Synthesis of Highly Flexible Difluorinated Cyclopropanoid Nucleoside Analogues

René Csuk and Leo Eversmann

Institut für Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Straße 2, D-06120 Halle (Saale), Germany

Reprint requests to Prof. Dr. R. Csuk. E-mail: csuk@chemie.uni-halle.de

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A novel class of (difluorocyclopropyl)propyl nucleoside analogues containing a propyl spacer between the cyclopropane moiety and the heterocycle has been prepared in an easy sequence.

Key words: Nucleoside Analogues, Cyclopropanes

Introduction

A large number of cyclopentanoid or cyclobutanoid carbocyclic nucleoside analogues [1 – 4] have been synthesized as potential chemotherapeutic agents. Recently, cyclopropane derived nucleoside analogues [5, 6] have been in the focus of interest and even more recently the first successful synthesis of several difluorocyclopropyl nucleoside analogues [7 – 11] has been accomplished. The incorporation of one or two fluorine substituents is known to be of advantage both for an improved biological activity, for higher bioavailability as well as for causing a retarded metabolism [12] of several drugs.

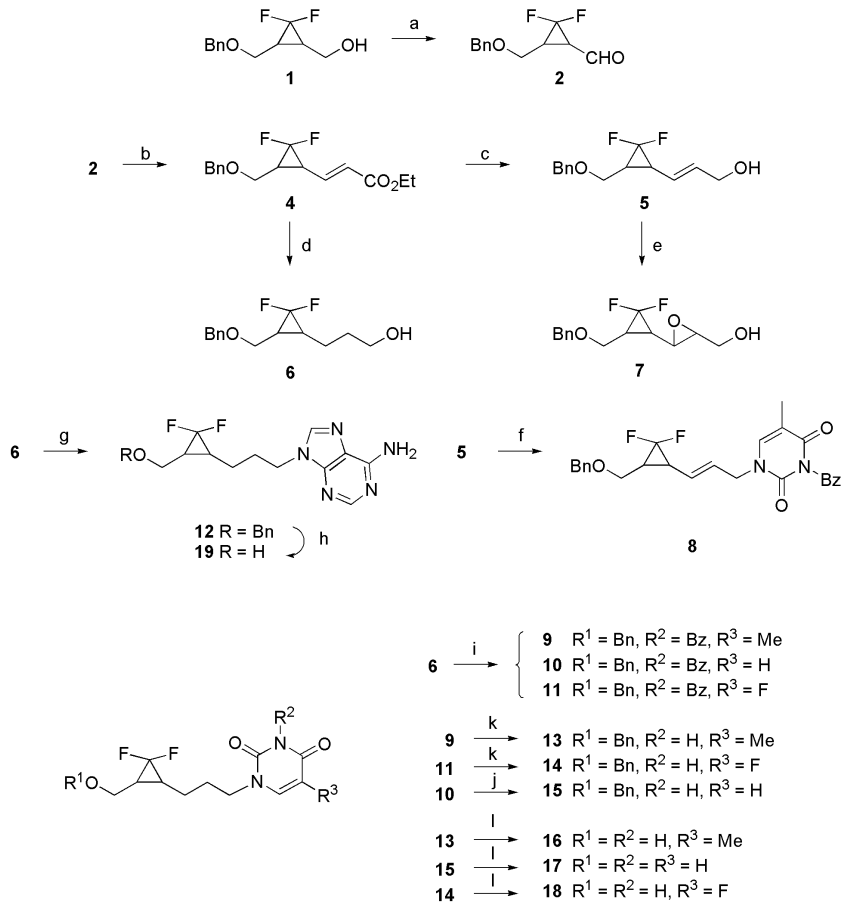
Results and Discussion

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 nucleoside analogues possessing both a higher flexibility as well as a medium chain spacer between the difluorocyclopropane moiety and the heterocycle. From the inspection of models it was concluded that compounds possessing a propyl spacer between the cyclopropane ring and the heterocycle seemed most suited for further biological evaluations. Nucleoside analogues possessing a propyl spacer between the carbo- or heterocyclic ring and the nitrogen base are hitherto unknown; only a few compounds possessing a C_2-spacer [13 – 17] have been described so far.

Retrosynthetic analysis revealed a strategy using the primary alcohol **1** [8] as a suitable starting material and it was assumed that its oxidation to the corresponding aldehyde **2** should be realized either by using the *Dess-Martin* reagent [18] or by applying *Swern* conditions [19] (Scheme 1). The oxidation of **1** using the latter conditions (dimethylsulfoxide, oxalylic chloride in dichloromethane at -60 °C), however, invariably resulted in the formation of a 1:1 mixture of the cyclopropane carbaldehydes **2** (*cis*) and **3** (*trans*) albeit in a yield of 97%. Due to only marginal difference in their chromatographic polarity, the separation of these two aldehydes was rather tedious and required multiple chromatographic separations.

In order to find reaction conditions that allowed the oxidation of **1** to proceed without any *cis*/*trans*-isomerization, pure samples of **2** were treated with triethylamine and with dichloromethane, respectively, both liquids containing traces of moisture. ^{19}F NMR spectroscopic investigations showed that the isomerization of *cis*-**2** in the presence of triethylamine proceeded very rapidly whereas under slightly acidic conditions no isomerization reactions could be observed ever after prolonged reaction times. This finding is in accordance with previous results obtained for several dihalogenated cyclopropane derivatives [20, 21].

Better results for the oxidation of **1** could be obtained, however, by oxidizing **1** with sodium hypochlorite in the presence of catalytic amounts of 2,2,6,6-tetramethylpiperidine-N-oxide (TEMPO) [22] using a biphasic reaction medium. Due to the very short reaction time (less than 15 min.) no isomerization reactions were observed and **2** was obtained in 73% isolated yield after work-up. Compound **2** was shown to



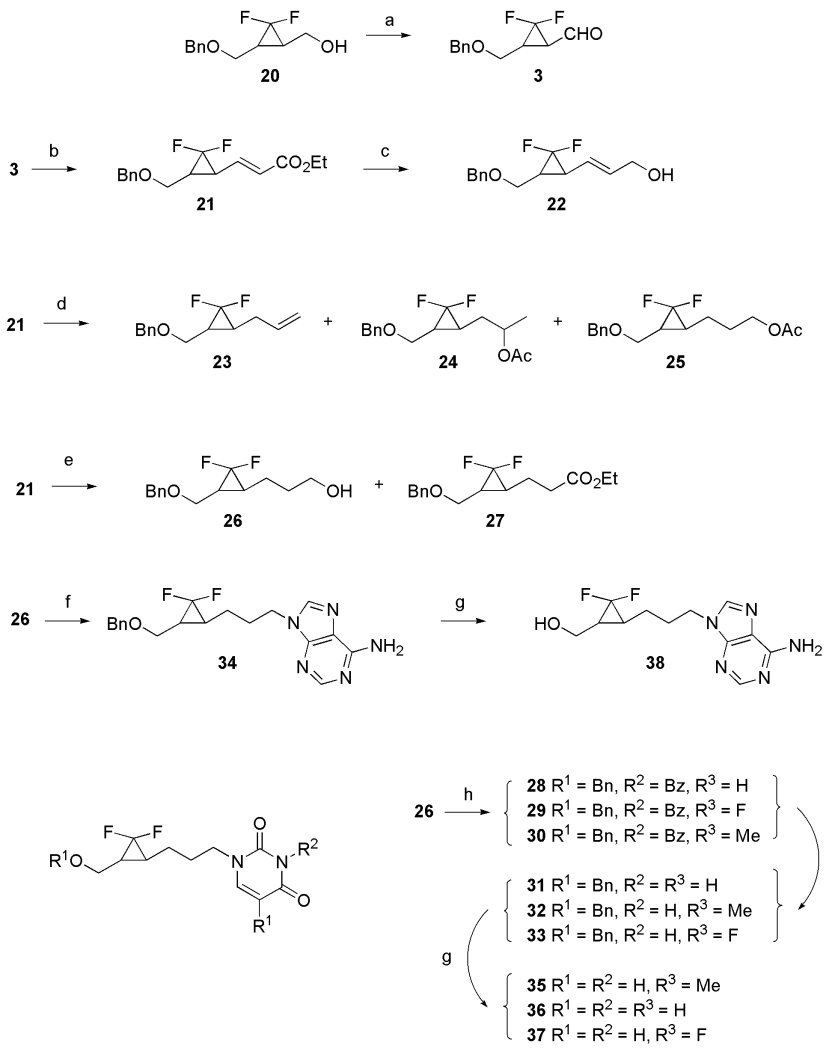
Scheme 1. Reactions: a) TEMPO, NaOCl; b) $(EtO)_2P(O)CH_2CO_2Et$/NaH; c) DIBAH, toluene; d) $NaBH_4$/LiCl/EtOH; e) mCPBA; f) triphenylphosphane, N^3-benzoyl-thymine, DEAD; g) triphenylphosphane, adenine, DEAD; h) $Pd(OH)_2$, cyclohexene, methanol; i) triphenylphosphane, N^3-benzoyl-thymine (for **9**), DEAD; triphenylphosphane, N^3-benzoyl-uracil (for **10**), DEAD; triphenylphosphane, N^3-5-fluoro-uracil (for **11**), DEAD; j) NaOH in dioxane; k) NH_4OH/MeOH; l) $Pd(OH)_2$, cyclohexene, MeOH.

be stable even for several weeks without any significant decomposition when kept refrigerated at -20 °C. Compound **2** showed in the ^{1}H NMR spectrum a coupling constant $^3J_{H,H} = 11.5$ Hz (whereas for the corresponding *trans*-configurated analogue **3** (*vide infra*) $^3J_{H,H} = 6.1$ Hz is observed).

Chain elongation of **2** using *Wittig-Horner* conditions [23] gave 80% of the difluorocyclopropylpropenoate **4**. Treatment of **4** with diisobutylaluminiumhydride (DIBAH) at -78 °C gave 94% of the allylic alcohol **5**. As shown by NMR no isomerization reactions occur during this reduction as long as low temperatures and an uninterrupted work-up is provided. Compound **5** shows in the ^{19}F NMR spectrum signals at $\delta = -125.19$ ppm ($^2J_{F,F} = 160.8$ Hz and $^3J_{F,H} = 12.8$ Hz) and $\delta = -150.22$ ppm ($^2J_{F,F} = 160.8$ Hz).

Reduction of the double bond in **5** under a variety of conditions ($Pd/C/H_2$, $Pd/Al_2O_3/H_2$, $Rh/C/H_2$, $Pd(OH)_2/C/H_2$) invariably led to complex reaction mixtures of numerous products; in addition, reduction of **4** with diborane [24, L-selectride [25] or superhydride [25–27] failed also to give clean reactions; invariably isomerization reactions as well as ring opening reactions were observed.

Reduction of **4** with sodium borohydride in the presence of lithium chloride gave 66% of desired **6** accompanied by the allylic alcohol **5**. Compounds **5** and **6** could not be separated by column chromatography un-



Scheme 2. a) TEMPO, NaOCl; b) $(EtO)_2P(O)CH_2CO_2Et$/NaH; c) DIBAH, toluene; d) BH_3, HOAc; e) $NaBH_4$/LiCl/EtOH; f) triphenylphosphane, adenine, DIAD; g) $Pd(OH)_2$, cyclohexene, methanol; h) DIAD/triphenylphosphane N^3-benzoyl-thymine, N^3-benzoyl-uracil or N^3-5-fluorouracil; i) NaOH in dioxane or NH_4OH in MeOH.

der a variety of different conditions; therefore the crude reaction mixture was subjected to an oxidation with *m*-chloroperbenzoic acid (*m*CPBA) to afford a mixture of unreacted **6** and 13% of the epoxide **7**; these two compounds were easily separated by chromatography.

Although the allylic alcohol **5** gave 64% of the *Mitsunobu* reaction product **8** upon reaction with triphenylphosphane, diethyl azodicarboxylate (DEAD) and N^3-benzoyl-thymine, hydrogenolysis of **8** with $Pd(OH)_2/H_2$ in methanol gave only minor amounts of the desired product invariably accompanied by several products formed either by cyclopropane ring opening reactions and/or simultaneous debenzylation.

Thus **6** was used as a starting material that gave under *Mitsunobu* conditions 49 – 88% of the protected precursors **9 – 12**, respectively. Debenzoylation of **9** with ammonium hydroxide in methanol gave 92% of **13**; in an analogous way from **11** 76% of **14** was obtained. Debenzoylation of **10** with 1 N sodium hydroxide in 1,4-dioxane gave **15**. The compounds **12 – 15** were debenzylated using *Pearlman's* catalyst and cyclohexene in methanol to afford target compounds **16 – 19**, respectively.

For the synthesis of *trans*-configurated compounds a similar strategy could be adopted (Scheme 2). Since the *Swern*-oxidation of **1** resulted in the formation of mixtures of the cyclopropanes **2** and **3** again the TEMPO mediated oxidation of **20** with NaOCl was used and gave the *trans*-aldehyde **3** in 71% yield whose reaction with triethyl phoshonoacetate/sodium hydride

yielded the chain-elongated olefin **21**. Reduction of **21** with DIBAH in toluene at −78 °C afforded the allylic alcohol **22** in 95% yield. Compound **22** is characterized in its ^{19}F NMR spectrum by an AB system at $\delta = -137.38$ and -139.15 ppm ($J_{AB} = 160.8$ Hz).

Reduction of **21** with the borane-THF complex followed by acidic work-up gave a mixture consisting of **23** (15%), **24** (4%) and **25** (11%). Reductions with L-selectride or superhydride failed to give clean reactions. Thus, **21** was reduced with sodium borohydride/lithium chloride and 77% of **26** together with 18% of **27** were isolated. *Mitsunobu* reactions of **26** with N^3-benzoylated pyrimidines gave **28 – 30**, respectively. Compounds **28** and **30** were debenzoylated with 1 N sodium hydroxide in dioxane to afford **31** and **32** whereas the debenzoylation of **29** had to be performed with ammonium hydroxide in methanol to yield **33**.

Mitsunobu reaction of **26** with adenine gave 51% of **34**. Deprotection of the precursors was performed under conditions of transfer-hydrogenolysis. Thus, the reaction of **31 – 34** with cyclohexene in methanol in the presence of *Pearlman's* catalyst gave the target compounds **35 – 38**, respectively.

As exemplified for the two adenine derivatives *cis*-**18** and *trans*-**38**, the differences in their respective ^{1}H, ^{13}C NMR as well as their MS data are rather small and not suited to assign the relative configurations unambiguously, whereas the ^{19}F NMR data are again very helpful. Thus, for *cis*-configurated **18** two signals at $\delta = -123.84$ and -153.03 ppm are found whereas for the geminal difluoro substituents of *trans*-configurated **38** an AB system at $\delta = -137.72$ and -138.62 ppm is observed.

Biological screening of the compounds as well as their incorporation in artificial DNA/RNA fragments is presently under investigation in our labs.

Experimental Section

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

General procedure for Mitsunobu reactions (GP1): The *Mitsunobu* reactions were carried out in dry 1,4-dioxane. Diisopropyl azodicarboxylate (DIAD) as well as diethyl azodicarboxylate (DEAD) were used as obtained. Triphenylphosphane (triphenylphosphane) was recrystallized three times from ethanol and dried. A solution of DIAD or DEAD (2 equiv.) in dry dioxane was added dropwise at room temperature over a period of 2 (for pyrimidines) or 4 h (for purine derivatives) to a suspension of the corresponding alcohol (1 equiv.), triphenylphosphane (2 equivs.) and the purine or pyrimidine derivative. Stirring was continued for 12 h, the solvents were removed under reduced pressure and the residue subjected to chromatography (silica gel or RP18 silica gel).

General procedure for hydrogenolytic debenzylations (GP2): The benzyl ether (1 mmol) was dissolved in methanol (17 ml) and cyclohexene (15 ml). Pearlman's catalyst (1.1 mmol, 20%, wet) was carefully added and the mixture heated under reflux until tlc indicated the completion of the reaction. After cooling to room temperature the catalyst was filtered off through a pad of Celite, the solvent was removed and the residue purified by chromatography.

