Synthesis of Spacered Nucleoside Analogues Comprising a Difluorocyclopropane Moiety

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A novel class of difluorinated cyclopropanoic nucleoside analogues containing a propyl spacer between the cyclopropane ring and the heterocycle has been prepared. Some of these compounds showed weak antitumor activity in prelimary screenings. The resolution of these racemic compounds on an analytical scale was performed by HPLC using chiral stationary phases.

Key words: Nucleoside Analogues, Cyclopropanes, HPLC

Introduction

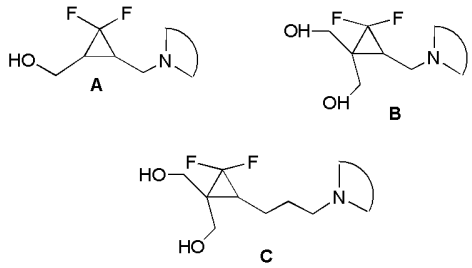
Cyclopropane derived drugs have gained considerable attraction due to their ability to show a variety of promising biological activities. More recently, cyclopropane derived nucleoside analogues have been in the focus of interest as potential chemotherapeutic agents [1 – 4]. Thus, a number of compounds possessing an additional spacer or an unsaturated group between the cyclopropane and the heterocycle as well as compounds with a (in)direct attachment of the heterocycle but with two vicinal or geminal hydroxymethyl units at the cyclopropane skeleton have been accessed but only recently the first successful syntheses of several difluoro-cyclopropyl nucleoside analogues of types **A** and **B** have been reported [5 – 7].

As shown for several acyclonucleosides as penciclovir [8 – 10] decreased conformational flexibility as a consequence of the rather rigid cyclopropyl ring seems to be unfavourable both for the interaction with phosphorylating enzymes as well as for the interaction of the corresponding triphosphates with viral RNA polymerases [8].

Results and Discussion

To obtain higher flexibility in the difluoro cyclopropanoid nucleoside analogues series the synthesis of compounds of type **C** was planned.

[2,2-Bis(benzyloxymethyl)-3,3-difluoro-cyclopropyl]methanol (which has previously been prepared in several steps from easily accessible 1,3-dibenzyloxy-2-propanol) [6, 11] was conveniently oxidized to the corresponding carbaldehyde with 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) [12, 13] in the presence of sodium hypochlorite and sodium bromide. Consequently, the carbaldehyde **1** was subjected to an *Emmons-Horner* reaction [14] to afford the chain elongated α,β-unsaturated ester **2** whose reduction with hydrogen in the presence of *Pearlman's* catalyst gave under simultaneous loss of the benzyl protecting groups the cyclopropylpropanoate **3**. Silylation of **3** with *tert*-butyldimethylsilyl chloride in dichloromethane/pyridine in the presence of catalytical amounts of dimethylaminopyridine gave 89% of **4** whose reduction with diisobutylaluminum hydride (DIBAH) at low temperatures yielded the corresponding (difluoro-cyclopropyl)propanol **5**.



Scheme 1. Target structures.

As previously shown, *Mitsunobu* reactions [15, 16] are well suited for the convenient introduction of heterocycles in good and reproducible high yields. Thus, **5** can be regarded as a well accessible starting material for the straightforward synthesis of the tar-

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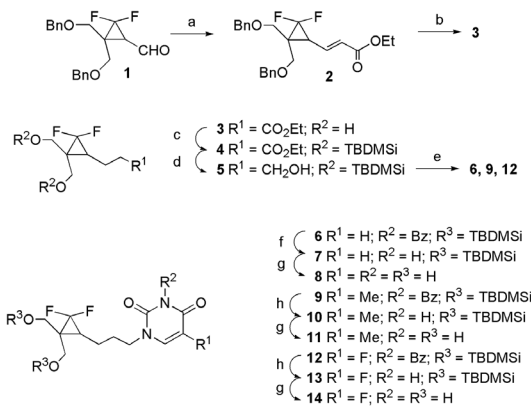

Scheme 2. Reactions: a) NaH/(EtO)P(O)CH_2CO_2Et; b) Pearlman's catalyst, MeOH, H_2; c) TBDMSiCl/DMAP; d) DIBAH, toluene, -40 °C; e) TPP, DIAD, N^3-benzoyl-uracil (for **6**), N^3-benzoyl-thymine (for **9**) and N^3-benzoyl-5-fluoro-uracil (for **12**), respectively; f) NaOH/MeOH; g) Bu_4NF trihydrate, THF; h) NH_4OH; i) TPP, DIAD, adenine.

get molecules. Reaction of **5** with triphenylphosphane (TPP)/diisopropyl azodicarboxylate (DIAD) with N^3-benzoyl-uracil [5, 17] followed by chromatographic work-up gave 92% of fully protected **6**. Consecutive deprotection starting with a debenzoylation reaction gave 99% of **7** whose desilylation was achieved with tetra-*n*-butylammonium fluoride (TBAF) trihydrate to yield 82% of **8**.

In a similar way the key intermediate **5** was allowed to react under *Mitsunobu* conditions with N^3-benzoyl-thymine [5, 18] to afford 83% of fully protected **9**. Debenzoylation of **9** gave **10** whose desilylation under the same conditions as described above finally gave 82% of the (difluoro-bishydroxymethyl-cyclopropyl)thymine **11**.

Accordingly, the 5-fluoro-uracil-analogue **14** was obtained from **5** *via* **12** and **13** [19]. Compound **14** is characterized by the presence of three distinct ^{19}F NMR signals two of them corresponding to the geminal difluoromethylene group showing $^2J_{F,F} = 162.2$ Hz whereas the fluorine substituent attached to the heterocycle is found at $\delta = -167.8$ ppm with $^3J_{F,H} = 7.3$ Hz as expected from analogues.

This approach is equally well suited for the synthesis of analogues of both the purine and the pyrimidine type. Thus, reaction of **5** with unprotected adenine using the same *Mitsunobu* conditions as described above afforded 54% of **15** whose desilylation gave the (difluoro-bishydroxymethyl-cyclopropyl)adenine **16** in 78% yield.

Table 1. HPLC separation of the enantiomers of nucleoside analogues [Daicel Chiralpak AD columns, 4.6 mm × 250 mm; 20 °C, hexane/2-propanol 90/10 (*v*/*v*)].

Compound	$t_{R(1)}$ (min)	$t_{R(2)}$ (min)	α	λ (nm)
8	21.55	37.49	1.73	270
14	28.03	40.77	1.45	278
16	15.92	23.87	1.49	266

Several of these compounds showed weak to moderate antitumor activity. Since it is well known that for many nucleoside analogues the biological activity of these compounds resides only in one enantiomer, a suitable chromatographic separation/analytical method had to be developed. Exploring a variety of different chiral stationary phases, best suited seems the use of a Daicel Chiralpak AD column at 20 °C using hexane/2-propanol (90/10 *v*/*v*) as eluent. Thus, compounds **8**, **14** and **16** were easily separated into their respective enantiomers (*cf*. Table 1).

The stereoselective synthesis of these enantiomers and their incorporation in short artificial DNA and RNA fragments is presently under investigation in our labs.

Experimental Section

General methods: Melting points are uncorrected (*Leica* hot stage microscope), 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'corresponds 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 (electron spray, voltage 4.5 kV, under nitrogen) instrument; Column chromatography was performed on silica gel 60 (FLUKA, 0.04 – 0.06 mm).

