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Synthesis of 3′-Deoxy-3′-difluoromethyl Azanucleosides from *trans*-4-Hydroxy-L-proline

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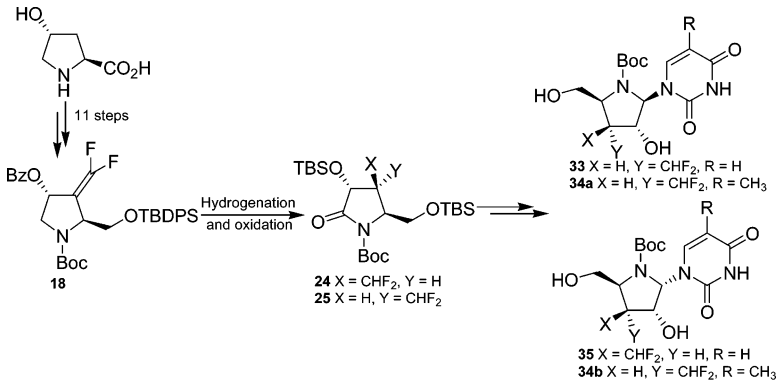

Two strategies were tried to synthesize 3′-deoxy-3′-difluoromethyl azanucleosides. After the failure of the first route, the key intermediate **12** from *trans*-4-hydroxyproline **7** in 8 steps was stereoselectively prepared. The alcohol **12** was subjected to selective protection, oxidation, and difluoromethylenation to afford the fluorinated compound **18**, whose hydrogenation was then systematically investigated. After a series of transformations of protecting groups, the resultant compounds **22** and **23** were oxidized to the desired lactams **24** and **25**, which were successfully utilized to synthesize our target molecules, 3′-deoxy-3′-difluoromethyl azanucleosides **33**, **34a**, **34b**, and **35**.

Introduction

In general, nucleosides, consisting of both a base moiety and a sugar moiety, are classified into two major divisions, that is, *N*-nucleosides and *C*-nucleosides.[1] *N*-Nucleosides feature a bond between the anomeric carbon of the sugar moiety and the nitrogen of the base moiety. *C*-Nucleosides have a bond between the anomeric moiety and the carbon of the base moiety. Further, the nucleosides, wherein carbon, sulfur, phosphorus, and nitrogen substitute for the sugar ring oxygen, are commonly defined as carbocyclic nucleosides,[2] thionucleosides,[3] phosphanucleosides,[4] and azanucleosides,[1] respectively. Nucleosides and nucleoside analogues, known to be DNA and RNA subunits, have achieved considerable success in the fight against viral infection. For the last two decades, some high biological nucleoside and nucleoside analogues have been synthesized, studied, and used. For example, the 5-iodo-2′-deoxyuridine (IDU) was licensed as the first nucleoside antiviral, and the first antiviral chemotherapeutic agent for use in humans.[5] The 2′,3′-dideoxynucleosides (ddNs) have thus far proven to be the most effective therapeutic agents against human immunodeficiency virus (HIV)[6] and hepatitis B virus (HBV).[7] 3′-Azido-2′,3′-dideoxythymidine (AZT),[8] 2′,3′-dideoxyinosine (DDI),[9] and 2′,3′-dideoxycytidine (DDC)[10]

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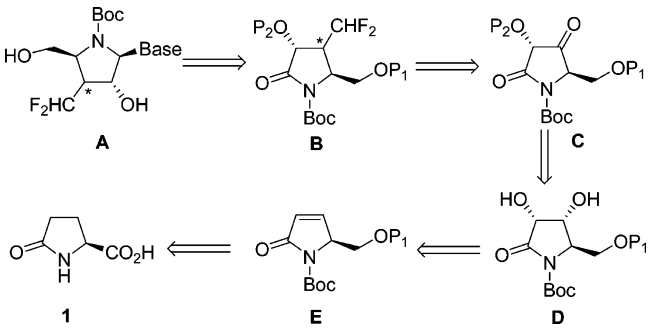
have also been approved for the treatment of AIDS. However, some nucleosides have shown limited stability, high toxicity, and lower bioactivity, so development of new antiviral and anticancer nucleoside analogues is intensively demanded despite great improvements against virus and cancer.

Recently, fluorinated nucleosides, containing fluorine atom(s) or fluorine-containing groups in the sugar moiety or the base moiety of nucleoside, have drawn increasing attention due to the introduction of the fluorine atom(s) into some nucleosides resulting in great improvement of bioactivity and stability of the corresponding compounds.[11] Perhaps the best known of the fluorinated nucleosides are 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-thymine (FMAU),[12] 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (FIAC),[12b] 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-ethyluracil (FEAU),[13] 3′-deoxy-3′-fluorothymidine (FLT),[14] 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC),[15] 1-(2-deoxy-2-*C*-fluoromethyl-β-D-arabinofuranosyl)cytosine(SFDC),[16] and 1-(2-deoxy-2,2-difluoro-β-D-arabinofuranosyl)cytosine (Gemcitabine),[17] all of which have high antiherpes activity, as well as antitumor activity in some cases. Although monofluorinated, *gem*-difluorinated, and trifluoromethylated sugar nucleosides, thionucleosides, and carbocyclic nucleosides have been widely studied, only a few fluorinated azanucleosides have been reported.[18] Difluoromethylated (CHF_2−) and monofluoromethylated (CH_2F−) azanucleosides are attractive potential bioactive targets because of the unique properties of the two groups and azanucluosides. First, two groups have synthesized a series of azanucleosides and some of azanucleosides have proved active against human tumor cell lines.[19] Second,

SCHEME 1



the CF_2 and CHF groups have been proposed as reasonable isosteric and isopolar replacements for neutral oxygen, conferring phosphatase stability on nucleotide phosphate moiety.[20] Third, the CHF_2 and CH_2F groups have been employed [21] as preferable replacements for CH_3 in oligo(deoxyribonucleotide methyl phosphonate) due to its ability to act as a hydrogen donor,[22] potentially allowing interaction with solvent and biological molecules. Fourth, replacements of the sugar ring oxygen of a nucleoside by nitrogen could cause the effects of biological significance. Besides the simple heteroatom effect of nitrogen,[23] nitrogen could bind with exceedingly high affinity and specificity to a variety of base-exicision DNA repair (BER) enzymes, which may suggest a transition-state model for the glycosyl transfer reaction leading to base excision.[24] On the basis of the above consideration and our ongoing efforts to develop new antiviral and anticancer agents, several difluoromethylated and monofluoromethylated azanucleosides were prepared in our group.[18b,25] Here reported is our recent synthesis of 3′-deoxy-3′-difluoromethyl azanucleosides, starting from natural, cheap, and commercially available *trans*-4-hydroxy-L-proline.

Results and Discussion

Attempt To Synthesize Target Molecules from L-Pyroglutamic Acid. On the basis of retrosynthetic analysis (Scheme 1), the target molecules **A** can be reached from the fluorinated intermediate **B**, which could be prepared from keto compound **C** via difluoromethylenation followed by hydrogenation. Selective protection of the two hydroxyl groups of **D** followed by oxidation of the residual hydroxyl group would furnish the lactam **C**. The alcohol **D** can be provided via dihydroxylation of the lactam **E**, which could be conveniently synthesized from L-pyroglutamic acid **1**. It is noteworthy that the Boc-protecting groups of target molecules **A** could not be removed because the *N*-azanucleosides having a free NH group have proved to be unstable.[26]

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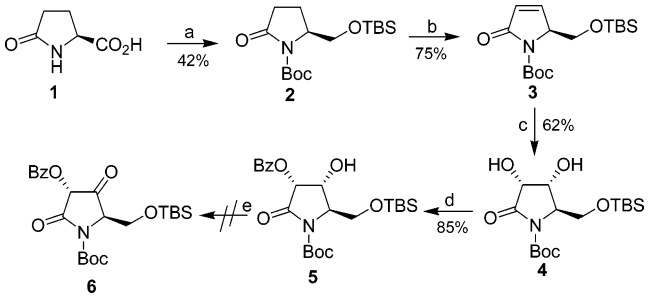
SCHEME 2[a]



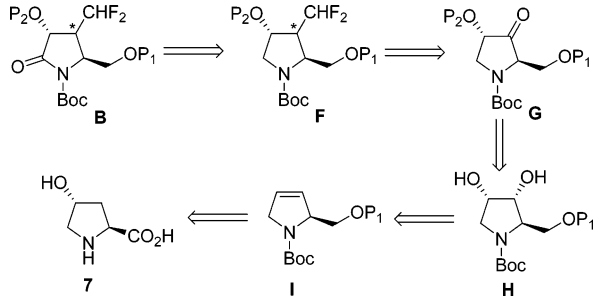
[a] Reagent and conditions: (a) (i) $SOCl_2$, MeOH; (ii) $NaBH_4$, EtOH; (iii) TBDMSCl, DMAP, imidazole, CH_2Cl_2; (iv) *t*-Boc_2O, Et_3N, DMAP, CH_2Cl_2; (b) (i) LiHMDS, THF, −78 °C then PhSeCl, THF, −78 °C; (ii) H_2O_2, pyridine; (c) OsO_4, 4-methylmorpholine *N*-oxide monohydrate (NMNO), acetone−H_2O, rt; (d) BzCl, pyridine, DMAP, CH_2Cl_2, −78 then −10 °C; (e) Dess−Martin Oxidant, CH_2Cl_2, rt.