*(±)-[(1SR, 3RS)-cis-3-Benzyloxymethyl-2,2-difluorocyclopropane]-carbaldehyde ((±)-**2**) and (±)-[(1SR, 3SR)-trans-3-benzyloxymethyl-2,2-difluorocyclopropane]-carbaldehyde ((±)-**3**)*

To a solution of oxalylic chloride (0.84 ml, 9.68 mmol) in dry dichloromethane (26 ml) dimethyl-sulfoxide (1.5 ml, 21 mmol) was added at −60 °C within 10 min. Stirring was continued for another 10 min at the same temperature and a solution of **(±)-1** (2 g, 8.8 mmol) in dichlormethane (14 ml) was added within 5 min followed by the addition of dry triethylamine (6.11 ml, 440 mmol). The reaction mixture was allowed to warm to room temperature, stirred for another 10 min and water (26 ml) was added, the layers were separated, the aqueous layer extracted with dichloromethane (3×10 ml) and the combined organic layers dried ($MgSO_4$) and evaporated. The residue was subjected to chromatography (twice, ethyl acetate/hexane 1:12) to afford the *cis*-aldehyde **(±)-2** (0.59 g, 30%) and the more polar *trans*-aldehyde **(±)-3** (0.73 g, 37%) together with a mixture of **2**/**3**.

Data for **(±)-2**: R_F (ethyl acetate/hexane 1:12) 0.14. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 252$ nm (3.38). – IR (film): $\nu = 3035$w, 2870w, 1715m, 1455m, 1410w, 1365w, 1280w, 1190m, 1075m, 1030w cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.32$ (dd, $^3J_{H,H} = 5.5$ Hz, $^4J_{F,H} = 1.6$ Hz, 1 H, CHO), 7.36 – 7.27 (m, 5 H, H_{Ph}), 4.51 (AB system, $J_{AB} =$

11.8 Hz, 2 H, CH_2-phenyl), 3.96 (dd, $^2J_{H,H} = -11.1$ Hz, $^3J_{H,H} = 7.4$ Hz, 1 H, H-CH'OBn), 3.84 (ddd, $^2J_{H,H} = -11.1$ Hz, $^3J_{H,H} = 8.5$ Hz, $^4J_{F,H} = 1.5$, 1.6 Hz, 1 H, H'-CHOBn), 2.59 (dddd, $^3J_{H,H} = 11.5$, 5.5 Hz, $^3J_{F,H} = 11.5$, 1.6 Hz, 1 H, 1-H), 2.47 (ddddd, $^3J_{F,H} = 11.8$, 2.2 Hz, $^3J_{H,H} = 11.5$, 8.5, 7.4 Hz, 1 H, 3-H). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 192.89$ (dd, $^3J_{C,F} = 4.5$, C=O), 137.24 (s, C_q (phenyl)), 128.63 (d, C_{ortho} (phenyl)), 128.15 (d, C_{meta} (phenyl)), 127.92 (d, C_{para} (phenyl)), 112.77 (dd, $^1J_{C,F} = 292.6$, 285.1 Hz, CF_2), 73.01 (t, CH_2-phenyl), 60.96 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OBn), 35.66 (virt dt, $^2J_{C,F} = 10.2$ Hz, C-1), 30.49 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -122.15$ (virt dt, $^2J_{F,F} = -164.5$ Hz, $^3J_{F,H} = 11.0$ Hz, F_{cis}), -147.00 (d, $^2J_{F,F} = 164.5$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 206(< 1), 177(< 1), 146(< 1), 128(< 1), 115(< 1), 99 (2), 91 (100). – Analysis for $C_{12}H_{12}O_2F_2$ (226.34): calcd. C 63.70, H 5.35; found C 63.54, H 5.37.

Data for **(±)-3**: R_F (ethyl acetate/ hexane 1:12) 0.12. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 262$ nm (3.24). – IR (film): $\nu = 3035$w, 2865w, 2750w, 1720s, 1495w, 1465m, 1395w, 1365m, 1305m 1255m, 1190m, 1100s, 1025m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.32$ (ddd, $^3J_{H,H} = 4.5$ Hz, $^4J_{H,H} = 1.7$ Hz, $^4J_{F,H} = 0.5$ Hz, 1 H, CHO), 7.39 – 7.26 (m, 5 H, H_{Ph}), 4.54 (AB system, $J_{AB} = 11.9$ Hz, 2 H, CH_2-phenyl), 3.69 – 3.60 (m, $^2J_{H,H} = -10.9$ Hz, $^3J_{H,H} = 7.4$, 6.9 Hz, $^4J_{F,H} = 2.8$, 1.5, 1.0, 0.2 Hz, 2 H, CH_2-OBn), 2.77 – 2.67 (ddddd, $^3J_{H,H} = 7.4$, 6.9 Hz, $^3J_{F,H} = 15.3$, 6.1 Hz, $^4J_{H,H} = 0.1$ Hz, 1 H, 3-H), 2.54 – 2.48 (m, $^3J_{H,H} = 4.5$ Hz, $^3J_{F,H} = 13.7$, 6.2 Hz, $^4J_{H,H} = 0.1$ Hz, 1 H, 1-H). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 192.28$ (dd, $^3J_{C,F} = 3.1$, 1 H, C=O), 137.27 (s, C_q (phenyl)), 128.46 (d, C_{ortho} (phenyl)), 127.94 (d, C_{meta} (phenyl)), 127.67 (d, C_{para} (phenyl)), 112.16 (virt t, $^1J_{C,F} = 289.0$ Hz, CF_2), 72.84 (t, CH_2-phenyl), 64.29 (dt, $^3J_{C,F} = 3.9$ Hz, CH_2-OBn), 37.57 (virt dt, $^2J_{C,F} = 11.2$ Hz, C-1), 28.27 (virt dt, $^2J_{C,F} = 9.6$ Hz, C-3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -133.96$ and -136.04 (dAB, $J_{AB} = 160.8$ Hz, $^3J_{F,H} = 13.7$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 225(14), 197 (4), 181 (4), 147 (9), 120 (6), 107 (98), 99 (41), 91 (100). – Analysis for $C_{12}H_{12}O_2F_2$ (226.34): calcd. C 63.70, H 5.35; found C 63.36, H 5.28.

*Compound (±)-**2** by TEMPO-mediated oxidation of (±)-**1***

To a suspension containing **(±)-1** (1.75 g, 7.76 mmol), TEMPO (0.014 g, 0.009 mmol), potassium bromide (0.12 g, 1 mmol), water (0.5 ml) and dichloromethane (14 ml) at -6 °C under stirring an aqueous solution of sodium hypochlorite (1 M, 11 ml, 0.82 mol) containing sodium hydrogencarbonate (0.074 g, 0.88 mmol) was added within 3 min. Stirring was continued for another 8 min and then dichloromethane (25 ml) was added. The layers were separated, the aqueous phase extracted with dichloromethane (3×10 ml), the organic phases were combined and washed with hydrochloric acid [10%, 5 ml containing potassium iodide (0.08 g, 5 mmol)], aq. sodium thiosulfate (10%, 5 ml) and water (5 ml), dried ($MgSO_4$) and the solvents were removed under reduced pressure. The residue was subjected to chromatography (ethyl acetate/hexane $1:4 \rightarrow 1:1$) to afford **(±)-2** (1.27 g, 73%) as an oil and unchanged starting material **(±)-1** (0.35 g, 20%).

*Compound (±)-**3** by TEMPO-mediated oxidation of (±)-**20***

As described above from the TEMPO-mediated oxidation of **(±)-20** (1.75 g, 7.76 mmol) **3** (1.24 g, 71%) and unchanged starting material **(±)-20** (0.35 g, 20%) was obtained.

*(±)-Ethyl 3-[(1SR, 3RS)-cis-3-benzyloxymethyl-2,2-difluorocyclopropyl]-prop-2-enoate ((±)-**4**)*

To a suspension of the ylide (*in situ* prepared from sodium hydride [(60% suspension in mineral oil, 0.73 g, 18.3 mmol) and triethyl phosphonoacetate (3.62 ml, 18.3 mmol) in toluene (70 ml)] at 0 °C a solution of **(±)-2** (4.1 g, 18 mmol) in toluene (14 ml), was added, stirred for 3 h and after aqueous work-up and chromatography (silica gel ethyl acetate/hexane 1:12) **(±)-4** (4.29 g, 80%) was obtained as an oil. – R_F (ethyl acetate/hexane 1:12) 0.24. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 231$ nm (3.06). – IR (film): $\nu =$ 3370m, 3150m, 2920w, 2850w, 1735s, 1650s, 1600s, 1575m, 1480m, 1415m, 1390w, 1365m, 1330m, 1310m, 1245s, 1145m, 1055m, 1030m, 1000m cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.37 - 7.26$ (m, 5 H, H_{Ph}), 6.64 (dddd, $^3J_{H,H} = 15.6$, 9.8 Hz, $^4J_{F,H} = 1.7$ Hz, 1.4, 3-H olefin.), 6.05 (d, $^3J_{H,H} = 15.6$ Hz, 1 H, 2-H olefin.), 4.54 and 4.45 (AB system, $J_{AB} = -11.9$ Hz, 2 H, CH_2-phenyl), 4.19 (q, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2-CH_3), 3.76 – 3.56 (m, 2 H, CH_2-OBn), 2.57 – 2.40 (m, 1 H, 1-H), 2.33 – 2.14 (m, 1 H, 3-H), 1.27 (t, $^3J_{H,H} = 7.2$ Hz, 3 H, CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 165.46$ (s, C=O), 137.50 (s, C_q(phenyl)), 137.37 (ddd, $^3J_{C,F} = 6.6$, 3.3 Hz, C-3 olefin.), 128.43 (d, C_{ortho}(phenyl)), 127.82 (d, C_{meta}(phenyl)), 127.68 (d, C_{para}(phenyl)), 125.17 (d, C-2 olefin.), 113.41 (dd, $^1J_{C,F} = 285.2$, 294.0 Hz, CF_2), 73.00 (t, CH_2-phenyl), 62.84 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OBn), 60.45 (t, CH_2-Me), 29.08 (virt dt, $^2J_{C,F} = 9.6$ Hz, C-1), 28.35 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-3), 14.20 (d, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -124.73$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), -148.30 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): m/z (%) = 276(< 1), 258(< 1), 247(< 1), 228(< 1), 201 (25), 189 (3), 170 (3), 159 (6), 127 (17), 115 (8), 91 (100). – Analysis for $C_{16}H_{18}O_3F_2$ (296.32): calcd. C 64.85, H 6.12; found C 64.86, H 6.36.

*(±) 3-[(1SR, 3RS)-cis-3-Benzyloxymethyl-2,2-difluorocyclopropyl]-prop-2-enol ((±)-**5**)*

Reduction of compound **(±)-4** (1.31 g, 4.43 mmol) DIBAH (1 M in toluene, 13.3 ml, 13.3 mmol) at -78 °C

followed by aqueous work-up and extraction with ethyl acetate (3×15 ml), drying ($MgSO_4$) and chromatography (silica gel, ethyl acetate/hexane 1:3→1:2) afforded **(±)-5** (1.07 g, 95%) as an oil. – R_F (ethyl acetate/hexane 1:3) 0.19. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 243$ nm (3.95). – IR (film): $\nu = 3395$m, 3065m, 3035m, 2870s, 1720s, 1705s, 1600m, 1585m, 1495m, 1470s, 1365s, 1285s, 1205s, 1180s, 1095s, 1025s cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 7.34 – 7.26 (t, 5 H, H_{Ph}), 5.92 (dd, $^3J_{H,H} = 15.4$, 5.5 Hz, 1 H, 2-H olefin.), 5.43 (ddd, $^3J_{H,H} = 15.4$, 8.8 Hz, $^4J_{F,H} =$ 1.7 Hz, 1 H, 3-H olefin.), 4.58 and 4.46 (AB system, $J_{AB} = -11.9$ Hz, 2 H, CH_2-phenyl), 4.09 (virt d, 2 H, CH_2-OH), 3.71 – 3.59 (t, 2 H, CH_2-OBn), 2.47 – 2.31 (t, 1 H, 1-H cyclopr.), 2.18 – 2.01 (t, 1 H, 3-H cyclopr.). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 137.74$ (s, C_q(phenyl)), 134.47 (d, C-2 olefin.), 128.40 (d, C_{ortho}(phenyl)), 127.81 (d, C_{meta}(phenyl)), 127.74 (d, C_{para}(phenyl)), 120.37 (ddd, C-3 olefin), 113.54 (dd, $^1J_{C,F} = 294.4$, 285.2 Hz, CF_2), 72.71 (t, CH_2-phenyl), 62.99 (t, CH_2-OBn), 62.92 (t, CH_2-OH), 27.91 and 27.10 (2×virt dt, $^2J_{C,F} = 10.2$ and 10.0 Hz, C-1 and C-3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -125.19$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), −150.22 (d, $^1J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): m/z (%) = 214(< 1), 199(< 1), 185 (2), 167(< 1), 170(< 1), 144 (1), 123 (3), 110 (1), 91 (100). – HR-MS for $C_{14}H_{16}O_2F_2$: calcd. 254.1118; found 254.1118. – Analysis for $C_{14}H_{16}O_2F_2$ (254.11): calcd. C 66.13, H 6.34; found C 66.03; 6.23.

*(±)-(1SR, 3RS)-cis-3-[3-Benzyloxymethyl-2,2-difluorocyclopropyl]-propanol ((±)-**6**) and (±)-3-[(1SR, 3RS)-3-benzyloxymethyl-2,2-difluorocyclopropyl]-2-hydroxymethyl-oxirane ((±)-**7**)*

Reduction of (±)-**4** (2.26 g, 7.63 mmol) with lithium chloride (1.7 g, 40 mmol) and sodium borohydride (1.5 g, 40 mmol) in THF (33 ml) and ethanol (66 ml) followed by aqueous work-up and chromatography (silica gel, ethyl acetate/hexane 1:2) gave crude **6** as an oil containing **(±)-5** as impurity. This crude mixture (1.35 g, 5.27 mmol, containing approx. 20% of **(±)-5** as determined by ^{1}H NMR) was treated with m-CPBA (0.31 g, 1.3 mmol) in chloroform (12 ml) for 17 h at room temperature, then diluted with additional chloroform (20 ml), washed with an saturated aqueous solution of $NaHCO_3$ (3×3 ml), dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was subjected to chromatography (silica gel, diethylether/pentane 1:2→1:1) to afford **(±)-6** (0.92 g, 66%) and the epoxide **(±)-7** (0.19 g, 13%).

Data for **(±)-6**: oil, R_F (ethyl acetate/hexane 1:4) 0.11. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 262$ nm (2.35). – IR (film): $\nu = 3415$m, 3065w, 3030w, 2875m, 1475m, 1455s, 1365m, 1265m, 1185m, 1155m, 1085s, 1030s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36 - 7.26$ (m, 5 H, H_{Ph}), 4.54 and 4.46 (AB system, $J_{AB} = -11.9$ Hz, 2 H, CH_2-phenyl), 3.68 – 3.52 (m, 4 H, CH_2-OBn, CH_2-OH), 1.93 – 1.83 (m, 1 H, 3-H), 1.69 – 1.48 (m, 6 H, OH, 1-H, CH_2-CH_2OH, CH_2-CH_2CH_2OH). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 137.77 (s, C_q(phenyl)), 128.52 (d,C_{ortho}(phenyl)), 127.91 (d, C_{meta}(phenyl)), 127.76 (d,C_{para}(phenyl)), 114.32 (dd, $^1J_{C,F} = 291.7$, 283.9 Hz, CF_2), 72.87 (t, CH_2-phenyl), 62.98 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OBn), 61.71 (t, CH_2-OH), 31.87 (dt, $^4J_{C,F} = 1.3$ Hz, CH$_2$-CH_2OH), 25.04 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-3), 24.44 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 17.80 (dt, $^3J_{C,F} = 3.3$ Hz, CH$_2$-CH_2CH_2OH). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -126.28$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 11.0$ Hz, F_{cis}), −153.73 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): m/z (%) = 256 (1), 238 (< 1), 159 (< 1), 148 (2), 130 (2), 117 (2), 112 (7), 108 (11), 97 (3), 91 (100). – HR-MS for $C_{14}H_{18}O_2F_2$: calcd. 256.1275; found 256.1275. – Analysis for $C_{14}H_{18}O_2F_2$ (256.13): calcd. C 65.61, H 7.08; found C 65.58; H 7.18.