(±)-[2,2-Bis(benzyloxymethyl)-3,3-difluoro-cyclopropane]-carbaldehyde ((±) – 1)

A solution of 2,2-[bis(benzyloxymethyl)-3,3-difluoro-cyclopropyl]methanol (12.36 g, 35.4 mmol), TEMPO (0.16 g, 0.7 mmol) in dichloromethane (88 ml) and a solution of KBr (0.83 g, 7.0 mmol) in water (0.81 ml) were vigorously stirred and cooled to -5 °C. The pH of NaOCl (70 ml, 1 M in water, 70 mmol) was adjusted to 9.5 by dissolving $NaHCO_3$ (0.45 g) immediately before use. This NaOCl solution was added over 10 min, keeping the temperature of the reaction mixture between 10 and 15 °C. The mixture was stirred for 10 min. The orange colored organic phase was separated and the aqueous phase was extracted with dichloromethane

(75 ml). The combined organic phases were washed with 10% aqueous HCl (150 ml) containing KI (2.2 g), 10% aqueous $Na_2S_2O_3$ (75 ml), water (75 ml) and brine (75 ml). The organic phase was dried over $MgSO_4$, the solvent removed under reduced pressure and the remaining yellowish liquid was subjected to column chromatography (silica gel, *n*-hexane/ethyl acetate 3:1) to afford **1** (11.2 g, 91%) as a colorless liquid. – R_F (*n*-hexane/ethyl acetate 3:1) 0.39. – UV/vis (methanol): λ_{max} (lg ε) = 260 nm (2.64). – IR (film): ν = 3064w, 3031s, 2868s, 1716s, 1586w, 1496w, 1454m, 1407w, 1364w, 1256w, 1207w, 1172w, 1143m, 1093s, 1028m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (dd, $^4J_{H,F}$ = 1.6 Hz, $^3J_{H,H}$ = 5.5 Hz, 1 H, COH); 7.41 – 7.26 (m, 10 H, phenyl); 4.58 – 4.49 (m, 4 H, CH_2-phenyl); 4.11 and 3.89 (AB system, $J_{A,B}$ = 10.5 Hz, $^4J_{H,F}$ = 3.5 Hz, 2 H, CH_2O_{cis}), 3.89 and 3.44 (AB system, $J_{A,B}$ = 10.5 Hz, $^4J_{H,F}$ = 1.2 Hz, 2 H, CH_2O_{trans}), 2.38 (dd, $^4J_{H,F}$ = 1.6 Hz, $^3J_{H,H}$ = 5.6 Hz, 1 H, cyclopropyl). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.60 (dd, $^3J_{C,F}$ = 4.0 Hz, HCO), 138.68 (s, C_q phenyl), 138.51 (s, $C_q$phenyl), 129.62 – 128.83 (m, C_{phenyl}), 115.04 (dd, $^1J_{C,F}$ = 288.7, 294.7 Hz, CF_2), 74.27 (t, CH_2-phenyl), 74.01 (t, CH_2-phenyl), 68.11 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2O_{trans}), 62.59 (dt, $^3J_{C,F}$ = 5.0 Hz, CH_2O_{cis}), 41.00 (t, $^2J_{C,F}$ = 9.0 Hz, C-2), 40.12 (dt, $^2J_{C,F}$ = 11.0 Hz, C-1). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −131.16 (dd, $^2J_{F,F}$ = 164.5 Hz, $^3J_{H,F}$ = 11.0 Hz, F), −141.58 (d, $^2J_{F,F}$ = 164.5 Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol, N_2): *m/z* (%) = 402.2 (22) $[MHNaMeOH]^+$, 401.2 (100) $[MNaMeOH]^+$, 385.4 (11) $[MLiMeOH]^+$, 369.3 (5) $[MNa]^+$, 353.4 (1) $[MLi]^+$.

Ethyl[2,2-bis(benzyloxymethyl)-3,3-difluoro-cyclopropyl]-propenoate ($(\pm)-$**2**)

To a cooled suspension of sodium hydride (1.25 g, 32.2 mmol) in toluene (21 ml) under argon triethyl phosphonoacetate (7.22 ml, 32.2 mmol) was slowly added and stirred at room temperature until the evolution of hydrogen had ceased. The reaction mixture was cooled once again and a solution of **1** (11.16 g, 32.2 mmol) in toluene (10 ml) added. After stirring for 45 min the mixture was dissolved by the addition of a minimum amount of absolute ethanol. Stirring was continued for further 45 min. Then it was quenched by the addition of water. The product was extracted into ethyl acetate, the organic phase dried ($MgSO_4$) and the solvent evaporated. Purification was achieved by column chromatography (silica gel, *n*-hexane/ethyl acetate 3:1) to afford **2** (12.34 g, 92%) as a colorless liquid. – R_F (*n*-hexane/ethyl acetate 7:3) 0.46. – UV/vis (methanol): λ_{max}(lg ε) = 231 nm (4.11). – IR (film): ν = 3492w, 3064m, 3031m, 2982m, 2871s, 1717s, 1650s, 1496m, 1454s, 1391m, 1367s, 1333m, 1254s, 1200s, 1145s, 1095s, 1029s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.24 (m, 10 H, phenyl), 6.70 (dd, $^3J_{H,H}$ = 9.8 Hz, $^4J_{H,F}$ = 1.6 Hz, 1 H, CH-cyclopropyl), 6.04 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H, CH-CO_2), 4.55 – 4.43 (m, 4 H, CH_2-phenyl), 4.20 (*t*, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2O), 3.78 and 3.66 (AB system, $J_{A,B}$ = 10.6 Hz, $^4J_{H,F}$ = 1.9 Hz, 2 H, CH_2O_{cis}), 3.74 and 3.57 (AB system, $J_{A,B}$ = 10.4 Hz, $^4J_{H,F}$ = 1.9 Hz, 2 H, CH_2O_{trans}), 2.28 (m, 1 H, cyclopropyl), 1.28 (*t*, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.65 (s, CO), 137.88 (dd, $^3J_{C,F}$ = 11.6 Hz, CH-cyclopropyl), 137.49 (s, C_q phenyl), 137.46 (s, $C_q$phenyl), 128.54 – 127.69 (m, C_{phenyl}), 125.44 (d, CH-CO_2), 114.69 (dd, $^1J_{C,F}$ = 290.1, 297.5 Hz, CF_2), 73.16 (t, CH_2-phenyl), 72.87 (t, CH_2-phenyl), 67.13 (dt, $^3J_{C,F}$ = 5.8 Hz, CH_2O_{trans}), 63.43 (*dt*, $^3J_{C,F}$ = 5.8 Hz, CH_2O_{cis}), 60.39 (t, CH_2O), 37.83 (t, $^2J_{C,F}$ = 8.8 Hz, C-2), 32.25 (dt, $^2J_{C,F}$ = 10.1 Hz, C-1), 14.08 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −133.63 (dd, $^2J_{F,F}$ = 160.1 Hz, $^3J_{H,F}$ = 10.9 Hz, F), −142.98 (d, $^2J_{F,F}$ = 160.1 Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol, N_2): *m/z* (%) = 440.1 (22) $[MHNa]^+$, 439.1 (100) $[MNa]^+$, 417.1 (6) $[MH]^+$. – HR-MS: calcd. for $C_{24}H_{26}F_2O_4$: 416.1799; found: 416.1799. – Analysis for $C_{24}H_{26}F_2O_4$(416.47): calcd. C 69.22, H 6.29; found C 69.01, H 6.00.

