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ADDITION OF MOLECULAR FLUORINE TO 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE AND RELATED COMPOUNDS: SYNTHESIS OF DIFLUORINATED CARBOCYCLIC NUCLEOSIDES[1]

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Abstract: Addition of molecular fluorine to bicyclo[2.2.1]hept-2-ene derivatives having electronegative substituent(s) on the ethano bridge has been found to give *exo,exo*-difluoro adducts with high stereoselectivity. The difluoro adducts derived from 2-azabicyclo[2.2.1]hept-5-en-3-ones having an electron-withdrawing group at 2-position were converted to the difluorinated carbocyclic nucleoside analogs.

Through a pioneering work by Barton[2] and later a series of works by Rozen,[3] fluorination of organic compounds using diluted molecular fluorine has become one of the useful methods for preparation of fluorinated organic compounds.[4] Addition to C-C double bonds[5] and substitution of C-H bonds[6] are two major types of reactions which permit selective fluorination. In our laboratory, general synthetic methods of 5-fluorinated 1,3-dioxin-4-ones,[7] 5α-fluorinated steroids,[8] and 3-fluorinated amino acids[9] have been elaborated using the addition to C-C double bond as the key step.

We also performed mechanistic studies on these fluorination reactions and, by using *ab initio* MO calculation with IRC (instrinstic reaction coordinate) method, have demonstrated that both of fluorine addition to ethylene[10] and fluorine substitution[11] of methane can be categorized as an electrophilic reaction. This conclusion when combined with the FMO theory[12] suggests that the smaller the energy gaps of corresponding MOs [i.e. $\sigma^*_{F\text{-}F}$ (the LUMO of F_2) and $\pi_{C=C}$ (the HOMO of carbon-carbon double bond) or $\sigma_{C\text{-}H}$ (the HOMO of carbon-hydrogen bond)] the more readily the C-H or C-C double bonds react with molecular fluorine.

In the present study, we were interested in the synthesis of fluorine containing carbocyclic nucleosides by using the above addition reaction as the key step. Our initial attempts to perform direct fluorination of some cyclopentenes shown in Figure 1 which belong to type D compounds in Scheme 1 were found to give complex mixtures and we reasoned that this failure was probably due to small differences in reactivity between the tertiary hydrogen and the double bond.

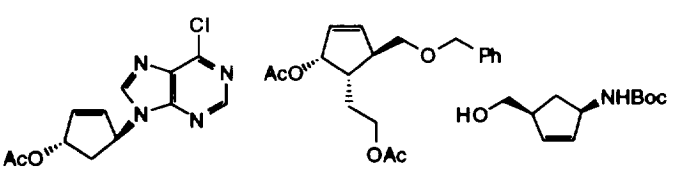
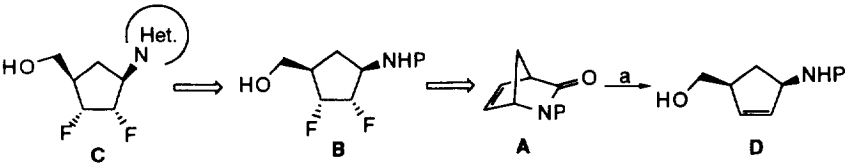


Figure 1

Hence, in order to obtain the fluorine-containing carbocyclic sugar units **B**, we chose 2-azabicyclo[2.2.1]hept-5-en-3-one derivatives **A** (P = an appropriate protecting group) instead of **D** as the substrates for fluorination. The reasons for this choice are as follows: 1) Compounds **A** have not only tertiary C-H with somewhat lower *p*-character,[13] but also a more activated double bond[14] than those incorporated in acyclic and monocyclic systems and 2) We have found that **A** having an electron-withdrawing group at 2-position (e.g. P = CO_2R, $COCH_3$ etc.) can be cleaved at the N_2-C_3 bond to give the corresponding ring-opened products (e.g. **D**).[15]



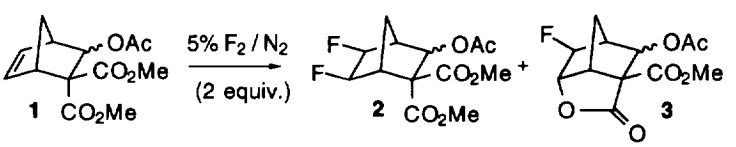
Scheme 1. Retrosynthesis of **C** from **A** and conversion of **A** to **D** by RAC reaction (a: $NaBH_4$/MeOH)

We describe here successful addition of fluorine to 2-azabicyclo[2.2.1]hept-5-en-3-one derivatives (**A**) and the conversion of the adducts to fluorine-containing carbocyclic purine and pyrimidine nucleosides (**C**).[16]

RESULTS AND DISCUSSION

Addition of Molecular Fluorine to Bicyclo[2.2.1]hept-2-ene Derivatives

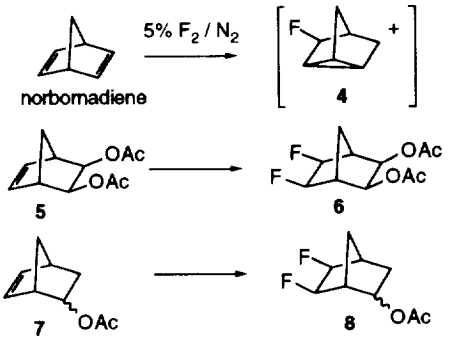
At first, the bicycloheptene **1**[17] which was readily available by Diels-Alder reaction of cyclopentadiene with dimethyl acetoxymethylenemalonate[18] was used as the substrate for the fluorine addition reaction. In a typical experiment, stream of 5% fluorine (2 mol equiv. to **1**) in nitrogen was passed through a solution of the bicyclic heptene **1** (*endo*/*exo* = *ca.* 6/5). In acetonitrile, the corresponding *cis* adduct **2** was obtained in 23% yield together with 61% of the lactone **3**. Using Rozen's conditions which employ $CFCl_3$-$CHCl_3$-EtOH (5:4:1) as the solvent,[5] the yield of the desired adduct **2** increased to 52%.



Temp.	Solvent	Yield	
-35 °C	MeCN	23%	61%
-78 °C	$CFCl_3$/$CHCl_3$/EtOH 5 : 4 : 1 v/v	52%	20%

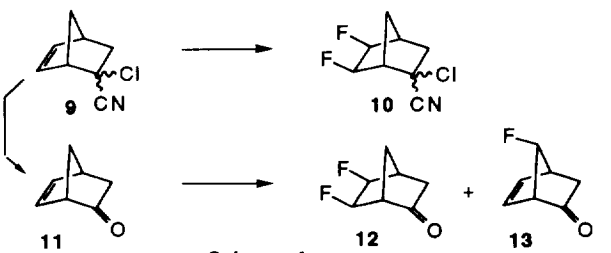
Scheme 2

Fluorination of norbornadiene under the Rozen's conditions gave only a complex mixture. We thought that the result would be due to formation of the carbocation intermediate **4**.[19] In order to prevent the formation of **4**, fluorination of the diacetate **5** obtained from norbornadiene by the known method[20] was examined. As expected, the *exo* adduct **6** was obtained in 40% yield. Fluorination of the monoacetate **7** (*endo*/*exo* = *ca.* 4)[21] gave the adduct **8** in a lower yield (23%).