Data for **(±)-7**: oil. – R_F (ethyl acetate/hexane 1:4) 0.06. – UV/vis (methanol): $\lambda_{max\,1}(\lg\varepsilon) = 262$ nm (2.35), $\lambda_{max\,2}(\lg\varepsilon) = 212$ nm (3.35). – IR (film): $\nu = 3415$m, 3065w, 3030w, 2875m, 1605w, 1475m, 1455s, 1365m, 1265m, 1185m, 1155m, 1085s, 1030m cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.36 - 7.26$ (m, 5 H, H-C(phenyl)), 4.59 and 4.52 (AB system, $J_{AB} = -12.0$ Hz, CH_2-phenyl), 3.88 (dd, $^2J_{H,H} = -12.7$ Hz, $^3J_{H,H} = 2.4$ Hz, H-CH'OH), 3.78 (dddd, $^2J_{H,H} = -11.0$ Hz, $^3J_{H,H} = 9.1$ Hz, $^4J_{F,H} = 1.4$, 1.5 Hz, H-CH'OBn), 3.72 (ddd, $^2J_{H,H} = -11.0$ Hz, $^3J_{H,H} =$ 7.9 Hz, $^4J_{F,H} = 1.6$ Hz, H'-CHOBn), 3.63 (dd, $^2J_{H,H} = -12.7$ Hz, $^3J_{H,H} = 3.7$ Hz, 1 H, H'-CHOH), 3.14 – 4.12 (m, 1 H, H_A oxirane), 2.97 (d, $^3J_{H,H} = 7.3$ Hz, 1 H, H_B oxirane), 2.17 – 1.96 (m, 1 H, 3-H), 1.85 (br s, 1 H, OH), 1.74 – 1.58 (m, 1 H, 1-H). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 137.81 (s, C_q(phenyl)), 128.53 (d, C_{ortho}(phenyl)), 127.91 (d, C_{meta}(phenyl)), 127.88 (d, C_{para}(phenyl)), 112.87 (dd, $^1J_{C,F} = 292.1$, 284.3, CF_2), 72.84 (t, CH_2-phenyl), 62.67 (dt, $^3J_{C,F} = 5.0$ Hz, CH_2-OBn), 60.73 (t, CH_2-OH), 58.50 (d, C_A oxirane), 49.19 (dd, $^3J_{C,F} = 5.0$, C_B oxirane), 25.65 and 25.35 (2 virt dt, $^2J_{C,F} = 10.5$ and 10.2 Hz, C-1, C-3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -125.94$ (virt dt, $^2J_{F,F} = -164.6$ Hz, $^3J_{F,H} = 11.9$ Hz, F_{cis}), −150.56 (d, $^2J_{F,F} = -164.6$ Hz, F_{trans}). – HR-MS for $C_{14}H_{16}O_3F_2$: calcd. 270.10674; found 270.10675.

*(±)-3-Benzoyl-1-[3-((1SR, 3RS)-cis-3-benzyloxymethyl-2,2-difluorocyclopropyl)-prop-2-enyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**8**)*

The synthesis of ±-**8** performed according to GP1 starting from **(±)-5** (0.50 g, 1.97 mmol), triphenylphosphane (1.03 g, 3.94 mmol), N^3-benzoyl-thymine (0.90 g, 3.94 mmol) and DEAD (0.62 ml, 3.94 mmol) in 1,4-dioxane (8 ml/12 ml) followed by chromatography (silica gel, ethyl acetate/hexane

1:3→1:1) to afford **(±)-8** (0.68 g, 74%) as an oil. – R_F (ethyl acetate/hexane 1:1) 0.46. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 281$ nm (4.00), $\lambda_{max\,2}(\lg\varepsilon) = 256$ nm (4.20). – IR (film): $\nu = 3340$w, 3065w, 3035w, 2930w, 2870w, 1750s, 1700s, 1650s, 1600m, 1440s, 1350m, 1315m, 1255s, 1180m, 1095m, 1075m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.92 – 7.26 (m, 10 H, H_{Ph}), 7.01 (d,$^4J_{H,H} = 1.2$ Hz, 6'-H), 5.81 (dt, $^3J_{H,H} = 15.4$, 6.5 Hz, 1 H, 2-H (olefin.)), 5.52 (dd, $^3J_{H,H} = 15.4$, 8.6 Hz, 1 H, 3-H (olefin.)), 4.53 and 4.45 (AB system, $J_{AB} = 12.1$ Hz, 2 H, CH_2-phenyl), 4.35 (dd, $^2J_{H,H} = -15.2$ Hz, $^3J_{H,H} = 6.2$ Hz, 1 H, H-CH'N), 4.22 (dd, $^2J_{H,H} = -15.2$ Hz, $^3J_{H,H} = 6.6$ Hz, 1 H, H'-CHN), 3.67 (ddd, $^2J_{H,H} = -10.9$ Hz, $^3J_{H,H} = 7.3$ Hz, $^4J_{F,H} = 1.6$ Hz, 1 H, H-CH'OBn), 3.56 (dd, $^2J_{H,H} = -10.9$ Hz, $^3J_{H,H} = 9.4$ Hz, 1 H, H'-CHOBn), 2.45 – 2.35 (m, 1 H, 1-H (cyclopr.)), 2.16 – 2.10 (m, 1 H, 3-H (cyclopr.)), 1 91 (s, 3 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.18$ (s, C=O (Bz)), 164,21 (s, C-2'), 150.85 (s, C-4'), 140.27 (s, C-6'), 138.80 (s, C_q(phenyl, Bn)), 136.11 (s, C_q(phenyl, Bz)), 132.77 (d, C-2 (olefin.)), 131.52 (d, C_{para}(phenyl, Bz)), 130.25 (d, C_{ortho}(phenyl, Bz)), 129.61 (d, C_{meta}(phenyl, Bz)), 129.37 (d, C_{ortho}(phenyl, Bn)), 129.04 (d, C_{meta}(phenyl, Bn)), 128.86 (d, C_{para}(phenyl, Bn)), 126.73 (dd, C-3 (olefin.)), 112.14 (dd, CF_2), 73.86 (t, CH_2-phenyl)), 63.85 (dt, $^3J_{C,F} = 4.0$ Hz, CH_2-OBn), 50.43 (t, CH_2-N), 28.71 and 28.39 (2 virt dt, $^2J_{C,F} = 11.0$ and 10.0 Hz, C-1, C-3), 13.24 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -125.43$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), −149.59 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 446 (6), 428 (3), 356 (6), 338 (9), 324 (6), 306 (4), 255 (6), 234 (7), 216 (9), 199 (11), 181 (5), 167 (4), 125 (7), 105 (100). – HR-MS for $C_{26}H_{24}O_4N_2F_2$: calcd. 466.1704; found: 466.1704. – Analysis for $C_{26}H_{24}O_4N_2F_2$ (466.17): calcd. C 66.94, H 5.19, N 6.01; found C 66.83, H 5.34, N 6.11.

*(±)-3-Benzoyl-1-[3-((1SR, 3RS)-cis-3-benzyloxymethyl-2,2-difluorocyclopropyl)-propyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**9**)*

Compound **(±)-9** was synthesized following GP1 starting from **6** (0.41 g, 1.60 mmol), triphenylphosphane (0.84 g, 3.2 mmol), N^3-benzoyl-thymine (0.74 g, 3.20 mmol), DIAD (0.62 ml, 3.2 mmol) in dioxane (23 ml) followed by chromatography (silica gel, ethyl acetate/hexane 1:2→1:1) to afford **9** (0.66 g, 88%) as an oil. – R_F (ethyl acetate/hexane 1:1) 0.44. – UV/vis (methanol): $\lambda_{max\,1}(\lg\varepsilon) =$ 287 nm (4.01), $\lambda_{max\,2}(\lg\varepsilon) = 257$nm (4.24). – IR (flm): $\nu =$ 3065w, 3030w, 2930w, 2865w, 1745m, 1700s, 1655s, 1600w, 1440m, 1350m, 1255m, 1225m, 1180m, 1075m, 1030w, 1000w cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.91 -$ 7.31 (m, 10 H, H-C(phenyl)), 6.99 (d, $^4J_{H,H} = 1.2$ Hz, 1 H, 6'-H), 4.52 and 4.42 (AB system, $J_{AB} = 11.7$ Hz, 2 H, CH_2-phenyl), 3.74 – 3.36 (m, 4 H, CH_2-OBn, CH_2-N), 2.07 – 1.54 (m, 6 H, CH_2-CH_2N, CH_2-CH_2CH_2N, 1-H, 3-H), 1.92 (d, $^4J_{H,H} = 1.2$ Hz, 3 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.21$ (s, C=O (Bz)), 164.26 (s, C-2'), 150.95 (s, C-4'), 141.00 (d, C-6'), 138.88 (s, C_q(phenyl, Bn)), 136.05 (s, C_q(phenyl, Bz)), 132.83 (d, C_{para}(phenyl, Bz)), 131.46 (d, C_{ortho}(phenyl, Bz)), 130.24 (d, C_{meta}(phenyl, Bz)), 129.60 (d, C_{ortho}(phenyl, Bn)), 128.98 (d, C_{meta}(phenyl, Bn)), 128.87 (d, C_{para}(phenyl, Bn)), 115.08 (dd, $^1J_{C,F} = 292.1$, 283.4 Hz, CF_2), 111.89 (s, C-5'), 73.94 (t, CH_2-phenyl), 63.94 (dt, $^3J_{C,F} = 3.6$ Hz, CH_2-OBn), 49.12 (t, CH_2-N), 29.40 (t, CH_2-CH_2N), 25.64 und 25.57 (2 virt dt, $^2J_{C,F} =$ 10.0 and 10.0 Hz, C-1, C-3), 19.70 (dt, $^3J_{C,F} = 4.1$ Hz, CH_2-CH_2CH_2N), 13.20 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -126.26$ (virt dt, $^2J_{F,F} = -160.7$ Hz, $^3J_{F,H} = 14.6$ Hz, F_{cis}), −153.44 (d, $^2J_{F,F} = -160.7$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 468 (4), 389 (5), 363 (9), 342 (13), 277 (10), 257 (74), 241 (9), 216 (4), 194 (3), 153 (5), 111 (3), 105 (100). – HR-MS for $C_{26}H_{26}O_4N_2F_2$: calcd. 468.1861; found 468.1860. – Analysis for $C_{26}H_{26}O_4N_2F_2$ (468.19): calcd. C 66.66, H 5.59, N 5.98; found C 66.79, H 5.39, N 5.71.

*(±)-3-Benzoyl-1-[3-((1SR, 3RS)-cis-3-benzyloxy-methyl-2,2-difluorocyclopropyl)-propyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**10**)*

The synthesis of **(±)-10** was performed according to GP1 starting from **6** (0.44 g, 1.72 mmol), triphenylphosphane (0.9 g, 3.44 mmol), N^3-benzoyl-uracil (0.74 g, 3.44 mmol) and DIAD (0.66 ml, 3.34 mmol) in dioxane (17 + 4 ml) to afford after chromatography (silica gel, ethyl acetate/hexane 1:1) **10** (0.63 g, 80%) as an oil. – R_F (ethyl acetate/hexane 1:1) 0.14. – UV/vis (methanol): $\lambda_{max\,1}(\lg\varepsilon) = 282$ nm (3.99), $\lambda_{max\,2}(\lg\varepsilon) = 258$ nm (4.31). – IR (film): $\nu = 3090$w, 2950w, 2870w, 2360w, 1750m, 1705m, 1660m, 1600w, 1470w, 1435m, 1385w, 1345m, 1255m, 1180w, 1090w, 1030w, 1000w cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.89$ (m, 2 H, H_{ortho} (Bz)), 7.62 (m, 1 H, H_{para} (Bz)), 7.64 (m, 2 H, H_{meta} (Bz)), 7.35-7.25 (m, 5 H, H_{Ph} (Bn)), 7.08 (d, $^3J_{H,H} = 8.0$, 1 H, 6'-H), 5.68 (d, $^3J_{H,H} = 8.0$, 1 H, H-C-5'), 4.51 and 4.42 (AB system, $J_{AB} = -11.7$ Hz, 2 H, CH_2-phenyl), 3.71 – 3.61 (m, 3 H, H-CH'OBn, CH_2-N), 3.52 – 3.47 (m, 1 H, H'-CHOBn), 1.96 – 1.71 (m, 3 H, 3-H, CH_2-CH_2N), 1 65 – 1.42 (m, 3 H, 1-H, CH_2-CH_2CH_2N). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.91$ (s, C=O (Bz)), 162.44 (s, C-2'), 149.79 (s, C-4'), 144.06 (d, C-6'), 137.79 (s, C_q(phenyl) (Bn)), 135.12 (s, C_q(phenyl) (Bz)), 131.51 (d, C_{para}(phenyl) (Bz)), 130.37 (d, C_{ortho}(phenyl) (Bz)), 129.19 (d, C_{meta}(phenyl) (Bz)), 128.51 (d, C_{ortho}(phenyl) (Bn)), 127.90 (d, C_{meta}(phenyl) (Bn)), 127.80 (d, C_{para}(phenyl) (Bn)), 112.57 (dd, $^1J_{C,F} = 292.1$, 283.4, CF_2), 102.03 (s, C-5'), 72.83 (t, CH_2-phenyl), 62.83 (dt, $^3J_{C,F} = 4.2$ Hz, CH_2-OBn), 48.30 (t, CH_2-N), 28.22 (t, CH_2-CH_2N), 24.51 and 24.44 (2 virt dt, $^2J_{C,F} = 10.4$ and 10.4 Hz, C-1, C-

3), 18.55 (dt, $^3J_{C,F}$ = 3.7 Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -126.17$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), −153.34 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): 454 (< 1), 384 (1), 349 (13), 328 (1), 277 (3), 243 (100). – HR-MS for $C_{25}H_{24}O_4N_2F_2$: calcd. 454.1704; found 454.1704. – Analysis for $C_{25}H_{24}O_4N_2F_2$ (454.17): calcd. C 66.07, H 5.32, N 6.16; found C 65.97, H 5.11, N 5.95.

*(±)-3-Benzoyl-1-[3-((1SR, 3RS)-cis-3-benzyloxymethyl-2,2-difluorocyclopropyl)-propyl]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-***11***)*

Compound **(±)-11** was synthesized by a Mitsunobu reaction according to GP1 starting from **6** (0.36 g, 1.40 mmol), triphenylphosphane (0.74 g, 2.80 mmol), N^3-benzoyl-5-fluoro-uracil (0.66 g, 2.80 mmol), DIAD (0.54 ml, 2.8 mmol) in dioxane (17 + 4 ml) followed by chromatography (silica gel, ethyl acetate/hexane 1:3→2:3) to afford 11 as an oil. – R_F (ethyl acetate/hexane 2:3) 0.45. – UV/vis (methanol): $\lambda_{max\,1}(\lg\varepsilon) = 287$ nm (4.03), $\lambda_{max}(\lg\varepsilon) = 259$ nm (4.35). – IR (film): ν = 3070m, 3030m, 2935m, 2870m, 1755s, 1715s, 1670s, 1600m, 1450s, 1360s, 1245s, 1180m, 1075m, 1030m cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (m, 2 H, H_{ortho}), 7.65 (m, 1 H, H_{para}), 7.48 (m, 2 H, H_{meta}), 7.36 – 7.26 (m, 5 H, H_{Ph} (Bn)), 7.21 (d, $^3J_{F,H}$ = 5.3 Hz, 1 H, 6'-H), 4.52 and 4.42 (AB system, J_{AB} = −11.5 Hz, 2 H, CH_2-phenyl), 3.71 – 3.61 (m, 3 H, CH_2-N, H-CH'OBn), 3.49 (dd, $^2J_{H,H} = -10.7$ Hz, $^3J_{H,H}$ = 9.0 Hz, 1 H, H'-CHOBn), 1.95 – 1.75 (m, 3 H, 3-H, CH_2-CH_2N), 1.63 – 1.44 (m, 3 H, 1-H, CH_2-CH_2CH_2N). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.39 (s, C=O (Bz)), 156.34 (d, $^2J_{C,F}$ = 26.9, C-4'), 148.39 (s, C-2'), 140.03 (d, $^1J_{C,F}$ = 240.8 Hz, C-5'), 137.77 (s, C_q(phenyl) (Bn)), 135.51 (s, C_q(phenyl) (Bz)), 131.10 (d, C_{para}(phenyl) (Bz)), 130.54 (d, C_{ortho}(phenyl) (Bz)), 129.35 (d, C_{meta}(phenyl) (Bz)), 128.58 (d, C_{ortho}(phenyl) (Bn)), 128.34 (dd, $^2J_{C,F}$ = 32.3 Hz, C-6'), 128.02 (d, C_{meta}(phenyl) (Bn)), 127.86 (d, C_{para}(phenyl) (Bn)), 113.96 (dd, $^1J_{C,F}$ = 291.7, 283.4 Hz, CF_2), 72.92 (t, CH_2-phenyl), 62.83 (dt, $^3J_{C,F}$ = 4.1, CH_2-OBn), 48.60 (t, CH_2-N), 28.08 (t, CH_2-CH_2N), 24.53 (2 virt dt, $^2J_{C,F}$ = 10.2 and 10.2 Hz, C-1, C-3), 18.56 (dt, $^3J_{C,F}$ = 4.2 Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -126.19$ (virt dt, $^2J_{F,F} = -160.9$ Hz, $^3J_{F,H}$ = 10.9 Hz, F_{cis}), −153.25 (d, $^2J_{F,F} = -160.9$ Hz, F_{trans}), −165.91 (s, F-C-5'). – MS (EI, 70 eV): *m/z* (%) = 472 (< 1), 402 (1), 367 (27), 261 (100). – HR-MS for $C_{25}H_{23}O_4N_2F_3$: calcd. 472.1610; found 472.1610. – Analysis for $C_{25}H_{23}O_4N_2F_3$ (472.16): calcd. C 63.56, H 4.91, N 5.93; found C 63.48, H 4.73, N 6.05.