(±)-Ethyl[3,3-bis(hydroxymethyl)-2,2-difluoro-cyclopropyl]propanoate ($(\pm)-$**3**)

Pearlman's catalyst (0.72 g, 20%) was added to a solution of **2** (12.34 g, 29.6 mmol) in methanol (200 ml) under hydrogen atmospheric pressure. The reaction mixture was stirred at room temperature overnight. After filtration and evaporation of all volatiles the remaining residue was subjected to column chromatography (silica gel, *n*-hexane/ethyl acetate 2:1) to give **3** (5.85 g, 83%) as a colorless liquid. – R_F (*n*-hexane/ethyl acetate 1:2) 0.28. – UV/vis (methanol): λ_{max} (lg ε) = 207 nm (2.40). – IR (film): ν = 3401m, 2982m, 2896m, 1732s, 1468s, 1421s, 1377m, 1263s, 1188s, 1138m, 1112m, 1033s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2O), 3.94 – 3.78 (m, 4 H, CH_2OH), 3.07 (br s, 2 H, OH), 2.46 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2CO), 1.86 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2-cyclopropyl), 1.48 (m, 1 H, cyclopropyl), 1.25 (q, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.52 (s, CO), 115.47 (dd, $^1J_{C,F}$ = 286.7, 295.0 Hz, CF_2), 63.57 (dt, $^3J_{C,F}$ = 5.8 Hz, CH_2O_{trans}), 60.78 (t, CH_2O), 58.36 (dt, $^3J_{C,F}$ = 6.6 Hz, CH_2O_{cis}), 35.31 (t, $^2J_{C,F}$ = 9.7 Hz, C-3), 29.24 (dt, $^2J_{C,F}$ = 9.9 Hz, C-1), 17.42 (dt, $^3J_{C,F}$ = 3.7 Hz, CH_2-cyclopropyl), 13.94 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −136.49 (dd, $^2J_{F,F}$ = 162.7 Hz, $^3J_{F,H}$ = 14.6 Hz, F), −148.99 (d, $^2J_{F,F}$ = 162.7 Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol, N_2): *m/z* (%) = 261.2 (60) $[MNa]^+$, 245.2 (15) $[MLi]^+$, 239.0 (100) $[MH]^+$. – HR-MS: calcd. for $C_{10}H_{16}F_2O_4$: 238.1016; found: 238.1016. – Analysis for $C_{10}H_{16}F_2O_4$ (238.23): calcd. C 50.42, H 6.77; found C 50.31, H 6.51.

(±)-Ethyl[2,2-bis(tert-butyldimethylsilyloxymethyl)-3,3-difluoro-cyclopropyl]propanoate ($(\pm)-$**4***)*

A solution of **3** (5.85 g, 24.6 mmol), *tert*-butyldimethylsilyl chloride (9.08 g, 59.0 mmol) and a catalytic amount of DMAP in dry dichloromethane (25 ml) and dry pyridine (9.8 ml) was stirred at room temperature under argon for 48 h. Then all volatiles were removed under vacuum and the residue subjected to column chromatography (silica gel, *n*-hexane/ethyl acetate 8:1) to give **4** (10.22 g, 89%) as a colorless liquid. – R_F (*n*-hexane/ethyl acetate 5:1) 0.62. – IR (film): $\nu = 3411$m, 2956s, 2930s, 2886m, 2858s, 1737s, 1473s, 1390m, 1377m, 1362m, 1257s, 1187s, 1139m, 1085s, 1034m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.12$ (t, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2O), 3.94 – 3.44 (m, 4 H, CH_2O), 2.44 – 2.41 (m, 2 H, CH_2CO), 1.83 (t, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2-cyclopropyl), 1.40 – 1.30 (m, 1 H, cyclopropyl), 1.24 (t, $^3J_{H,H} = 7.2$ Hz, CH_3), 0.88 (m, 18 H, CH_3C), 0.06 – 0.03 (m, 12 H, CH_3Si). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.98$ (s, CO), 117.01 (dd, $^1J_{C,F} = 287.6$, 295.0 Hz, CF_2), 61.90 (dt, $^3J_{C,F} = 7.0$ Hz, CH_2O_{trans}), 61.32 (t, CH_2O), 56.88 (dt, $^3J_{C,F} = 6.2$ Hz, CH_2O_{cis}), 37.33 (t, $^2J_{C,F} = 9.5$ Hz, C-2), 29.12 (dt, $^2J_{C,F} = 9.9$ Hz, C-1), 26.69 (q, CH_3C), 19.07 (s, CCH_3), 18.64 (dt, $^3J_{C,F} = 3.7$ Hz, CH_2-cyclopropyl), 15.05 (q, CH_3), −4.80 (q, CH_3Si). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -136.98$ (dd, $^2J_{F,F} = 160.9$ Hz, $^3J_{F,H} = 14.7$ Hz, F), −149.33 (d, $^2J_{F,F} = 160.9$ Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol, N_2): *m/z* (%) = 489.3 (100) $[MNa]^+$, 467.2 (20) $[MLi]^+$. – HR-MS calcd. for $C_{22}H_{44}F_2O_4Si_2$: 466.2746; found: 466.2746. – Analysis for $C_{22}H_{44}F_2O_4Si_2$ (466.76): calcd. C 56.61, H 9.50; found C 56.52, H 9.47.

(±)-[2,2-Bis(tert-butyldimethylsilyloxymethyl)-3,3-difluoro-cyclopropyl]propanol ($(\pm)-$**5***)*

DIBAH (74.8 ml, 1.2 M in toluene, 89.8 mmol) was cooled to −40 °C under argon. A solution of **4** (10.22 g, 21.9 mmol) in dry toluene (31 ml) was added at this temperature. The reaction mixture was stirred at −40 °C for 2 h. and then quenched by the addition of methanol and water. The product was extracted into ethyl acetate, the organic phase dried ($MgSO_4$) and the solvent evaporated. Purification was achieved by column chromatography (silica gel, *n*-hexane/ethyl acetate 4:1) to afford **5** (8.00 g, 86%) as a colorless liquid. – R_F (*n*-hexane/ethyl acetate 3:1) 0.43. – IR (film): $\nu = 3350$w, 2955s, 2930s, 2885m, 2858s, 1473s, 1390w, 1362w, 1257s, 1196w, 1169w, 1083s, 1006m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.88$ and 3.63 (AB system, $J_{AB} = 10.8$ Hz, $^4J_{H,F} = 2.1$ Hz, 2 H, CH_2O_{cis}), 3.79 (m, 2 H, CH_2OH), 3.66 and 3.51 (AB system, $J_{AB} = 10.3$ Hz, $^4J_{H,F} = 2.1$ Hz, 2 H, CH_2O_{trans}), 1.80 (br s, 1 H, OH), 1.67 – 1.61 (m, 2 H, CH_2-cyclopropyl), 1.31 – 1.25 (m, 1 H, cyclopropyl), 0.87 (m, 18 H, CH_3C), 0.05 – 0.02 (m, 12 H, CH_3Si). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 116.17$ (dd, $^1J_{C,F} = 286.7$, 295.4 Hz, CF_2), 61.41 (dt, $^3J_{C,F} = 5.8$ Hz, CH_2OH_{trans}), 60.97 (t, CH_2OH), 56.17 (dt, $^3J_{C,F} = 6.7$ Hz, CH_2OH_{cis}), 36.16 (t, $^2J_{C,F} = 10.1$ Hz, C-2), 32.02 (t, CH_2CH_2OH), 28.90 (dt, $^2J_{C,F} = 10.1$ Hz, C-1), 25.72 (q, CH_3C), 18.20 (dt, $^3J_{C,F} = 3.3$ Hz, CH_2-cyclopropyl), −5.7 (q, CH_3Si). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -136.95$ (dd, $^2J_{F,F} = 160.8$ Hz, $^3J_{F,H} = 14.6$ Hz, F), −149.22 (d, $^2J_{F,F} = 160.8$ Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol, N_2): *m/z* (%) = 447.2 (87.5) $[MNa]^+$, 431.2 (67.5) $[MLi]^+$, 425.1 (100) $[MH]^+$. – HR-MS calcd. for $C_{20}H_{42}F_2O_3Si_2$: 424.2640; found: 424.2640. – Analysis for $C_{20}H_{42}F_2O_3Si_2$ (424.72): calcd. C 56.56, H 9.97; found C 56.32, H 10.13.