Thus, according to our retrosynthetic analysis, the lactam **2** was prepared from L-pyroglutamic acid over 4 steps in 42% yield (Scheme 2).[27] Treatment of the compound **2** with LiHMDS/PhSeCl in THF at −78 °C followed by elimination of the resulting phenylselenyl derivative with H_2O_2/pyridine smoothly gave the alkene **3** in 75% yield.[28] Then, dihydroxylation of the compound **3** resulted in only isomer **4** in 62% yield along with recovery of 30% starting material.[29] Selective protection of the two hydroxyl groups of **4** with BzCl afforded the desired alcohol **5** in 85% yield and there are no other products detected by TLC except a few starting materials. Oxidation of the residual hydroxyl group in the compound **5** with the Dess−Martin oxidant was carried out; however, the reaction was very complicated and no expected compound **6** was isolated. In our opinion, the special structure of the desired compound **6** bearing a benzoyl-protected hydroxy group between two keto groups was responsible for the failure of the reaction. The compounds containing this similar structure are unstable and prone to racemization and isomerization.[30]

Synthesis of Target Molecules from *trans*-4-Hydroxy-L-proline. In view of the above failure, we changed our synthetic strategy; the new synthetic strategy is outlined in Scheme 3. In our opinion, the lactam skeleton of the intermediate **B** could be constructed via oxidation of the pyrrolidine **F**, which might be prepared by difluoromethylenation of the keto **G** followed by hydrogenation. Similarly to the first route, dihydroxylation of the alkene **I** followed by selective protection of the resulting hydroxyl groups in **H** and oxidation of the residual hydroxyl group could provide the keto **G**. The intermediate **I** could be conveniently prepared from *trans*-4-hydroxy-proline **7**.

Although the protective ester **8** was first prepared from *trans*-4-hydroxyproline **7** over three steps in 78% yield,[31] treatment of the compound **8** with PhSeSePh/MeOH under reflux conditions following elimination of the resulting phenylselenyl derivative smoothly afforded the alkene **9** in 63% yield over two steps.[32] Then, reduction of the compound **9** with $LiAlH_4$ in Et_2O at room temperature gave the alcohol **10** in 89% yield. The protecting group for the primary hydroxy group was a key point because the diastereoselectivity of the following dihydroxylation was controlled by this protecting group. Thus, the big-blocking-effect protecting group, *tert*-butyldiphenylsilyl, was utilized and the favorable alkene **11** was provided in 82% yield. Dihydroxylation reaction was carried out on compound **11** and the only isomer **12** was obtained in 92% yield.

SCHEME 3



Selective protection of the hydroxyl groups in **12** was studied. According to the previous reports[33] and following transformation, the *tert*-butyldimethylsilyl group would be the appropriate protecting group. However, exposure of compound **12** to TBDMSCl/imidazole at 0 °C in DMF or CH_2Cl_2 only resulted in the recovery of the starting material, even when catalytic DMAP was added (Scheme 5). Increasing the reaction temperature to room temperature also gave the disappointing outcome and both the expected product **13** and the protective compound **14** were isolated in 31% and 49% yield, respectively. Slightly surprisingly, treatment of compound **12** with BzCl/pyridine/DMAP at −10 °C for 24 h in CH_2Cl_2 gave the acceptable result and the favorable compound **15** was afforded in 70% yield along with isomer **16** in 17% yield and recovery of 7% starting material.

With compound **15** in hand, oxidation of the residual hydroxy group with Dess−Martin oxidant in CH_2Cl_2 at room temperature smoothly provided the keto **17** in 92% yield (Scheme 6). Then, difluoromethylenation of the carbonyl group with CF_2Br_2/Zn/HMPT in THF successfully afforded the fluorinated compound **18** in 83% yield.[34]

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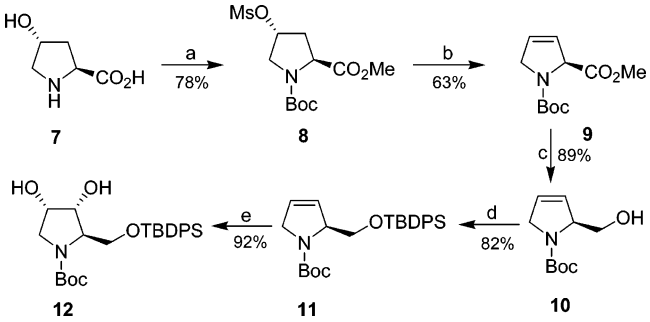
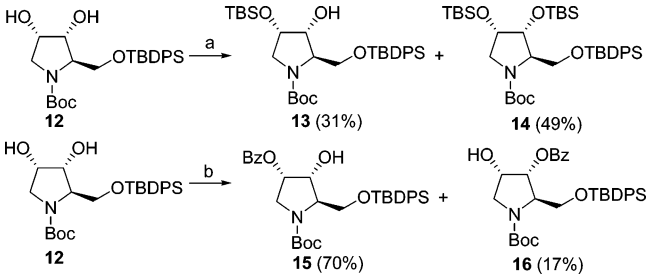
SCHEME 4[a]



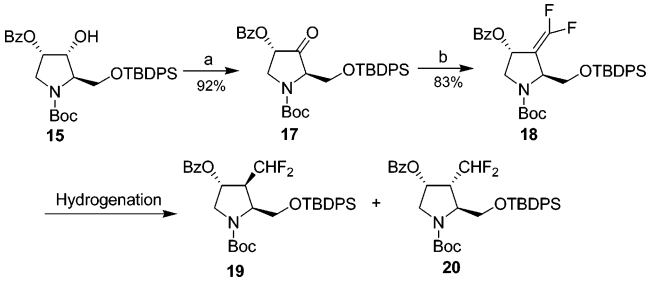
[a] Reagent and conditions: (a) (i) $SOCl_2$, MeOH, 0 °C to room temperature; (ii) Boc_2O, CH_2Cl_2, Et_3N, DMAP, rt; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt; (b) (i) PhSeSePh, MeOH, reflux; (ii) H_2O_2, pyridine, rt.; (c) $LiAlH_4$, Et_2O, rt; (d) TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt; (e) OsO_4, 4-methylmorpholine *N*-oxide monohydrate (NMNO), acetone−H_2O, rt.

SCHEME 5[a]



[a] Reagent and conditions: (a) TBDMSCl, DMAP, imidazole, DMF, rt, 3 h; (b) BzCl, pyridine, CH_2Cl_2, −10 °C, 24 h.

SCHEME 6[a]



[a] Reagent and conditions: (a) Dess−Martin oxidant, CH_2Cl_2, rt; (b) CF_2Br_2, HMPT, Zn, THF, reflux.