*(±)-9-[3-((1SR, 3RS)-cis-3-Benzyloxymethyl-2,2-difluorocyclopropyl)-propyl]-9H-6-purinamine ((±)-***12***)*

Compound **(±)-12** was obtained following GP1 from 6 (0.31 g, 1.21 mmol), triphenylphosphane (0.64 g, 2.42 mmol), adenine (0.33 g, 2.42 mmol), DIAD (0.47 ml, 2.42) in dioxane (21 ml) followed by chromatography (silica gel, ethyl acetate/methanol 7:1) to yield **12** (0.22 g, 49%) as a white solid after recrystalization from ethyl acetate. – M.p. 91 – 92 °C. – R_F (ethyl acetate/methanol 7:1) 0.33. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 267$ nm (4.14). – IR (film): ν = 3300m, 2870m, 2285w, 1675m, 1605m, 1575m, 1480m, 1415m, 1365w, 1310m, 1245m, 1190m, 1105m, 1075m, 1030w cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 8.33 (s, 1 H, 2'-H), 7.71 (s, 1 H, 8'-H), 7.36 – 7.26 (m, 5 H, H_{Ph}), 5.61 (br s, 2 H, NH_2), 4.50 and 4.40 (AB system, J_{AB} = −11.7 Hz, 2 H, CH_2-phenyl), 4.21 – 4.10 (m, 2 H, CH_2-N), 3.65 – 3.57 (m, 1 H, H-CH'OBn), 3.51-3.41 (m, 1 H, H'-CHOBn), 2.12 – 1.47 (m, 6 H, 1-H, 3-H, CH_2-CH_2CH_2N, CH_2-CH_2N). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.70 (s, C-6'), 152.91 (d, C-2'), 149.95 (s, C-4'), 140.08 (d, C-8'), 137.61 (s, C_q(phenyl)), 128.40 (d, C_{ortho}(phenyl)), 127.80 (d, C_{meta}(phenyl)), 127.70 (d, C_{para}(phenyl)), 119.53 (s, C-5'), 113.93 (dd, $^1J_{C,F}$ = 291.7, 283.2, CF_2), 72.85 (t, CH_2-phenyl), 62.83 (dt, $^3J_{C,F}$ = 3.9 Hz, CH_2-OBn), 43.24 (t, CH_2-N), 29.43 (t, CH_2-CH_2N), 24.63 und 24.57 (2 virt dt, $^2J_{C,F}$ = 10.4, 10.4 Hz, C-1, C-3), 18.94 (dt, $^3J_{C,F}$ = 3.9 Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -126.24$ (virt d, $^2J_{F,F} = -160.8$ Hz, F_{cis}), −153.32 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 373 (3), 322 (1), 282 (3), 266 (16), 262 (36), 252 (2), 247 (100). – HR-MS for $C_{19}H_{21}ON_5F_2$: calcd. 373.1714; found 373.1714. – Analysis for $C_{19}H_{21}ON_5F_2$ (373.17): calcd. C 61.12, H 5.67, N 18.76; found C 61.00, H 5.49, N 18.51.

*(±)-1-[3-((1SR, 3RS)-cis-3-Benzyloxymethyl-2,2-difluorocyclopropyl)-propyl]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-***13***)*

A solution of (±)-**9** (0.62 g, 1.32 mmol) in methanol (20 ml) and ammonium hydroxide (25%, 14 ml) was kept at room temperature for 2 h. The solvents were removed under diminished pressure and the residue subjected to chromatography (1. silica gel, ethyl acetate/hexane 1:1→ ethyl acetate; 2. silica gel, ethyl acetate) to afford (±)-**13** (0.45 g, 92%) as an oil. – R_F (ethyl acetate/hexane 1:1) 0.19. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 277$ nm (4.02). – IR (film): ν = 3175w, 3035w, 2950w, 1680m, 1470m, 1360m, 1275w, 1245w, 1220w, 1190w, 1075m, 1030w cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 9.90 (br s, 1 H, NH), 7.31 – 7.23 (m, 5 H, H_{Ph}, 6.88 (d, $^4J_{H,H}$ = 1.1 Hz, 1 H, 6'-H), 4.51 and 4.43 (AB system, J_{AB} = 11.7 Hz, 2 H, CH_2-phenyl), 3.70 – 3.58 (m, 3 H, CH_2-N, H-CH'OBn), 3.51 – 3.47 (m, 1 H, H'-CHOBn), 1.95 – 1.37 (m, 6 H, CH_2-CH_2N, CH_2-CH_2CH_2N, 1-H, 3-H), 1.84 (d, $^4J_{H,H}$ = 1.1 Hz, 3 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.61 (s, C-2'), 151.15 (s, C-4'), 140.09 (d, C-6'), 137.77 (s, C_q(phenyl) (Bn)), 128.42 (d, C_{ortho}(phenyl)), 127.79 (d, C_{meta}(phenyl)), 127.71 (d,

C_{para}(phenyl)), 114.00 (dd, $^1J_{C,F} = 292.1$, 283.4 Hz, CF_2), 110.71 (s, C-5'), 72.74 (t, CH_2-phenyl), 62.82 (dt, $^3J_{C,F}$ = 4.6 Hz, CH_2-OBn), 47.56 (t, CH_2-N), 28.29 (t, CH_2-CH_2N), 24.55 and 24.39 (2 virt dt, $^2J_{C,F} = 10.3$ and 10.0 Hz, C-1, C-3), 18.50 (dt, $^3J_{C,F} = 4.1$ Hz, CH_2-CH_2CH_2N), 11.98 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -126.22$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), −153.95 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 364 (10), 283 (< 1), 273 (2), 257 (18), 243 (12), 238 (29), 214 (2), 191 (6), 179 (1), 167 (3), 154 (12), 140 (10), 127 (21), 112 (47), 96 (15), 91 (100). – HR-MS for $C_{19}H_{22}O_3N_2F_2$: calcd. 364.1598; found 364.1598. – Analysis for $C_{19}H_{22}O_3N_2F_2$ (364.16): calcd. C 62.63, H 6.09, N 7.69; found C 62.78, H 6.00, N 7.42.

*(±)-1-[3-((1SR, 3RS)-cis-3-Benzyloxymethyl-2,2-difluorocyclopropyl)-propy l]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-***14***)*

A solution of **(±)-11** (0.64 g, 0.97 mmol) in methanol (10 ml) containing ammonium hydroxide (25%, 14 ml) was stirred overnight and the solvents were removed under diminished pressure. The remaining residue was suspended in water (20 ml), extracted with ethyl acetate (3 × 25 ml), the combined organic layers were dried ($MgSO_4$) and the solvents removed. The residue was purified by chromatography (silica gel, ethyl acetate/hexane 1:1) to yield **(±)-14** (0.27 g, 76%) as an oil. – R_F (ethyl acetate/hexane 1:1) 0.34. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 279$ nm (4.01). – IR (film): ν = 3185m, 3065m, 2955, 2870m, 1715m, 1695m, 1680m, 1470m, 1455m, 1370m, 1290m, 1275m, 1240m, 1215m, 1195m, 1170m, 1075m, 1030m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.85$ (br s, 1 H, NH), 7.35 – 7.25 (m, 5 H, H_{Ph}), 7.10 (d, $^3J_{F,H} = 6.5$ Hz, 1 H, 6'-H), 4.53 and 4.43 (AB system, $J_{AB} = -11.7$ Hz, 2 H, CH_2-phenyl), 3.69 – 3.61 (m, 3 H, CH_2-N, H-CH'OBn), 3.50 (dd, $^2J_{H,H} = -10.7$ Hz, $^3J_{H,H} = 9.0$ Hz, 1 H, H'-CHOBn), 1.97 – 1.71 (m, 3 H, 3-H, CH_2-CH_2N), 1.64 – 1.42 (m, 3 H, 1-H, CH_2-CH_2CH_2N). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.39$ (d, $^2J_{C,F} = 26.1$ Hz, C-4'), 149.70 (s, C-2'), 140.55 (d, $^1J_{C,F} = 238.3$ Hz, C-5'), 137.77 (s, C_q(phenyl) (Bn)), 128.55 (d, C_{ortho}(phenyl) (Bn)), 128.33 (dd, $^2J_{C,F} = 32.3$ Hz, C-6'), 127.98 (d, C_{meta}(phenyl) (Bn)), 127.84 (d, C_{para}(phenyl) (Bn)), 113.99 (dd, $^1J_{C,F} = 293.4$, 283.4 Hz, CF_2), 72.87 (t, CH_2-phenyl), 62.85 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OBn), 48.23 (t, CH_2-N), 28.12 (t, CH_2-CH_2N), 24.58 and 24.48 (2 virt dt, $^2J_{C,F} = 10.4$ and 10.0 Hz, C-1, C-3), 18.52 (dt, $^3J_{C,F} = 4.2$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -126.19$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), −153.27 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}), −167.02 (s, 5'-F). – MS (EI, 70 eV): *m/z* (%) = 368 (9), 349 (< 1), 277 (1), 262 (27), 247 (13), 242 (31), 234 (6), 221 (7), 195 (10), 176 (4), 158 (4), 143 (9), 131 (8), 112 (31), 100 (9), 91 (100). – HR-MS for $C_{18}H_{19}O_3N_2F_3$: calcd. 368.1348; found 368.1348. – Analysis for $C_{18}H_{19}O_3N_2F_3$ (368.13): calcd. C 58.69, H 5.20, N 7.60; found C 58.49, H 4.96, N 7.62.

*(±)-1-[3-((1SR, 3RS)-cis-3-Benzyloxymethyl-2,2-difluorocyclopropyl)-propyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-***15***)*

A solution of **(±)-10** (0.62 g, 1.36 mmol) in 1,4-dioxane (17 ml) containing aq. sodium hydroxide (1 N, 7 ml) was stirred overnight at room temperature, then neutralized by the addition of hydrochloric acid (10%), and the solvents were removed under diminished pressure. The oily residue was suspended in water (20 ml) and extracted with ethyl acetate (3 × 35 ml). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (5 ml) and brine (5 ml), dried ($MgSO_4$), the solvents were removed and the residue was purified by chromatography (silica gel, ethyl acetate/hexane 5:1) to afford **(±)-15** (0.22 g, 50%) as an oil. – R_F (ethyl acetate/hexane 2:1) 0.36. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) =$ 269 nm (4.00). – IR (film): ν = 3190m, 3055m, 2950m, 2870m, 1680s, 1470s, 1420m, 1375m, 1275m, 1245m, 1205m, 1180m, 1075s, 1030m cm^{-1}. – ^{1}H NMR (200 MHz, CD_3OD): $\delta = 7.41$ (d, $^3J_{H,H} = 7.8$ Hz, 1 H, 6'-H), 7.37 – 7.26 (m, 5 H, H_{Ph}), 5.59 (d, $^3J_{H,H} = 7.8$, 1 H, 5'-H), 4.50 and 4,42 (AB system, $J_{AB} = -11.7$ Hz, 2 H, CH_2-phenyl)), 3.68 (virt t, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2-N), 3.59 – 3.47 (m, 2 H, CH_2-OBn), 2.03 – 1.40 (m, 6 H, 1-H, 3-H, CH_2-CH_2N, CH_2-CH_2CH_2N). – ^{13}C NMR (50 MHz, CD_3OD): $\delta = 166.56$ (s, C-2'), 152.64 (s, C-4'), 146.96 (d, C-6'), 139.28 (s, C_q(phenyl) (Bn)), 129.37 (d, C_{ortho}(phenyl) (Bn)), 128.89 (d, C_{meta}(phenyl) (Bn)), 128.77 (d, C_{para}(phenyl) (Bn)), 115.75 (dd, $^1J_{C,F} = 290.6$, 282.1 Hz, CF_2), 102.27 (s, C-5'), 73.69 (t, CH_2-phenyl), 63.99 (dt, $^3J_{C,F} = 4.5$, CH_2-OBn), 48.94 (t, CH_2-N), 29.40 (t, CH_2-CH_2N), 25.87 and 25.57 (2 virt dt, $^2J_{C,F} = 10.4$ and 10.4 Hz, C-1, C-3), 19.67 (dt, $^3J_{C,F} = 3.9$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -123.51$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 13.7$ Hz, F_{cis}), −151.37 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 350 (10), 243 (24), 229 (10), 224 (37), 216 (1), 200 (2), 177 (4), 165 (4), 153 (3), 140 (11), 126 (7), 121 (11), 112 (26), 105 (21), 97 (7), 91 (100). – HR-MS for $C_{11}H_{14}O_3N_2F_2$: calcd. 260.0972; found 260.0972. – Analysis for $C_{11}H_{14}O_3N_2F_2$ (260.10): calcd. C 50.77, H 5.42, N 10.76; found C 50.71, H 5.31, N 10.74.

*(±)-1-[3-((1SR, 3RS)-cis-2,2-Difluoro-3-hydroxymethyl-cyclopropyl)-propyl]-5-methyl-1,2,3,4-tetra-hydro-2,4-pyrimidinedione ((±)-***16***)*

Compound **(±)-16** was obtained by debenzylation of **(±)-13** following GP2 starting from **13** (0.45 g, 1.23 mmol), cyclohexene (19 ml), Pearlman's catalyst (0.95 g) in methanol (21 ml) followed by chromatography (silica gel,

ethyl acetate → ethyl acetate/methanol 7:1) to afford **16** (0.18 g, 53%) as an oil. – R_F (ethyl acetate) 0.20. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 276$ nm (3.93). – IR (KBr): $\nu = 3510$m, 3180m, 3035m, 2965m, 2830w, 2605w, 1680s, 1470s, 1420m, 1390m, 1355m, 1280m, 1230m, 1215m, 1185w, 1130m, 1110m, 1100m, 1050m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.43$ (d, $^4J_{H,H} = 1.2$ Hz, 1 H, 6'-H), 3.80 – 3.59 (m, 4 H, CH_2-N, CH_2-OH), 1.86 (d, $^4J_{H,H} = 1.2$ Hz, 3 H, CH_3). – 1.91 – 1.42 (m, 6 H, CH_2-CH_2N, CH_2-CH_2CH_2N, 1-H, 3-H). – ^{13}C NMR (100 MHz, CD_3OD): 167.06 (s, C-2'), 153.16 (s, C-4'), 143.16 (d, C-6'), 116.05 (dd, $^1J_{C,F} = 290.9$, 282.2 Hz, CF_2), 111.39 (s, C-5'), 55.98 (dt, $^3J_{C,F} = 5.8$ Hz, CH_2-OH), (CH_2-N), 29.59 (t, CH_2-CH_2N), 27.83 (virt dt, $^2J_{C,F} = 10.3$ Hz, C-3), 25.84 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 19.56 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-CH_2CH_2N), 12.08 (q, CH_3). – ^{13}C NMR (100 MHz, d_6-acetone): $\delta = 165.14$ (s, C-2'), 152.10 (s, C-4'), 141.94 (d, C-6'), 113.26 (dd, $^1J_{C,F} = 290.0$, 282.2 Hz, CF_2), 110.31 (s, C-5'), 55.60 (dt, $^3J_{C,F} = 5.8$ Hz, CH_2OH), 48.01 (t, CH_2-N), 29.35 (dt, $^4J_{C,F} = 1.7$ Hz, CH_2-CH_2N), 27.88 (virt dt, $^2J_{C,F} = 10.3$ Hz, C-3), 25.44 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 19.22 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-CH_2CH_2N), 12.18 (q, CH_3). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -123.85$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), −153.05 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 274 (50), 257 (12), 243 (31), 236 (8), 226 (12), 206 (2), 191 (19), 177 (15), 164 (15), 152 (39), 139 (47), 126 (60), 117 (6), 111 (23), 96 (100). – HR-MS for $C_{12}H_{16}O_3N_2F_2$: calcd. 274.1129; found 274.1129. – Analysis for $C_{12}H_{16}O_3N_2F_2$ (274.11): calcd. C 52.55, H 5.88, N 10.21; found C 52.33, H 5.64, N 10.06.