(±)-3-Benzoyl-1-[(2,2-bis(tert-Butyldimethylsilyloxy-methyl)-3,3-difluoro-cyclopropyl-propyl]1,2,3,4-tetra-hydro-pyrimidine-2,4-dione) ($(\pm)-$**6***)*

To a mixture of **5** (2.00 g, 4.7 mmol), TPP (2.41 g, 9.4 mmol) and N^3-benzoyluracil (2.03 g, 9.4 mmol) in dry 1,4-dioxane (29 ml) a solution of DIAD (1.91 g, 9.4 mmol) in dry 1,4-dioxane (60 ml) was added dropwise under argon 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, *n*-hexane/ethyl acetate 3:1) to afford **6** (2.69 g, 92%) as a white solid, 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); m.p. 78 – 79 °C. – R_F (*n*-hexane/ethyl acetate 3:1) 0.30. – UV/vis (methanol): λ_{max} (lg $\varepsilon = 257$ nm (4.26). – IR (film): $\nu = 3089$m, 2955s, 2930s, 2885s, 2857s, 1750s, 1706s, 1668s, 1599m, 1560m, 1472s, 1438s, 1389s, 1347s, 1255s, 1177s, 1083s, 1005m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.94 – 7.53$ (m, 5 H, benzoyl), 7.55 (d, $^3J_{H,H} = 8.2$ Hz, 1 H, 6-H), 5.79 (d, $^3J_{H,H} = 8.0$ Hz, 1 H, 5-H), 3.93 and 3.69 (AB, $J_{AB} = 10.7$ Hz, $^4J_{H,F} = 1.8$ Hz, 2 H, CH_2O_{cis}), 3.86 and 3.55 (AB, $J_{AB} = 10.4$ Hz, $^4J_{H,H} = 1.7$ Hz, 2 H, CH_2O_{trans}), 3.81 (t, $^3J_{H,H} = 7.3$ Hz, 2 H, CH_2N), 1.88 – 1.78 (m, 2 H, CH_2-cyclopropyl), 1.62 – 1.54 (m, 2 H, CH_2), 1.47 – 1.42 (m, 1 H, cyclopropyl), 0.90 – 0.88 (m, 18 H, CH_3C), 0.07 – 0.00 (m, 12 H, CH_3Si). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 170.36$ (s, CO), 164.89 (s, C-4'), 151.55 (s, C-2'), 147.54 (d, C-6'), 136.48 (s, C_q), 133.15 (d, C_{para}phenyl), 131.53 (d, C_{ortho}phenyl), 130.55 (d, C_{meta} phenyl), 117.57 (dd, $^1J_{C,F} = 286.7$, 294.6 Hz, CF_2), 102.33 (*d*, C-5'), 62.15 (dt, $^3J_{C,F} = 6.6$ Hz, CH_2O_{trans}), 57.13 (dt, $^3J_{C,F} = 6.3$ Hz, CH_2O_{cis}), 49.54 (t, CH_2N), 37.66 (t, $^2J_{C,F} = 9.9$ Hz, C-2), 29.69 (dt, $^2J_{C,F} = 9.9$ Hz, C-1), 29.56 (s, CCH_3), 26.35 (q, CH_3C), 26.32 (q, CH_3C), 20.05 (dt, $^3J_{C,F} = 3.3$ Hz, CH_2-cyclopropyl), 19.05 (dt, $^4J_{C,F} = 1.2$ Hz, CH_2), −5.35 – −5.43 (m, CH_3Si). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -134.26$ (dd, $^2J_{F,F} = 162.6$ Hz, $^3J_{F,H} = 14.7$ Hz, F), −146.70 (d, $^2J_{F,F} = 162.6$ Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol, N_2): *m/z* (%)

= 645.3 (100) $[MNa]^+$, 623.2 (10) $[MH]^+$. – HR-MS: calcd. for $C_{31}H_{48}F_2N_2O_5Si_2$: 622.3069; found: 622.3069. – Analysis for $C_{31}H_{48}F_2N_2O_5Si_2$ (622.81): calcd. C 59.78, H 7.77, N 4.50; found C 59.59, H 7.42, N 4.49.

*(±)-1-[(2,2-Bis(tert-butyldimethylsilyloxymethyl)-3,3-difluoro-cyclopropyl-propyl]1,2,3,4-tetrahydro-pyrimidine-2,4-dione) ((±) – **7**)*

A solution of **6** (2.69 g, 4.3 mmol) in methanol (45 ml) was treated with ammonium hydroxide (18 ml, 25%) overnight. The volatiles were evaporated and the remaining oil was subjected to column chromatography (silica gel, *n*-hexane/ethyl acetate 1:1) to give **7** (2.20 g, 99%) as a white solid; m.p. 82 – 84 °C. – R_F (*n*-hexane/ethyl acetate 1:1) 0.47. – UV/vis (methanol): λ_{max}(lg ε) = 269 nm (3.97). – IR (KBr): ν = 2957s, 2931s, 2886s, 2858s, 1681s, 1473s, 1430m, 1390m, 1361m, 1257s, 1198m, 1173m, 1081s, 1006m cm^{-1}. – ^{1}H-NMR (400 MHz, CD_3OD): δ = 7.55 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 6'-H), 5.63 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 5'-H), 3.92 and 3.68 (AB system, J_{AB} = 10.7 Hz, $^4J_{H,F}$ = 1.9 Hz, 2 H, CH_2O_{cis}), 3.86 and 3.55 (AB system, J_{AB} = 10.4 Hz, $^4J_{H,F}$ = 1.8 Hz, 2 H, CH_2O_{trans}), 3.76 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH_2N), 1.82 – 1.77 (m, 2 H, CH_2-cyclopropyl), 1.58 – 1.54 (m, 2 H, CH_2), 1.46 – 1.42 (m, 1 H, cyclopropyl), 0.89 (s, 18 H, CH_3C), 0.78 – 0.06 (m, 12 H, CH_3Si). – ^{13}C-NMR (100 MHz, CD_3OD): δ = 166.88 (s, C-4'), 152.93 (s, C-2'), 147.23 (d, C-6'), 117.61 (dd, $^1J_{C,F}$ = 286.7, 295.0 Hz, CF_2), 102.41 (d, C-5'), 62.16 (dt, $^3J_{C,F}$ = 7.0 Hz, CH_2O_{trans}), 57.09 (dt, $^3J_{C,F}$ = 6.2 Hz, CH_2O_{cis}), 48.95 (t, CH_2N), 37.63 (t, $^2J_{C,F}$ = 9.9 Hz, C-2), 29.74 (dt, $^2J_{C,F}$ = 9.9 Hz, C-1), 29.64 (s, CCH_3), 26.32 (q, CH_3C), 26.31 (q, CH_3C), 19.99 (dt, $^3J_{C,F}$ = 3.7 Hz, CH_2-cyclopropyl), 19.04 (dt, $^4J_{C,F}$ = 1.7 Hz, CH_2), −5.36 – −5.45 (m, CH_3Si). – ^{19}F NMR (188 MHz, CD_3OD): δ = −134.29 (dd, $^2J_{F,F}$ = 164.4 Hz, $^3J_{F,H}$ = 14.7 Hz, F), −146.77 (d, $^2J_{F,F}$ = 164.4 Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol, N_2): *m/z* (%) = 541.2 (100) $[MNa]^+$, 519.2 (63) $[MH]^+$. – HR-MS calcd. for $C_{24}H_{44}F_2N_2O_4Si_2$: 518.2807; found: 518.2807. – Analysis for $C_{24}H_{44}F_2N_2O_4Si_2$ (518.80): calcd. C 55.56, H 8.55, N 5.40; found C 55.43, H 8.34, N 5.23.

