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Optically Pure and Fluoro Substituted Acyclovir Analogues

Pierfrancesco Bravo*,[a] Giuseppe Resnati*,[b] Fiorenza Viani[b]

[a]Dipartimento di Chimica del Politecnico,
[b]CNR - Centro di Studio sulle Sostanze Organiche Naturali,
Via Mancinelli 7, I-20131 Milano, Italy

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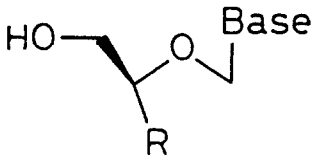
Abstract 1',2'-Seco-2'-nor-nucleosides carrying a fluorine atom, instead of hydroxyl group, on C-3' are synthesized in enantiomerically pure form, starting from (2S)-1-fluoro-3-(R)-[(4-methylphenyl)sulfinyl]-2-propanol.

Selective substitution of a fluorine for an hydroxyl group in the sugar part of a nucleoside frequently allowed to obtain compounds endowed with useful antiviral activity.[1]

Acyclovir 1 is a drug commonly employed for the treatment of HSV infections and is the first successful specimen of the so called "acyclic nucleosides". Several other similar compounds showed interesting pharmacological properties and DHPG 2 emerged as a particularly attractive product.[2]

We thus decided to prepare some acyclic nucleosides in which one of the two hydroxyl groups of DHPG was replaced by fluorine. Here we describe the synthesis of two examples of these nucleoside analogues, namely (*R*)-1-[(1-fluoro-3-hydroxy-2-propoxy)methyl]thymine 3 and its 9-adenine analogue 4. Both compounds have been prepared in enantiomerically pure form as different pharmacological activities have been frequently reported for the two enantiomers of acyclic nucleosides.[3]



	R	Base
1	H	guanin-9-yl
2	CH_2OH	guanin-9-yl
3	CH_2F	thymin-1-yl
4	CH_2F	adenin-9-yl

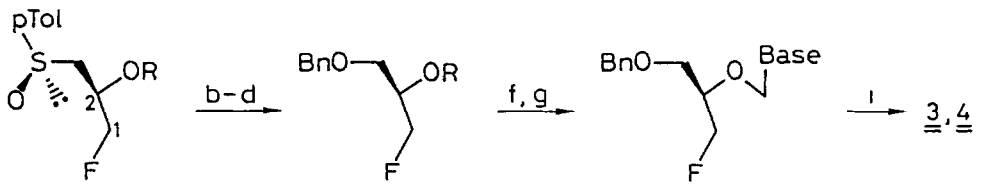
(2S)-1-Fluoro-3-(R)-[(4-methylphenyl)sulfinyl]-2-propanol 5, prepared in two steps from commercially available (+)-(R)-methyl-4-methylphenylsulfoxide, was used as starting material.[4] The reaction of this propanol derivative with dimethoxymethane and phosphorus pentoxide[5] afforded the corresponding methoxymethyl ether 6 (84% yield).

Under these reaction conditions no loss of chirality at the carbon stereocentre occurred, but partial racemization of the sulfinyl group was observed. This is unimportant as in the next step of the synthetic sequence the sulfoxide residue is replaced by an hydroxyl group. Specifically the so formed mixture of fluoro-sulfinyl-ethers $(2S,R_S)$-6 and $(2S,S_S)$-6 was treated with trifluoroacetic anhydride and 2,4,6-trimethylpyridine in acetonitrile solution and a clean Pummerer rearrangement took place.[6]

A geminal trifluoroacetyloxy-tolylthio intermediate formed and this masked aldehyde was hydrolyzed *in situ* with mercury(II) chloride to give (R)-3-fluoro-2-methoxymethoxypropanal. This aldehyde had a marked proclivity for becoming hydrated[7] so that it was not isolated in pure form, but the crude product was reduced with sodium borohydride and the so formed alcohol was benzylated under standard conditions to give the (R)-1-benzyloxy-3-fluoro-2-methoxymethoxypropane 7 in 52% overall yield starting from 6.