Although hydrogenations of similar substrates were reported,[35] hydrogenation of alkene **18** was still a challenge to us due to bulky block effects of the neighboring groups. Thus, different solvents, catalysts, and hydrogen pressure were used to investigate the hydrogenation reaction (Table 1). Pd/C was first selected as catalyst (entries 1−5). Hydrogenation of **18** in MeOH at room temperature and 1 atm (H_2) for 17 h gave a disappointing outcome and the desired compounds **19** and **20** were isolated in 11% and <1% yield, respectively, along with recovery of 9% starting material (entry 1). The low yield was attributed to the decomposition of **18** under proton solvent. However, there was no reaction that occurred

TABLE 1. Hydrogenation of Compound 18

entry	catalyst	pressure (atm)	solvent	time (h)	yield (%) **19**	yield (%) **20**	recovery (%)
1	10% Pd/C	1	MeOH	17	11	<1	9
2	10% Pd/C	1	EtOAc	24	0	0	83
3	10% Pd/C	20	EtOAc	24	31	<1	46
4	10% Pd/C	70	EtOAc	17	41	12	9
5	10% Pd/C	80	THF	17	27	7	38
6	$Pd(OH)_2$/C	80	THF	7	<1	<1	87
7	$Pd(OH)_2$/C	80	EtOAc	7	13	20	48
8	$Pd(OH)_2$/C	80	dioxane	7	<4	13	77
9	$Pd(OH)_2$/C	80	dioxane	65	<4	48	37
10	$Pd(OH)_2$/C	100	dioxane	31	10	54	22

with substitution of EtOAc for MeOH under the same conditions (entry 2). Thus, 20 atm of H_2 was used for this reaction and after 24 h, compound **19** was afforded in 31% yield besides a small amount of compound **20** and 46% recovery of **18** (entry 3). When the hydrogen pressure was increased to 70 atm, the yield of **19** was increased to 41%. However, the decomposition was also obvious with only 9% recovery of **18** (entry 4). The replacement of EtOAc with THF did not give a better hydrogenation outcome (entry 5). $Pd(OH)_2$/C was also used as a catalyst to investigate this reaction (entries 6−10). Using THF as a solvent under 80 atm of H_2 also gave a bad result (entry 6). Besides 48% recovery of starting material, compounds **19** and **20** were provided in 13% and 20% yield, respectively, with utilization of EtOAc as solvent (entry 7). When the reaction was carried out under 80 atm of H_2 with dioxane as solvent, the main compound **20** was afforded in 13% yield after 7 h (entry 8). Prolongation of reaction time to 65 h could increase the yield of **20** to 48% (entry 9). Finally, when the hydrogen pressure was added to 100 atm also with dioxane as solvent, compounds **19** and **20** were furnished in 10% and 54% yield, respectively (entry 10). It was evident from the above hydrogenation outcome that pressure and solvent were two important points to the hydrogenation of **18**. Also obvious was that the catalysts Pd/C and $Pd(OH)_2$/C could give different stereoselectivity. That was, diasteroisomer **19** was the main product with Pd/C being used, and diastersoisomer **20** was provided as the main product with $Pd(OH)_2$/C as catalyst. In our opinion, when Pd/C was used, the blocking effect of the substrate induced the attack of hydrogen on the *Re* side of the double bound, which resulted in the main product **19**. However, hydrogen mainly attacked the *Si* side to afford the main product **20** with $Pd(OH)_2$/C as catalyst, perhaps due to the influence of the hydrogen bond between the hydroxy group and the oxygen atoms of substrate.

Then, oxidation of compounds **19** and **20** with $RuO_2 \cdot xH_2O/NaIO_4$ under ethyl acetate/water biphase condition was carried out, respectively (Scheme 7). However, the reactions were complicated and only a few expected compounds were detected by TLC. Although many successful examples about the oxidation of the pyrrolidine substrates containing silyl group(s) to the corresponding lactams with $RuO_2 \cdot xH_2O/NaIO_4$ were reported, Young et al.[36] reported that the *tert*-butyldiphenylsilyl group could be oxidated to the *tert*-butylhydroxylphenylsilyl group by

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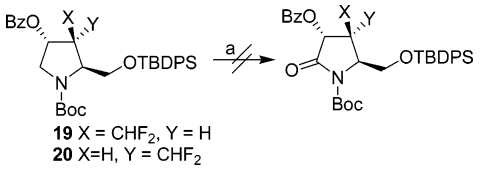
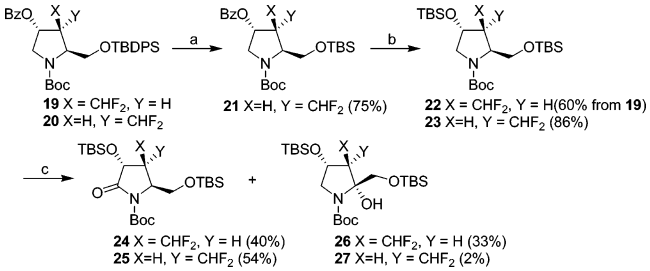
SCHEME 7 [a]



[a] Reagent and conditions: (a) $RuO_2 \cdot xH_2O$, $NaIO_4$, EtOAc, H_2O, rt.

SCHEME 8 [a]



[a] Reagent and conditions: (a) (i) TBAF, THF, rt; (ii) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt; (b) (i) saturated NH_3/MeOH, rt; (ii) TBDMSCl, imidazole, DMAP, DMF, rt; (c) $RuO_2 \cdot xH_2O$, $NaIO_4$, EtOAc, H_2O, rt.

$RuO_2 \cdot xH_2O/NaIO_4$. While no *tert*-butylhydroxylphenylsilyl-containing compound was isolated, it is our opinion that the failures of the reactions were attributed to the existence of the *tert*-butyldiphenylsilyl group.

In view of the above failure and following transformation, we decided to replace the protecting groups of hydroxy groups with *tert*-butyldimethylsilyl groups. Thus, exposure of compound **20** to TBAF in THF followed by protection of the resultant primary hydroxyl group with the *tert*-butyldimethylsilyl group provided compound **21** in 75% yield over two steps (Scheme 8). The absolute configuration of compound **21** was confirmed by X-ray. Then, treatment of **21** with a saturated solution of ammonia in methanol followed by protection of the resultant hydroxyl group also with the *tert*-butyldimethylsilyl group smoothly afforded compound **23** in 86% yield. Similarly, compound **22** was furnished from **19** in 60% yield over four steps. Next oxidation of the pyrrolidine **22** with $RuO_2 \cdot xH_2O/NaIO_4$ under ethyl acetate/water biphase condition was carried out and the desired lactam **24** was provided in 40% yield after 16 h. However, tertiary alcohol **26** was also isolated in 33% yield, which resulted from the oxidation of the hydrogen atom in the 2′-C position of compound **22**, just as reported by Ikota.[37] Treatment of compound **23** with the same condition for 13.5 h gave the desired compound **25** and alcohol **27** in 54% and 2% yield, respectively, along with the 11% recovery of starting material. Obviously from the yield of alcohols **26** and **27**, besides the electron effect,[38] the RuO_4 oxidation procedure was also influenced by the blocking effect. That is, the hydrogen atom in the 2′-C position of compound **23** is more efficiently shielded than that of compound **22**, which directly resulted in the lower yield of the byproduct **27** than that of **26**.

Lactam **24** was reduced by $LiBEt_3H$ in anhydrous THF to provide exclusively β-anomeric isomer, which was then treated with acetic anhydride to afford anomeric acetate **28** in 95% yield over two steps (Scheme 9). Similarly, lactam **25** was transformated predominantly, but not exclusively, into anomeric acetate **29a** (55%) and **29b** (11%) under the same conditions. Coupling of **28** with silylated uracil under Vorbrüggen conditions[39] gave mainly the α-anomer **30b** in 67% yield along with the β-anomer **30a** in 7% yield. Silyl-protected azanucleosides **30a** and **30b** could be separated by column chromatography. However, acetate **29a** was condensed with silylated uracil, as described for **28**, to afford mainly β-anomer **31a** in 77% yield along with the α-anomer **31b** in 13% yield. Coupling of acetate **29a** with silylated thymine gave β-anomer **32a** and α-anomer **32b** in 49% and 31% yield, respectively. Finally, removal of the silyl protective groups with TBAF in THF smoothly gave 3′-deoxy-3′-difluoromethyl azanucleosides **33**, **34a**, **34b**, and **35**. The opposite stereochemical outcome in coupling acetate **28** and **29a** with silylated uracil could be elucidated from Figure 1. That is, the silylated uracil mainly attacked the less shielded *Re* side of the double bond in intermediate **28′**, which resulted in the formation of α-anomer **30b**. However, the *Si* diastereoface of intermediate **29′** was less shielded, which was mainly subjected to the attack of silylated uracil to provide β-anomer **31a** as the main product.

The stereochemical assignments of the silylated azanucleosides were made on the base of 1D and 2D NMR spectroscopy and X-ray crystallography. The configuration of the anomeric center was assigned mainly by ^1H NMR, in which the anomers with H4′ at lower field were assigned as the α-anomers and the ones at higher field were assigned as the β-anomers on the base of the deshielding effect of the base moiety (Figure 2).[40] This assignment was further confirmed by the NOESY experiment of **30a**, **30b**, **31a**, and **31b** (Figure 2) as well as the X-ray crystallography of **30a**.

In summary, two strategies were used to synthesize 3′-deoxy-3′-difluoromethyl azanucleosides. After the failure of the first route, we stereoselectively prepared the key intermediate **12** from *trans*-4-hydroxy-proline **7** in eight steps. Alcohol **12** was subjected to selective protection, oxidation, and difluoromethylenation to afford the fluorinated compound **18**, whose hydrogenation was then systematically investigated. After a series of transformations of protecting groups, the resultant compounds **22** and **23** were oxidized to the desired lactams **24** and **25**, which were successfully utilized to synthesize our target molecules, 3′-deoxy-3′-difluoromethyl azanucleosides **33**, **34a**, **34b**, and **35**. Furthermore, work is in progress to use the intermediates **24** and **25** for the synthesis of other biologically potential active compounds. Antiviral and cytotoxicity evaluations of compounds **33**, **34a**, **34b**, and **35** are also currently in progress.