*(±)-1-[(2,2-Difluoro-3,3-bis(hydroxymethyl)-cyclopropyl)-propyl]-1,2,3,4-tetrahydro-pyrimidine-2,4-dione ((±) – **8**)*

To a solution of **7** (2.20 g, 4.2 mmol) in THF (40 ml) was added tetra-*n*-butylammonium fluoride trihydrate (7.95 g, 25.2 mmol). After stirring overnight the solvent was evaporated and the residue subjected to column chromatography (silica gel, ethyl acetate/methanol 8:1) to afford **8** (1.00 g, 82%) as a white solid; m.p. 136 – 138 °C. – R_F (ethyl acetate/methanol 5:1) 0.61. – UV/vis (methanol): λ_{max} (lg ε) = 258 nm (3.93). – IR (KBr): ν = 3462m, 3421m, 2959m, 2564w, 1678s, 1467m, 1402w, 1364w, 1351m, 1276m, 1238w, 1195w, 1158w, 1119w, 1033m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 7.57 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 6'-H), 5.65 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, 5'-H), 3.81 and 3.71 (AB system, J_{AB} = 10.5 Hz, $^4J_{H,F}$ = 1.9 Hz, 2 H, CH_2O_{cis}), 3.79 – 3.74 and 3.66 (AB system, J_{AB} = 11.7 Hz, $^4J_{H,F}$ = 1.9 Hz, 2 H, CH_2O_{trans}), 3.79 – 3.74 (m, 2 H, CH_2N), 1.82 – 1.74 (m, 2 H, CH_2-cyclopropyl), 1.62 – 1.48 (m, 2 H, CH_2), 1.39 – 1.29 (m, 1 H, cyclopropyl). – ^{13}C NMR (100 MHz, CD_3OD): δ = 166.70 (s, C-4'), 152.80 (s, C-2'), 147.17 (d, C-6'), 117.52 (dd, $^1J_{C,F}$ = 286.2, 293.6 Hz, CF_2), 102.30 (d, C-5'), 61.46 (dt, $^3J_{C,F}$ = 6.9 Hz, CH_2O_{trans}), 56.58 (dt, $^3J_{C,F}$ = 6.9 Hz, CH_2O_{cis}), 40.08 (t, CH_2N), 37.18 (t, $^2J_{C,F}$ = 9.3 Hz, C-3), 30.20 (dt, $^2J_{C,F}$ = 10.0 Hz, C-1), 19.20 (dt, $^3J_{C,F}$ = 3.9 Hz, CH_2-cyclopropyl). – ^{19}F NMR (188 MHz, CD_3OD): δ = −134.21 (dd, $^2J_{F,F}$ = 162.7 Hz, $^3J_{F,H}$ = 162.7 Hz, $^3J_{F,H}$ = 14.6 Hz, F), −146.69 (d, $^2J_{F,F}$ = 162.7 Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol, N_2): *m/z* (%) = 602.8 (36) $[M_2Na]^+$, 586.9 (53) $[M_2Li]^+$, 313.2 (25) $[MNa]^+$, 297.2 (100) $[MLi]^+$. – HR-MS calcd. for $C_{12}H_{16}F_2N_2O_4$: 290.1078; found: 290.1078. – Analysis for $C_{12}H_{16}F_2N_2O_4$ (290.27): calcd. C 49.66, H 5.56, N 9.65; found C 49.51, H 5.29, N 9.42.

*(±)-3-Benzoyl-1-[(2,2-bis(tert-butyldimethylsilyloxymethyl)-3,3-difluoro-cyclopropyl)propyl]-5-methyl-1,2,3,4-tetrahydro-pyrimidine-2,4-dione ((±) – **9**)*

The reaction was performed under the conditions as described for **6** using **5** (2.00 g, 4.7 mmol), TPP (2.41 g, 9.4 mmol), N^3-benzoylthymine (2.16 g, 9.4 mmol), 1,4-dioxane (28 ml) and DIAD (1.91 g, 9.4 mmol) in 1,4-dioxane (59 ml). After evaporation of the solvents and purification by column chromatography (silica gel, *n*-hexane/ethyl acetate 7:3) **9** (2.48 g, 83%) 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 10:1). – R_F (*n*-hexane/ethyl acetate = 7:3) 0.27. – UV/vis (methanol): λ_{max} (lg ε) = 258 nm (4.25). – IR (KBr): ν = 3436m, 3069m, 2956s, 2930s, 2886m, 2856s, 2363w, 1751s, 1702s, 1660s, 1600m, 1472s, 1463s, 1438s, 1388m, 1352m, 1257s, 1172m, 1082s, 1005m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 7.91 – 7.52 (m, 6 H, phenyl, 6'-H), 3.92 and 3.68 (AB system, J_{AB} = 10.8 Hz, $^4J_{H,F}$ = 1.6 Hz, 2 H, CH_2O_{cis}), 3.86 and 3.54 (AB system, J_{AB} = 10.5 Hz, $^4J_{H,F}$ = 1.6 Hz, 2 H, CH_2O_{trans}), 3.78 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2N), 1.84 – 1.82 (m, 2 H, CH_2-cyclopropyl), 1.61 – 1.54 (m, 2 H, CH_2), 1.48 – 1.43 (m, 1 H, cyclopropyl), 0.90 – 0.89 (m, 18 H, CH_3C), 0.07 – 0.06 (m, 12 H, CH_3Si). – ^{13}C NMR (100 MHz, CD_3OD): δ = 170.57 (s, CO), 165.40 (s, C-4'), 151.59 (s, C-2'), 143.47 (d, C-6'), 136.49 (s, C_q phenyl), 133.16 (d, C_{para} phenyl), 131.53(d, C_{ortho} phenyl), 130.56 (d, C_{meta} phenyl), 117.66 (dd, $^1J_{C,F}$ = 286.3, 294.6 Hz, CF_2), 110.91 (d, C-5'), 62.17 (dt, $^3J_{C,F}$ = 6.6 Hz,

CH_2O_{trans}), 57.13 (dt, $^3J_{C,F} = 6.2$ Hz, CH_2O_{cis}), 37.66 (t, C-2), 29.38 (dt, $^2J_{C,F} = 9.5$ Hz, C-1), 29.58 (s, CCH_3), 26.34 (q, CH_3C), 26.32 (q, CH_3C), 20.03 (dt, CH_2-cyclopropyl), 18.61 (dt, $^4J_{C,F} = 2.0$ Hz, CH_2), −5.79 – −5.88 (m, CH_3Si). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -134.26$ (dd, $^2J_{F,F} = 164.4$ Hz, $^3J_{F,H} = 14.6$ Hz,F), −146.73 (d, $^2J_{F,F} = 164.4$ Hz, F"). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol + $LiClO_4$, N_2): *m/z* (%) = 643.3 (100) $[MLi]^+$. – HR-MS calcd. for $C_{32}H_{50}F_2N_2O_5Si_2$: 636.3226; found: 636.3226. – Analysis for $C_{32}H_{50}F_2N_2O_5Si_2$ (636.86): calcd. C 60.34, H 7.91, N 4.40; found C 60.22, H 8.09, N 4.25.