In order to transform the methoxymethylene substituent on C-2 of (R)-7 into a more suitable leaving group for the alkylation of the nucleoside bases, this protective group was hydrolyzed by acid treatment (acetic acid/water/dioxane/reflux) (84% yield). The so formed (R)-1-benzyloxy-3-fluoro-2-propanol 8 was reacted with paraformaldehyde and hydrogen chloride in dichloromethane solution[8] and (R)-3-benzyloxy-2-chloromethoxy-1-fluoropropane was produced in nearly pure form (^1H NMR analyses).

Scheme: a) dimethoxymethane /phosphorus pentoxide /r.t.; b) trifluoroacetic anhydride /2,4,6-trimethylpyridine /acetonitrile /r.t.; then mercury(II) chloride /acetonitrile /K_2CO_3/r.t.; c) sodium borohydride / acetonitrile / r.t.; d) sodium hydride / benzyl bromide / dimethylformamide / r.t.; e) acetic acid / water-dioxane /reflux; f) paraformaldehyde /dichloromethane/hydrogen chloride $_{(gas)}$ /-10°C; g) nitrogen base /hexamethyldisilazane/ ammonium sulfate; then mercury(II) cyanide / benzene; h) $NH_{3\ (gas)}$ / methanol / 80 °C; i) palladium(II) oxide / cyclohexene /hydrogen /ethanol /r.t.



		R			R		Base
a	(2S,R_S)- 5	H	e	(R)-7	CH_2OCH_3	(R)-9a	thymin-1-yl
	(2S,S_S/R_S)-6	CH_2OCH_3		(R)-8	H	-9b	6-chloropurin-9-yl
						h -9c	6-chloropurin-7-yl
						-9d	adenin-9-yl

The chlorine atom of this crude reaction product was replaced by thymine and 6-chloropurine (persilylated base/benzene/reflux) to give acyclic nucleosides 9a-c. Tetra n-butylammonium iodide or mercury(II) cyanide were employed as catalysts for the condensation reaction and the latter salt gave better results.[9]

When 6-chloropurine was employed, the N-9 alkylation product 9b formed preferentially, but minor amounts of the N-7 isomer 9c were also isolated.

The 6-chloropurine nucleoside 7b was cleanly transformed into the desired adenine derivative 7d with methanolic ammonia at 80 °C in stainless steel bomb.[8]

The removal of the protecting benzyl group was performed by catalytic transfer reduction (palladium oxide/cyclohexene/hydrogen/ethanol/) (80% yields ca.) and target nucleosides (R)-3 and (R)-4 were obtained starting from 9a and 9d, respectively. The esters of alcohol 8 with (+)-(S) and (-)-(R)-2-phenylpropionic acids have been prepared. The absolute configuration of the alcohol was thus confirmed as well as its optical purity.[10] It is known that the chloromethylation reaction and successive steps do not cause racemisation.[11]

Final nucleosides 3 and 4 have thus been prepared in enantiomerically pure form.

These acyclic nucleosides have the same chirality of natural nucleosides assuming that oxygenated and fluorinated carbons of 3 and 4 mimic, respectively, C-5′ and C-3′ of natural compounds. The biological and pharmacological properties of 3 and 4 is being tested.

E X P E R I M E N T A L

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker AC 250L spectrometer in $CDCl_3$. C_6F_6 was used as internal standard (δ_F - 162.90) for ^{19}F. $[\alpha]_D^{20}$ values were determined on a Jasco DIP-181 Polarimeter. Mps are uncorrected and were obtained on a capillary apparatus. TLC were run on silica gel 60 F_{254} Merck; flash column chromatography was performed with silica gel 60 (60-200 μm, Merck). Methylene chloride was freshly distilled from phosphorus pentoxide (P_2O_5) and from calcium chloride ($CaCl_2$), C_6H_6 was freshly distilled from $CaCl_2$; in other cases commercially available reagent-grade solvents were employed. Pummerer reaction and conjugation of the nitrogen bases were performed under a positive argon pressure.