Experimental Section

THF was distilled from sodium metal. CH_2Cl_2 and pyridine were distilled from CaH_2. All the melting points and optical rotations are uncorrected. Chemical shifts (δ) of ^1H NMR, ^{13}C

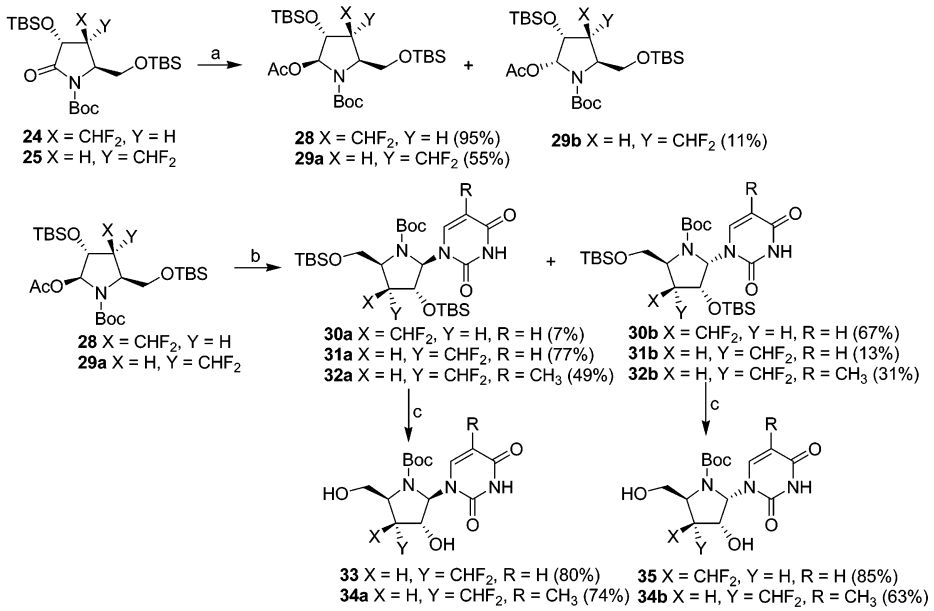
(37) Ikota, N. *Heterocycles* **1993**, *36*, 2035.

(38) Lee, D. G.; Van den Engh, M. *Can. J. Chem.* **1972**, *50*, 3129.

(39) (a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234. (b) Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, *114*, 1256.

(40) Chun, B. K.; Olgen, S.; Hong, J. H.; Newton, M. C.; Chu, C. K. *J. Org. Chem.* **2000**, *65*, 685.

SCHEME 9[a]



[a] Reagent and conditions: (a) (i) $LiBEt_3H$, THF, −78 °C; (ii) Ac_2O, CH_2Cl_2, Et_3N, DMAP, rt; (b) silylated uracil or thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMSOTf, 0 °C to rt. (c) TBAF, THF, rt.

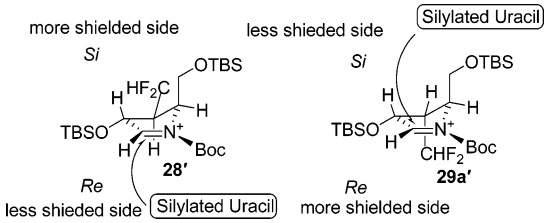


FIGURE 1. Explanation of the opposite stereochemical outcome in the glycosylation reaction.

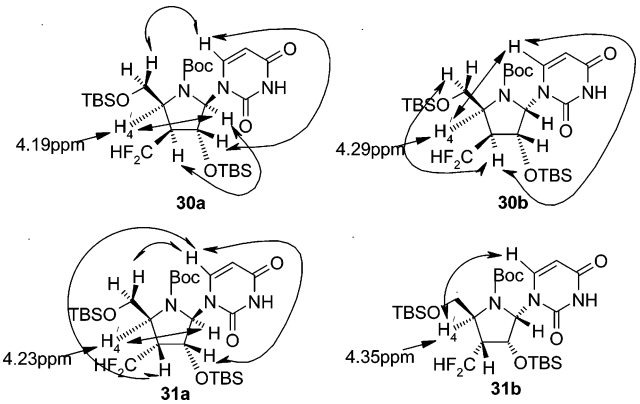


FIGURE 2. Selective NOE correlation from NOESY spectra of **30a**, **30b**, **31a**, and **31b** and ^{1}H NMR data of H4′.

NMR, and ^{19}F NMR ($CFCl_3$ as external standard and low field is positive) spectra are reported in ppm, and coupling constants (*J*) are in Hz.

Compounds **2** and **3** were prepared according to the literature procedure.[27,28]

(3*R*,4*R*,5*R*)-*N*-*tert*-Butoxycarbonyl-3,4-dihydroxy-5-(*tert*-butyldimethylsiloxymethyl)pyrrolidin-2-one (4). To a cooled solution of compound **3** (323 mg, 0.98 mmol) and 4-methylmorpholine *N*-oxide monohydrate (NMNO) (222 mg, 1.49 mmol) in acetone (15 mL) and H_2O (4 mL) was added OsO_4 (0.50 mL, 0.1 M in toluene, 0.05 mmol) dropwise. The resulting mixture was stirred at room temperature for 4 days. The reaction was quenched with H_2O and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 2:3) to afford **4** as a white solid (219 mg, 62%) and the starting material (95 mg). Compound **4**: mp 74−76 °C; $[\alpha]^{20}_D$ −10.6 (*c* 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (d, J = 4.8 Hz, 1H), 4.32 (d, J = 4.8 Hz, 1H), 4.09 (br, 1H), 3.94 (dd, J = 3.0, 2.4 Hz, 1H), 3.80 (d, J = 10.2 Hz, 2H), 3.39 (br, 1H), 1.50 (s, 9H), 0.83 (s, 9H), 0.01, −0.01 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.9, 149.7, 83.6, 71.6, 69.3, 64.7, 61.8, 28.0, 25.8, 18.2, −5.6; IR (thin film) 3440, 2957, 1776, 1739, 1695, 1473, 1367, 1286 cm^{-1}; MS (ESI) *m/z* 384.2 (M + Na$^+$). Anal. Calcd for $C_{16}H_{31}NO_6Si$: C, 53.18; H, 8.59; N, 3.88. Found: C, 53.20; H, 8.53; N, 3.67.

(3*R*,4*R*,5*R*)-*N*-*tert*-Butoxycarbonyl-3-benzoyloxy-4-hydroxy-5-(*tert*-butyldimethylsiloxymethyl)pyrrolidin-2-one (5). To a solution of compound **4** (213 mg, 0.59 mmol) and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) and pyridine (2 mL) at −78 °C was added BzCl (71 μL, 0.61 mmol) dropwise. The mixture was then warmed to −10 °C and stirred for 12 h. The reaction was quenched with H_2O (5 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with 1 M citric acid and brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 4:1) to afford **5** as a oil (235 mg, 85%) and the starting material (8 mg). Compound **5**: $[\alpha]^{20}_D$ −32.3 (*c* 0.78, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 5.92 (d, J = 5.4 Hz, 1H), 4.57 (d, J = 5.4 Hz, 1H), 4.19 (s, 1H), 4.04 (dd, J = 2.7, 2.4 Hz, 1H), 3.86 (d, J = 10.8 Hz, 1H), 2.66 (br, 1H), 1.54 (s, 9H), 0.90 (s, 9H), 0.08, 0.06 (2s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.2, 165.2, 149.9, 133.6, 130.1, 128.8, 128.5, 83.6, 72.8, 69.1, 64.9, 61.7, 28.0, 25.8, 18.6, −5.6; IR (thin film) 3486, 2957, 1789, 1728, 1603, 1473, 1371, 1309, 1258, 838 cm^{-1}; MS (ESI) *m/z* 488.3 (M + Na$^+$); ESI-HRMS *m/z* 488.2072 (M + Na$^+$, $C_{23}H_{35}NO_7Si$ required 488.2075).