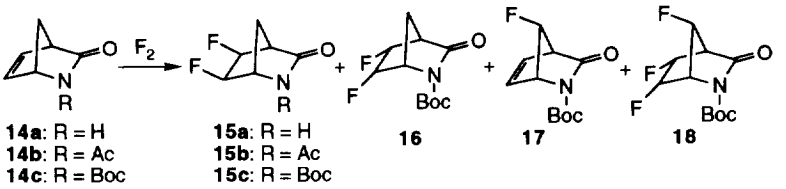
Scheme 3

Treatment of the bicyclic heptene **9** (*endo*/*exo* = *ca.* 6)[22] with F_2 gave **10** in 52% yield. The same reaction if applied to the ketone **11**[23] obtained from **9** provided **12** in 17% yield, together with **13** (11%).



Scheme 4

Addition of fluorine to 2-azabicyclo[2.2.1]hept-5-en-3-one (**14a**)[24] and its acetate **14b** afforded the corresponding adducts **15a** and **15b** in 27% and 32% yields, respectively. Since the presence of an electron-withdrawing group in their 2-position is essential for RAC reaction of the bicyclic lactams (**14**, **15** etc.), only **15b** could serve as the substrate for RAC reaction. However, the yield of **14b** from **14a** was only 17%. After searching a ready and efficient way to introduce an electron-withdrawing group, we found that *tert*-butoxycarbonyl group could be introduced to **14a** by reacting di-*tert*-butyl dicarbonate[25] under Grieco's conditions to give **14c**, quantitatively. Hence, the fluorination reaction of **14c** was then investigated in details. As a result, the *exo* difluoro adduct **15c** (41%) was obtained as the major product and the *endo* isomer **16** (5%), monofluoro product **17** (2%) and trifluoro product **18** (4%) were identified as the minor products. Addition of tetrabutylammonium fluoride to the reaction system decreased the formation of **15c** (31%), but increased the formation of **17** (7%) and **18** (8%).

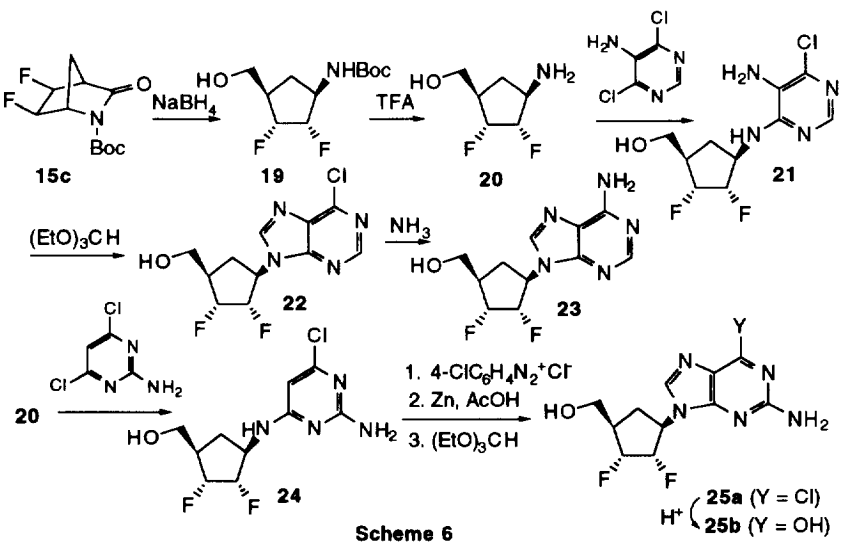


Scheme 5

The *exo* configuration of two fluorine groups in **15c** was evident both from the larger coupling ($J = 7$ Hz) of C_4-H (3.17 ppm) with C_5-F compared to the absence of the corresponding coupling constant in **16** and from lowfield shift of C_{7anti}-H (2.34 ppm) compared to the corresponding proton (1.44 ppm) of **16** due to deshielding effect of the fluorine groups. Long range couplings ($J = 9$ Hz) of C_{7syn}-H (2.13 ppm) with C_5-F and C_6-F in **16** also supported its *endo* structure. The similar long-range couplings ($J = 8$ Hz) were observed in C_{7syn}-H (5.07 ppm) of **18** . The monofluorinated product **17** was considered to be formed *via* addition-rearrangement with nitrogen participation which was well precedented in the bromination of similar system.[26] It is reasonable to assume that **18** was formed from **17**, since the fluorine at the 7-position of **17** would restrict the access of fluorine to its *exo* face.[27]

Synthesis of Fluorine Containing Carbocyclic Nucleosides

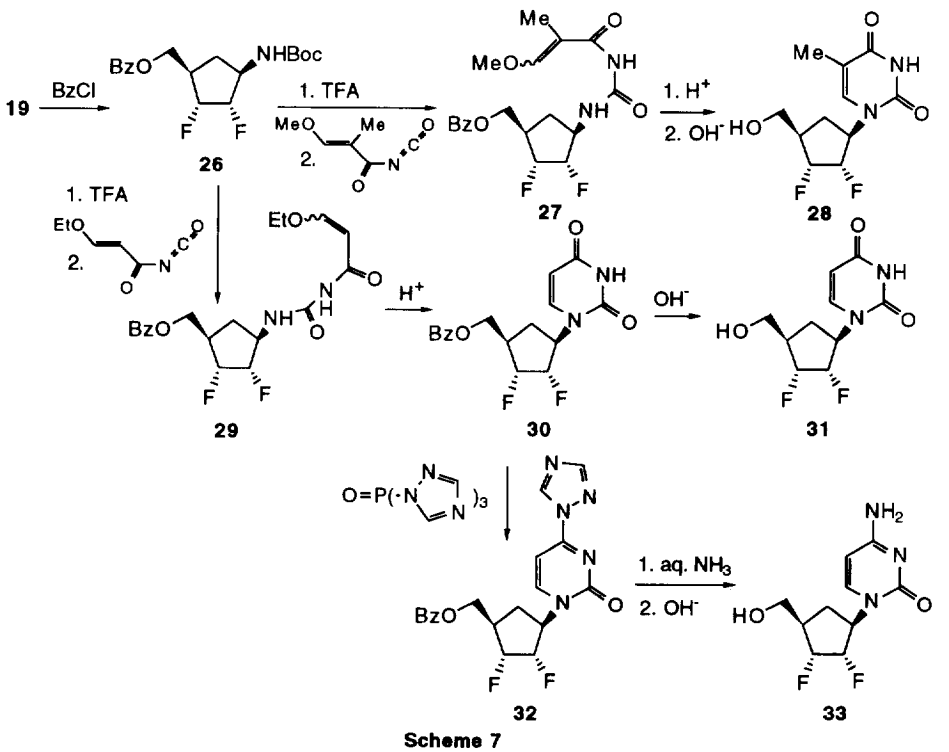
Reductive amide bond cleavage of **15c** with sodium borohydride in methanol at room temperature gave the alcohol **19** in 53% yield. When the reaction was carried out at -20 °C→0 °C, **19** was obtained in 84% yield. Usual construction of purine rings[28] from **20** derived from **19** then afforded the desired carbocyclic fluorinated nucleosides **23** and **25b**. Thus, coupling of the resulted aminoalcohol **20** with 5-amino-4,6-dichloro-pyrimidine furnished the diamine **21** in 40% yield. Treatment of **21** with triethyl orthoformate under acidic



Scheme 6

conditions followed by amination led to the adenosine derivative **23** in 49% yield. Coupling of **20** with 2-amino-4,6-dichloropyrimidine gave **24** in 52% yield. Diazotization of **24** using 4-chlorophenyldiazonium chloride and reduction of the diazo compound with zinc-acetic acid, followed by ring closure as in the case of **21** and subsequent acidic hydrolysis, afforded the guanosine analog **25b** in 21% overall yield.