Synthesis of (2S,R_S)-1-Fluoro-3-[(4-methylphenyl)sulphinyl]-2-propyl methoxymethyl ether (6). - To a solution of secondary alcohol 5 (2.16 g, 10 mmol) in dimethoxymethane (50 ml) at room temperature, phosphorus pentoxide (28.5 g, 20.0 mmol) was added portionwise After 4 h the reaction mixture was filtered on celite and the solution was concentrated to a yellowish oil which was purified by flash chromatography (n-hexane/ethyl acetate 5:2) to give (2S, R_S)-6 (1.50 g, 60% yield) and (2S,S_S)-6 (600 mg,24% yield). (2S,R_S)-6 R_f 0.30; $[\alpha]_D^{20}$ + 168.8° (c 1.1, $CHCl_3$); m.p. 35 °C (diethylether); ^{1}H NMR δ: 2.42 (3H, s, ArCH_3), 2.89 (1H, dd, CH_aS, $^{2}J_{H-H}$=13 Hz, $^{3}J_{H-H}$=3.3 Hz), 3 00 (1H, dd, CH_bS, $^{3}J_{H-H}$=9.8 Hz), 3.50 (3H, s, OCH_3), 4 43 (1H, dddd, CH_aF, $^{2}J_{H-F}$=49.0 Hz), 4.65 (1H, dddd, CH_bF, $^{2}J_{H-F}$=47.0 Hz, $^{3}J_{H-H}$=9.8 Hz), 4.37 (1H, m, CHO, $^{3}J_{H-F}$=22.3 Hz, $^{3}J_{H-H}$=9.8, 6.5, 3.3 Hz), 4.85 (1H, d, OCH_aO, $^{2}J_{H-H}$=6.8 Hz), 4.89 (1H, d, OCH_bO), 7.30-7.80 (4H, m, ArH); ^{13}C NMR δ: 21.41 (ArCH_3), 55.99 (OCH_3), 60.53 (d, CH_2S, J_{C-F}=4 4 Hz), 70.89 (d, CHO, J_{C-F}=19.5 Hz), 84.24 (d, CH_2F, J_{C-F}=174.2 Hz), 96 85 (OCH_2O), 123 75 and 130 13 (ArC); ^{19}F NMR δ -231.9.

(2S,S_S)-6 : R_f 0.35; $[\alpha]_D^{20}$ - 117.6° (c 0.9, $CHCl_3$); ^1H NMR δ: 2.42 (3H, s, $ArCH_3$), 3.05 (1H, ddd, CH_aS, $^2J_{H-H}$=13.5 Hz, $^3J_{H-H}$=6.3 Hz, $^4J_{H-F}$=1.0 Hz), 3.13 (1H, ddd, CH_bS, $^3J_{H-H}$=5.5 Hz), 3.37 (3H, s, OCH_3), 4.10 (1H, m, CHO, $^3J_{H-H}$=6.25, 5.5, 5.0, and 4.0 Hz, $^3J_{H-F}$=23.0 Hz), 4.61 (1H, dd, CH_aF, $^2J_{H-F}$=47.0 Hz, $^3J_{H-H}$=4.0 Hz), 4.62 (1H, dd, CH_bF, $^2J_{H-F}$=47.0 Hz, $^3J_{H-H}$=5.0 Hz), 4.64 (2H, brs, OCH_2O), 7.30-7.60 (4H, m, ArH); ^{19}F NMR δ: -229.1