(4*R*)-*N*-*tert*-Butoxycarbonyl-4-methylsulfonyloxy-l-proline Methyl Ester (8). To a cooled solution of *trans*-4-hydroxy-

L-proline **7** (10.00 g, 76.26 mmol) in anhydrous MeOH (100 mL) was added $SOCl_2$ (6.5 mL, 89.06 mmol) dropwise. After the mixture was refluxed for 2 h, it was cooled to room temperature and stirred overnight. After the solvent was removed in vacuo, the residue was washed twice with anhydrous Et_2O to provide white solid (14.00 g). Then, to a cooled solution of the above white solid (14.00 g) and DMAP (2.00 g, 16.39 mmol) in anhydrous CH_2Cl_2 (150 mL) was added Et_3N (25 mL), followed by a solution of Boc_2O (19.0 mL, 88.79 mmol) in CH_2Cl_2 (50 mL) dropwise. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with 1 M citric acid and brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 1:1) to afford a white solid (15.529 g), which was then solved in CH_2Cl_2 (250 mL). After the miture was cooled to 0 °C, DMAP (2.00 g, 16.39 mmol) and Et_3N (13 mL) were added, followed by MsCl (7.3 mL, 94.32 mmol) dropwise. The mixture was stirred for 2 h and H_2O (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2. Then, the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 2:1) to afford **8** as a white solid (19.317 g, 78%). $[\alpha]^{25}_D$ −48.4 (*c* 1.58, $CHCl_3$) (lit.[31] $[\alpha]^{25}_D$ −50.7 (*c* 1.5 $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (br, 1H), 4.47−4.37 (m, 1H), 3.86−3.75 (m, 1H), 3.82 (s, 3H), 3.08 (s, 3H), 2.68−2.55 (m, 1H), 2.32−2.23 (m, 1H), 1.47, 1.42 (2s, 9H); MS (ESI) *m/z* 346.1 ($M + Na^+$).

Methyl (2*S*)-*N*-*tert*-Butyloxycarbonyl-3,4-dehydroprolinate (9). To a 0 °C solution of **8** (19.317 g, 59.80 mmol) and PhSeSePh (11.222 g, 35.95 mmol) in MeOH (450 mL) was added $NaBH_4$ (3.0 g, 78.95 mmol) in several portions. Then, the mixture was refluxed about 11 h and the solution was removed in vacuo. H_2O (100 mL) was added and the mixture was extracted with Et_2O (3 × 80 mL). The combined organic was washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 2:1) to afford an oil (20.213 g), which was then resolved in CH_2Cl_2 (320 mL) and pyridine (6.5 mL) and 30% aqueous H_2O_2 (15 mL) were added. After about 2 h, H_2O (100 mL) was added. The organic layer was then washed with 1 M citric acid, saturated aqueous Na_2SO_3, and brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 10:1) to afford **9** as a clear oil (8.57 g, 63%). $[\alpha]^{20}_D$ −261.0 (*c* 1.11, $CHCl_3$) (lit.[32d] $[\alpha]^{20}_D$ −131.0 (*c* 1.22, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.98−5.95 (m, 1H), 5.69−5.66 (m, 1H), 4.94−4.91 (m, 1H), 4.25−4.15 (m, 2H), 3.71, 3.70 (2s, 3H), 1.45, 1.39 (2s, 9H), rotamers; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9 and 170.6, 153.8 and 153.3, 129.3 and 129.2, 124.7 and 124.6, 80.1, 66.5 and 66.2, 53.4 and 53.2, 52.1, 52.0 and 51.9, 28.3 and 28.2, rotamers.

(2*S*)-*N*-*tert*-Butyloxycarbonyl-2-hydroxymethyl-3-pyrroline (10). To a 0 °C solution of **9** (8.57 g, 37.75 mmol) in anhydrous Et_2O (200 mL) was added $LiAlH_4$ (1.55 g, 41.2 mmol). The mixture was then warmed to room temperature and stirred for 1 h. The reaction was quenched with H_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 3:1 then 2:1) to afford **10** as a clear oil (6.72 g, 89%). $[\alpha]^{20}_D$ −107.8 (*c* 1.23, $CHCl_3$) (lit.[31] $[\alpha]^{20}_D$ −107.2 (*c* 13.9, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (br, 1H), 5.65 (br, 1H), 4.72 (br, 1H), 4.22−4.04 (m, 3H), 3.79−3.75 (dd, *J* = 2.7, 2.4 Hz, 1H), 3.62−3.60 (br, 1H), 1.51, 1.49 (2s, 9H), rotamers.

(2*S*)-*N*-*tert*-Butyloxycarbonyl-2-(*tert*-butyldiphenylsiloxymethyl)-3,4-dehydropyrrolidine (11). To a 0 °C solution of **10** (6.72 g, 33.77 mmol) and imidazole (6.88 g, 101.18 mmol) in CH_2Cl_2 (130 mL) was added DMAP (420 mg, 3.44 mmol), followed by TBDPSCl (14 mL, 53.48 mmol) dropwise. The mixture was then stirred overnight and the reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 15:1) to afford **11** as a white foam (12.10 g, 82%). $[\alpha]^{20}_D$ −90.1 (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.64 (m, 4H), 7.39−7.37 (m, 6H), 5.89−5.78 (m, 2H), 4.64−4.52 (2br, 1H), 4.29−3.99 (m, 2.4H), 3.85 (ddd, *J* = 16.7, 3.0, 2.9 Hz, 1H), 3.69 (dd, *J* = 6.3, 6.6 Hz, 0.6H), 1.48, 1.36 (2s, 9H), 1.00 (s, 9H), rotamers; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.0, 135.6, 129.6, 129.5, 128.7, 127.6, 126.2, 79.3 and 79.1, 65.5 and 65.3, 65.1, 63.7, 54.2 and 54.0, 28.5 and 28.4, 26.7, 19.3, 19.2, rotamers; IR (thin film) 3073, 3051, 2860, 1960, 1741, 1701, 1627, 1590, 1402, 1114, 702 cm^{-1}; MS (ESI) *m/z* 438.3 ($M + H^+$); ESI-HRMS *m/z* 438.2460 ($M + H^+$, $C_{26}H_{36}NO_3Si$ required 438.2459).

(2*R*,3*R*,4*S*)-*N*-*tert*-Butyloxycarbonyl-3,4-dihydroxy-2-(*tert*-butyldiphenylsiloxymethyl)pyrrolidine (12). To a 0 °C solution of **11** (10.00 g, 22.88 mmol) and 4-methylmorpholine *N*-oxide monohydrate (NMNO) (9.10 g, 67.41 mmol) in acetone (250 mL) and H_2O (60 mL) was added OsO_4 (5.0 mL, 0.1 M in toluene, 0.5 mmol). The resulting mixture was warmed to room temperature and stirred for 5 h. Then, Na_2SO_3 (5.0 g) was added and after 30 min of stirring, the mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 1:1) to afford **12** as a white foam (9.65 g, 92%). $[\alpha]^{20}_D$ −30.5 (*c* 1.01, MeOH); ^1H NMR (300 MHz, MeOH-d_4) δ 7.64−7.61 (m, 4H), 7.42−7.35 (m, 6H), 4.40−4.30 (m, 2H), 4.08 (dd, *J* = 3.9, 3.6 Hz, 0.48H), 3.88 (dd, *J* = 4.2, 4.5 Hz, 0.62H), 3.77−3.66 (m, 2H), 3.59−3.39 (m, 2H), 1.47, 1.28 (2s, 9H), 1.03, 1.02 (2s, 9H), rotamers; ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 156.4, 136.6, 135.7, 135.6, 134.5, 134.4, 134.3, 131.0, 128.9, 81.1 and 80.9, 75.0 and 74.5, 71.3 and 70.8, 66.3 and 66.0, 63.8 and 63.0, 52.8 and 52.1, 28.9 and 28.8, 27.4, 20.1, rotamers; IR (thin film) 3395, 3073, 3051, 2932, 1698, 1670, 1590, 1427, 1113, 702 cm^{-1}; MS (ESI) *m/z* 472.3 ($M + H^+$); ESI-HRMS *m/z* 494.2322 ($M + Na^+$, $C_{26}H_{37}NO_5NaSi$ required 494.2333).