*(±)-1-[3-((1SR, 3RS)-cis-2,2-Difluoro-3-hydroxymethyl-cyclopropyl)-propyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**17**)*

Compound **(±)-17** was obtained by debenzylation of **(±)-15** following GP2 starting from **15** (0.2 g, 0.57 mmol), cyclohexene (8.6 ml), Pearlman's catalyst (0.44 g) in methanol (10 ml) followed by chromatography (silica gel, ethyl acetate/methanol) to afford **17** (0.12 g, 81%) as an oil. – R_F (ethyl acetate/methanol) 0.50. – UV (methanol): $\lambda_{max}(\lg\varepsilon) = 271$ nm (3.99). – IR (film): $\nu = 3400$m, 3195m, 3050m, 2955m, 2875m, 1680s, 1470s, 1420m, 1395m, 1360m, 1275m, 1245m, 1205m, 1170m, 1110m, 1040m, 1000m cm^{-1}. – ^{1}H NMR (200 MHz, CD_3OD): $\delta = 7.58$ (d, $^3J_{H,H} = 7.8$ Hz, 1 H, 6'-H), 5.65 (d, $^3J_{H,H} = 7.8$ Hz, 1 H, H-C-5'), 3.81 – 3.65 (m, 4 H, CH_2-OH, CH_2-N), 1.96 – 1.38 (m, 6 H, CH_2-CH_2N, CH_2-CH_2CH_2N, 1-H, 3-H). – ^{13}C NMR (50 MHz, CD_3OD): $\delta = 166.70$ (s, C-2'), 152.80 (s, C-4'), 147.17 (d, C-6'), 115.93 (dd, $^1J_{C,F} = 290.2$, 281.7 Hz, CF_2), 102.30 (d, C-5'), 55.93 (dt, $^3J_{C,F} = 5.4$ Hz, CH_2-OH), 29.57 (dt, $^4J_{C,F} = 1.5$ Hz, CH_2-CH_2N), 27.82 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-3), 25.83 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 19.60 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-CH_2CH_2N). – ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 164.72$ (s, C-2'), 152.09 (s, C-4'), 146.21 (d, C-6'), 116.10 (dd, $^1J_{C,F} = 290.2$, 281.7 Hz, CF_2), 102.06 (d, C-5'), 55.53 (dt, $^3J_{C,F} = 5.4$ Hz, CH_2-OH), 48.35 (t, CH_2-N), 29.28 (dt, $^4J_{C,F} = 1.3$ Hz, CH_2-CH_2N), 27.82 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-3), 25.40 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1) 19.20 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -123.77$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), −152.94 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 260 (6), 243 (4), 229 (20), 222 (5), 207 (4), 192 (3), 177 (25), 163 (11), 150 (15), 138 (32), 130 (8), 125 (34), 117 (12), 113 (37), 97 (19), 82 (100). – HR-MS for $C_{11}H_{14}O_3N_2F_2$: calcd. 260.0972; found 260.0972. – Analysis for $C_{11}H_{14}O_3N_2F_2$ (260.10): calcd. C 50.77, H 5.42, N 10.76; found C 50.65, H 5.31, N 10.53.

*(±)-1-[3-((1SR, 3RS)-cis-2,2-Difluoro-3-hydroxymethyl-cyclopropyl)-propyl]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**18**)*

Compound **(±)-18** was obtained by debenzylation following GP2 starting from **(±)-14** (0.19 g, 0.52 mmol), cyclohexene (8 ml), Pearlman's catalyst (0.4 g) in methanol (9 ml) followed by chromatography (1. silica gel ethyl acetate/hexane 10:1 → ethyl acetate, 2. silica gel ethyl acetate) to afford **18** (0.11 g, 81%) as an oil. – R_F (ethyl acetate) 0.47. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 284$ nm (3.87). – IR (KBr): $\nu = 3400$m, 3190m, 3065m, 2960m, 2830w, 1695s, 1475m, 1365m, 1275m, 1240s, 1190w, 1160m, 1110m, 1035m, 1000m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.84$ (d, $^3J_{F,H} = 6.3$ Hz, 6'-H), 3.79 – 3.59 (m, 4 H, CH_2-OH, CH_2-N), 1.89 – 1.40 (m, 6 H, CH_2-CH_2N, CH_2-CH_2CH_2N, 1-H, 3-H). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 159.88$ (d, $^2J_{C,F} = 25.8$ Hz, C-4'), 151.65 (s, C-2'), 141.84 (d, $^1J_{C,F} = 232.9$ Hz, C-5'), 131.18 (dd, $^2J_{C,F} = 33.2$ Hz, C-6'), 116.04 (dd, $^1J_{C,F} = 290.9$, 282.2 Hz, CF_2), 55.96 (dt, $^3J_{C,F} = 5.4$ Hz, CH_2-OH), 49.08 (t, CH_2-N), 29.33 (t, CH_2-CH_2N), 27.79 (virt dt, $^2J_{C,F} = 10.2$ Hz, C-3), 25.78 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 19.48 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -123.78$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 12.8$ Hz, F_{cis}), −152.92 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}), −167.76 (s, 5'-F). – MS (EI, 70 eV): *m/z* (%) = 278 (24), 261 (7), 247 (26), 240 (4), 230 (5), 210 (5), 195 (49), 181 (21), 176 (4), 168 (23), 156 (41), 149 (10), 143 (74), 130 (57), 128 (10), 117 (14), 111 (21), 100 (100). – HR-MS for $C_{11}H_{13}O_3N_2F_3$: calcd. 278.0878; found 278.0878.

*(±)-9-[3-((1SR, 3RS)-cis-2,2-Difluoro-3-hydroxymethyl-cyclopropyl)-propyl]-9H-6-purinamine ((±)-**19**)*

Compound **(±)-19** was obtained by debenzylation according to GP2 starting from **(±)-12** (0.22 g, 0.59 mmol), cy-

clohexene (9 ml), Pearlman's catalyst (0.44 g) in methanol followed by chromatography (silica gel, ethyl acetate/hexane 6:1→3:1) to afford **19** (0.11 g, 66%) as a white solid. – M.p. 140 – 142 °C. – R_F (ethyl acetate/methanol 3:1) 0.29. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 267$ nm (4.14). – IR (KBr): $\nu = 3305$m, 3105m, 2935w, 1680m, 1605s, 1575m, 1475m, 1420m, 1360w, 1335m, 1305m, 1250m, 1205w, 1180w, 1105w, 1080w, 1040m, 1005m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 8.20$ (s, 1 H, 2'-H), 8.12 (s, 1 H, 8'-H), 4.30 – 4.19 (m, 2 H, CH_2-N), 3.66 – 3.58 (m, 2 H, CH_2-OH), 2.10 – 1.92 (m, 2 H, CH_2-CH_2N), 1.88 – 1.78 (m, 1 H, 3-H), 1.75 – 1.65 (m, 1 H, 1-H), 1.60 – 1.44 (m, 2 H, CH_2-CH_2CH_2N). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 157.52$ (s, C-6'), 153.87 (d, C-2'), 150.83 (s, C-4'), 142.81 (d, C-8'), 120.18 (s, C-5'), 116.00 (dd, $^1J_{C,F} = 291.1$, 282.4 Hz, CF_2), 55.90 (dt, $^3J_{C,F} = 3.4$ Hz, CH_2-OH), 44.44 (t, CH_2-N), 30.63 (t, CH_2-CH_2N), 27.82 (virt dt, $^2J_{C,F} = 10.2$ Hz, C-3), 25.70 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 19.75 (dt, $^3J_{C,F} = 4.2$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -123.84$ (virt dt, $^2J_{F,F} = -160.8$ Hz, $^3J_{F,H} = 10.9$ Hz, F_{cis}), -153.03 (d, $^2J_{F,F} = -160.8$ Hz, F_{trans}). – MS (EI, 70 eV): *m/z* (%) = 283 (14), 263 (58), 252 (11), 246 (99), 232 (23), 226 (6), 214 (2), 206 (1), 188 (12), 176 (11), 162 (15), 148 (82), 135 (100). – HR-MS for $C_{12}H_{15}ON_5F_2$: calcd. 283.1245; found 283.1245. – Analysis for $C_{12}H_{15}ON_5F_2$ (283.12): calcd. C 50.88, H 5.34, N 24.72; found C 50.64, H 5.49, N 24.83.

*(±)-Ethyl 3-[(1SR, 3SR)-3-benzyloxymethyl-2,2-difluorocyclopropyl]-prop-2-enoate ((±)-**21**)*

To a solution of sodium hydride (60% suspension in mineral oil, 0.9 g, 22.1 mmol) at 0 °C in dry toluene (86 ml) triethyl phosphonoacetate (4.4 ml, 22.1 mmol) was added. Stirring was continued at room temperature until the evolution of hydrogen had ceased. The resulting clear solution was cooled to 0 °C and **(±)-3** (5 g, 22.1 mmol) dissolved in toluene (17 ml) was added dropwise. After 1 hour the reaction mixture was allowed to warm to room temperature and the precipitated viscous oil was dissolved by adding a little amount of absolute ethanol. Stirring was continued for another two hours and water (70 ml) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (4 × 30 ml). The combined organic layers were dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The remaining crude oil was purified by column chromatography (silica gel, ethyl acetate/hexane 1:7) to afford **(±)-21** (5.42 g, 83%) as a colorless oil. – R_F (ethyl acetate/ hexane 1:9) 0.47. – UV/vis (methanol): $\lambda_{max\,1}(\lg\varepsilon) = 219$ nm (4.3), $\lambda_{max\,2}(\lg\varepsilon) = 229$ nm (4.2). – IR (film): $\nu = 3065$w, 3030w, 2985w, 2930w 2865m, 1720s, 1655m, 1495w, 1470m, 1455m, 1390w, 1370m, 1340m, 1310m, 1275s, 1205s, 1175m, 1140s, 1095m, 1025m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36 - 7.25$ (m, 5 H, H_{Ph}), 6.59 (dddd, $^3J_{H,H} = 15.6$, 9.6 Hz, $^4J_{F,H} = 1.6$, 1.2 Hz, 1 H, 3-H propen.), 5.97 (d, $^3J_{H,H} = 15.6$ Hz, 1 H, 2-H propen.), 4.53 and 4.48 (AB system, $J_{AB} = -11.9$ Hz, 2 H, CH_2-phenyl), 4.18 (q, $^3J_{H,H} = 7.1$ Hz, 2 H, CH_2-Me), 3.61 (ddd, $^2J_{H,H} = -11.0$ Hz, $^3J_{H,H} = 7.7$ Hz, $^4J_{F,H} = 1.1$ Hz, 1 H, H-CH'OBn), 3.59 (dddd, $^2J_{H,H} = -11.0$ Hz, $^3J_{H,H} = 6.7$ Hz, $^4J_{F,H} = 3.4$, 1.2 Hz, 1 H, H'-CHOBn), 2.18 (ddd, $^3J_{F,H} = 13.4$, 6.5 Hz, $^3J_{H,H} = 9.6$ Hz, 1 H, 1-H), 2.03 (dddd, $^3J_{F,H} = 14.7$, 6.0 Hz, $^3J_{H,H} = 7.7$, 6.7 Hz, 1 H, 3-H), 1.27 (t, $^3J_{H,H} = 7.1$ Hz, 3 H, CH_3). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 165.56$ (s, C=O), 140.12 (dd, $^3J_{C,F} = 3.1$, C-3 propen.), 137.56 (s, C_q(phenyl)), 128.42 (d, C_{ortho}(phenyl)), 127.81 (d, C_{meta}(phenyl)), 127.63 (d, C_{para}(phenyl)), 123.62 (d, C-2 propen.), 113.70 (dd, $^1J_{C,F} = 291.3$, 289.0 Hz, CF_2), 72.69 (t, CH_2-phenyl), 65.30 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OBn), 60.45 (t, CH_2-Me), 30.75 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-1), 29.78 (ddd, $^2J_{C,F} = 13.1$, 10.1 Hz, C-3), 14.17 (d, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -135.35$ and -138.21 (d-AB system, $J_{AB} = 157.2$ Hz, $^3J_{F,H} = 13.7$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 295 (2), 246 (1), 205 (3), 189 (11), 140 (4), 122 (4), 105 (30), 91(100). – Analysis for $C_{16}H_{18}O_3F_2$ (296.32): calcd. C 64.85, H 6.12; found C 64.80, H 6.39.

*(±) 3-[(1SR, 3SR)-trans-3-Benzyloxymethyl-2,2-difluorocyclopropyl]-prop-2-en-1-ol ((±)-**22**)*

To a solution of diisobutylaluminium hydride (1 M in toluene, 7.4 ml, 7.4 mmol) at −76 °C a solution of **(±)-21** (0.73 g, 2.46 mmol) in dry toluene (6 ml) was added within 15 min, stirring was continued for another 3 h, then a mixture of methanol (1 ml) in toluene (9 ml), methanol (1 ml) and finally water (12.5 ml) was carefully added to the reaction mixture. After warming to room temperature, the reaction mixture was filtered, the residue washed with ethyl acetate (3 × 15 ml), the combined organic layers were dried ($MgSO_4$) and the solvents evaporated. The oily residue was subjected to column chromatography (ethyl acetate/hexane 1:3→1:2) to afford **(±)-22** (0.59 g, 94%) as an oil. – R_F (ethyl acetate/hexane 1:3) 0.19. – IR (film): $\nu = 3395$m, 3065w, 3030w, 2865m, 1735w, 1670w, 1495m, 1470s, 1455s, 1365m, 1250m, 1180s, 1090s, 1020s cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.37 - 7.26$ (m, 5 H, H_{Ph}), 5.84 (dt, $^3J_{H,H} = 15.4$, 5.5 Hz, 1 H, 2-H(olefin.)), 5.44 (ddd, $^3J_{H,H} = 15.4$, 8.2, 7.0 Hz, 1 H, 3-H(olefin.)), 4.55 and 4.47 (AB system, $J_{AB} = 12.1$ Hz, 2 H, CH_2-phenyl), 4.12 (virt d, $^3J_{H,H} = 5.5$ Hz, 2 H, CH_2-OH), 3.68 – 3.50 (m, 2 H, CH_2-OBn), 2.11 – 2.01 (m, 1 H, 1-H(cyclopr.)), 1.97 – 1.74 (m, 1 H, 3-H(cyclopr.)). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.88$ (s, C_q(phenyl)), 132.71 (d, C-2(olefin.)), 128.50 (d, C_{ortho}(phenyl)), 127.84 (d, C_{meta}(phenyl)), 127.75 (d, C_{para}(phenyl)), 123.99 (dd, $^3J_{C,F} = 4.2$ Hz, C-3(olefin)), 114.01 (dd, $^1J_{C,F} = 292.1$, 288.8 Hz, CF_2), 72.53 (t, CH_2-

phenyl), 65.82 (dt, $^3J_{C,F} = 5.0$ Hz, CH_2-OBn), 62.83 (t, CH_2-OH), 29.46 and 29.26 (2 virt dt, $^2J_{C,F} = 10.5$ Hz, C-1 and C-3(cyclopr.)). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -137.38$ and -139.15 (dAB system, $J_{AB} = 160.8$ Hz, $^3J_{F,H} = 14.6$ Hz, 2 F). – MS (EI, 70 eV): *m/z* (%) = 254(< 1), 237 (< 1), 224 (< 1), 206 (< 1), 186 (< 1), 173 (< 1),160 (< 1), 147 (< 1), 116 (2), 108 (7), 91 (100). – HR-MS for $C_{14}H_{16}O_2F_2$: calcd. 254.1118; found 254.1118. – Analysis for $C_{14}H_{16}O_2F_2$ (254.11): calcd. C 66.13, H 6.34; found C 66.28, H 6.12.