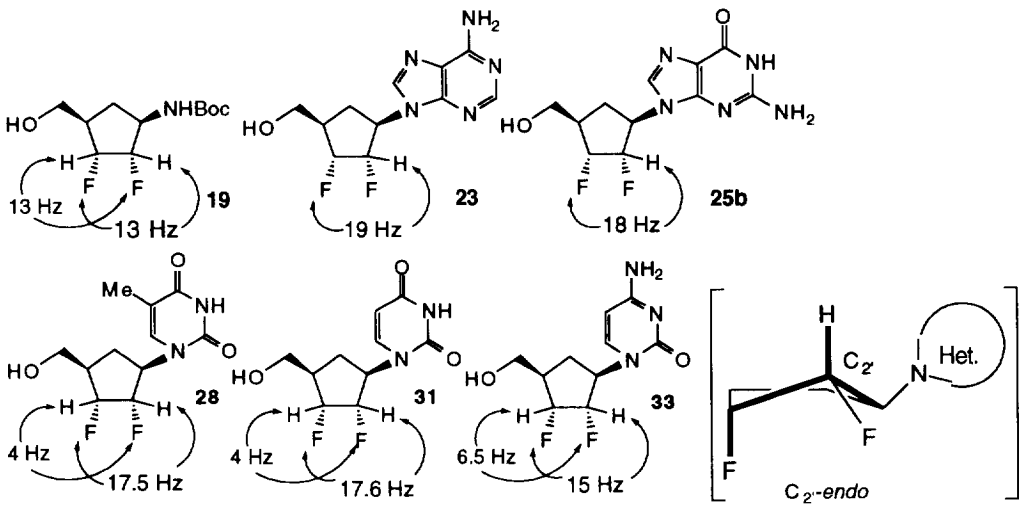
The synthesis of the uridine and thymidine analogs **28** and **31** were based on the general method developed initially Shaw and Warrener.[29] After benzoylation of hydroxyl group of **19** in 88% yield, the benzoate **26** was treated with TFA followed by coupling with 3-methoxy-2-methylacryloyl isocyanate to give **27** in 61% yield. Cyclization of **27** under acidic conditions[30] followed by deprotection of the primary hydroxyl group furnished the thymidine analog **28** in 77% yield. Coupling reaction of the cyclopentanylamine derived from **26** with 3-ethoxyacryloyl isocyanate gave **29** in 85% yield. Similar cyclization of **29** and deprotection provided the uridine analog **31** in 77% overall yield from **29**. The cytidine analog **33** was prepared according to the procedure of Reese.[31] Treatment of **30** with tri(1*H*-1,2,4-triazol-1-yl)phosphine oxide gave the triazole **32** in 76% yield. Ammonolysis of **32** with aqueous ammonia followed by deprotection by NaOH-MeOH afforded **33** in 82% yield.



Scheme 7

The coupling constant (19 Hz) of $C_{2'}$-H with $C_{3'}$-F in adenosine analog **23** and that (18 Hz) in guanosine analog **25b** after construction of nucleobase were larger than that (13 Hz) of their precursor **19** without the purine base. Comparably larger coupling constants 17.5, 17.6 and 15 Hz were also observed in the spectra of the pyrimidine analogs **28**, **31** and **33**, respectively. The result could be correlated with $C_{2'}$-*endo*

conformation of the cyclopentane ring. This fact is interesting when compared with the fact that most of furanose rings in helical DNA duplexes exist in $C_{2'}$-*endo* conformation.[32]



Scheme 8

In conclusion, we have found that fluorination of bicyclo[2.2.1]hept-2-ene derivatives by diluted fluorine affords selectively the *exo* adducts. This reaction could be used for the synthesis of not only fluorinated carbocyclic nucleoside analogs as demonstrated above but also other fluorine containing compounds.

Acknowledgment. This work is supported in part by a Grant-in-Aid for Scientific Research to A. T. (Grant No. 07772084) from the Ministry of Education, Science and Culture, Japan.

Experimental Section

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. IR spectra were measured on a JASCO A-102 spectrophotometer and UV spectra were measured on a Hitachi 320 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI, Hitachi R-300 or JEOL JNM-GX 500 spectrometer with tetramethylsilane as an internal standard. If otherwise noted, all spectra were mesured by 60 MHz. High-resolution mass spectra were recorded on a JEOL JMS-DX-303 or JMS-AX-500 spectrometer.

The fluorine gas [5% (v/v) in N_2] was donated from Asahi Glass Co., Ltd. and the amount of fluorine was determined by means of Kusano KG-2 flowmeter. Merck Silicagel 60 (230-400 mesh ASTM) and Merck Kieselgel 60 F_{254} were employed for flash chromatography and preparative thin layer chromatography (TLC), respectively.

Dimethyl 3-Acetoxy-5-*exo*,6-*exo*-difluorobicyclo[2.2.1]cyclopentane-2,2-dicarboxylate (2) and 5-Acetoxy-9-*exo*-fluoro-4-*exo*-methoxycarbonyl-2-oxatricyclo[4.2.1.0]nonan-3-one (3)

5% F_2/N_2 was passed into a solution of **1** (*endo/exo* = 6/5) (267 mg, 1.0 mmol) in $CFCl_3$ (25 ml)-$CHCl_3$ (20 ml)-EtOH (5 ml) at -78 °C until 2 mmol of F_2 had passed through the flowmeter (*ca.* 10 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (4 ml)-water (40 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (5 : 1)] to give the recovered **1** (*endo/exo* = *ca.* 6/5) (62 mg, 23%) and **2** (3-*endo* /3-*exo* = 6/5) (160 mg, 52%) as a colorless oil. **2**: IR ($CHCl_3$): 1741 cm^{-1}. **2** (3-*endo*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.44 (1H, d, J = 11 Hz, C_{7s}-H), 2.02 (3H, s, Ac), 2.14 (1H, d, J = 11 Hz, C_{7a}-H), 2.89 (1H, m, C_4-H), 3.03 (1H, d, J = 10 Hz, C_1-H), 3.69 and 3.79 (each 3H, s, Me x 2), 5.00 (1H, dm, J = 52 Hz, C_6-H), 5.80 (1H, dm, J = 51 Hz, C_5-H), 6.05 (1H, dd, J = 5 and 4 Hz, C_3-H). **2** (3-*exo*): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.03 (3H, s, Ac), 2.18 and 2.30 (each 1H, d, J = 12 Hz, C_7-H_2), 2.57 (1H, d, J = 11 Hz, C_1-H), 3.12 (1H, m, C_4-H), 3.73 and 3.78 (each 3H, s, Me x 2), 4.36 (1H, dd, J = 51 and 5 Hz, C_6-H), 4.78 (1H, ddd, J = 50.5, 5 and 3 Hz, C_5-H), 5.60 (1H, s, C_3-H). High-resolution MS *m/z* Calcd for $C_{13}H_{17}F_2O_6$ (M^++1): 307.0989. Found: 307.0993.

Further elution with hexane-AcOEt (3 : 1) gave **3** (5-*endo*/5-*exo* = *ca.* 6/5) (55 mg, 20%) as a colorless oil. IR ($CHCl_3$): 1801, 1757 cm^{-1}. **3** (5-*endo*/5-*exo* = *ca.* 6/5) : ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.67 and 1.90 (each 1H, m, C_7-H_2), 2.08 ($^6/_{11}$ x 3H, s, Ac), 2.11 ($^5/_{11}$ x 3H, s, Ac), 3.02 (1H, m, C_8-H), 3.57 (1H, ddd, J = 6, 2 and 2 Hz, C_6-H), 3.84 (3H, s, Me), 4.81 (1H, ddd, J = 19, 6 and 2 Hz, C_1-H), 4.91 (1H, d, J = 52 Hz, C_9-H), 5.76 (1H, m, C_5-H). High-resolution MS *m/z* Calcd for $C_{12}H_{13}FO_6$ (M^++1): 273.0775. Found: 273.0774.