(2*R*,3*R*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-3-hydroxy-2-(*tert*-butyldiphenylsiloxymethyl)pyrrolidine (13) and (2*R*,3*R*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-3-*tert*-butyldimethylsilyloxy-2-(*tert*-butyldiphenylsiloxymethyl)pyrrolidine (14). To a 0 °C solution of **12** (90 mg, 0.19 mmol) and DMAP (3 mg, 0.02 mmol) in DMF (0.5 mL) was added imidazole (68 mg, 0.49 mmol), followed by TBDMSCl (32 mg, 0.21 mmol). Then, the mixture was warmed to room temperature and stirred for 3 h. EtOAc (40 mL) was added and the resulting mixture was washed with brine (3 × 15 mL). The organic phase was dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 10:1) to afford **13** as a white foam (35 mg, more polar, 31%) and **14** as a white foam (65 mg, less polar, 49%). Compound **13**: $[\alpha]^{24}_D$ −12.4 (*c* 1.32, acetone); ^1H NMR (300 MHz, acetone-d_6) δ 7.70−7.68 (m, 4H), 7.46−7.42 (m, 6H), 4.60−4.55 (m, 1H), 4.33−4.29 (m, 1H), 4.12−3.88 (m, 1H), 3.84−3.71 (m, 2H), 3.64−3.52 (m, 1H), 3.47−3.35 (m, 2H), 1.47, 1.32 (2s, 9H), 1.07 (s, 9H), 0.93 (s, 9H), 0.15, 0.14 (2s, 6H), rotamers; ^{13}C NMR (75.5 MHz, acetone-d_6) δ 155.4 and 155.2, 136.6, 136.5, 135.6, 134.6, 134.5, 134.4, 130.9, 128.9, 79.7, 75.5 and 74.9, 72.8 and 72.3, 66.2 and 66.1, 64.4 and 63.5, 52.8 and 52.4, 29.0 and 28.9, 27.6, 26.5, 20.1, 19.0, −4.3, rotamers; IR (thin film) 3439, 3073, 3053, 2956, 1699, 1681, 1590, 1409, 1113, 838 cm^{-1}; MS (ESI)

m/z 608.3 (M + Na^+), 586.3 (M + H^+); ESI-HRMS *m/z* 586.3375 (M + H^+, $C_{32}H_{52}NO_5Si_2$ required 586.3379). Compound **14**: $[\alpha]^{20}_D$ −5.5 (*c* 2.33, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.73−7.70 (m, 4H), 7.45−7.42 (m, 6H), 4.45−4.39 (m, 2H), 3.95−3.76 (m, 3H), 3.51−3.34 (m, 2H), 1.45, 1.32 (2s, 9H), 1.08 (s, 9H), 0.92, 0.91 (2s, 18H), 0.17−0.12 (m, 12H), rotamers; ^{13}C NMR (75.5 MHz, acetone-d_6) δ 155.6 and 155.3, 136.4, 135.5, 134.4, 134.2, 134.0, 130.9, 130.8, 128.9, 128.8, 128.7, 79.6, 75.8 and 75.3, 72.5 and 72.0, 67.1 and 66.8, 63.9 and 63.1, 28.8, 28.7, 27.5, 26.5, 26.4, 20.0 and 19.9, 18.9, −3.8, −4.4, −4.2, −4.2, −4.3, rotamers; IR (thin film) 2957, 2859, 1702, 1473, 1393, 1254, 1113, 837 cm^{-1}; MS (ESI) *m/z* 722.5 (M + Na^+), 700.5 (M + H^+); ESI-HRMS *m/z* 700.4245 (M + H^+, $C_{38}H_{66}NO_5Si_3$ required 700.4243).

(2*R*,3*R*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-benzoyloxy-3-hydroxy-2-(*tert*-butyldiphenylsiloxymethyl)pyrrolidine (15) and (2*R*,3*R*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-hydroxy-3-benzoyloxy-2-(*tert*-butyldiphenylsiloxymethyl)pyrrolidine (16). To a −78 °C solution of **12** (716 mg, 1.52 mmol) and DMAP (10 mg, 0.08 mmol) in CH_2Cl_2 (4.5 mL) was added pyridine (3.0 mL), followed by BzCl (176 μL, 1.52 mmol) dropwise. Then, the mixture was warmed to −10 °C and stirred for 24 h. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with 1 M citric acid and brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 8:1) to afford **15** as a white foam (614 mg, less polar, 70%) and **16** as a white foam (145 mg, more polar, 17%) and the starting material (52 mg, 7%). Coumpound **15**: $[\alpha]^{20}_D$ −26.3 (*c* 0.94, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.11−7.44 (m, 15H), 5.67−5.62 (m, 1H), 4.85−4.71 (m, 2H), 4.19−3.96 (m, 1H), 3.90−3.69 (m, 4H), 1.49−1.34 (m, 9H), 1.09, 1.08 (2s, 9H), rotamers; ^{13}C NMR (75.5 MHz, acetone-d_6) δ 166.6, 155.2, 136.5, 134.1, 131.4, 130.8, 130.6, 129.5, 128.9, 79.9, 74.5 and 74.2, 73.5 and 72.9, 66.5 and 66.3, 64.0 and 63.1, 50.1 and 49.7, 28.9, 27.5, 20.0, rotamers; IR (thin film) 3434, 3073, 2933, 1964, 1725, 1699, 1677, 1603, 1589, 1275, 1114, 709 cm^{-1}; MS (ESI) *m/z* 598.2 (M + Na^+), 576.2 (M + H^+); ESI-HRMS *m/z* 598.2575 (M + Na^+, $C_{33}H_{41}NO_6NaSi$ required 598.2595). Compound **16**: $[\alpha]^{20}_D$ −16.0 (*c* 0.57, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.09 (d, *J* = 7.8 Hz, 2H), 7.72−7.39 (m, 13H), 5.73−5.68 (m, 1H), 4.76 (br, 1H), 4.60−4.58 (m, 1H), 4.21−3.85 (m, 3H), 3.77−3.55 (m, 2H), 1.49, 1.31 (2s, 9H), 1.05 (s, 9H), rotamers; ^{13}C NMR (75.5 MHz, acetone-d_6) δ 166.6, 155.2 and 154.9, 136.5, 134.1, 131.5, 130.9, 130.7, 129.5, 128.9, 79.9, 77.8 and 77.2, 70.1 and 69.5, 64.1 and 63.1, 63.6, 53.0 and 52.6, 28.8, 27.5, 20.0, rotamers; IR (thin film) 3441, 3073, 2933, 1725, 1699, 1679, 1603, 1589, 1473, 1276, 1114, 709 cm^{-1}; MS (ESI) *m/z* 576.3 (M + H^+); ESI-HRMS *m/z* 598.2584 (M + Na^+, $C_{33}H_{41}NO_6NaSi$ required 598.2596).

(2*R*,4*S*)-*N*-*tert*-Butyloxycarbonyl-4-benzoyloxy-3-oxo-2-(*tert*-butyldiphenylsiloxymethyl)pyrrolidine (17). To a cooled solution of Dess−Martin oxidant (618 mg, 1.46 mmol) in CH_2Cl_2 (6 mL) was added a solution of **15** (536 mg, 0.93 mmol) in CH_2Cl_2 (12 mL) dropwise. The mixture was warmed to room temperature and stirred for 1.5 h. Then, the mixture was cooled again and a solution of $Na_2S_2O_4$ (1.0 g) and $NaHCO_3$ (200 mg) in H_2O (10 mL) was added dropwise. The resulting mixture was stirred for about 0.5 h and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 10:1) to afford **17** as a white foam (489 mg, 92%). $[\alpha]^{20}_D$ −30.8 (*c* 1.2, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.11−8.07 (m, 2H), 7.72−7.66 (m, 5H), 7.58−7.44 (m, 8H), 5.67 (dd, *J* = 7.5, 7.8 Hz, 1H), 4.48−4.18 (m, 3H), 3.96 (t, *J* = 10.2 Hz, 1H), 3.82 (t, *J* = 8.9 Hz, 1H), 1.55, 1.38 (2s, 9H), 1.07 (s, 9H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 207.3, 166.1, 155.0, 136.5, 134.8, 133.7, 131.1, 130.8, 130.1, 129.8, 129.0, 81.0, 74.0, 65.0, 64.2, 48.8, 28.8, 27.4, 20.0; IR (thin film) 3073, 2933, 1780, 1731, 1702, 1602, 1589, 1396, 1273, 1115, 709 cm^{-1}; MS (ESI) *m/z* 574.3 (M + H^+); ESI-HRMS *m/z* 596.2426 (M + Na^+, $C_{33}H_{39}NO_6NaSi$ required 596.2439).