*(±)-3-[(1SR,3SR)-trans-3-Benzyloxymethyl-2,2-difluorocyclopropyl]-prop-1-ene ((±)-***23***), (±)-2-[(1SR,3SR)-trans-3-benzyloxymethyl-2,2-difluorocyclopropyl]-1-methylethyl acetate ((±)-***24***) and (±)-3-[(1SR, 3SR)-trans-3-benzyloxymethyl-2,2-difluorocyclopropyl]-propyl acetate ((±)-***25***)*

To a solution of **(±)-21** (1.55 g, 5.23 mmol) in dry THF (30 ml) BH_3·THF (1 N in THF, 1.87 ml) was slowly added at 0 °C within 1 hour; stirring was continued for another 2 h, then additional BH_3·THF (1 N in THF, 1.87 ml) was added, and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and glacial acetic acid (45 ml) and dry diglyme (45 ml) were added. After heating under reflux for 6 h the reaction was quenched by the addition of water (100 ml) and extracted with ethyl acetate (3 × 30 ml). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (10 ml), water (10 ml) and brine (10 ml), dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was subjected to chromatography (silica gel, ethyl acetate/hexane 1:14→1:3) to yield compounds **(±)-23** (0.19 g, 15%), (±)-**25** (0.18 g, 11%) and **(±)-24** (0.06 g, 4%).

Data for **(±)-23**: oil. – R_F (ethyl acetate/hexane 1:3) 0.63. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 260$ nm (2.35). – IR (film): ν = 3065w, 3030w, 2860w, 1645w, 1495w, 1475m, 1455m, 1415w, 1365w, 1340w, 1260m, 1185m, 1100m, 1030w, 1005m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 − 7.26 (m, 5 H, H_{Ph}), 5.91 – 5.84 (m, 1 H, H-C=CH_2), 5.20 – 5.07 (m, 2 H, CH_2=CH), 4.58 und 4.52 (AB-system, $J_{AB} = -12.0$ Hz, 2 H, CH_2-phenyl), 3.64 – 3.61 (m, 1 H, H-CH'OBn), 3.58 – 3.53 (m, 1 H, H'-CHOBn), 2.30 – 2.23 (m, 2 H, CH_2-$CHCH_2$), 1.62 – 1.57 (m, 1 H, H-C (cyclopr.), 1.48 – 1.41 (m, 1 H, H-C (cyclopr.). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.20 (s, C_q (phenyl)), 136.46 (dd, $^4J_{C,F}$ = 2.0 Hz, C-2 (olefin.)), 129.54 (d, C_{ortho} (phenyl)), 128.81 (d, C_{meta} (phenyl)), 128.74 (d, C_{para} (phenyl)), 117.02 (t, C-1 (olefin.)), 116.04 (dd, $^1J_{C,F}$ = 288.7, 287.7, CF_2), 73.52 (t, CH_2-phenyl), 67.45 (dt, $^3J_{C,F} = 4.0$ Hz, CH_2-OBn), 31.05 (dt, $^3J_{C,F} = 3.0$ Hz, CH_2-$CHCH_2$), 28.70 and 26.62 (2 virt dt, $^2J_{C,F} = 10.1$ Hz, C-1 und C-3 (cyclopr.)). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -139.36$ and -141.04 (AB, J_{AB} = 160.8 Hz, $^3J_{F,H} = 14.6$ Hz, 2 F). – MS (EI, 70 eV): *m/z* (%) = 237(< 1), 223 (< 1), 209 (< 1), 196 (< 1), 166 (< 15), 159 (< 1), 132 (< 1), 117 (< 1), 105 (5), 91 (100). – Analysis for $C_{14}H_{16}OF_2$ (238.28): calcd. C 70.57, H 6.77; found C 70.66, H 7.09.

Data for **(±)-24**: oil. – R_F (ethyl acetate/hexane 1:3) 0.37. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 260$ nm (2.37). – IR (film): ν = 3065w, 3030w, 2980w, 2930m, 2860m, 1740s, 1480m, 1455m, 1375s, 1330w, 1295w, 1240s, 1190m, 1130m, 1100m, 1045m, 1030m, 1015m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 − 7.27 (m, 5 H, H_{Ph}), 5.04 – 4.96 (m, 1 H, CH-OAc), 4.56/4.55 und 4.49/4.48 (2 AB systems, J_{AB} = 12.1 Hz, 2 H, CH_2-phenyl), 3.59 – 3.50 (m, 2 H, CH_2-OBn), 2.03/2.01 (2 s, 3 H, CH_3-CO), 1.76 – 1.72 (m, 2 H, CH_2-CHOAc), 1.56 – 1.51 (m, 1 H, H-C (cyclopr.)), 1.38 – 1.30 (m, 1 H, H-C (cyclopr.)), 1.27/1.26 (2 s, 3 H, CH_3-CH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.68 (s, C=O), 139.11 (s, C_q(phenyl)), 129.52 (d, C_{ortho} (phenyl)), 128.83 (d, C_{meta}(phenyl)), 128.73 (d, C_{para}(phenyl)), 115.77/115.57 (2 dd, $^1J_{C,F}$ = 288.4/288.4 and 288.0/287.2 Hz, CF_2), 73.63 (t, CH_2-phenyl), 70,77/70.36 (2 d, CH-OAc), 67.31 (t, CH_2-OBn), 33.42/33.22 (2 t, CH_2-CHOAc), 28.51/28.78 and 24.27 (4 virt dt, $^2J_{C,F}$ = 10.5/10.6, 10.6 Hz, C-1 and C-3 (cyclopr.)), 22.10/22.03 (2 q, CH_3-CH), 20.39/20.32 (2 q, CH_3-CO). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -139.26/-139.74$ and $-140.40/-140.64$ (2 AB systems, J_{AB} = 160.9/160.8 Hz, 2 F). – MS (EI, 70 eV): *m/z* (%) = 255(< 1), 237 (1), 223 (< 1), 207 (< 1), 196 (1), 166 (< 1), 159 (1), 145 (2), 117 (5), 112 (20), 91 (100). – Analysis for $C_{12}H_{20}O_3F_2$ (298.14): calcd. C 64.42, H 6.76; found C 64.31, H 6.83.

Data for **(±)-25**: R_F (ethyl acetate/hexane 1:9) 0.23. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 267$ nm (2.36). – IR (film): ν = 3380w, 3030w, 2955m, 2870m, 1740s, 1480m, 1455m, 1365m, 1245s, 1180m, 1100m, 1075m, 1040m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 − 7.26 (m, 5 H, H_{Ph}), 4.56 and 4.49 (AB, $J_{AB} = -12.0$ Hz, 2 H, CH_2-phenyl), 4.10 (virt t, $^3J_{H,H} = 6.5$ Hz, 2 H, CH_2-OAc), 3.59 – 3.51 (m, 2 H, CH_2-OBn), 2.04 (s, 3 H, CH_3), 1.79 – 1.72 (m, 2 H, CH_2-CH_2OAc), 1.61 – 1.48 (m, 3 H, 3-H, CH_2-CH_2CH_2OAc), 1.38 – 1.29 (m, 1 H, 1-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.02 (s, C=O), 137.96 (s, C_q(phenyl)), 128.38 (d, C_{ortho}(phenyl)), 127.68 (d, C_{meta}(phenyl)), 127.57 (d, C_{para}(phenyl)), 115.05 (dd, $^1J_{C,F}$ = 286.7, 288.2 Hz, CF_2), 72.56 (t, CH_2-phenyl), 66.40 (dt, $^3J_{C,F} = 5.6$ Hz, CH_2-OBn), 63.53 (t, CH_2-OAc), 27.96 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-3), 27.72 (dt, $^4J_{C,F} = 2.3$ Hz, CH_2-CH_2OAc), 26.38 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-1), 22.91 (dt, $^3J_{C,F} = 3.9$ Hz, CH_2-CH_2CH_2OAc), 20.86 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -139.12$ and -141.38 (d-AB system, J_{AB} = 159.0 Hz, $^3J_{F,H} = 13.7$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 298(1), 129 (15), 117 (18), 112 (87), 107 (30), 97 (26), 91 (100). – Analysis for $C_{16}H_{20}O_3F_2$: C 64.42, H 6.76; found C 64.58, H 6.99.

*(±)-(1SR, 3SR)-3-[3-Benzyloxymethyl-2,2-difluoro-cyclopropyl]-propanol ((±)-**26**)*

To a solution of **(±)-21** (3 g, 0.01 mol) in dry THF (58 ml) were added anhydrous lithium chloride (1.9 g, 0.045 mol), sodium borohydride (1.7 g, 0.045 mol) and then absolute ethanol (115 ml) with vigorous stirring. The reaction mixture was stirred at room temperature overnight. The mixture was cooled with an ice-bath, adjusted to pH 4 by the gradual addition of 10% aqueous citric acid and the volatiles were evaporated under reduced pressure. The resulting concentrated mixture was diluted with water (50 ml) and extracted with ethyl acetate (3×100 ml). The combined organic layers were dried ($MgSO_4$) and the solvents evaporated. The remaining oil was subjected to column chromatography (silica gel, ethyl acetate/hexane $1:4 \rightarrow 1:1$) to give **26** (1.98 g, 77%) as a viscous colorless oil and oily by-product **27** (0.53 g, 18%).

Data for **(±)-26**: R_F (ethyl acetate/hexane 1:3) 0.14. – UV/vis (methanol): $\lambda_{max}(\lg \varepsilon) = 265$ nm (2.35). – IR (film): $\nu = 3375$m, 3090w, 3065w, 3030w, 2940s, 2870s, 1720w, 1605w, 1480s, 1455s, 1365m, 1265s, 1210s, 1175s, 1075s, 1030s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38 - 7.56$ (m, 5 H, H_{Ph}), 4.56 and 4.49 (AB system, $J_{AB} = 11.9$ Hz, 2 H, CH_2-phenyl), 3.71 – 3.68 (m, $^3J_{H,H} = 5.9$ Hz, 2 H, CH_2-OH), 3.60 – 3.53 (m, $^3J_{H,H} = 7.1$ Hz, $^4J_{F,H} = 1.6$ Hz, 2 H, CH_2-OBn), 1.73 – 1.35 (m, $^3J_{H,H} = 5.9$, 7.1 Hz, 7 H, $2 \times CH_2$, 1-H, 3-H, OH). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 137.89$ (s, C_q(phenyl)), 128.42 (d,C_{ortho}(phenyl)), 127.74 (d, C_{meta}(phenyl)), 127.65 (d,C_{para}(phenyl)), 115.24 (dd, $^1J_{C,F} = 288.2$ Hz, CF_2), 72.62 (d, CH_2-phenyl), 66.48 (dd, $^3J_{C,F} = 4.6$ Hz, CH_2-OBn), 61.98 (d, CH_2-OH), 31.56 (d, CH_2-CH_2OH), 27.99 (dt, $^2J_{C,F} = 10.0$ Hz, C-3), 26.76 (dt, $^2J_{C,F} = 10.0$ Hz, C-1), 22.82 (dd, $^3J_{C,F} = 3.8$ Hz, CH_2-CH_2CH_2OH). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -140.10$ (d-AB system, $J_{AB} = 159.1$ Hz, $^3J_{F,H} = 12.7$, 11.0 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 256 (2), 205 (< 1), 187 (2), 159 (2), 148 (7), 130 (6), 117 (18), 112 (20), 108 (32), 97 (6), 91 (100). – HR-MS for $C_{14}H_{18}O_2F_2$: calcd. 256.12747; found 256.12747. – Analysis for $C_{14}H_{18}O_2F_2$ (256.30): calcd. C 65.61, H 7.08; found C 65.47, H 7.13.

Data for **(±)-27**: colorless oil. – R_F (ethyl acetate/hexane 1:9) 0.20. – UV/vis (methanol): $\lambda_{max}(\lg \varepsilon) = 213$ nm (3.89). – IR (film): $\nu = 3065$m, 3030m, 2985m, 2940m, 2865m, 1730s, 1480s, 1455s, 1415m, 1375s, 1335m, 1250s, 1195s, 1100s, 1020s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37 - 7.27$ (m, 5 H, H_{Ph}), 4.55 and 4.48 (AB system, $J_{AB} = -12.1$ Hz, 2 H, CH_2-phenyl), 4.13 (q, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2-Me), 3.59 – 3.48 (m, 2 H, CH_2-OBn), 2.42 (dt, $^3J_{H,H} = 7.0$ Hz, $^4J_{H,H} = 1.5$ Hz, 2 H, CH_2-COOEt), 1.87 – 1.78 (m, 2 H, CH_2-CH_2COOEt), 1.60 – 1.51 (m, 1 H, H-C(cyclopr.)), 1.46 – 1.37 (m, 1 H, H-C(cyclopr.)), 1.25 (t, $^3J_{H,H} = 7.2$ Hz, 3 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.76$ (s, C=O), 139.16 (s, C_q(phenyl)), 129.51 (d, C_{ortho}(phenyl)), 128.79 (d, C_{meta}(phenyl)), 128.69 (d, C_{para}(phenyl)), 116.06 (dd, $^1J_{C,F} = 288.7$, 286.7 Hz, CF_2), 73.54 (t, CH_2-phenyl)), 67.34 (dt, $^3J_{C,F} = 5.0$ Hz, CH_2-OBn), 61.44 (t, CH_2-Me), 34.14 (dt, $^4J_{C,F} = 2.0$ Hz, CH_2-COOEt), 28.91 and 27.03 (2 virt dt, $^2J_{C,F} = 10.1$ Hz, C-1 and C-3(cyclopr.)), 22.73 (dt, $^3J_{C,F} = 4.0$ Hz, CH_2-CH_2COOEt), 15.04 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -139.26$ and -141.54 (dAB system, $J_{AB} = 160.8$ Hz, $^3J_{F,H} = 13.7$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 297(< 1), 269 (< 1), 246 (< 1), 224 (< 1), 191 (2), 172 (16), 163 (4), 143 (2), 115 (3), 98 (5). – Analysis for $C_{16}H_{20}O_3F_2$ (298.32): calcd. C 64.42, H 6.76; found C 64.71, H 6.95.

*(±)-3-Benzoyl-1-[(1SR, 3SR)-[3-(3-benzyloxymethyl-2,2-difluorocyclopropyl)-pr opyl]]-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**28**)*

The reaction was performed according to GP1 using **26** (0.31 g, 1.21 mmol), triphenylphosphane (0.634 g, 2.42 mmol), N^3-benzoyluracil (0.523 g, 2.42 mmol), 1,4 dioxane (3 ml) and DEAD (0.382 ml, 2,42 mmol) in 1,4-dioxane (12 ml) followed by column chromatography (silica gel, ethyl acetate/hexane 1:2→1:1) to afford **(±)-28** (0.48 g, 87%) as a viscous oil. – R_F (ethyl acetate/hexane 1:2) 0.08. – UV/vis (methanol): $\lambda_{max}(\lg \varepsilon) = 257$ nm (4.27). – IR (film): $\nu = 3090$w, 3030w, 2935w, 2865w, 1750s, 1705s, 1660s, 1600m, 1480m, 1440s, 1390m, 1350m, 1255s, 1220m, 1180m, 1100m, 1030m, 1000m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92 - 7.32$ (m, 10 H, H_{Ph}), 7.08 (d, $^3J_{H,H} = 8.0$ Hz, 1 H, 6'-H), 5.65 (d, $^3J_{H,H} = 7.8$ Hz, 1 H, 5'-H), 4.53 and 4.47 (AB system, $J_{AB} = -11.7$ Hz, 2 H, CH_2-phenyl), 3.80 – 3.61 (m, 3 H, H-CH'OBn, CH_2-N), 3.49 (m, 1 H, H'-CHOBn), 1.82 – 1.78 (m, 2 H, CH_2-CH_2N), 1.56 – 1.51 (m, 3 H, CH_2-CH_2CH_2N, 3-H), 1.38 – 1.36 (m, 1 H, 1-H). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.01$ (s, C=O(Bz)), 163.57 (s, C-2'), 150.90 (s, C(4')), 145.23 (d, C-6'), 138.97 (s, C_q(phenyl, Bn)), 136.21 (s, C_q(phenyl, Bz)), 131.48 (d, C_{para}(phenyl, Bz)), 130.29 (d, C_{ortho}(phenyl, Bz)), 129.68 (d, C_{meta}(phenyl, Bz)), 129.63 (d, C_{ortho}(phenyl, Bn)), 129.05 (d, C_{meta}(phenyl, Bn)), 128.94 (d, C_{para}(phenyl, Bn)), 115.90 (dd, $^1J_{C,F} = 289.7$, 286.7 Hz, CF_2), 103.12 (d, C-5'), 73.94 (t, CH_2-phenyl), 67.46 (dt, $^3J_{C,F} = 4.0$ Hz, CH_2-OBn), 49.22 (t, CH_2-N), 28.92 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-3), 28.91 (t, CH_2-CH_2N), 27.18 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-1), 23.74 (dt, $^3J_{C,F} = 4.0$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -138.73$ and -140.62 (dAB system, $J_{AB} = 159.0$ Hz, $^3J_{F,H} = 13.7$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 464 (< 1), 349 (21), 277 (3), 243 (88), 223 (5), 194 (4), 105 (100). – HR-MS for $C_{25}H_{24}O_4N_2F_2$: calcd. 454.1704; found: 454.1704. – Analysis for $C_{25}H_{24}O_4N_2F_2$ (454.17): calcd. C 66.07, H 5.32, N 6.16; found C 65.91, H 5.31, N 6.31.