Synthesis of (R)-1-benzyloxy-3-fluoro-2-methoxy-methoxypropane (7). - To an acetonitrile solution (14 ml) of (2S, R_S)-6 and (2S, S_S)-6 (10 mmol, 2.48 g) and 2,4,6-trimethylpyridine (20 mmol, 2.65 ml) cooled at -20 °C under Argon, a solution of trifluoroacetic anhydride (15 mmol, 2.08 ml) in the same solvent (4 ml) was added dropwise. After 1 hour at room temperature, some solid K_2CO_3 was added (up to pH 7) and a solution of $HgCl_2$ (14 mmol, 3.80 g) in acetonitrile (2 ml) was added at 0 °C. A white precipitate slowly formed and reaction was stirred for 1 h at room temperature. The solid was filtered through celite and the solution was cooled to 0 °C and treated with an acetonitrile solution (4 ml) of $NaBH_4$ (20 mmol, 790 mg). Some CH_3COOH was added (up to pH 6), solvent removed and the residue purified by flash chromatography (methylene chloride/ethyl acetate 4:1) to give (R)-1-hydroxy-3-fluoro-2-methoxy-methoxypropane (1.05 g, 76% yield): $[\alpha]_D^{20}$ + 24.4° (c 0.6, $CHCl_3$), $[\alpha]_{365}^{20}$ + 72.5° (c 0.6, $CHCl_3$); ^1H NMR δ: 2.50 (1H, brt, OH), 3.44 (3H, s, OCH_3), 3.67 (1H, ddd, CH_aOH, $^2J_{H-H}$=12.0 Hz, $^3J_{H-H}$=6.2 Hz, $^4J_{H-F}$=1.2 Hz), 3 75 (1H, ddd, CH_bOH, $^3J_{H-H}$=3.2 Hz, $^4J_{H-F}$=1.6 Hz), 3.87 (1H, m ,CHO, $^2J_{H-H}$=6 2, 5 2, 3 2 Hz, $^3J_{H-F}$=19.6 Hz), 4 51 (2H, dd, CH_2F, $^2J_{H-F}$=46.8 Hz, $^3J_{H-H}$=5 2 Hz), 4 78 (2H,br s, OCH_2O); ^{19}F NMR δ: -232.0. A DMF (10 ml) solution of the so-obtained alcohol (10 mmol, 1.38 g) and benzyl bromide (100 mmol, 11.88 ml) was added dropwise to a suspension of NaH (20 mmol, 0.95 g) in DMF (20 ml) at 0 °C After 20 min at room temperature, an usual work up and a flash chromatography (n-hexane/diethyl ether 4:1), afforded the benzyloxy derivative 7 (1.75 g, 82% yield). $[\alpha]_D^{20}$ -25 3° (c 1.0 in $CHCl_3$), $[\alpha]_{365}^{20}$ -80.3° (c 1.0, $CHCl_3$); ^1H NMR δ: 3.38 (3H, s, OCH_3), 3.60 (2H, dd, CH_2O, $^3J_{H-H}$=5.5 Hz, $^4J_{H-F}$=1 5 Hz), 4.00 (1H, dddd, CHO, $^3J_{H-F}$=21.0 Hz, $^2J_{H-H}$=5.5, 5.0, 4.0 Hz), 4.52 (1H, ddd, CH_aF, $^2J_{H-F}$=47 0 Hz, $^2J_{H-H}$=10.0 Hz, $^3J_{H-H}$=5.0 Hz), 4.57 (1H, ddd, CH_bF, $^2J_{H-F}$=47.0 Hz, $^3J_{H-H}$=4.0 Hz), 4.73 and 4.76 (2H, AB system, OCH_2O), 7.30-7.40 (5H, m, ArH); ^{19}F NMR δ -232.3.