(2*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-benzoyloxy-3-difluoromethylenyl-2-(*tert*-butyldiphenylsiloxymethyl)-pyrrolidine (18). To a −15 °C solution of **17** (2.149 g, 3.75 mmol) in THF (80 mL) was added HMPT (3.5 mL, 18.5 mmol) followed by CF_2Br_2 (1.75 mL, 19.10 mmol). The mixture was stirred at room temperature for 0.5 h and then Zn dust (1.20 g, 18.5 mmol) was added. The mixture was heated to reflux for 0.5 h and cooled to room temperature. H_2O (50 mL) and Et_2O (100 mL) were added. The aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with saturated aqueous $CuSO_4$ and brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 25:1) to afford **18** as a white foam (1.886 g, 83%). $[\alpha]^{20}_D$ +22.4 (*c* 1.0, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.70−7.64 (m, 5H), 7.55−7.46 (m, 8H), 6.22 (br, 1H), 4.90 (br, 1H), 4.24−3.92 (m, 3H), 3.79 (t, *J* = 12.5 Hz, 1H), 1.47, 1.40 (2s, 9H), 1.08 (s, 9H), rotamers; ^{19}F NMR (282 MHz, $CDCl_3$) δ −84.17 to −84.38 (m, 1F), −84.64 to −84.89 (m, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 166.5, 154.5 and 154.1, 153.3 (t, *J* = 290.1 Hz) and 153.2 (t, *J* = 288.8 Hz), 136.5, 136.4, 134.5, 131.1, 131.0, 130.6, 129.7, 129.0, 92.6 (t, *J* = 21.2 Hz) and 91.9 (t, *J* = 21.0 Hz), 80.7, 72.6 (d, *J* = 6.6 Hz) and 72.0 (d, *J* = 4.8 Hz), 65.3 and 64.2, 59.3, 55.1 and 54.6, 28.8, 27.4, 20.0, rotamers; IR (thin film) 3073, 2933, 1961, 1772, 1724, 1702, 1602, 1580, 1474, 1403, 1278, 1265, 1174, 1106, 710 cm^{-1}; MS (ESI) *m/z* 630.2 (M + Na^+), 608.2 (M + H^+); ESI-HRMS *m/z* 630.2453 (M + Na^+, $C_{34}H_{39}F_2NO_5NaSi$ required 630.2458).

(2*S*,3*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-benzoyloxy-3-difluoromethyl-2-(*tert*-butyldiphenylsiloxymethyl)pyrrolidine (19) and (2*S*,3*R*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-benzoyloxy-3-difluoromethyl-2-(*tert*-butyldiphenylsiloxymethyl)pyrrolidine (20). Typical procedure: To a solution of **18** in solvent was added catalyst. Then, the mixture was hydrogenated under different press. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 25:1) to afford **19** as a white foam (less polar) and **20** as a white foam (more polar). Compound **19**: $[\alpha]^{20}_D$ −11.0 (*c* 0.22, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.09−8.06 (m, 2H), 7.73−7.45 (m, 13H), 6.41 (tt, *J* = 55.7, 7.8 Hz, 1H), 6.10−6.04 (m, 1H), 4.29−4.16 (m, 2H), 4.12−3.98 (m, 1H), 3.72 (t, *J* = 12.9 Hz, 1H), 3.51 (dd, *J* = 6.3, 6.0 Hz, 1H), 3.40−3.22 (m, 1H), 1.48, 1.32 (2s, 9H), 1.13 (s, 9H), rotamers; ^{19}F NMR (282 MHz, acetone-d_6) δ −114.12 to −115.40 (m, 1F), −119.66 to −121.04 (ddd, *J* = 313.8, 18.0, 19.0 Hz, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 166.5, 154.2, 136.6, 136.5, 134.4, 133.5, 131.1, 131.0, 130.8, 130.6, 129.6, 129.0, 117.7 (t, *J* = 238.9 Hz), 80.5, 72.8 and 72.3, 64.3 and 63.4, 59.1 and 58.9, 52.5, 50.5 (t, *J* = 21.1 Hz) and 49.7 (t, *J* = 21.7 Hz), 28.8, 27.5, 19.8, rotamers; IR (thin film) 3074, 2933, 1728, 1700, 1603, 1589, 1474, 1395, 1270, 1111 cm^{-1}; MS (ESI) *m/z* 648.4 (M + K^+), 632.2 (M + Na^+), 610.3 (M + H^+); ESI-HRMS *m/z* 632.2622 (M + Na^+, $C_{34}H_{41}F_2NO_5NaSi$ required 632.2614). Compound **20**: $[\alpha]^{20}_D$ −14.4 (*c* 0.74, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.06−8.05 (m, 2H), 7.75−7.44 (m, 13H), 6.50 (td, *J* = 55.8, 5.4 Hz, 1H), 5.82 (br, 1H), 4.36−4.14 (m, 2H), 4.03−3.91 (m, 1H), 3.83−3.69 (m, 2H), 3.58−3.41 (m, 1H), 1.41, 1.32 (2s, 9H), 1.08 (s, 9H), rotamers; ^{19}F NMR (282 MHz, acetone-d_6) δ −116.47 to −117.75 (ddd, *J* = 293.1, 10.2, 10.7 Hz, 1F), −123.22 to −124.62 (dddd, *J* = 291.3, 55.8, 16.4, 16.9 Hz, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 166.1, 154.9 and 154.7, 136.3, 135.4, 134.4, 134.0, 130.8, 130.7, 130.4, 129.5, 128.8, 120.7, 117.5 (t, *J* = 240.6 Hz), 80.2 and 80.1, 73.8 and 73.5, 64.8 and 63.9, 58.8 (t, *J* = 6.9 Hz), 53.9 and 53.3, 48.1 (t, *J* = 21.4 Hz) and 47.3 (t, *J* = 20.3 Hz), 28.6, 27.2, 19.9, rotamers; IR (thin film)

3073, 2933, 1728, 1700, 1602, 1589, 1473, 1394, 1270, 1113, 709 cm^{-1}; MS (ESI) *m/z* 648.3 ($M + K^+$), 632.2 ($M + Na^+$), 610.3 ($M + H^+$); ESI-HRMS *m/z* 632.2628 ($M + Na^+$, $C_{34}H_{41}F_2NO_5NaSi$ required 632.2614).

(2*S*,3*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-*tert*-butyldimethylsiloxy-3-difluoromethyl-2-(*tert*-butyldimethylsiloxymethyl)pyrrolidine (22). To a 0 °C solution of **19** (460 mg, 0.76 mmol) in THF (20 mL) was added TBAF (0.76 mL, 1 M in THF, 0.76 mmol) dropwise. The mixture was warmed to room temperature and stirred until the reaction was shown to be complete by TLC. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 3:1) to afford a clear oil (207 mg), which was solved in CH_2Cl_2 (10 mL) and cooled to 0 °C. To the solution was added DMAP (10 mg, 0.08 mmol) and imidazole (125 mg, 1.84 mmol), followed by a solution of TBDMSCl (138 mg, 0.91 mmol) in CH_2Cl_2 (2 mL). The mixture was warmed to room temperature and stirred for 2 h. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 4:1) to afford a clear oil (258 mg), which was solved in MeOH (3.5 mL) and cooled to 0 °C. Then, to the resulting solution was added a saturated solution of ammonia in methanol (15 mL). The mixture was stirred at room temperature for 28 h. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 4:1) to afford a clear oil (180 mg), which was solved in DMF (3 mL) and cooled to 0 °C. To the resulting solution was added DMAP (40 mg, 0.33 mmol) and imidazole (1.20 g, 17.6 mmol), followed by a solution of TBDMSCl (2.00 g, 13.27 mmol) in DMF (4 mL). The mixture was then stirred for 2.5 h at room temperature. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 50:1) to afford **22** as a clear oil (225 mg, 60%). $[\alpha]^{20}_D$ +6.1 (*c* 0.59, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 6.37−5.96 (m, 1H), 4.75 (q, J = 7.5 Hz, 1H), 4.06−3.95 (m, 2H), 3.77−3.64 (m, 2H), 3.13 (dd, J = 6.6, 6.9 Hz, 1H), 2.80−2.65 (m, 1H), 1.45 (s, 9H), 0.94, 0.89 (2s, 18H), 0.08 (s, 12H), rotamers; ^{19}F NMR (282 MHz, acetone-d_6) δ −113.24 to −114.72 (m, 1F), −119.20 to −120.98 (dddd, J = 294.3, 137.5, 11.6, 12.5 Hz, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 154.2 and 153.9, 118.4 (t, J = 240.1 Hz) and 118.3 (t, J = 240.0 Hz), 80.0 and 79.9, 71.3 (d, J = 3.5 Hz) and 70.7 (d, J = 3.8 Hz), 62.7 and 61.6, 59.2 (t, J = 9.3 Hz), 55.1, 53.4 (t, J = 20.2 Hz) and 52.7 (t, J = 20.2 Hz), 28.8, 26.4, 26.2, 18.8, 18.6, −4.4, −4.8, −5.2, −5.3, rotamers; IR (thin film) 2957, 2932, 1702, 1393, 1257, 1132, 1116, 838 cm^{-1}; MS (ESI) *m/z* 496.3 ($M + H^+$); ESI-HRMS *m/z* 518.2917 ($M + Na^+$, $C_{23}H_{47}F_2NO_5NaSi_2$ required 518.2904).