*(±)-3-Benzoyl-1-[(1SR, 3SR)-[3-(3-benzyloxymethyl-2,2-difluorocyclopropyl)-propyl]]-5-fluoro-1,2,3,4-tetra-hydro-2,4-pyrimidinedione ((±)-**29**)*

The reaction was performed according to GP1 using DIAD (0.60 ml, 3.20 mmol) in 1,4-dioxane (17 ml), **26** (0.40 g, 1.60 mmol), triphenylphosphane (0.82 g, 3.20 mmol) and N^3-benzoyl-5-fluorouracil (0.73 g, 3.20 mmol) in 1,4-dioxane (4 ml) followed by chromatography (silica gel, ethyl acetate/hexane 1:3→1:1) to afford **(±)-29** (0.61 g, 80%) as a viscous oil. – R_F (ethyl acetate/hexane 1:3) 0.12. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 277$ nm (4.05). – IR (film): ν = 3365w, 3070m, 3030m, 2935m, 2865m, 1750m, 1665m, 1600m, 1450m, 1360m, 1250m, 1175m, 1095m, 1030m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.89 - 7.87$ (m, 2 H, H_{ortho}, Bz), 7.65 – 7.61 (m, 1 H, H_{para}, Bz), 7.49 – 7.45 (m 2 H, H_{meta}, Bz), 7.35 – 7.26 (m, 6 H, H_{Ph}), 6'-H), 4.51 and 4.45 (AB system, $J_{AB} = -11.7$ Hz, 2 H, CH_2-phenyl), 3.76 – 3.56 (m, 3 H, CH_2-N, H-CH'OBn), 3.50 – 3.36 (m, 1 H, H'-CHOBn), 1.81 – 1.69 (m, 2 H, CH_2-CH_2N), 1.58 – 1.42 (m, 3 H, 3-H, CH_2-CH_2CH_2N), 1.38 – 1.29 (m, 1 H, 1-H). – ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.49$ (s, C=O (Bz)), 156.33 (d, $^2J_{C,F} = 26.9$ Hz, C-4'), 148.27 (s, C-2'), 139.76 (d, $^1J_{C,F} = 240.0$ Hz, C-5'), 137.83 (s, C_q(phenyl, Bn)), 135.46 (s, C_q(phenyl, Bz)), 130.96 (d, C_{para}(phenyl, Bz)), 130.38 (d, C_{ortho}(phenyl, Bz)), 129.27 (d, C_{meta}(phenyl, Bz)), 128.70 (dd, $^2J_{C,F} = 32.7$ Hz, C-6'), 128.43 (d, C_{ortho}(phenyl, Bn)), 127.82 (d, C_{meta}(phenyl, Bn)), 127.70 (d, C_{para}(phenyl, Bn)), 114.81 (dd, $^1J_{C,F} = 289.0$, 287.0 Hz, CF_2), 72.65 (t, CH_2-phenyl), 66.19 (dt, $^3J_{C,F} = 4.1$ Hz, CH_2-OBn), 48.13 (t, CH_2-N), 27.68 (virt dt, $^2J_{C,F} = 10.5$ Hz, C-3), 27.49 (t, CH_2-CH_2N), 25.87 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 22.46 (dt, $^3J_{C,F} = 3.7$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -138.74$ and -139.67 (d-AB system, $J_{AB} = 157.0$ Hz, $^3J_{F,H} = 12.8$ Hz, F_A and F_B), -166.57 (s, 5'-F). – MS (EI, 70 eV): *m/z* (%) = 472 (1), 402 (1), 367 (45), 347 (1), 299 (1), 261 (100), 241 (5), 218 (1), 194 (5), 183 (2), 143 (2), 111 (2), 105 (98), 91 (24), 77 (13), 65 (1). – HR-MS for $C_{25}H_{23}O_4N_2F_3$: calcd. 472.1610; found 472.1610. – Analysis for $C_{25}H_{23}O_4N_2F_3$ (472.16): calcd. C 63.56, H 4.91, N 5.93; found C 63.72, H 4.83, N 5.81.

*(±)-3-Benzoyl-1-[(1SR, 3SR)-[3-(3-benzyloxymethyl-2,2-difluorocyclopropyl)-propyl]]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-**30**)*

Following GP1 from **26** (0.19 g, 0.74 mmol), DEAD (0.23 ml, 1.48 mmol) in 1,4-dioxane (10 ml), triphenylphosphane (0.39 g, 1.48 mmol) and N^3-benzoylthymine (0.34 g, 1.48 mmol) in 1,4-dioxane (3 ml) followed by column chromatography (silica gel, ethyl acetate/hexane 1:2) **(±)-30** (0.26 g, 75%) was obtained as a viscous oil contaminated with some impurities that were easily separated in the next reaction step; an analytical sample was obtained by chromatography (1. silica gel RP-18; methanol/water 8:3; 2. silica gel ethyl acetate/hexane 1:1). – R_F (ethyl acetate/hexane 1:1) 0.39. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 257$ nm (4.26). – IR (film): $\nu = 3065$w, 3030w, 2920m, 2865m, 1750s, 1695s, 1650s, 1600m, 1435s, 1355m, 1255s, 1225s, 1180m, 1100m, 1030m cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.90 - 7.24$ (m, 10 H, H_{Ph}), 7.00 (d, $^4J_{H,H} = 1.0$, 1 H, 6'-H), 4.53 and 4.44 (AB system, $J_{AB} = -11.9$, 2 H, CH_2-phenyl), 3.81 – 3.66 (m, 2 H, CH_2-N), 3.62 – 3.44 (m, 2 H, CH_2-OBn), 1.88 (d, $^4J_{H,H} = 1.0$ Hz, 3 H, CH_3), 1.84 – 1.73 (m, 2 H, CH_2-CH_2N), 1.57 – 1.24 (m, 4 H, 1-H, 3-H, CH_2-CH_2CH_2N). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 169.01$ (s, C=O(Bz)), 163.05 (s, C-2'), 149.75 (s, C-4'), 139.96 (d, C-6'), 137.81 (s, C_q(phenyl, Bz)), 134.91 (s, C_q(phenyl, Bn)), 131.60 (d, C_{para}(phenyl, Bz)), 130.30 (d, C_{ortho}(phenyl, Bz)), 129.08 (d, C_{meta}(phenyl, Bz)), 128.42 (d, C_{otho}(phenyl, Bn)), 127.77 (d, C_{meta}(phenyl, Bn)), 127.60 (d, C_{para}(phenyl, Bn)), 114.81 (dd, $^1J_{C,F} = 289.0$, 286.7 Hz, CF_2), 110.72 (s, C-5'), 72.74 (t, CH_2-phenyl), 66.32 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OBn), 47.88 (t, CH_2-N), 28.07 (t, CH_2-CH_2N), 27.93 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-3), 26.17 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-1), 22.97 (dt, $^3J_{C,F} = 3.8$ Hz, CH_2-CH_2CH_2N), 12.28 (q, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -138.89$ and -140.79 (d-AB system, $J_{AB} = 160.9$ Hz, $^3J_{F,H} = 13.7$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 468 (1), 398 (4), 363 (18), 342 (11), 257 (75), 241 (7), 105 (100). – HR-MS for $C_{26}H_{26}O_4N_2F_2$: calcd. 468.1861; found 468.1861. – Analysis for $C_{26}H_{26}O_4N_2F_2$ (468.19): calcd. C 66.66, H 5.59, N 5.98; found C 66.47, H 5.81, N 6.13.

*(±)-1-[(1SR, 3SR)-[3-(3-Benzyloxymethyl-2,2-difluoro-cyclopropyl)-propyl]]-1,2,3,4-tetrahydro-2,4-pyrimidine-dione ((±)-**31**)*

A solution of **28** (0.4 g, 0.88 mmol) in 1,4-dioxane (11 ml) was treated with sodium hydroxide (N, 11 ml) overnight. After neutralization with 10% aqueous hydrochloric acid the volatiles were evaporated and the residue was suspended in water (20 ml) and extracted with ethyl acetate (3 × 25 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate, brine and were dried ($MgSO_4$). Evaporation of the solvents was followed by column chromatography (silica gel, ethyl acetate/hexane 2:1→1:10) of the remaining residue to afford (±)-**31** (0,19 g, 62%) as a viscous colorless oil. – R_F (ethyl acetate/hexane 2:1) 0.24. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 270$ nm (4.01). – IR (film): $\nu = 3175$m, 3055m, 2945m, 2865m, 1680s, 1455m, 1420m, 1360m, 1245m, 1205m, 1180m, 1150m, 1095m, 1030m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.39$ (br s, 1 H, NH), 7.34 – 7.25 (m, 5 H, H_{Ph}), 6.96 (d, $^3J_{H,H} = 8.0$ Hz, 1 H, 6'-H), 5.55 (d, $^3J_{H,H} = 7.9$ Hz, 1 H, 5'-H), 4.52 and 4.45 (AB system, $J_{AB} = -11.7$ Hz, 2

H, CH_2-phenyl), 3.80 – 3.61 (m, 3 H, H-CH'OBn, CH_2N), 3.49 – 3.44 (m, 1 H, H'-CHOBn), 1.81 – 1.72 (m, 2 H, CH_2-CH_2N), 1.61 – 1.44 (m, 3 H, CH_2-CH_2CH_2N, 3-H), 1.40 – 1.32 (m, 1 H, 1-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.90 (s, C-2'), 150.95 (s, C-4'), 144.32 (d, C-6'), 137.89 (s, C_q(phenyl)), 128.57(d, C_{ortho}(phenyl)), 127.99 (d, C_{meta}(phenyl)), 127.87 (d, C_{para}(phenyl)), 114.83 (dd, $^1J_{C,F}$ = 288.7, 287.6 Hz, CF_2), 102.24 (d, C-5'), 72.89 (t, CH_2-phenyl), 66.41 (dt, $^3J_{C,F}$ = 4.2 Hz, *C*H_2-OBn), 47.80 (t, CH_2-N), 27.90 (t, *C*H_2-CH_2N), 27.88 (virt dt, $^2J_{C,F}$ = 10.3 Hz, C-3), 26.22 (virt dt, $^2J_{C,F}$ = 10.9 Hz, C-1), 22.68 (dt, $^3J_{C,F}$ = 3.7 Hz, *C*H_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −138.72 and −140.66 (dAB system, J_{AB} = 159.0 Hz, $^3J_{F,H}$ = 13.7 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 339 (6), 298 (4), 277 (16), 209 (8), 193 (14), 179 (9), 105 (88), 91 (100). – HR-MS for $C_{18}H_{20}O_3N_2F_2$: calcd. 350.1442; found 350.1442. – Analysis for $C_{18}H_{20}O_3N_2F_2$ (350.14): calcd. C 61.71, H 5.75, N 8.00; found C 61.59, H 5.81, N 8.12.

*(±)-1-[(1SR, 3SR)-[3-(3-Benzyloxymethyl-2,2-difluoro-cyclopropyl)-pro pyl]]-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-***32***)*

A solution of **(±)-30** (0.08 g, 0.17 mmol) in 1,4-dioxane (2 ml) was treated with sodium hydroxide (1 N, 2 ml) for an hour. The reaction mixture was neutralized by diluted hydrochloric acid (10%) and extracted with ethyl acetate (3 × 20 ml). The combined organic layers were evaporated and the remaining oil was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:1) to afford (±)-**32** (0.04 g, 65%) as an oil. – R_F (ethyl acetate/hexane 2:1) 0.43. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon)$ = 276 (4.04). – IR (film): ν = 3185m, 3035m, 2930m, 2865m, 2635w, 2520w, 1680s, 1605m, 1585m, 1475s, 1455m, 1415m, 1385m, 1360s, 1315m, 1270s, 1220s, 1190m, 1095m, 1075m, 1025m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (br s, 1 H, NH), 7.34 – 7.25 (m, 5 H, H_{Ph}), 6.90 (d, $^4J_{H,H}$ = 1.3 Hz, 1 H, 6'-H), 4.53 and 4.47 (AB system, J_{AB} = −11.9 Hz, 2 H, CH_2-phenyl), 3.76 – 3.65 (m, 2 H, CH_2-N), 3.59 (ddd, $^2J_{H,H}$ = −11.6 Hz, $^3J_{H,H}$ = 7.2 Hz, $^4J_{F,H}$ = 2.1 Hz, 1 H, H-CH'OBn), 3.49 (ddd, $^2J_{H,H}$ = −11.6 Hz, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 2.3 Hz, 1 H, H'-CHOBn), 1.85 (d, $^4J_{H,H}$ = 1.3 Hz, 3 H, CH_3), 1.82 – 1.73 (m, 2 H, CH_2-CH_2N), 1.57 – 1.48 (m, 3 H, 3-H, CH_2-CH_2CH_2N), 1.40 – 1.32 (m, 1 H, 1-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.84 (s, C-2'), 151.11 (s, C-4'), 140.23 (d, C-6'), 137.66 (s, C_q(phenyl)), 128.23 (d, C_{ortho}(phenyl)), 127.47 (d, C_{meta}(phenyl)), 127.28 (d, C_{para}(phenyl)), 114.76 (dd, $^1J_{C,F}$ = 288.2, 286.7 Hz, CF_2), 110.48 (s, C-5'), 72.48 (t, CH_2-phenyl), 66.19 (dt, $^3J_{C,F}$ = 3.9 Hz, *C*H_2-OBn), 47.38 (t, CH_2-N), 27.88 (t, *C*H_2-CH_2N), 27.68 (dt, $^2J_{C,F}$ = 10.9 Hz, C-3), 26.03 (dt, $^2J_{C,F}$ = 10.9 Hz, C-1), 22.76 (dt, $^3J_{C,F}$ = 3.9 Hz, *C*H_2-CH_2CH_2N), 12.05 (d, CH_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −138.83 and −140.77 (d-AB system, J_{AB} = 157.2 Hz, $^3J_{F,H}$ = 13.7 Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 364 (10), 258 (14), 243 (8), 238 (25), 191 (8), 154 (10), 139 (8), 127 (14), 112 (44), 96 (17), 91 (100). – HR-MS for $C_{19}H_{22}O_3N_2F_2$: calcd. 364.1598; found 364.1598. – Analysis for $C_{19}H_{22}O_3N_2F_2$ (364.16): calcd. C 62.63, H 6.09, N 7.69; found C 62.43, H 6.23, N 7.41.

*(±)-1-[(1SR, 3SR)-[3-(3-Benzyloxymethyl-2,2-difluoro-cyclopropyl)-propyl]]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione ((±)-***33***)*

A solution of (±)-**29** (0.60 g, 1.27 mmol) in methanol (10 ml) was treated with ammonium hydroxide (2 ml) for one hour. The volatiles were evaporated and the residue was suspended in water (10 ml), extracted with ethyl acetate (3 × 20 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated. The remaining oil was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:2) to afford (±)-**33** (0.22 g, 47%) as an oil. – R_F (ethyl acetate/hexane 1:1) 0.66. – UV/vis (methanol): $\lambda_{max\,1}(\lg\varepsilon)$ = 286 nm (3.81), $\lambda_{max\,2}(\lg\varepsilon)$ = 257 nm (4.12). – IR (film): ν = 3185w, 3065m, 2865w, 1695m, 1475m, 1365m, 1240m, 1170w, 1095w, 1030w cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.46 (br s, 1 H, NH), 7.31 – 7.27 (m, 5 H, H_{Ph}), 7.17 (d, $^3J_{F,H}$ = 5.3 Hz, 6'-H), 4.52 and 4.46 (AB system, J_{AB} = −11.7 Hz, 2 H, CH_2-phenyl), 3.80 – 3.30 (m, 4 H, CH_2-N, CH_2-OBn), 1.78 – 1.26 (m, 6 H, 1-H, 3-H, CH_2-CH_2N, CH_2-CH_2CH_2N). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.48 (d, $^2J_{C,F}$ = 26.2 Hz, C-4'), 149.66 (s, C-2'), 140.17 (d, $^1J_{C,F}$ = 237.0 Hz, C-5'), 137.61 (s, C_q(phenyl)), 128.50 (dd, $^2J_{C,F}$ = 29.3 Hz, C-6'), 128.25 (d, C_{ortho}(phenyl,)), 127.65 (d, C_{meta}(phenyl)), 127.56 (d, C_{para}(phenyl)), 114.76 (dd, $^1J_{C,F}$ = 287.0, 287.0 Hz, CF_2), 72.53 (t, CH_2-phenyl), 66.16 (dt, $^3J_{C,F}$ = 3.9 Hz, CH_2-OBn), 47.79 (t, CH_2-N), 27.64 (virt dt, $^2J_{C,F}$ = 10.4 Hz, C-3), 27.59 (t, CH_2-CH_2N), 25.98 (virt dt, $^2J_{C,F}$ = 10.4 Hz, C-1), 22.48 (dt, $^3J_{C,F}$ = 3.8 Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −138.71 and −140.64 (dAB system, J_{AB} = 161.0 Hz, $^3J_{F,H}$ = 13.8 Hz, F_A and F_B), −167.37 (s, 5'-F). – MS (EI, 70 eV): *m/z* (%) = 368 (2), 261 (9), 247 (6), 242 (13), 234 (3), 221 (3), 195 (6), 176 (2), 158 (3), 143 (6), 130 (5), 112 (37), 100 (8), 91 (100). – HR-MS for $C_{18}H_{19}O_3N_2F_3$: calcd. 368.1348; found 368.1348. – Analysis for $C_{18}H_{19}O_3N_2F_3$ (368.13): calcd. C 58.69, H 5.20, N 7.70; found C 58.42, H 5.89, N 7.84.