Synthesis of (R)-3-benzyloxy-1-fluoro-propane (8). - A dioxane solution (14 ml) of the methoxymethyl derivative 7 (10 mmol, 2.28 g) was added to a 4:1 solution of CH_3COOH/H_2O (28 ml). The reaction mixture was refluxed under argon and acetic acid solution was added in order to adjust pH to 4.5 (20 ml). After 4 hours removal of solvent stripping CH_3COOH with benzene (3x10 ml) and flash chromatographic purification (n-hexane/diisopropylether 3·7) gave the alcohol 8 (1 54 g, 84% yield). $[\alpha]_D^{20}$ -11.5° (c 1 0, EtOH), $[\alpha]_{365}^{20}$ -32.4° (c 1.0, EtOH), ^1H NMR δ: 2.44 (1H, d, OH, $^3J_{H-H}$=5.0 Hz), 3.55 (1H, ddd, OCH_a, $^2J_{H-H}$=9 6 Hz, $^3J_{H-H}$=5 8 Hz, $^4J_{H-F}$=1.4 Hz), 3 60 (1H, ddd, OCH_b, $^3J_{H-H}$=4.7 Hz), 4.05 (1H, m, CHO, $^3J_{H-OH}$=5.0 Hz, $^3J_{H-H}$=5.8, 4.7, 5.4, 4.4 Hz, $^3J_{H-F}$=18.6 Hz), 4.45 (1H, ddd, CH_aF, $^2J_{H-F}$=47 0 Hz, $^2J_{H-H}$=9.6 Hz, $^3J_{H-H}$=5.4, Hz $^2J_{H-H}$=0.2 Hz), 4.51 (1H, ddd, CH_bF, $^2J_{H-F}$=47.0 Hz, $^3J_{H-H}$=4.4 Hz), 4.58 (2H, brs, CH_2O), 7.30-7.40 (5H, m, ArH); ^{19}F NMR δ· -233.0

