (100%), 466.3 $[MLi-H]^+$ (8.8%); Anal. calcd. for $C_{24}H_{23}F_3N_2O_4$ (460.45); C, 62.60; H, 5.03; N, 6.08; found: C, 62.49; H, 4.88; N, 6.23.

*(±)-[(1* RS*)-2,2-Difluoro-3,3-di(hydroxymethyl-cyclopropylmethyl)-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione (= (±)-1-(2,2-difluoro-3,3-di(hydroxymethyl)-5-fluoro-uracil)* [(±)-**16**]. Removal of the benzyl group was performed as described for **10** by treating **15** (0.57 g, 1.2 mmol) with cyclohexene (14 *ml*) and *Pearlman's* catalyst (0.92 g, 20%) in refluxing methanol (14 *ml*) for 6 h. After column chromatography (silica gel, ethyl acetate/hexane 5:1) **16** (0.17 g, 56%) was obtained as a white solid; mp: 148-150 °C, $R_F$ (ethyl acetate/hexane 5:1) 0.35; UV (methanol): $\lambda_{max}$= 275 nm (log ε = 3.90); IR (KBr) ν 3380*m*, 3150*w*, 3077*m*, 3027*m*, 2961*m*, 2934w, 2817*w*, 2508*m*, 2293*w*, 1693*s* 1473*s*, 1373*s*, 1241*s*, 1148*m*, 1062*m*, 1028*s*; $^1$H NMR (400 MHz, $CD_3OD$): δ 7.86 (*d*, $^3J_{H,F}$ = 6.2, 1 H, H-C(6')), 4.08 and 3.89 (AB, $J_{AB}$ = –14.8, $^3J_{H,H}$ = 7.2, $^4J_{H,F}$ = 3.1, 2 H, $CH_2N$), 3.98 and 3.75 (AB, $J_{AB}$ = –12.0, $^4J_{H,F}$ = 2.1, 2 H, $CH_2O_{cis}$), 3.80 and 3.59 (AB, $J_{AB}$ = –11.8, $^4J_{H,F}$ = 2.1, $CH_2O_{trans}$), 2.03-1.97 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (100 MHz, $CD_3OD$): δ 159.53 (*d*, $^2J_{C,F}$ = 6.1, C(4')), 151.16 (*s*, C(2')), 141.45 (*d*, $^1J_{C,F}$ =233.3, C(5')), 130.33 (*d*, $^2J_{C,F}$ = 34.2, C(6')), 116.10 (*dd*, $^1J_{C,F}$ = 284.6, 294.7, $CF_2$), 60.53 (*dt*, $^3J_{C,F}$ = 6.0, $CH_2O_{trans}$), 55.60 (*dt*, $^3J_{C,F}$ = 6.0, $CH_2O_{cis}$), 43.07 (*dt*, $^3J_{C,F}$ = 5.0, $CH_2N$), 37.88 (*t*, C(3)), 28.21 (*dt*, C(1)); $^{19}$F NMR (188 MHz, $CD_3OD$): δ –134.27 (*dd*, $^2J_{F,F}$ = 164.4, $^3J_{H,F}$ = 14.7, F), –144.44 (*d*, $^2J_{F,F}$ = 164.4, F'), –167.49 (*d*, $^3J_{H,F}$ = 7.3, F-C(5')); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 287.2 $[MLi]^+$ (100%), 286.3 $[MLi-H]^+$ (18%); Anal. calcd. for $C_{10}H_{11}F_3N_2O_4$ (280.202); C, 42.87; H, 3.96; N, 10.00; found: C, 42.58; H, 3.79; N, 10.13.