5-*exo*,6-*exo*-Difluorobicyclo[2.2.1]heptane-2-*exo*,3-*exo*-diyl Diacetate (6)

5% F_2/N_2 was passed into a solution of **5** (210 mg, 1.0 mmol) in $CFCl_3$ (25 ml)-$CHCl_3$ (20 ml)-EtOH (5 ml) at -78 °C until 3 mmol of F_2 had passed through the flowmeter (*ca.* 15 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (7 ml)-water (40 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (10 : 1)] to give **6** (100 mg, 40%) as colorless needles, mp 78-79 °C (hexane). IR ($CHCl_3$): 3020, 2990, 2910, 1755 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.00 and 2.08 (each 1H, ddd, J = 10, 1.5 and 1.5 Hz, C_7-H_2), 2.06 (6H, s, Ac x 2), 2.59 (2H, dd, J = 7 and 7 Hz, C_1-H and C_4-H), 4.67 (2H, ddd, J = 41, 12 and 1.5 Hz, C_5-H and C_6-H), 4.68 (2H, d, J = 1.5 Hz, C_2-H and C_3-H). High-resolution MS *m/z* Calcd for $C_{11}H_{14}F_2O_4$ (M^+): 248.0859. Found: 248.0861. *Anal.* Calcd for $C_{11}H_{14}F_2O_4$: C, 53.22; H, 5.68. Found: C, 53.00; H, 5.67.

5-*exo*,6-*exo*-Difluorobicyclo[2.2.1]heptan-2-yl Acetate (8)

5% F_2/N_2 was passed into a solution of **7**[33] (152 mg, 1.0 mmol) in $CFCl_3$ (25 ml)-$CHCl_3$ (20 ml)-EtOH (5 ml) at -78 °C until 2 mmol of F_2 had passed through the flowmeter (*ca.* 10 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (3 ml)-water (40 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (20 : 1)] to give **8** (44 mg, 23%) as a colorless oil. IR ($CHCl_3$): 2950, 2860, 1725 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (1H, ddd, J = 14, 4 and 4 Hz, C_{3exo}-H), 1.42 (1H, d, J = 14 Hz, C_{3endo}-H), 2.05 (3H, s, Ac x 2), 2.05-2.08 (2H, m, C_7-H_2), 2.47 (1H, m, C_4-H), 2.74 (1H, m, C_1-H), 4.69 (1H, dm, J = 53 Hz, C_5-H),

4.99 (1H, ddd, J = 8, 4 and 4 Hz, C_2-H), 5.05 (1H, dm, J = 52 Hz, C_6-H). High-resolution MS *m/z* Calcd for $C_9H_{12}F_2O_2$ (M^+): 190.0804. Found: 190.0799.

2-Chloro-2-cyano-5-*exo*,6-*exo*-difluorobicyclo[2.2.1]heptane (10)

5% F_2/N_2 was passed into a solution of **9** (154 mg, 1.0 mmol) in $CFCl_3$ (25 ml)-$CHCl_3$ (20 ml)-EtOH (5 ml) at -78 °C until 2 mmol of F_2 had passed through the flowmeter (*ca.* 10 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (3 ml)-water (40 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (50 : 1)] to give the recovered **9** (68 mg, 44%). Further elution with hexane-AcOEt (20 : 1) gave **10** (99 mg, 52%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.5-3.3 (6H, m, C_1-H, C_3-H_2, C_4-H and C_7-H_2), 4.72 (1H, dm, J = 52 Hz, C_5-H), 5.23 (1H, dm, J = 50 Hz, C_6-H). High-resolution MS *m/z* Calcd for $C_8H_8ClF_2N$ (M^+): 191.0313. Found: 191.0289.

5-*exo*,6-*exo*-Difluorobicyclo[2.2.1]heptan-2-one (12)

5% F_2/N_2 was passed into a solution of **11** (200 mg, 1.85 mmol) in $CFCl_3$ (25 ml)-$CHCl_3$ (20 ml)-EtOH (5 ml) at -78 °C until 3 mmol of F_2 had passed through the flowmeter (*ca.* 15 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (3 ml)-water (40 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (30 : 1)] to give the recovered **11** (88 mg, 44%). Further elution with hexane-AcOEt (20 : 1) gave **13** (25 mg, 11%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (2H, m, C_3-H_2), 3.35 (2H, m, C_1-H and C_4-H), 5.10 (1H, dm, J = 58 Hz, C_7-H), 6.05 and 6.55 (each 1H, m, C_5-H and C_6-H).

Further elution with hexane-AcOEt (10 : 1) gave **12** (46 mg, 17%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.5-2.7 (4H, m, C_3-H_2 and C_7-H_2), 2.85 (1H, m, C_4-H), 3.00 (1H, m, C_1-H), 4.83 (each 1H, dm, J = 50 Hz, C_5-H and C_6-H).

5-*exo*,6-*exo*-Difluoro-2-azabicyclo[2.2.1]heptan-3-one (15a)

5% F_2/N_2 was passed into a solution of **14a** (109 mg, 1.0 mmol) in $CFCl_3$ (25 ml)-$CHCl_3$ (20 ml)-EtOH (5 ml) at -78 °C until 2 mmol of F_2 had passed through the flowmeter (*ca.* 10 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (3 ml)-water (10 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give **15a** (40 mg, 27%) as a colorless oil. Further elution with hexane-AcOEt (1 : 2) gave the recovered **14a** (14 mg, 25%). **15a**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.25 and 2.36 (each 1H, dd, J = 11 Hz, C_7-H_2), 2.95 (1H, d, J = 6.5 Hz, C_4-H), 4.00 (1H, d, J = 1.5 Hz, C_1-H), 4.81 (1H, dm, J = 48 Hz, C_6-H), 4.98 (1H, dm, J = 52 Hz, C_5-H), 6.17 (1H, br m, NH).

2-Acetyl-5-*exo*,6-*exo*-difluoro-2-azabicyclo[2.2.1]heptan-3-one (15b)

5% F_2/N_2 was passed into a solution of **14b** (150 mg, 1.0 mmol) in $CFCl_3$ (25 ml)-$CHCl_3$ (20 ml)-EtOH (5 ml) at -78 °C until 1.6 mmol of F_2 had passed through the flowmeter (*ca.* 8 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (3 ml)-water (10 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give **15b** (60 mg, 32%) as a colorless oil. Further elution with hexane-AcOEt (1 : 2) gave the recovered **14b**

(29 mg, 19%). **15b**: IR ($CHCl_3$): 3025, 2990, 1770, 1755, 1710 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.18 (1H, d, J = 11 Hz, C_{7s}-H), 2.40 (1H, d, J = 11 Hz, C_{7a}-H), 2.42 (3H, s, Ac), 3.17 (1H, d, J = 7 Hz, C_4-H), 4.84 (1H, dm, J = 55 Hz, C_6-H), 4.93 (1H, br s, C_1-H), 5.02 (1H, dm, J = 52 Hz, C_5-H). High-resolution MS *m/z* Calcd for $C_8H_9F_2NO_2$ (M^+): 189.0601. Found: 189.0590.