Synthesis of acyclic nucleosides 9a-c - General procedure: A solution of alcohol

8 (10 mmol, 1.84 g) and paraformaldehyde (30 mmol, 2.80 g) in methylene chloride (30 ml) was stirred at 0 °C under protection from moisture as a stream of gaseous hydrogen chloride was bubbled through it. After 4 h, the resulting solution was purged with a stream of Argon in order to remove excess HCl and then dried over molecular sieves and filtered. Solvent was removed under reduced pressure to give the (R)-3-benzyloxy-2-chloromethoxy-1-fluoropropane as a yellowish residual oil which was not purified, but was immediately utilized. ^{1}H NMR δ: 3.55 (1H, dd, OCH_a), 3.70 (1H, dd, OCH_b), 4.20 (1H, ddd, CH_aF, $^2J_{H-F}$=45.0 Hz), 4.50 (2H, br s, $ArCH_2O$), 4.80 (1H, ddd, CH_bF, $^2J_{H-F}$=50.0 Hz), 5.58 (2H, s, CH_2Cl), 7.20-7.40 (5H, m, ArH). Tymine or 6-chloro-purine (10 mmol) and ammonium sulfate (1.0 mmol, 132 mg) were added to hexamethyldisilazane (40 ml). The mixture was heated at reflux for 3 hours, HMDS was removed, the residue dissolved in C_6H_6 (30 ml) and $Hg(CN)_2$ (12 mmol, 3.02 g) was added. The mixture was heated at reflux and a solution of the chloromethyl ether derivative in the same solvent (11.0 mmol, 2.42 g) was added dropwise. After 1 hour, the solution was filtered, solvent evaporated off and dichloromethane (70 ml) was added. The solution was washed with 30% aqueous KI, saturated aqueous NaCl and 10% aqueous K_2CO_3 solutions, the collected organic layers were dried over sodium sulfate, concentrated to give a residue which was purified by flash chromatography. From thymine, (R)-9a was obtained (n-hexane/ethyl acetate 2:3) in 50% yield (1.51 g): $[\alpha]_D^{20}$ - 17.9° (c 1.1, $CHCl_3$), $[\alpha]_{365}^{20}$ - 72.1° (c 1.1, $CHCl_3$), ^{1}H NMR δ: 1.89 (3H, d, CH_3C=CH, $^4J_{H-H}$=1.3 Hz), 3.55 (1H, ddd, OCH_a, $^3J_{H-H}$=5 5 Hz), 4.09 (1H, m, CH_bO, $^3J_{H-F}$=20.0 Hz, $^2J_{H-H}$=5.8, 5.5, 3 8 Hz), 4.45 (1H, ddd, CH_aF, $^2J_{H-F}$=42.5 Hz, $^2J_{H-H}$=10.0 Hz, $^3J_{H-H}$=5.8 Hz), 4.52 (1H, ddd, CH_bF, $^2J_{H-H}$=10.0 Hz, $^3J_{H-H}$=3.8 Hz), 4.51 (2H, s, $ArCH_2O$), 5.24 (2H, s, NCH_2O), 7.14 (1H, d, CH=CMe, $^4J_{H-H}$=1.3 Hz), 7.20-7.40 (5H, m, ArH), 9.25 (1H, brs, NH); ^{13}C NMR δ· 12.28 (CH_3), 66.69 (d, OCH_2, J_{C-F}=8.19 Hz), 73.53 (NCH_2O), 76.27 ($ArCH_2O$), 76 92 (d, CHO, J_{C-F}=17.0 Hz), 83.06 (d, CH_2F, J_{C-F}=172.0 Hz), 127.64-128.48 (ArC), 111.57 ($CH_3\underline{C}$=CH), 139.21 (N$\underline{C}$H=C), 151.27 (HNCON), 164.12 (HN$\underline{C}$OC); ^{19}F NMR δ: -231.3. From 6-chloro-purine, flash chromatography (n-hexane/ethyl acetate 1:1) gave (R)-6-chloropurin-9-yl derivative 9b in 20% yield and (R)-6-chloropurin-7-yl derivative 9c in 12% yield. 9b: R_f 0.35; $[\alpha]_D^{20}$ - 20.3° (c 1 0, $CHCl_3$), $[\alpha]_{365}^{20}$ - 70.3° (c 1.0, $CHCl_3$); ^{1}H NMR δ: 3.50 (2H, dd, OCH_2, $^3J_{H-H}$=5.5 Hz, $^4J_{H-F}$=1.3 Hz), 4.10 (1H, dddd, CHO, $^3J_{H-F}$=19.5 Hz, $^3J_{H-H}$= 5.5, 4.0, 1.3 Hz), 4.46 (1H, ddd, CH_aF, $^2J_{H-F}$=47.5 Hz, $^3J_{H-H}$=10.0 Hz, $^2J_{H-H}$=8.0 Hz), 4.48 (1H, ddd, CH_bF, $^2J_{H-F}$=47 5 Hz, $^3J_{H-H}$=5 8 Hz), 4.44 (2H, AB system, $ArCH_2O$), 5.81 (1H, d, OCH_aN, $^2J_{H-H}$=11.3 Hz), 5 86 (1H, d, OCH_bN), 7.18-7.36 (5H, m, ArH), 8.25 (1H, s, H-8), 8.77 (1H, s, H-2); ^{13}C NMR δ. 68.79 (O$\underline{C}H_2$CH), 72.99 (NCH_2O), 73.55 (Ar$\underline{C}H_2$), 77 49 (d, CHO, J_{C-F}=19.0 Hz), 83.15 (d, CH_2F, J_{C-F}=172.0 Hz), 128.48, 127.96, 127.86, 137.22 (ArC), 131 60 (C-5), 145.33 (C-8), 151.30 (C-6), 151.92 (C-4), 152.39 (C-2), ^{19}F NMR δ: -231.0 9c: R_f 0.5; $[\alpha]_D^{20}$ - 14.3° (c 0.6, $CHCl_3$), $[\alpha]_{365}^{20}$ - 43.1° (c 0 6, $CHCl_3$), ^{1}H NMR δ: 3.54 (2H, AB system, OCH_2), 3.98 (1H, dddd, CHO), 4.46 and 4.48 (2H, ddd, CH_2F, $^2J_{H-F}$=47.5 Hz), 4.46 (2H, br s, $ArCH_2$), 5.94 (1H, d, NCH_aO, $^2J_{H-H}$=10.5 Hz), 6.01 (1H, d, NCH_bO), 7.20-7.40 (5H, m, ArH), 8.32 (1H, s, H-8), 8.88 (1H, s, H-2); ^{13}C NMR δ: 69.28 (d, CH_2O, $^3J_{C-F}$=7.0 Hz), 73.66 ($ArCH_2$), 75.59 (NCH_2O), 76 37 (d, CHO, J_{C-F}=19 0 Hz), 83.59 (d, CH_2F, J_{C-F}=171.5 Hz), 122.18 (C-5), 127.83, 128.01, 128.40, 137.12 (ArC), 143.44 (C-6), 149.50 (C-8), 152.77 (C-2), 162 38(C-4); ^{19}F NMR δ: -229.4