*(±)-9-[(1SR, 3SR)-[3-(3-Benzyloxymethyl-2,2-difluoro-cyclopropyl)-propyl]]-9H-6-purinamine ((±)-***34***)*

Following GP1 from **(±)-26** (0.49 g, 1.93 mmol), triphenylphosphane (1.01 g, 3.94 mmol) and adenine (0.52 g, 3.94 mmol) in dry 1,4-dioxane (6 ml) and DEAD (0.61 ml, 3.94 mmol) in 1,4-dioxane (24 ml) followed by column chromatography (silica gel, ethyl acetate/methanol 10:1→5:1)

and recrystallization (ethyl acetate/hexane/methanol), **34** (0.37 g, 51%) was obtained as a white solid. – M.p. 126 – 127 °C. – R_F (ethyl acetate/methanol 5:1) 0.68. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 265$ nm (4.28). – IR (KBr): $\nu = 3445$s, 2925m, 1680m, 1605s, 1575m, 1475m, 1415m, 1365m, 1310m, 1250m, 1205m, 1115m cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.32$ (br s, 1 H, 2'-H), 7.68 (br s, 1 H, 8'-H), 7.34 – 7.22 (m, 5 H, H_{Ph}), 4.51 and 4.43 (AB system, $J_{AB} = -11.7$ Hz, 2 H, CH_2-phenyl), 4.19 (virt t, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2-N), 3.60 – 3.41 (m, 2 H, CH_2-OBn), 2.07 – 1.92 (m, 2 H, CH_2-CH_2N), 1.59 – 1.21 (m, 4 H, 1-H, 3-H, CH_2-CH_2CH_2N). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 155.73$ (s, C-6'), 152.86 (d, C-2'), 149.96 (s, C-4'), 140.12 (d, C-8'), 137.78 (s, C_q(phenyl)), 128.36 (d, C_{ortho}(phenyl)), 127.71 (d, C_{meta}(phenyl)), 127.57 (d, C_{para}(phenyl)), 119.59 (s, C-5'), 114.78 (dd, $^1J_{C,F} = 287.0$, 287.0 Hz, CF_2), 72.66 (t, CH_2-phenyl), 66.23 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OBn), 42.98 (t, CH_2-N), 29.09 (dt, $^4J_{C,F} = 1.5$ Hz, CH_2-CH_2N), 27.93 (virt dt, $^2J_{C,F} = 10.5$ Hz, C-3), 26.12 (virt dt, $^2J_{C,F} = 10.5$ Hz, C-1), 23.20 (dt, $^3J_{C,F} = 3.8$ Hz, CH_2-CH_2CH_2N)). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -138.89$ and -140.76 (dAB system, $J_{AB} = 159.0$ Hz, $^3J_{F,H} = 13.7$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 373 (2), 322 (< 1), 282 (3), 266 (14), 262 (23), 247 (100), 226 (5), 188 (6), 175 (3), 162 (6), 149 (43), 135 (31). – HR-MS for $C_{19}H_{21}ON_5F_2$: calcd. 373.1714; found 373.1714. – Analysis for $C_{19}H_{21}ON_5F_2$ (373.17): calcd. C 61.12, H 5.67, N 18.76; found C 61.10, H 5.76, N 18.98.

*(±)-1-[(1SR, 3SR)-[3-(2,2-Difluorocyclopropyl-3-hydroxymethyl)-propyl]] -5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione (=(±)-1-[3-(2,2-difluoro-3-hydroxymethyl-cyclopropyl)-propyl]-thymine ((±)-***35****))*

Reaction of **(±)-32** (0.19 g, 0.52 mmol) in methanol (9 ml) / cyclohexene (8 ml) with Pearlman's catalyst (0.4 g, 20%) according to GP2 followed by column chromatography (silica gel, ethyl acetate→ethyl acetate/methanol 3:1) afforded **(±)-35** (0.1 g, 70%) as a clear oil. – R_F (ethyl acetate) 0.23. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 275$ nm (3.99). – IR (film): $\nu = 3410$m, 3185m, 3055m, 2950m, 2825w, 1680s, 1475s, 1385m, 1360s, 1265m, 1245m, 1220s, 1185m, 1160m, 1035m, 1005m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.43$ (d, $^4J_{H,H} = 1.2$ Hz, 1 H, 6'-H), 3.74 (virt t, $^3J_{H,H} = 7.3$ Hz, 2 H, CH_2-N), 3.60 (virt d, $^3J_{H,H} = 6.8$ Hz, 2 H, CH_2-OH), 1.86 (d, $^4J_{H,H} = 1.2$ Hz, 3 H, CH_3), 1.82 – 1.72 (m, 2 H, CH_2-CH_2N), 1.59 – 1.41 (m, 4 H, 1-H, 3-H, CH_2-CH_2CH_2N)). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 164.88$ (s, C-2'), 151.52 (s, C-4'), 140.50 (d, C-6'), 115.22 (dd, $^1J_{C,F} = 288.4$, 287.6 Hz, CF_2), 110.97 (s, C-5'), 58.75 (dt, $^3J_{C,F} = 3.7$ Hz, CH_2-OH), 47.38 (t, CH_2-N), 30.05 (virt dt, $^2J_{C,F} = 9.8$ Hz, C-3), 27.75 (t, CH_2-CH_2N), 25.89 (virt dt, $^2J_{C,F} = 10.2$ Hz, C-1), 22.42 (dt, $^3J_{C,F} = 2.9$ Hz, CH_2-CH_2CH_2N), 11.92 (q, CH_3). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -139.40$ and -140.41 (d-AB system, $J_{AB} = 160.9$ Hz, $^3J_{F,H} = 11.0$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 247 (28), 257 (9), 243 (25), 236 (6), 191 (36), 177 (21), 164 (16), 152 (24), 139 (43), 126 (54), 117 (13), 111 (34), 96 (100). – HR-MS for $C_{12}H_{16}O_3N_2F_2$: calcd. 274.1129; found: 274.1129. – Analysis for $C_{12}H_{16}O_3N_2F_2$ (274.11): calcd. C 52.55, H 5.88, N 10.21; found C 52.49, H 6.04, N 10.43.

*(±)-1-[(1SR, 3SR)-[3-(2,2-Difluorocyclopropyl-3-hydroxymethyl)-propyl]]-1,2,3,4-tetrahydro-2,4-pyrimidinedione (= (±)-1-[3-(2,2-difluoro-3-hydroxymethyl-cyclopropyl)-propyl]-uracil ((±)-***36****)*

Following GP2 from **(±)-31** (0.185 g, 0.53 mmol) in methanol (9 ml) / cyclohexene (8 ml) and Pearlman's catalyst (0.41 g, 20%) followed by column chromatography (silica gel, ethyl acetate/methanol 15:1) **(±)-36** (0.09 g, 66%) was obtained as a viscous oil. – R_F (ethyl acetate) 0.14. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 272$ (4.19). – IR (film): $\nu = 3400$w, 3195w, 3050w, 2950w, 2875w, 1680m, 1465m, 1420m, 1395m, 1355m, 1245m, 1205w, 1170w, 1030m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.58$ (d, $^3J_{H,H} = 7.8$ Hz, 1 H, 6'-H), 5.65 (d, $^3J_{H,H} = 7.8$ Hz, 1 H, 5'-H), 3.77 (virt t, $^3J_{H,H} = 7.3$ Hz, 2 H, CH_2-N), 3.59 (virt d, $^3J_{H,H} = 7.0$ Hz, 2 H, CH_2-OH), 1.83 – 1.75 (m, 2 H, CH_2-CH_2N), 1.58 – 1.41 (m, 4 H, CH_2-CH_2CH_2N, 3-H), 1-H). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 166.93$ (s, C-2'), 153.02 (s, C-4'), 147.34 (d, C-6'), 117.05 (dd, $^1J_{C,F} = 287.6$, 286.8 Hz, CF_2), 102.43 (d, C-5'), 59.57 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OH), 31.39 (virt dt, $^2J_{C,F} = 10.2$ Hz, C-3), 29.05 (t, CH_2-CH_2N), 27.25 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 24.08 (dt, $^3J_{C,F} = 3.3$ Hz, CH_2-CH_2CH_2N). – ^{13}C NMR (100 MHz, D_2O): $\delta = 168.00$ (s, C-2'), 153.42 (s, C-4'), 148.35 (d, C-6'), 117.05 (dd, CF_2), 102.53 (d, C-5') 59.42 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OH), 49.26 (t, CH_2-N), 30.08 (virt dt, $^2J_{C,F} = 10.2$ Hz, C-3), 28.15 (t, CH_2-CH_2N), 26.80 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 23.35 (dt, $^3J_{C,F}$ = 3.3 Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -137.68$ and -138.59 (AB system, $J_{AB} = 171.8$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 260 (4), 243 (4), 229 (11), 177 (24), 163 (11), 150 (18), 138 (19), 125 (24), 113 (36), 97 (25), 82 (100). – HR-MS for $C_{11}H_{14}O_3N_2F_2$: calcd. 260.0972; found 260.0972. – Analysis for $C_{11}H_{14}O_3N_2F_2$ (260.10): calcd. C 50.77, H 5.42, N 10.76; found C 50.61, H 5.40, N 10.81.

*(±)-1-[(1SR, 3SR)-[3-(2,2-Difluorocyclopropyl-3-hydroxymethyl)-propyl]]-5-fluoro-1,2,3,4-tetrahydro-2,4-pyrimidinedione (= (±)-1-[3-(2,2-difluoro-3-hydroxymethyl-cyclopropyl)-propyl]-5-fluorouracil ((±)-***37****)*

Following GP2 from **(±)-33** (0.17 g, 0.46 mmol) in methanol (8 ml) / cyclohexene (7 ml) and Pearlman's catalyst (0.36 g, 20%) followed by chromatography (silica gel, ethyl

acetate/hexane 10:1) **(±)-37** (0.11 g, 47%) was obtained as a clear oil. – R_F (ethyl acetate) 0.49. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 279$ nm (3.96). – IR (film): $\nu = 3430$s, 3185s, 3065s, 2955s, 2825m, 2570w, 2375w, 1695s, 1480s, 1370s, 1240s, 1195s, 1160s, 1110s, 1035s, 1005s cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.87$ (d, $^3J_{F,H} = 6.3$ Hz, 6'-H), 3.80 – 3.69 (m, 2 H, CH_2-N), 3.60 (virt d, $^3J_{H,H} = 7.0$ Hz, CH_2-OH), 1.85 – 1.72 (m, 2 H, CH_2-CH_2N), 1.60 – 1.39 (m, 4 H, 3-H, 1-H, CH_2-CH_2CH_2N). – ^{13}C NMR (100 MHz, CD_3OD): $\delta = 159.97$ (d, $^2J_{C,F} = 25.7$ Hz, C-4'), 151.65 (s, C-2'), 141.86 (d, $^1J_{C,F} = 233.0$ Hz, C-5'), 131.20 (dd, $^2J_{C,F} = 33.1$ Hz, C-6'), 117.05 (dd, $^1J_{C,F} = 286.8$, 287.6 Hz, CF_2), 59.56 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OH), 49.08 (t, CH_2-N), 31.35 (virt dt, $^2J_{C,F} = 10.0$ Hz, C-3), 28.85 (t, CH_2-CH_2N), 27.23 (virt dt, $^2J_{C,F} = 10.4$ Hz, C-1), 23.99 (dt, $^3J_{C,F} = 2.9$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -137.25$ and -138.49 (AB system, $J_{AB} = 172.0$ Hz, F_A and F_B), -167.78 (s, 5'-F). – MS (EI, 70 eV): *m/z* (%) = 278 (33), 261 (7), 247 (31), 240 (5), 233 (7), 212 (7), 195 (100), 181 (28), 168 (44), 156 (24), 143 (58), 130 (40), 117 (11), 111 (20), 100 (54), 97 (18). – HR-MS for $C_{11}H_{13}O_3N_2F_3$: calcd. 278.0878; found 278.0878.

*(±)-(1SR, 3SR)-3-[3-(6-Amino-9H-9-purinyl)-propyl]-2,2-difluorocyclopropyl-methanol [= 9-[3-(3-hydroxymethyl-2,2-difluorocyclopropyl)-propyl]-adenine] ((±)-**38**)*

To a solution of **34** (0.37 g, 1 mmol) in methanol (17 ml) were added cyclohexene (15 ml) and Pearlman's catalyst (0.75 g, 20%) and the reaction mixture was heated under reflux for 6 hours. After filtration and evaporation of the volatiles the resulting crude product was subjected to column chromatography (silica gel, ethyl acetate/methanol 6:1) to afford **38** (0.22 g, 78%) as a white solid. – M.p. 165 – 167 °C. – R_F (ethyl acetate/methanol 7:1) 0.13. – UV/vis (methanol): $\lambda_{max}(\lg\varepsilon) = 265$ nm (4.15). – IR (KBr): $\nu = 3425$s, 2935m, 1685m, 1615s, 1575m, 1485m, 1420m, 1365m, 1335m, 1305m, 1235m, 1180m, 1040m, 1020m cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): $\delta = 8.20$ (s, 1 H, 2'-H), 8.12 (s, 1 H, 8'-H), 4.26 (virt dt, $^3J_{H,H} = 7.2$ Hz, $^4J_{H,H} = 1.2$ Hz, 2 H, CH_2-N), 3.58 (virt d, $^3J_{H,H} = 7.2$ Hz, 2 H, CH_2-OH), 2.04 – 1.96 (m, 2 H, CH_2-CH_2N), 1.60-1.41 (m, 4 H, 1-H, 3-H, CH_2-CH_2CH_2N). – ^{13}C NMR (100 MHz, CD_3OD):$\delta = 157.55$ (s, C-6'), 153.89 (d, C-2'), 150.85 (s, C-4'), 142.82 (d, C-8'), 120.19 (s, C-5'), 117.01 (dd, $^1J_{C,F} = 287.2$, 287.2 Hz, CF_2), 59.55 (dt, $^3J_{C,F} = 4.6$ Hz, CH_2-OH), 44.30 (t, CH_2-N), 31.42 (virt dt, $^2J_{C,F} = 10.3$ Hz, C-3), 30.18 (t, CH_2-CH_2N), 27.16 (virt dt, $^2J_{C,F} = 10.3$ Hz, C-1), 24.27 (dd, $^3J_{C,F} = 3.3$ Hz, CH_2-CH_2CH_2N). – ^{19}F NMR (188 MHz, CD_3OD): $\delta = -137.72$ and -138.62 (AB system, $J_{AB} = 170.0$ Hz, F_A and F_B). – MS (EI, 70 eV): *m/z* (%) = 283 (21), 263 (48), 266 (14), 246 (89), 252 (11), 232 (21), 226 (6), 219 (3), 204 (1), 188 (10), 176 (13), 162 (16), 148 (49), 135 (100). – HR-MS for $C_{12}H_{15}ON_5F_2$: calcd. 283.1244; found 283.1244. – Analysis for $C_{12}H_{15}ON_5F_2$ (283.12): calcd. C 50.88, H 5.34, N 24.72; found C 50.61, H 5.43, N 24.59.

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