2-*tert*-Butoxycarbonyl-2-azabicyclo[2.2.1]hept-5-en-3-one (14c)

To a solution of **14a** (5.46g, 50.0 mmol) in CH_2Cl_2 (100 ml) were added NEt_3 (7.0 ml, 50 mmol), di-*tert*-butyl dicarbonate (*t*-Boc_2O) (21.8 g, 100 mmol) and DMAP (6.11g, 50.0 mmol) at room temperature. After 24 h of stirring at the same temperature, the mixture was evaporated *in vacuo* and the residue was diluted with water and extracted with Et_2O. The organic extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (5 : 1)] to give **14c** (10.5 g, 100%) as colorless prisms, mp 55-57 °C (hexane). IR ($CHCl_3$): 3025, 2995, 1790, 1755, 1705 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.51 (9H, s, *t*-Bu), 2.14 and 2.35 (each 1H, dm, J = 8 Hz, C_7-H_2), 3.39 (1H, br s, C_4-H), 4.96 (1H, m, C_1-H), 6.66 (1H, dm, J = 5.5 Hz, C_5-H), 6.89 (1H, dd, J = 5.5 and 2 Hz, C_6-H). High-resolution MS *m/z* Calcd for $C_{10}H_{12}NO_3$ (M^+-CH_3): 194.0816. Found: 194.0820. *Anal.* Calcd for $C_{10}H_{12}NO_3$: C, 63.14; H, 6.74; N, 6.69. Found: C, 63.38; H, 6.70; N, 6.55.

Fluorination of 14c

5% F_2/N_2 was passed into a solution of **14c** (1.05 g, 5.0 mmol) in $CFCl_3$ (125 ml)-$CHCl_3$ (100 ml)-EtOH (25 ml) at -78 °C until 3 mmol of F_2 had passed through the flowmeter (*ca.* 75 min). The reaction mixture was poured into sat. aq. $NaHCO_3$ (20 ml)-water (10 ml). After neutralization, the organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was separated by flash chromatography [hexane-AcOEt (10 : 1)] to give **17** (11 mg, 1%) as a yellow oil, **15c** (503 mg, 41%) as colorless needles and the recovered **14c** (75 mg, 7%). Further elution with hexane-AcOEt (5 : 1) gave **18** (46 mg, 4%) as a colorless oil. Additional further elution with hexane-AcOEt (1 : 1) gave **16** (58 mg, 5%) as colorless prisms.

2-*tert*-Butoxycarbonyl-5-*exo*,6-*exo*-difluoro-2-azabicyclo[2.2.1]heptan-3-one (15c): mp 133-136 °C (hexane). IR ($CHCl_3$): 3020, 2990, 1795, 1770, 1720 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.53 (9H, s, *t*-Bu), 2.21 (1H, dm, J = 11 Hz, C_{7s}-H), 2.34 (1H, dm, J = 11 Hz, C_{7a}-H), 3.10 (1H, dm, J = 7 Hz, C_4-H), 4.62 (1H, m, C_1-H), 4.88 (1H, dm, J = 47 Hz, C_6-H), 5.04 (1H, dm, J = 48 Hz, C_5-H). High-resolution MS *m/z* Calcd for $C_{11}H_{16}F_2NO_3$ (M^++1): 248.1097. Found: 248.1079. *Anal.* Calcd for $C_{11}H_{15}F_2NO_3$: C, 53.43; H, 6.12; N, 5.67. Found: C, 53.21; H, 6.16; N, 5.63.

2-*tert*-Butoxycarbonyl-5-*endo*,6-*endo*-difluoro-2-azabicyclo[2.2.1]heptan-3-one (16): mp 138-141 °C (hexane). IR ($CHCl_3$): 3025, 2990, 1795, 1775, 1720 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.53 (9H, s, *t*-Bu), 1.44 (1H, dm, J = 12 Hz, C_{7a}-H), 2.13 (1H, ddddd, J = 12, 9, 9, 2 and 2 Hz, C_{7s}-H), 3.25 (1H, m, C_4-H), 4.80 (1H, m, C_1-H), 5.05 (1H, dddd, J = 50, 7, 3 and 3 Hz, C_6-H), 5.13 (1H, dddd, J = 47, 8, 4 and 3 Hz, C_5-H). High-resolution MS *m/z* Calcd for $C_{10}H_{12}F_2NO_3$ (M^+-CH_3): 232.0784. Found: 232.0789.

2-*tert*-Butoxycarbonyl-7-*anti*-fluoro-2-azabicyclo[2.2.1]hept-5-en-3-one (17): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.51 (9H, s, *t*-Bu), 3.51 (1H, d, J = 2 Hz, C_4-H), 5.02 (1H, br s, C_1-H), 5.18 (1H, d, J = 60 Hz, C_7-H), 6.57 (1H, dm, J = 5.5 Hz, C_5-H), 6.78 (1H, dd, J = 5.5 and 2 Hz, C_6-H).

2-*tert*-Butoxycarbonyl-7-*anti*-5-*endo*,6-*endo*-trifluoro-2-azabicyclo-[2.2.1]hept-5-en-3-one (18): IR ($CHCl_3$): 3040, 2995, 1805, 1780, 1730 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ: 1.54 (9H, s, *t*-Bu), 3.56 (1H, br s, C_4-H), 4.88 (1H, br s, C_1-H), 5.07 (1H, ddddd, *J* = 53, 7.7, 7.7, 2.6 and 2.6 Hz, C_7-H), 5.34 (1H, dddd, *J* = 50, 10, 4 and 3.3 Hz, C_6-H), 5.41 (1H, dddd, *J* = 51, 7.3, 4 and 3.3 Hz, C_5-H). High-resolution MS *m/z* Calcd for $C_{10}H_{11}F_3NO_3$ (M^+-CH_3): 250.0690. Found: 250.0678.

[*c*-3-(*N*-*tert*-Butoxycarbonyl)amino-*t*-4,*t*-5-difluorocyclopent-*r*-1-yl]methanol (19)

To a stirred sloution of **15c** (407 mg, 1.65 mmol) in MeOH (20 ml) was added portionwise $NaBH_4$ (187 mg, 5 mmol) at -20 °C and the mixture was stirred at the same temperature for 45 min. The stirred mixture was gradually warmed to room temperature over 2.5 h and neutralized with 10% HCl at 0 °C. After removal of methanol, the residue was diluted with water and extracted with AcOEt (3 x 20 ml). The organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give **19** (350 mg, 84%) as colorless needles (hexane-Et_2O), mp 72-75 °C. IR ($CHCl_3$): 3365, 2990, 1710 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$) δ: 1.45 (9H, s, *t*-Bu), 2.24 and 2.44 (each 1H, m, C_2-H_2), 2.49 (1H, m, C_1-H), 3.68 and 3.82 (each 1H, dm, *J* = 10.5 Hz, CH_2O), 4.07 (1H, m, C_3-H), 4.96 (2H, dddd, *J* = 51, 13, 4 and 4 Hz, C_4-H and C_5-H), 4.97 (1H, m, NH). High-resolution MS *m/z* Calcd for $C_{11}H_{19}F_2NO_3$ (M^+): 251.1332. Found: 251.1361. *Anal.* Calcd for $C_{11}H_{19}F_2NO_3$: C, 52.58; H, 7.62; N, 5.57. Found: C, 52.33; H, 7.63; N, 5.48.

(*c*-3-Amino-*t*-4,*t*-5-difluorocyclopent-*r*-1-yl)methanol (20)

19 (112 mg, 0.45 mmol) was dissolved in TFA (1 ml) and the solution was stirred at room temperature for 45 min. After evaporation of the solvent, the residue was treated with C_6H_6 and the solvent was evaporated *in vacuo* to give the crude **20**, which was used in the following reaction without purification.