*(±)-1-[(2,2-Bis(tert-butyldimethylsilyloxymethyl)-3,3-difluoro-cyclopropyl)propyl]-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione ((±) − **10**)*

A solution of **9** (2.48 g, 3.9 mmol) in methanol (40 ml) was treated with ammonium hydroxide (16 ml) overnight. The volatiles were evaporated and the remaining oil was subjected to column chromatography (silica gel, *n*-hexane/ethyl acetate 6:4) to give **10** (1.43 g, 69%) as a white solid; m. p. 133 °C. – R_F (*n*-hexane/ethyl acetate 6:4) 0.33. – UV/vis (methanol): λ_{max} (lg ε) = 277 nm (3.96). – IR (KBr): ν = 3438m, 3162w, 3030m, 2955m, 2932m, 2887m, 2859m, 1682s, 1475m, 1428w,1387w, 1361w, 1332w, 1256m, 1222w, 1154w, 1077m, 1009w cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.40$ (d, $^4J_{H,H} = 1.2$ Hz, 1 H, 6'-H), 3.92 and 3.68 (AB, $J_{AB} = 10.8$ Hz, $^4J_{H,F} = 2.1$ Hz, 2 H, CH_2O_{cis}), 3.86 and 3.55 (AB, $J_{AB} = 10.7$ Hz, $^4J_{H,F} = 1.9$ Hz, 2 H, CH_2O_{trans}), 3.73 (t, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2N), 1.85 (d, $^4J_{H,H} = 1.2$ Hz, 3 H, CH_3) 1.83 (m, 2 H, CH_2-cyclopropyl), 1.57 – 1.51 (m, 2 H, CH_2), 1.47 – 1.40 (m, 1 H, cyclopropyl), 0.90 – 0.88 (m, 18 H, CH_3C), 0.07 – 0.06 (m, 12 H, CH_3Si). – ^{13}C-NMR (100 MHz, CD_3OD): δ = 166.58 (s, C-4'), 152.64 (s, C-2'), 142.64 (d, C-6'), 117.18 (dd, $^1J_{C,F} = 286.3$, 294.6 Hz, CF_2), 110.88 (s, C-5'), 61.73 (dt, $^3J_{C,F} = 7.0$ Hz, CH_2O_{trans}), 56.50 (dt, $^3J_{C,F} = 6.6$ Hz, CH_2O_{cis}), 48.24 (t, CH_2N), 37.20 (t, $^2J_{C,F} = 9.1$ Hz, C-2), 29.32 (dt, $^2J_{C,F} = 9.7$ Hz, C-1), 25.86 (q, CH_3C), 19.55 (dt, $^3J_{C,F} = 3.7$ Hz, CH_2-cyclopropyl), 18.59 (dt, $^4J_{C,F} = 2.9$ Hz, CH2), −5.60 – −5.91 (m, CH_3Si). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -134.29$ (dd, $^2J_{F,F} = 162.6$ Hz, $^3J_{F,H} = 14.6$ Hz, F), −146.80 (d, $^2J_{F,F} = 162.6$ Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol + $LiClO_4$, N_2): *m/z* (%) = 539.3 (100) $[MLi]^+$. – HR-MS calcd. for $C_{25}H_{46}F_2N_2O_4Si_2$: 532.2964; found: 532.2964. – Analysis for $C_{25}H_{46}F_2N_2O_4Si_2$ (532.82): calcd. C 56.36, H 8.70, N 5.26; found C 56.11, H 8.51, N 5.01.

*(±)-1-[(2,2-Difluoro-3,3-bis(hydroxymethyl)-cyclopropyl)-propyl]-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione ((±) − **11**)*

To a solution of **10** (1.43 g, 2.7 mmol) in THF (36 ml) was added tetra-*n*-butylammonium fluoride trihydrate (5.06 g, 16 mmol). After stirring overnight the solvent was evaporated and the residue subjected to column chromatography (silica gel, ethyl acetate/methanol 3:1) to afford **8** (6.74 g, 82%) as a white solid; m.p. 108 °C. – R_F (ethyl acetate/methanol 3:1) 0.23. – UV/vis (methanol): λ_{max} (lg ε) = 277 nm (3.98). – IR (film): ν = 3399s, 2955s, 2519m, 2369m, 2071m, 1682s, 1472s, 1360s, 1284m, 1217s, 1133m, 1117m, 1033m cm^{-1}. – ^{1}H NMR (400MHz, CD_3OD): δ = 7.45 (d, $^4J_{H,H} = 1.2$ Hz, 1 H, 6'-H), 3.82 – 3.64 (m, 6 H, CH_2OH, CH_2N), 1.81 – 1.71 (m, 2 H, CH_2-cyclopropyl), 1.64 – 1.47 (m, 3 H, cyclopropane, CH_2). – ^{13}C NMR (100 MHz, CD_3OD): δ = 167.06 (s, C-4'), 153.15 (s, C-2'), 143.18 (d, C-6'), 117.68 (dd, $^1J_{C,F} = 286.0$, 294.6 Hz, CF_2), 111.40 (s, C-5'), 61.55 (dt, $^3J_{C,F} = 6.2$ Hz, CH_2O_{trans}), 56.66 (dt, $^3J_{C,F} = 5.8$ Hz, CH_2O_{cis}), 48.72 (t, CH_2N), 37.17 (t, $^2J_{C,F} = 9.9$ Hz, C-3), 30.21 (dt, $^2J_{C,F} = 9.9$ Hz, C-1), 19.87 (dt, $^3J_{C,F} = 3.7$ Hz, CH_2-cyclopropyl), 12.08 (q, CH_3). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -134.26$ (dd, $^2J_{F,F} = 162.5$ Hz, $^3J_{F,H} = 14.6$ Hz, F), −146.76 (d, $^2J_{F,F} = 162.5$ Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol + $LiClO_4$, N_2): *m/z* (%) = 311.2 (100)$[MLi]^+$. – HR-MS calcd. for $C_{13}H_{18}F_2N_2O_4$: 304.1234; found: 304.1234. – Analysis for $C_{13}H_{18}F_2N_2O_4$ (304.30): calcd. C 51.31, H 5.96, N 9.21; found C 51.09, H 6.02, N 9.31.

*(±)-3-Benzoyl-1-[(2,2-bis(tert-butyldimethylsilyloxy-methyl)-3,3-difluorocyclopropyl)propyl]-5-fluoro-1,2,3,4-tetrahydropyrimidine-2,4-dione ((±) − **12**)*

The reaction was performed under the conditions described for compound **6** using **5** (2.00 g, 4.7 mmol), TPP (2.41 g, 9.4 mmol), N^3-benzoyl-5-fluorouracil (2.40 g, 9.4 mmol), 1,4-dioxane (28 ml) and DIAD (1.91 g, 9.4 mmol) in 1,4-dioxane (42 ml). After evaporation of the solvents and purification by column chromatography (silica gel, *n*-hexane/ethyl acetate 3:1) **12** (1.50 g, 50%) was obtained as a white solid, 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 10:1); m.p. 92 °C. – R_F (*n*-hexane/ethyl acetate 3:1) 0.30. – UV/vis (methanol): λ_{max} (lg ε) = 258 nm (4.24). – IR (KBr): ν = 3457s, 2956s, 2930s, 2886s, 2856s, 1755s, 1715s, 1674s, 1600m, 1472s, 1450s, 1361m, 1257s, 1163m, 1081s cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 8.02$ (d, $^3J_{H,H} = 6.2$ Hz, 1 H, 6'-H), 7.97 – 7.54 (m, 5 H, phenyl), 3.93 and 3.68 (AB system, $J_{AB} = 10.7$ Hz, $^4J_{H,F} = 1.9$ Hz, 2 H, CH_2O_{cis}), 3.87 and 3.55 (AB system, $J_{AB} = 10.4$ Hz, $^4J_{H,F} = 1.8$ Hz, 2 H, CH_2O_{trans}), 3.79 (t, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2N), 1.89 (m, 2 H, CH_2-cyclopropyl), 1.62 – 1.55 (m, 2 H, CH_2), 1.48 – 1.40 (m, 1 H, cyclopropyl), 0.89 (m, 18 H, CH_3C), 0.07 – 0.05 (m, 12 H, CH_3Si). – ^{13}C NMR (100 MHz, CD_3OD): δ = 169.08 (s, CO), 158.55 (d, $^2J_{C,F} = 27.3$ Hz, C-4'), 150.28 (s, C-2'),141.37 (d, $^1J_{C,F} = 235.4$ Hz, C-5',