Conversion of 9b into adenine derivative 9d. - 9b (10 mmol, 3.5 g) was dissolved

in methanol (10 ml) and 50 ml of saturated methanolic ammonia solution was added. The mixture was sealed into a steel bomb which was then maintained at 80°C for 12 hours. The mixture was then concentrated to give a residue which after flash chromatography (methanol/dichloromethane/ethyl acetate) gave 9d (73.4% yield): $[\alpha]_D^{20}$ - 17.3°(c 0.6, EtOH), $[\alpha]_{365}^{20}$ - 63.9° (c 0.6, EtOH); m.p. 120-122 °C (ethyl acetate/cyclohexane 1:1); ^{1}H NMR δ: 3.46 (1H, dt, OCH_a, $^2J_{H-H}$=10.8 Hz, $^3J_{H-H}$=6.0 Hz, $^4J_{H-F}$=1.5 Hz), 3.50 (1H, ddd, OCH_b, $^3J_{H-H}$=4.8 Hz, $^4J_{H-F}$=1.2 Hz), 4 12 (1H, m, CHO, $^3J_{H-F}$=24.9 Hz), 4.38 (2H, br s, $ArCH_2O$), 4.40 (1H, ddd, CH_aF, $^2J_{H-F}$=48.0 Hz, $^2J_{H-H}$=10.5 Hz, $^3J_{H-H}$=5.7 Hz), 4.48 (1H, ddd, CH_bF, $^2J_{H-F}$=46.5 Hz, $^3J_{H-H}$=3.9 Hz), 5.72 (1H, d, NCHO, $^2J_{H-H}$=11.4 Hz), 5.78 (1H, d, NCHO), 7.14-7.32 (5H, m, ArH), 8.21 (2H, br s, H-2 and H-8); ^{13}C NMR δ: 69.85 (d, OCH_2, J_{C-F}=8.2 Hz), 73.83 (NCH_2O), 74.31 ($ArCH_2$), 78.62 (d, CHO, J_{C-F}=18.9 Hz), 84.12 (d, CH_2F, J_{C-F}=90.1 Hz), 120.0 (C-5), 128.66, 129.39 (ArC), 142.93 (C-8), 150.1 (C-4), 154.17 (C-2), 157.5 (C-6); ^{19}F NMR δ: -230.0.