5-Amino-6-chloro-4-[*t*-2,*t*-3-difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]aminopyrimidine (21)

To a solution of the above **20** and 5-amino-4,6-dichloropyrimidine (164 mg, 1.00 mmol) in *n*-BuOH (2.5 ml) was added *i*-Pr_2NEt (0.87 ml, 5 mmol) at room temperature and the mixture was refluxed for 25 h. After removal of the solvent, the residue was purified by flash chromatography (AcOEt) to give **21** (50 mg, 40% overall yield from **19**) as a yellow oil. ^1H-NMR (300 MHz, $CDCl_3$) δ: 1.79 (1H, m, C_5-H), 2.54 (2H, m, C_4-H and C_5-H), 3.71 and 3.81 (each 1H, dd, *J* = 11 and 3 Hz, CH_2O), 4.74 (1H, m, C_1-H), 5.06 (1H, dm, *J* = 52 Hz, C_3-H), 5.07 (1H, dm, *J* = 52 Hz, C_2-H), 6.76 (1H, d, *J* = 6.6 Hz, NH), 7.93 (1H, s, pyrimidine's C_2-H).

6-Chloro-9-[*t*-2,*t*-3-difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]-9*H*-purine (22)

To a suspension of **21** (79 mg, 0.28 mmol) in ethyl orthoformate (1 ml, 6.0 mmol) was added 10 N HCl (0.025 ml) at room temperature and the mixture was stirred at the same temperature for 6 h. After neutralization with NEt_3, the mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt (10 ml) and washed with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give **22** (64 mg, 72%) as a colorless oil. ^1H-NMR (300 MHz, $CDCl_3$) δ: 2.41 (1H, m, C_5-H), 2.6-2.5 (2H, m, C_4-H and C_5-H), 3.84 and 3.95 (each 1H, d, *J* =

11 Hz, CH_2O), 5.16 (1H, dm, J = 53 Hz, C_3-H), 5.23 (1H, m, C_1-H), 5.66 (1H, dddd, J = 50, 22, 9 and 4 Hz, C_2-H), 8.25 and 8.76 (each 1H, s, purine-H x 2).

9-[*t*-2,*t*-3-Difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]-9*H*-adenine (23)

A solution of **22** (60 mg, 0.15 mmol) in MeOH (10 ml) saturated with NH_3 at -10 °C was heated in a sealed tube at 80 °C for 18 h. The residue obtained after evaporation of the solvent *in vacuo* was purified by flash chromatography [AcOEt-MeOH (10 : 1)] to give **23** (28 mg, 68%) as colorless needles, mp 212-214 °C [AcOEt-MeOH (3 : 1)]. UV (MeOH) λmax: 260 nm. ^{1}H-NMR (300 MHz, CD_3OD) δ: 2.08 and 2.54 (each 1H, m, C_5-H_2), 2.60 (1H, m, C_4-H), 3.30 (2H, br s, NH_2), 3.67 (1H, dd, J = 11 and 5.5 Hz, C*H*H'O), 3.76 (1H, dd, J = 11 and 4.5 Hz, CH*H'*O), 5.09 (1H, dm, J = 53 Hz, C_3-H), 5.22 (1H, m, C_1-H), 5.57 (1H, dddd, J = 50, 19, 9 and 4 Hz, C_2-H), 8.20 and 8.24 (each 1H, s, purine -H x 2). High-resolution MS *m/z* Calcd for $C_{11}H_{13}F_2N_5O$ (M^+): 269.1087. Found: 269.1081. *Anal.* Calcd for $C_{11}H_{13}F_2N_5O$: C, 49.07; H, 4.87; N, 26.01. Found: C, 49.29; H, 5.05; N, 26.01.

2-Amino-6-chloro-4-[*t*-2,*t*-3-difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]aminopyrimidine (24)

To a solution of **20** obtained from **19** (251 mg, 1.0 mmol) and 2-amino-4,6-dichloropyrimidine (328 mg, 2.00 mmol) in *n*-BuOH (5 ml) was added *i*-Pr_2NEt (0.87 ml, 5.0 mmol) at room temperature and the mixture was refluxed for 33 h. After removal of the solvent, the residue was purified by flash chromatography (AcOEt) to give **24** (146 mg, 52% overall yield from **19**) as a foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.57 (1H, ddd, J = 13, 5 and 5Hz, C_5-H), 2.45-2.65(2H, m, C_4-H and C_5-H), 3.73 and 3.90 (each 1H, dd, J = 10 and 3 Hz, CH_2O), 4.85-5.15 (3H, m, C_1-H, C_2-H and C_3-H), 5.39 (1H, m, NH), 5.84 (1H, s, pyrimidine's C_5-H). High-resolution MS *m/z* Calcd for $C_{10}H_{13}ClF_2N_4O$ (M^+): 278.0745. Found: 278.0722.

2-Amino-6-chloro-9-[*t*-2,*t*-3-difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]-9*H*-purine (25a)

A solution of the diazonium salt prepared from *p*-chloroaniline (44 mg, 0.35 mmol) and $NaNO_2$ (36 mg, 0.52 mmol) in 3 N HCl (0.75 ml)-water (0.38 ml) was added dropwise to a stirred solution of **24** (84 mg, 0.30 mmol) and AcONa (600 mg) in AcOH (1.5 ml)-water (1.5 ml) at 0 °C and the mixture was stirred at room temperature for 15 h . The precipitate obtained after removal of the solvent and addition of water was collected by filtration and dried *in vacuo*, which was used in the following step without further purification.

To a stirred solution of the above precipitate in EtOH (4.5 ml)-water (4.5 ml)-AcOH (0.09 ml) was added zinc powder (195 mg, 2.98 mmol) at room temperature and the mixture was refluxed for 4 h. After filtration, the filtrate was concentrated *in vacuo* and purified by preparative TLC (AcOEt) to give the crude 5-aminopyrimidine derivative (48 mg).

To a suspension of the above 5-aminopyrimidine derivative (16 mg, 0.054 mmol) in ethyl orthoformate (0.25 ml, 1.5 mmol) was added 10 N HCl (0.035 ml) at room temperature and the mixture was stirred at the same temperature for 3 h. After neutralization with NEt_3, the mixture was evaporated *in vacuo*. The residue was dissolved in AcOEt (2 ml) and washed with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by preparative TLC [$CHCl_3$-MeOH (20 : 1)] to give **25a** (8 mg, 26% overall yield from **24**). ^{1}H-NMR (300 MHz, $CDCl_3$-CD_3OD) δ: 2.20 (1H, m, C_5-H), 2.58 (2H, m, C_4-

H and C_5-H), 3.69 (1H, m, C*H*H'O), 3.83 (1H, dd, J = 11 and 3.5 Hz, CH*H'*O), 5.09 (1H, m, C_1-H), 5.11 (1H, dm, J = 53 Hz, C_3-H), 5.49 (1H, dddd, J = 51, 20.5, 8.5 and 4 Hz, C_2-H), 7.39 (1H, s, purine-H). High-resolution MS *m/z* Calcd for $C_{11}H_{12}ClF_2N_5O$ (M^+): 303.0698. Found: 303.0709.

9-[*t*-2,*t*-3-Difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]-9*H*-guanine (25b)

A solution of **25a** (8.0 mg, 0.026 mmol) in 4% HCl (0.44 ml) was refluxed for 1 h. After neutralization with sat. aq. $NaHCO_3$, the mixture was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$-MeOH (1 : 1). After filtration, the filtrate was evaporated *in vacuo* and purified by TLC [$CHCl_3$-MeOH (4 : 1)] to give **25b** (6.1 mg, 82%) as an amorphous solid, mp 265-270 °C (MeOH). UV (MeOH) λmax: 254 nm. ^{1}H-NMR (300 MHz, CD_3OD) δ: 1.98 (1H, m, C_5-H), 2.4-2.6 (2H, m, C_4-H and C_5-H), 3.65 and 3.73 (each 1H, dd, J = 11 and 5 Hz, CH_2O), 5.03 (1H, m, C_1-H), 5.08 (1H, dm, J = 53 Hz, C_3-H), 5.46 (1H, dddd, J = 51, 18, 8 and 4 Hz, C_2-H), 7.84 (1H, s, purine -H). High-resolution MS *m/z* Calcd for $C_{11}H_{13}F_2N_5O_2$ (M^+): 285.1036. Found: 285.1037.