136.73 (s, C_q-phenyl), 132.8 (d, C_{para}-phenyl), 131.70 (d, $^2J_{C,F}$ = 33.6 Hz, C-6'), 131.69 (d, C_{ortho}-phenyl), 130.62 (d, C_{meta}-phenyl), 117.60 (dd, $^1J_{C,F}$ = 295.0 Hz, CF_2), 62.16 (dt, $^3J_{C,F}$ = 7.4 Hz, CH_2O_{trans}), 57.16 (dt, $^3J_{C,F}$ = 6.2 Hz, CH_2O_{cis}), 49.70 (t, CH_2N), 37.66 (t, $^2J_{C,F}$ = 9.7 Hz, C-2), 29.65 (dt, $^2J_{C,F}$ = 10.2 Hz, C-1), 29.36 (s, CCH_3), 26.29 (q, CH_3C), 20.01 (dt, $^3J_{C,F}$ = 3.7 Hz, CH_2-cyclopropyl), 19.03 (dt, $^4J_{C,F}$ = 2.4 Hz, CH_2), −5.38 – −5.47 (m, CH_3Si). – ^{19}F NMR (188 MHz, CD_3OD): δ = −134.32 (dd, $^2J_{F,F}$ = 164.5 Hz, $^3J_{F,H}$ = 14.6 Hz, F), −146.75 (d, $^2J_{F,F}$ = 164.5 Hz, F'), −166.75 (s, F"). – HR-MS calcd. for $C_{31}H_{47}F_3N_2O_5Si_2$: 640.2975; found: 640.2975. – Analysis for $C_{31}H_{47}F_3N_2O_5Si_2$ (640.90): calcd. C 58.10, H 7.39, N 4.37; found C 57.98, H 7.19.

(±)-1-[(2,2-Bis(tert-butyldimethylsilyloxymethyl)-3,3-difluoro-cyclopropy)lpropyl]-5-fluoro-1,2,3,4-tetrahydropyrimidine-2,4-dione ((±) − **13***)*

A solution of **12** (1.50 g, 2.3 mmol) in methanol (60 ml) was treated with ammonium hydroxide (15 ml, 25%) overnight. The volatiles were evaporated and the remaining oil was subjected to column chromatography (silica gel, *n*-hexane/ethyl acetate 1:1) to give **13** (1.06 g, 86%) as a white solid; m.p. 86 – 88 °C. – R_F (*n*-hexane/ethyl acetate 1:1) 0.19. – UV/vis (methanol): λ_{max} (lg ε) = 278 nm (3.97). – IR (KBr): ν = 3433m, 3063w, 2957m, 2932m, 2886w, 2859m, 2289w, 1723m, 1660m, 1473m, 1388m, 1362w, 1329w, 1254m, 1170w, 1154w, 1104m, 1077m, 1006w cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 7.82 (d, $^3J_{H,F}$ = 6.3 Hz, 1 H, 6'-H), 3.93 and 3.68 (AB system, J_{AB} = 10.7 Hz, $^4J_{H,F}$ = 1.9 Hz, 2 H, CH_2O_{cis}), 3.87 and 3.53 (AB system, J_{AB} = 10.4 Hz, $^4J_{H,F}$ = 1.8 Hz, 2 H, CH_2O_{trans}), 3.73 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2N), 1.83 – 1.77 (m, 2 H, CH_2-cyclopropyl), 1.58 – 1.49 (m, 2 H, CH_2), 1.46 – 1.42 (m, 1 H, cyclopropyl), 0.90 (s, 18 H, CH_3C), 0.08 – 0.06 (m, 12 H, CH_3Si). – ^{13}C NMR (100 MHz, CD_3OD): δ = 159.93 (d, $^2J_{C,F}$ = 26.1 Hz, C-4'), 151.59 (s, C-2'), 141.82 (*d*, $^1J_{C,F}$ = 233.3 Hz, C-5', 130.13 (d, $^2J_{C,F}$ = 33.1 Hz, C-6', 117.57 (dd, $^1J_{C,F}$ = 286.3, 296.0 Hz, CF_2), 62.17 (dt, $^3J_{C,F}$ = 7.0 Hz, CH_2O_{trans}), 57.11 (dt, $^3J_{C,F}$ = 6.2 Hz, CH_2O_{cis}), 49.09 (t, CH_2N), 37.64 (t, $^2J_{C,F}$ = 9.0 Hz, C-2), 29.71 (dt, $^2J_{C,F}$ = 9.7 Hz, C-1), 29.46 (s, CCH_3), 26.30 (q, CH_3C), 19.94 (dt, $^3J_{C,F}$ = 3.7 Hz, CH_2-cyclopropyl), 19.03 (dt, $^4J_{C,F}$ = 2.5 Hz), −5.37 – −5.45 (m, CH_3Si). – ^{19}F NMR (188 MHz, CD_3OD): δ = −134.31 (dd, $^2J_{F,F}$ = 162.6 Hz, $^3J_{F,H}$ = 14.6 Hz, F), −146.82 (d, $^2J_{F,F}$ = 162.6 Hz, F'), −167.86 (d, $^3J_{F,H}$ = 7.3 Hz, F"). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol + $LiClO_4$): *m/z* (%) = 543.3 (100) $[MLi]^+$. – HR-MS calcd. for $C_{24}H_{43}F_3N_2O_4Si_2$: 536.2713; found: 536.2713. – Analysis for $C_{24}H_{43}F_3N_2O_4Si_2$ (536.79): calcd. C 53.70, H 8.07, N 5.22; found C 53.56, H 8.15, N 5.33.

(±)-1-[(2,2-Difluoro-3,3-bis(hydroxymethyl)-cyclopropyl)-propyl]-5-fluoro-1,2,3,4-tetrahydro-pyrimidine-2,4-dione ((±) − **14***)*