Conversion of benzylic derivatives 9a,d into 3,4. - General procedure: benzyloxy derivatives 9a,d (10 mmol) were dissolved in ethanol (40 ml), cyclohexene (8 ml) and palladium oxide (640 mg) were added. The mixture was stirred under hydrogen atmosphere at room temperature for a period of time depending on the substrate. PdO was carefully filtered off, solvent was removed under reduced pressure and the residue was purified by flash chromatography. Starting from 9a, the thymin-1-yl derivative 3 was obtained in 81% yield (flash chromatography: ethyl acetate): $[\alpha]_D^{20}$ -9.8° (c 0.6, EtOH), $[\alpha]_{365}^{20}$ - 25.4° (c 0.6, EtOH); m.p. 122-124 °C (ethyl acetate); ^{1}H NMR δ. 1 77 (3H, d, $C\underline{H}_3C$=CH, $^4J_{H-H}$=1.3 Hz), 2.51 (1H, brt, OH, $^3J_{H-H}$= 3.0, 1.5 Hz), 3 43 (2H, dt, OCH_2, $^3J_{H-H}$=5.5 Hz, $^4J_{H-F}$=1.3 Hz), 3.81 (1H, dddd, CHO, $^3J_{H-F}$=21.0 Hz, $^3J_{H-H}$=5.7, 3.3, 3.0 Hz), 4.39 (1H, ddd, CH_aF, $^2J_{H-F}$=47.8 Hz, $^2J_{H-H}$=10.5 Hz, $^3J_{H-H}$=5 8 Hz), 4.51 (1H, ddd, CH_bF, $^2J_{H-F}$=47.5 Hz, $^3J_{H-H}$=3.3 Hz), 5.13 (1H, d, OCH_aN, $^2J_{H-H}$=10.8 Hz), 5.18 (1H, d, OCH_bN), 7.58 (1H, d, CH=C, $^4J_{H-H}$=1.3 Hz), 11.32 (1H, brs, NH); ^{13}C NMR δ: 11 60 (CH_3), 59.36 (d, OCH_2, J_{C-F}=8.8 Hz), 75.58 (NCH_2O), 77.86 (d, CHO, J_{C-F}=17.01Hz), 82.85 (d, CH_2F, J_{C-F}=168.21 Hz), 109.13 ($CH_3\underline{C}H$), 140.51 (NCH), 151.07 (NCONH), 164.18 ($HN\underline{C}OC$); ^{19}F NMR δ: -232.0. Starting from 9d, the adenin-9-yl derivative 4 was obtained in 42% yield (flash chromatography: ethyl acetate/ methanol 4:1): $[\alpha]_D^{20}$ - 8.9 °C (c 0.6, MeOH), $[\alpha]_{365}^{20}$ - 25.8° (c 0.6, MeOH), m.p. 170-172 °C (ethyl acetate); ^{1}H NMR δ: 3.53 (1H, ddd, $HOC\underline{H}_a$, $^2J_{H-H}$=11.7 Hz, $^3J_{H-H}$=6.0 Hz, $^4J_{H-F}$=1.5 Hz), 3.60 (1H, ddd, $HOC\underline{H}_b$, $^3J_{H-H}$= 6.6Hz, $^4J_{H-F}$=1.2 Hz), 3.96 (1H, m, CHO, $^3J_{H-F}$=18.9 Hz, $^3J_{H-H}$=6.6, 6.0, and 3.6 Hz), 4.39 (1H, ddd, CH_aF, $^2J_{H-F}$=47.7 Hz, $^2J_{H-H}$=10.2 Hz, $^3J_{H-H}$=6.0 Hz), 4.48 (1H, ddd, CH_bF, $^2J_{H-F}$=47.4 Hz, $^3J_{H-H}$=3.6 Hz), 5 77 (2H, s, NCH_2O), 8.21 (1H, s, H-8), 8.25 (1H, s, H-2); ^{13}C NMR δ: 62.03 (d, $HOCH_2$, J_{C-F}=8.8 Hz), 74.26 (NCH_2O), 80.52 (d, CHO, J_{C-F}=18.3 Hz), 84.57 (d, CH_2F, J_{C-F}=169.8 Hz), 120.55 (C-5), 143.57 (C-8), 151.47 (C-4), 154.82 (C-2), 158.00 (C-6); ^{19}F NMR δ: -230.45.

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