[*c*-3-(*N*-*tert*-Butoxycarbonyl)amino-*t*-4,*t*-5-difluorocyclopent-*r*-1-yl]methyl Benzoate (26)

To a solution of **19** (885 mg, 3.52 mmol) in pyridine (13 ml, 163 mmol) was added benzoyl chloride (BzCl) (0.41 ml, 3.53 mmol) at room temperature and the mixture was stirred at the same temperature for 11 h. After addition of ice-water, the mixture was extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (5 : 1)] to give the benzoate **26** (1.13 g, 88%) as colorless prisms, mp 109-112 °C (hexane). IR ($CHCl_3$): 3450, 2990, 1720, 1710, 1500, 1370, 1270, 1160, 1070 cm^{-1}. 1H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (1H, dm, J = 14 Hz, C_2-H), 1.45 (9H, s, *t*-Bu), 2.49 (1H, ddd, J = 14, 9 and 9 Hz, C_2-H'), 2.73 (1H, dm, J = 20 Hz, C_1-H), 4.08 (1H, m, C_3-H), 4.40 and 4.43 (each 1H, dd, J = 11.5 and 5 Hz, CH_2O), 4.72 (1H, d, J = 6 Hz, NH), 4.88 (1H, dm, J = 53 Hz, C_5-H), 4.96 (1H, dddd, J = 52, 12, 5.5 and 5 Hz, C_4-H), 7.46 (2H, m, Ph-H x 2), 7.59 (1H, m, Ph x 1), 8.04 (2H, m, Ph x 2). High-resolution MS *m/z* Calcd for $C_{14}H_{15}F_2NO_4$ (M^+-*t*-Bu+H): 299.0969. Found: 299.0952. *Anal.* Calcd for $C_{18}H_{23}F_2NO_4 \cdot {}^1/_2H_2O$: C, 59.33; H, 6.64; N, 3.84. Found: C, 59.34; H, 6.43; N, 3.69.

1-[*t*-2,*t*-3-Difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]thymine (28)

A solution of **26** (133 mg, 0.37 mmol) in TFA (0.8 ml)-CH_2Cl_2 (0.8 ml) was stirred at room temperature for 30 min. Evaporation of the solvent gave the crude amine, which was used in the following step without purification.

To a suspension of AgOCN (187 mg, 1.23 mmol) in C_6H_6 (1.5 ml) was added 3-methoxy-2-methylacryloyl chloride (96 mg, 0.72 ml) at room temperature and the mixture was refluxed for 30 min. After cooling to room temperature, the mixture was filtrated and the filtrate was added to the amine described above. After 24 h of stirring at room temperature, the mixture was evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give **27** (90 mg, 61% from **26**) as a colorless glass. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.54 (1H, ddd, J = 14, 8.8 and 8.8 Hz, C_5-H), 1.78 (3H, dd, J = 3 and 1 Hz, Me), 2.54 (1H, ddd, J = 14, 9 and 9 Hz, C_5-H), 2.78 (1H, m, C_4-H), 3.89 (3H, s, OMe), 4.38 (1H, dd, J = 11.5 and 5.8 Hz, C*H*H'O), 4.44 (1H, dd, J = 11.5 and 5 Hz, CH*H'*O), 4.45 (1H, m, C_1-H), 4.95 and 5.01 (each

1H, dm, J = 51 Hz, C_2-H and C_3-H), 7.35-7.65 (4H, m, olefinic-H, Ph-H x 3), 8.10 (2H, m, Ph-H x 2), 8.67 (1H, br s, C_1-NH), 9.11 (1H, d, J = 7 Hz, CONHCO).

To a solution of **27** (90 mg, 0.23 mmol) in 1,4-dioxane (1.8 ml) was added 2 N H_2SO_4 (3 ml) at room temperature, and the mixture was refluxed for 3 h. After neutralization with 10% aq. NaOH, the mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$, evaporated *in vacuo*. The residue was dissolved in 1% $^{w}/_{v}$ NaOH-MeOH (0.56 ml) and the mixture was stirred at room temperature for 14 h. After neutralization with 10% aq. HCl, the mixture was extracted with AcOEt. The organic layer was evaporated *in vacuo* and the residue was purified by preparative TLC (AcOEt) to give **28** (46 mg, 77% from **27**) as colorless prisms, mp 183-185 °C (AcOEt). UV (MeOH) λmax: 269 nm.^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.85 (1H, m, C_5-H), 1.92 (3H, s, Me), 2.35 (1H, m, C_5-H), 2.48 (1H, m, C_4-H), 3.64 (1H, dd, J = 10.6 and 3.3 Hz, C*H*H'O), 3.76 (1H, dd, J = 10.6 and 4 Hz, CH*H'*O), 4.83 (1H, m, C_1-H), 5.00 (1H, dddd, J = 52.4, 4, 4 and 3 Hz, C_3-H), 5.29 (1H, dddd, J = 51, 17.5, 4 and 2 Hz, C_2-H), 7.26 (1H, s, pyrimidine-H). High-resolution MS *m/z* Calcd for $C_{11}H_{14}F_2N_2O_3$ (M^+): 260.0973. Found: 260.1005. *Anal.* Calcd for $C_{11}H_{14}F_2N_2O_3 \cdot {}^1/_4H_2O$: C, 49.90; H, 5.52; N, 10.58. Found: C, 49.79; H, 5.44; N, 10.34.

1-[*c*-4-(Benzoyloxy)methyl-*t*-2,*t*-3-difluorocyclopent-*r*-1-yl]uracil (30)

A solution of **26** (506 mg, 1.42 mmol) in TFA (3.0 ml)-CH_2Cl_2 (3.0 ml) was stirred at room temperature for 30 min. Evaporation of the solvent gave the crude amine, which was used in the following step without purification.

To a suspension of AgOCN (1.28 g, 8.54 mmol) in C_6H_6 (8.5 ml) was added 3-ethoxyacryloyl chloride (766 mg, 5.69 ml) at room temperature and the mixture was refluxed for 30 min. After cooling to room temperature, the mixture was filtrated and the filtrate was added to the amine described above. After 43 h of stirring at room temperature, the mixture was evaporated *in vacuo*. The residue was purified by flash chromatography [hexane-AcOEt (1 : 1)] to give **29** (480 mg, 85% from **26**) as a colorless glass. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.54 (1H, ddd, J = 14, 8.8 and 8.8 Hz, C_5-H), 1.78 (3H, dd, J = 3 and 1 Hz, Me), 2.54 (1H, ddd, J = 14, 9 and 9 Hz, C_5-H), 2.78 (1H, m, C_4-H), 3.89 (3H, s, OMe), 4.38 (1H, dd, J = 11.5 and 5.8 Hz, C*H*H'O), 4.44 (1H, dd, J = 11.5 and 5 Hz, CH*H'*O), 4.45 (1H, m, C_1-H), 4.95 and 5.01 (each 1H, dm, J = 51 Hz, C_2-H and C_3-H), 7.35-7.65 (4H, m, olefinic-H, Ph-H x 3), 8.10 (2H, m, Ph-H x 2), 8.67 (1H, br s, C_1-NH), 9.11 (1H, d, J = 7 Hz, CONHCO).