To a solution of **13** (1.06 g, 2.0 mmol) in THF (20 ml) was added tetra-*n*-butylammonium fluoride trihydrate (3.78 g, 12 mmol). After stirring overnight the solvent was evaporated and the residue subjected to column chromatography (silica gel, ethyl acetate/methanol 8:1) to afford **14** (0.61 g, 99%) as a white solid; m.p. 152 – 154 °C. – R_F (ethyl acetate/methanol 8:1) 0.40. – UV/vis (methanol): λ_{max} (lg ε) = 278 nm (3.94). – IR (KBr): ν = 3462m, 3409m, 3073m, 2959m, 2883w, 2841w, 2565s, 2530s, 2358w, 2219m, 2127w, 1674s, 1524w, 1476m, 1444m, 1388m, 1364s, 1320m, 1300m, 1282m, 1263m, 1227s, 1186m, 1159m, 1132m, 1116m, 1060m, 1044s, 1026s cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 7.83 (d, $^3J_{H,F}$ = 6.2 Hz, 1 H, 6'-H), 3.83 – 3.64 (m, 6 H, CH_2OH, CH_2N), 1.83 – 1.73 (m, 2 H, CH_2-cyclopropyl), 1.65 – 1.47 (m, 3 H, cyclopropane, CH_2). – ^{13}C NMR (100 MHz, CD_3OD): δ = 159.98 (d, $^2J_{C,F}$ = 25.7 Hz, C-4'), 151.66 (s, C-2'), 141.84 (d, $^1J_{C,F}$ = 232.8 Hz, C-5'), 131.16 (d, $^2J_{C,F}$ = 33.1 Hz, C-6'), 117.66 (dd, $^1J_{C,F}$ = 285.9, 294.6 Hz, CF_2), 61.57 (dt, $^3J_{C,F}$ = 6.6 Hz, CH_2O_{trans}), 56.65 (dt, $^3J_{C,F}$ = 6.6 Hz, CH_2O_{cis}), 49.17 (t, CH_2N), 37.16 (t, $^2J_{C,F}$ = 9.9 Hz, C-3), 30.16 (dt, $^2J_{C,F}$ = 9.9 Hz, C-1), 19.82 (dt, $^3J_{C,F}$ = 3.7 Hz, CH_2-cyclopropyl). – ^{19}F NMR (188 MHz, CD_3OD): δ = −134.27 (dd, $^2J_{F,F}$ = 162.6 Hz, $^3J_{F,H}$ = 14.6 Hz, F), −146.74 (d, $^2J_{F,F}$ = 162.6 Hz, F'), −167.78 (d, $^3J_{F,H}$ = 7.3 Hz, F"). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol + $LiClO_4$, N_2): *m/z* (%) = 315.1 (100) $[MLi]^+$. – HR-MS calcd. for $C_{12}H_{15}F_3N_2O_4$: 308.0984; found: 308.0984. – Analysis for $C_{12}H_{15}F_3N_2O_4$ (308.26): calcd. C 46.76, H 4.90, N 9.09; found C 46.51, H 4.73, N 9.15.

(±)-9-[(2,2-Bis(tert-butyldimethylsilyloxymethyl)-3,3-difluoro-cyclopropyl)propyl]-9H-6-purineamine ((±) − **15***)*

The reaction was performed under the conditions as described for compound **6** using **5** (2.00 g, 4.7 mmol), TPP (2.41 g, 9.4 mmol), adenine (1.28 g, 9.4 mmol), 1,4-dioxane (52 ml) and DIAD (1.91 g, 9.4 mmol) in 1,4-dioxane (25 ml). After evaporation of the solvents and purification by column chromatography (silica gel, ethyl acetate/methanol 20:1) **15** (1.37 g, 54%) was obtained as a white solid, 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 10:1); m.p. 79 °C. – R_F (ethyl acetate/methanol = 20:1) 0.16. – UV/vis (methanol): λ_{max} (lg ε) = 266 nm (4.08). – IR (KBr): ν = 3425m, 2956m, 2930m, 2888m, 2858m, 1648m, 1601m, 1575m, 1474m, 1439m, 1418w, 1361w, 1326w, 1304m, 1257m, 1189m, 1082m, 1006w cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 8.18 (s, 1 H, 2'-H), 8.11 (s, 1

H, 8'-H), 4.26 (t, $^3J_{H,H} = 6.8$ Hz, 2 H, CH_2N), 3.83 and 3.60 (AB system, $J_{AB} = 10.6$ Hz, 2 H, CH_2O_{cis}), 3.82 and 3.53 (AB system, $J_{AB} = 10.4$ Hz, 2 H, CH_2O_{trans}), 2.02 – 1.96 (m, 2 H, CH_2-cyclopropyl), 1.53 – 1.50 (m, 2 H, CH_2), 1.47 – 1.42 (m, 1 H, cyclopropyl) 0.87 – 0.82 (m, 18 H, CH_3C), 0.04 – 0.01 (m, 12 H, CH_3Si). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 157.54$ (s, C-6'), 153.91 (s, C-2'), 150.92 (d, C-4'), 142.72 (d, C-8'), 117.60 (dd, $^1J_{C,F} = 286.1$, 295.4 Hz, CF_2), 62.10 (dt, $^3J_{C,F} = 7.0$ Hz, CH_2O_{trans}), 57.03 (dt, $^3J_{C,F} = 6.2$ Hz, CH_2O_{cis}), 44.29 (t, CH_2N), 37.59 (t, $^2J_{C,F} = 10.4$ Hz, C-2), 30.70 (s, CCH_3), 29.65 (dt, $^2J_{C,F} = 9.5$ Hz, C-1), 26.28 (q, CH_3C), 26.26 (q, CH_3C), 20.20 (dt, $^3J_{C,F} = 3.7$ Hz, CH_2-cyclopropyl), 19.00 (dt, CH_2), −5.38 – −5.51 (m, CH_3Si). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -134.30$ (dd, $^2J_{F,F} = 162.6$ Hz, $^3J_{F,H} = 14.7$ Hz, F), −146.83 (d, $^2J_{F,F} = 162.6$ Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol + TFA, N_2): *m/z* (%) = 542.3 (100) $[MH]^+$. – HR-MS calcd. for $C_{25}H_{44}F_2N_5O_2Si_2$: 541.3079; found: 541.3079. – Analysis for $C_{27}H_{49}F_2N_5O_2Si_2$ (541.84): calcd. C 55.42, H 8.37, N 12.93; found C 55.39, H 8.28, N 12.99.

(±)-[3-(6-Amino-9H-purinylpropyl)-2,2-difluoro-1,1-bis-(hydroxymethyl)-cyclopropyl]methanol ($(\pm) - \mathbf{16}$*)*

To a solution of **15** (1.37 g, 2.5 mmol) in THF (25 ml) was added tetra-*n*-butylammonium fluoride trihydrate (4.72 g, 15 mmol). After stirring overnight the solvent was evaporated and the residue subjected to column chromatography (silica gel, ethyl acetate/methanol) to afford **16** (0.61 g, 78%) as a white solid; m.p. 158 °C. – R_F (ethyl acetate/methanol 1:1) 0.27. – UV/vis (methanol): λ_{max} (lg ε) = 266 nm (4.11). – IR (KBr): ν = 3387w, 2930w, 2385w, 1671m, 1610m, 1578w, 1473w, 1335w, 1302w, 1262w, 1163w, 1037w cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 8.20$ (s, 1 H, 2'-H), 8.12 (s, 1 H, 8'-H), 4.27 – 4.23 (m, 2 H, CH_2N), 3.78 – 3.63 (m, 4 H, CH_2OH), 2.03 – 1.91 (m, 2 H, CH_2-cyclopropyl), 1.66 – 1.39 (m, 3 H, CH_2, cyclopropyl). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 157.52$ (s, C-6'), 153.87 (d, C-2'), 150.83 (s, C-4'), 142.84 (d, C-8'), 120.19 (s, C-5'), 117.65 (dd, $^1J_{C,F} = 285.9$, 294.6 Hz, CF_2), 61.48 (dt, CH_2O_{trans}), 56.61 (dt, CH_2O_{cis}), 44.41 (t, CH_2N), 37.21 (t, $^2J_{C,F} = 9.3$ Hz, C-3), 30.09 (dt, $^2J_{C,F} = 9.7$ Hz, C-1), 20.10 (dt, $^3J_{C,F} = 3.7$ Hz, CH_2-cyclopropyl). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -134.37$ (dd, $^2J_{F,F} = 162.6$ Hz, $^3J_{F,F} = 14.6$ Hz, F), −146.83 (d, $^2J_{F,F} = 162.6$ Hz, F'). – HPLC-MS (ESI, 4.1 kV, 8 μl/min, methanol + TFA, N_2): *m/z* (%) = 314.3 (100) $[MH]^+$. – HR-MS calcd. for $C_{13}H_{17}F_2N_5O_2$: 313.1250; found: 313.1251. – Analysis for $C_{13}H_{17}F_2N_5O_2$ (313.31): calcd. C 49.84, H 5.47, N 22.35; found C 49.75, H 5.51, N 22.46.

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