*(±)-9-[(1* RS*)-2,2-Di(benzyloxymethyl)-3,3-difluoro-cyclopropylmethyl]-9H-6-purinamine* [(±)-**17**]. The reaction was performed under the conditions as described for **8** using **7** (0.76 g, 2.2 mmol), TPP (1.15 g, 4.4 mmol), adenine (0.60 g, 4.4 mmol) suspended in dry 1,4-dioxane (24 *ml*) and DEAD (0.77 g, 4.4 mmol) dissolved in 1,4-dioxane (12 *ml*). The reaction mixture was stirred overnight. The solvent was evaporated and the residue was purified by column chromatography (silica gel, ethyl acetate/methanol 20:1) to afford **17** (0.74 g, 72%) as a white solid; mp: 123-125 °C; $R_F$ (ethyl acetate/methanol 20:1) 0.23; UV (methanol): $\lambda_{max}$= 262 nm (log ε = 4.20); IR (KBr): ν 3332*m*, 3152*m*, 3030*m*, 2879*m*, 2515*m*, 2322 *m*,1653*s*, 1607*s*, 1577*s*, 1485*s*, 1453*m*, 1418*m*, 1360*m*, 1331*m*, 1307*s*, 1232*s*, 1211*m*, 1186*m*, 1166*m*, 1088*s*, 1076*s*, 1042*m*, 1028 *m*; $^1$H NMR (500 MHz, $CD_3OD$): δ 8.18 (*s*, 1 H, H-C(2')), 8.09 (*s*, 1 H, H-C(8')), 7.26-7.17 (*m*, 10 H, phenyl), 4.44-4.39 (*m*, 4 H, $CH_2$-phenyl), 4.44-4.39 (*m*, 2 H, $CH_2N$), 3.86 and 3.69 (AB system, $J_{AB}$ = –10.6, $^4J_{H,F}$ = 2.1, 2 H, $CH_2O_{cis}$), 3.74 and 3.46 (AB system, $J_{AB}$ = –10.3, $^4J_{H,F}$ = 2.6, 2 H, $CH_2O_{trans}$), 2.33-2.30 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (100 MHz, $CD_3OD$): δ 157.24 (*s*, C(6')), 153.75 (*s*, C(2')), 150.64 (*d*, C(4')), 142.16 (*d*, C(8')), 139.30 (*s*, $C_q$ phenyl), 139.10 (*s*, $C_q$ phenyl), 129.35-128.65 (*m*, CH phenyl), 119.90 (*s*, C(5')), 115.87 (*dd*, $^1J_{C,F}$ = 285.5, 294.6, $CF_2$), 74.22 (*t*, $CH_2$-phenyl), 73.83 (*t*, $CH_2$-phenyl), 68.65 (*dt*, $^3J_{C,F}$ = 5.0, $CH_2O_{trans}$), 64.16 (*dt*, $^3J_{C,F}$ = 6.0, $CH_2O_{cis}$), 38.57 (*dt*, $^3J_{C,F}$ = 6.0, $CH_2N$), 35.60 (*t*, $^2J_{C,F}$ = 9.5, C(2)), 29.35 (*dt*, $^2J_{C,F}$ = 10.0, C(1)); $^{19}$F NMR (188 MHz, $CD_3OD$): δ –133.56 (*dd*, $^2J_{F,F}$ = 164.5, $^3J_{H,F}$ = 14.6, F), –144.90 (*d*, $^2J_{F,F}$ = 164.5, F'); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol): 467.3 $[MH]^+$ (37%); 466.3 $[M]^+$ (100%); HRMS calcd. for $C_{11}H_{13}F_2N_5O_2$: 285.1037; found: 285.1038.

*(±) (3* RS*) 3-(6-Amino-9H-purinylmethyl)-2,2-difluoro-1,1-dihydroxymethylcyclopropyl-methanol (= (±)-9-(2,2-difluoro-3,3-di(hydroxymethyl)-cyclopropylmethyl) adenine)* [(±)-**18**]. To a solution of **17** (0.62 g, 1.3 mmol) in methanol (23 *ml*) added cyclohexene (23 *ml*) and *Pearlman's* catalyst (3.06 g, 20%) were added and the reaction was heated under reflux for 6 h. After filtration and evaporation of the volatiles the resulting crude product was subjected to column chromatography (silica gel, ethyl acetate/methanol 3:1) to give **18** (0.18 g, 54%) as a light yellowish solid; mp: 121-123°C; $R_F$ (ethyl acetate/methanol 3:1) 0.33; UV (methanol): $\lambda_{max}$ = 263 nm (log ε = 4.08); IR (KBr): ν 3381*s*, 1649*s*, 1606*s*, 1578*m*, 1475*m*, 1421*m*, 1383*m*, 1334*m*, 1306*m*, 1246*m*, 1185*m*, 1152*m*, 1049*m*, 1018*m*, 1001 *m*; $^1$H NMR (500 MHz, $CD_3OD$): δ 8.20 (*s*, 1 H, H-C(2')), 8.18 (*s*, 1 H, H-C(8')), 4.51-4.48 (*m*, 2 H, $CH_2N$), 4.04 and 3.83 (AB system, $J_{AB}$ = –11.93, $^4J_{H,F}$ = 1.92, 2 H, $CH_2$-$OH_{trans}$), 3.83 and 3.60 (AB system, $J_{AB}$ = –11.41, 2 H, $CH_2$-$OH_{cis}$), 2.20-2.15 (*m*, 1 H, cyclopropyl); $^{13}$C NMR (125 MHz, $CD_3OD$): δ 157.37 (*s*, C(6')), 153.75 (*d*, C(2')), 150.59 (*s*, C(4')), 142.46 (*d*, C(8')), 120.01 (*s*, C(5')), 116.31 (*dd*, $^1J_{C,F}$ = 284.2, 294.2, $CF_2$), 61.03 (*dt*, $^3J_{C,F}$ = , $CH_2O_{trans}$), 56.14 (*dt*, $^3J_{C,F}$ = , $CH_2O_{cis}$), 38.76 (*dt*, $^3J_{C,F}$ = 5.9, $CH_2N$), 38.47 (*t*, $^2J_{C,F}$ = 10.0, C(1)), 29.54 (*dt*, $^2J_{C,F}$ = 10.0, C(3)); $^{19}$F NMR (188 MHz, $CD_3OD$): –134.63 (*dd*, $^2J_{F,F}$ = 166.1, $^3J_{H,F}$ = 14.7, F), –145.55 (*d*, $^2J_{F,F}$ = 168.2, F'); HPLC-MS (ESI, 4.1 kV, 8 µl/min, $N_2$, methanol/TFA (0.1%)): 293.1 (13%) $[MHLi]^+$, 292.1 (100%) $[MLi]^+$; HRMS calcd. for $C_{25}H_{25}F_2N_5O_2$: 465.1976; found: 465.1977.

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