To a solution of **29** (480 mg, 1.21 mmol) in 1,4-dioxane (9.6 ml) was added 2 N H_2SO_4 (16.5 ml) at room temperature, and the mixture was refluxed for 3 h. After neutralization with 10% aq. NaOH, the mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$, evaporated *in vacuo* and the residue was purified by flash chromatography [hexane-AcOEt (1 : 1)]preparative TLC (AcOEt) to give **30** (377 mg, 89% from **29**) as a colorless powder, mp 119-121 °C ($CHCl_3$). UV (MeOH) λmax: 263.5 nm.^{1}H-NMR (300 MHz, $CDCl_3$-CD_3OD, 10:1) δ: 2.11 (1H, ddd, J = 13.5, 9.9 and 9.9 Hz, C_5-H), 2.40 (1H, ddd, J = 13.5, 9 and 9 Hz, C_5-H'), 2.81 (1H, m, C_4-H), 4.36 (1H, m, C_1-H), 4.48 (2H, d, J = 5.5 Hz, CH_2O), 5.21 (1H, dddd, J = 51, 10.2, 5.5 and 5.1 Hz, C_3-H), 5.46 (1H, dddd, J = 51, 11, 5.5 and 5.5 Hz, C_2-H), 5.72 (1H, d, J = 8 Hz, pyrimidine's C_5-H), 7.14 (1H, d, J = 8 Hz, pyrimidine's C_6-H), 7.46 (2H, dd, J = 7 and 7 Hz, Ph-H x 2), 7.59 (1H, dd, J = 7 and 7 Hz, Ph-H), 8.05 (2H, d, J = 7 Hz, Ph-H x 2). High-resolution MS *m/z* Calcd for $C_{17}H_{16}F_2N_2O_4$ (M^+): 350.1078. Found: 350.1070. *Anal.* Calcd for $C_{17}H_{16}F_2N_2O_4$: C, 58.28; H, 4.60; N, 8.00. Found: C, 58.03; H, 4.55; N, 8.07.

1-[*t*-2,*t*-3-Difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]uracil (31)

A solution of **30** (28 mg, 0.080 mmol) in 1% $^{w}/_{v}$ NaOH-MeOH (0.32 ml) was stirred at room temperature for 14 h. After neutralization with 10% aq. HCl, the mixture was extracted with AcOEt. The organic layer was evaporated *in vacuo* and the residue was purified by preparative TLC (AcOEt) to give **31** (17.5 mg, 88%) as a colorless glass. UV (MeOH) λmax: 263 nm. ^{1}H-NMR (300 MHz, $CDCl_3$-CD_3OD, 10:1) δ: 1.84 (1H, ddd, J = 16, 13 and 6.6 Hz, C_5-H), 2.40 (1H, ddd, J = 16, 10 and 10 Hz, C_5-H'), 2.49 (1H, dm, J = 24 Hz, C_4-H), 3.63 (1H, dd, J = 11 and 4 Hz, C*H*H'O), 3.76 (1H, dd, J = 11 and 4 Hz, CH*H'*O), 4.89 (1H, m, C_1-H), 5.00 (1H, dddd, J = 52.7, 4, 4 and 3 Hz, C_3-H), 5.29 (1H, dddd, J = 52, 17.6, 8 and 4 Hz, C_2-H), 5.75 (1H, d, J = 8 Hz, pyrimidine's C_5-H), 7.48 (1H, d, pyrimidine's C_6-H). High-resolution MS *m/z* Calcd for $C_{10}H_{12}F_2N_2O_3$ (M^+): 246.0816. Found: 246.0817.

1-[*t*-2,*t*-3-Difluoro-*c*-4-(hydroxymethyl)cyclopent-*r*-1-yl]cytosine (33)

To a stirred mixture of 1,2,4-triazole (590 mg, 8.54 mmol) and phosphoryl chloride (0.16 ml, 2.2 mmol) in acetonitrile (2.5 ml) was added dropwise NEt_3 (1.1 ml, 7.9 mmol) at 0 °C and the mixture was stirred at room temperature for 40 min. To the resulting mixture was added a solution of **30** in acetonitrile (3.2 ml) at 0 °C and the mixture was stirred at room temperature for 4 d. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ and the solution was neutralized with sat. aq. $NaHCO_3$. The mixture was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by preparative TLC (AcOEt) to give **32** (97 mg, 76%) as a colorless powder, mp 171-172 °C (AcOEt). UV (MeOH) λmax: 314, 248 (sh), 224 nm. ^{1}H-NMR (300 MHz, $CDCl_3$-CD_3OD, 20:1) δ: 2.35 (1H, m, C_5-H), 2.40 (1H, m, C_5-H'), 2.75-3.0 (1H, m, C_4-H), 4.35-4.6 (1H, m, C_1-H), 4.55 (2H, d, J = 6 Hz, CH_2O), 5.37 (1H, dddd, J = 51, 11, 6 and 5 Hz, C_3-H), 5.68 (1H, dddd, J = 52, 9.5, 5 and 5 Hz, C_2-H), 7.08 (1H, d, J = 7 Hz, pyrimidine's C_5-H), 7.47 (2H, dd, J = 7.5 and 7.5 Hz, Ph-H x 2), 7.59 (1H, dd, J = 7.5 and 7.5 Hz, Ph-H), 7.85 (1H, d, J = 7 Hz, pyrimidine's C_6-H), 8.08 (2H, d, J = 7.5 Hz, Ph-H x 2), 8.13 (1H, s, triazole's C_3-H), 9.25 (1H, s, triazole's C_5-H). High-resolution MS *m/z* Calcd for $C_{19}H_{17}F_2N_5O_3$ (M^+): 401.1299. Found: 401.1287. *Anal.* Calcd for $C_{19}H_{17}F_2N_5O_3 \cdot {}^1/_8H_2O$: C, 56.54; H, 4.25; N, 17.35. Found: C, 56.61; H, 4.19; N, 17.05.

To a suspension of **32** (30.5 mg, 0.0760 mmol) in dioxane (0.3 ml) was added 25% aq. NH_3 (0.05 ml, 0.9 mmol) and the solution was stirred at room temperature for 18 h. After evaporation of the solvent, the residue was dissolved in 1% NaOH-MeOH (0.3 ml) and stirred at room temperature for 22 h. The mixture was neutralized with 10% aq. HCl and extracted with AcOEt. After evaporation of the solvent, the residue was purified by preparative TLC [$CHCl_3$-MeOH (5 : 1)] to give **33** (15 mg, 82%) as colorless prisms, mp 194-196 °C (dec.) [AcOEt-MeOH (10 :1)]. UV (MeOH) λmax: 272 nm. ^{1}H-NMR (300 MHz, $CDCl_3$-CD_3OD, 10:1) δ: 2.01 (1H, m, C_5-H), 2.33 (1H, ddd, J = 13, 9.5 and 9.5 Hz, C_5-H'), 2.49 (1H, dm, J = 25 Hz, C_4-H), 3.69 and 3.73 (each 1H, dd, J = 11 and 5 Hz, CH_2O), 4.53 (1H, dm, J = 22 Hz, C_1-H), 5.07 (1H, dddd, J = 52.5, 6.5, 4 and 4 Hz, C_3-H), 5.45 (1H, dddd, J = 52, 15, 5.5 and 5.5 Hz, C_2-H), 5.81 (1H, d, J = 7.3 Hz, pyrimidine's C_5-H), 7.38 (1H, d, J = 7.3 Hz, pyrimidine's C_6-H). High-resolution MS *m/z* Calcd for $C_{17}H_{16}F_2N_2O_4$ (M^+): 350.1078. Found: 350.1070. *Anal.* Calcd for $C_{10}H_{13}F_2N_3O_2 \cdot {}^1/_4H_2O$: C, 48.09; H, 5.45; N, 16.83./ Found: C, 48.36; H, 5.42; N, 16.55.

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