(2*S*,3*R*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-benzoyloxy-3-difluoromethyl-2-(*tert*-butyldimethylsiloxymethyl)pyrrolidine (21). To a 0 °C solution of **20** (579 mg, 0.95 mmol) in THF (25 mL) was added TBAF (0.95 mL, 1 M in THF, 0.95 mmol) dropwise. The mixture was warmed to room temperature and stirred for 4.5 h. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 3:1) to afford a clear oil (280 mg), which was solved in CH_2Cl_2 (20 mL) and cooled to 0 °C. To the solution was added DMAP (26 mg, 0.21 mmol) and imidazole (373 mg, 5.48 mmol), followed by a solution of TBDMSCl (382 mg, 2.53 mmol) in CH_2Cl_2 (0.5 mL). The mixture was warmed to room temperature and stirred overnight. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 20:1) to afford **21** as a white solid (344 mg, 75%). Mp 96−97 °C; $[\alpha]^{20}_D$ −27.2 (*c* 0.66, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.05 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 6.44 (td, J = 55.7, 5.7 Hz, 1H), 5.73−5.69 (m, 1H), 4.27−4.12 (m, 2H), 3.93−3.55 (m, 3H), 3.32−3.16 (m, 1H), 1.47, 1.38 (2s, 9H), 0.94 (s, 9H), 0.12−0.09 (m, 6H), rotamers; ^{19}F NMR (282 MHz, acetone-d_6) δ −116.85 to −118.10 (dd, J = 56.4, 54.1 Hz, 1F), −123.44 to −124.68 (m, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 166.1, 154.7, 134.4, 130.5, 129.5, 117.5 (t, J = 239.4 Hz) and 117.4 (t, J = 239.6 Hz), 80.2 and 80.0, 73.7 and 73.4, 64.1 and 63.0, 58.9 and 58.7, 53.7 and 53.3, 48.1 (t, J = 21.3 Hz) and 47.1 (t, J = 21.4 Hz), 28.6 and 28.5, 26.3, 18.9, −5.2, −5.3, rotamers; IR (thin film) 2956, 1718, 1695, 1602, 1584, 1474, 1403, 1280, 1122, 1086, 775 cm^{-1}; MS (ESI) *m/z* 508.1 ($M + Na^+$), 486.2 ($M + H^+$). Anal. Calcd for $C_{24}H_{37}F_2NO_5Si$: C, 59.38; H, 7.63; N, 2.89. Found: C, 59.51; H, 7.85; N, 2.86.

(2*S*,3*R*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-*tert*-butyldimethylsiloxy-3-difluoromethyl-2-(*tert*-butyldimethylsiloxymethyl)pyrrolidine (23). To a solution of **21** (344 mg, 0.71 mmol) in MeOH (5 mL) at 0 °C was added a saturated solution of ammonia in methanol (10 mL). The mixture was stirred at room temperature for 6 h. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 3:1) to afford a clear oil (250 mg), which was solved in DMF (7 mL) and cooled to 0 °C. To the resulting solution was added DMAP (38 mg, 0.31 mmol) and imidazole (600 mg, 8.82 mmol), followed by a solution of TBDMSCl (1.04 g, 6.89 mmol) in DMF (1 mL). The mixture was then stirred overnight at room temperature. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 40:1) to afford **23** as a clear oil (302 mg, 86%). $[\alpha]^{20}_D$ −20.4 (*c* 0.47, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 6.11 (td, J = 56.7, 6.7 Hz, 1H), 4.57 (br, 1H), 4.13 (dd, J = 9.9, 10.5 Hz, 1H), 3.98 (d, J = 7.8 Hz, 1H), 3.72−3.53 (m, 2H), 3.27 (ddd, J = 17.1, 3.6, 3.6 Hz, 1H), 2.92−2.85 (m, 1H), 1.46, 1.45 (2s, 9H), 0.90 (s, 18H), 0.14−0.04 (m, 12H), rotamers; ^{19}F NMR (282 MHz, acetone-d_6) δ −115.75 to −117.20 (m, 1F), −125.4 to −126.9 (m, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 155.0, 118.9 (t, J = 238.1 Hz) and 118.8 (t, J = 238.3 Hz), 79.8 and 79.6, 72.0 (d, J = 6.5 Hz) and 71.6 (d, J = 5.4 Hz), 63.8 and 62.7, 58.8 (t, J = 8.6 Hz), 56.4 and 55.8, 49.7 (t, J = 21.1 Hz) and 48.7 (t, J = 20.7 Hz), 28.8, 26.4, 26.2, 18.9, 18.7, −4.5, −5.0, −5.1, −5.2, rotamers; IR (thin film) 2957, 1702, 1473, 1398, 1257, 1151, 1118, 837, 778 cm^{-1}; MS (ESI) *m/z* 496.3 ($M + H^+$); ESI-HRMS *m/z* 518.2925 ($M + Na^+$, $C_{23}H_{47}F_2NO_5NaSi_2$ required 518.2904).

(5*S*,4*S*,3*R*)-*N*-*tert*-Butyloxycarbonyl-5-*tert*-butyldimethylsilyloxymethyl-4-difluoromethyl-3-(*tert*-butyldimethylsilyloxy)pyrolidin-2-one (24) and (2*R*,3*R*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-*tert*-butyldimethylsiloxy-3-difluoromethyl-2-(*tert*-butyldimethylsiloxymethyl)-2-hydroxypyrrolidine (26). To a solution of $NaIO_4$ (330 mg, 1.54 mmol) in H_2O (6 mL) was added $RuO_2{\cdot}xH_2O$ (15 mg). The mixture was stirred at room temperature for 5 min and a solution of **22** (225 mg, 0.45 mmol) in EtOAc (6 mL) was added dropwise. Then, the mixture was stirred at room temperature for 16 h. H_2O (20 mL) and EtOAc (20 mL) were added and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 60:1, then 10:1) to afford **24** as a clear oil (92 mg, less polar, 40%) and **26** as a clear oil (76 mg, more polar, 33%). Compound **24**: $[\alpha]^{20}_D$ +18.7 (*c* 0.57, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 6.28 (td, J = 55.6, 7.2 Hz, 1H), 4.72 (d, J = 10.2 Hz, 1H), 4.32 (d, J = 8.7 Hz, 1H), 4.10 (d, J = 11.1 Hz, 1H), 3.86 (d, J = 12.3 Hz, 1H), 2.95−2.84 (m, 1H), 1.52 (s, 9H), 0.91, 0.90 (2s, 18H), 0.19−0.06 (m, 12H), rotamers; ^{19}F NMR (282 MHz, acetone-d_6) δ −115.06 to −116.39 (dd, J = 54.1, 54.4 Hz, 1F), −119.00 to −120.31 (m, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 171.8 and 171.7, 150.6, 118.1 (t, J = 239.0 Hz), 83.8, 72.5 and 72.4, 61.5, 56.6 and 56.5, 49.0 (t, J = 22.1 Hz), 28.5, 26.5, 26.3, 19.0, 18.9, 1.6, −3.5, −4.8, −5.3, rotamers; IR (thin film) 2955, 1789, 1771, 1714, 1473, 1165, 1019, 841 cm^{-1}; MS (ESI) *m/z* 532.3 ($M + Na^+$); ESI-HRMS *m/z* 532.2702 ($M + Na^+$, $C_{23}H_{45}F_2NO_5NaSi_2$ required 532.2697). Compound **26**: $[\alpha]^{20}_D$ −3.9 (*c* 1.78, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6) δ 6.43−6.01 (m, 1H), 5.25−5.18 (m, 1H), 4.61 (dd, J = 4.8, 5.1 Hz, 1H), 4.40 (d, J = 5.1 Hz, 0.34H) and 4.44 (d, J = 5.4 Hz, 0.66H), 4.16 (d, J = 11.4 Hz, 0.66H) and 4.05 (d, J = 11.1 Hz, 0.34H), 3.92 (d, J = 8.7

Hz, 1H), 3.72−3.62 (m, 1H), 2.98−2.81 (m, 1H), 1.48 (s, 9H), 0.93, 0.92 (2s, 18H), 0.13−0.07 (m, 12H), rotamers; ^{19}F NMR (282 MHz, acetone-d_6) δ −112.39 to −114.31 (dddd, J = 298.36, 174.00, 14.66, 12.69 Hz, 1F), −117.63 to −119.52 (dddd, J = 297.37, 168.14, 11.21, 13.32 Hz, 1F); ^{13}C NMR (75.5 MHz, benzene-d_6) δ 154.0 and 153.8, 117.5 (t, J = 240.1 Hz), 80.5, 80.2, 71.6 (d, J = 9.2 Hz) and 70.9 (d, J = 5.8 Hz), 61.2 and 60.2, 57.1 (d, J = 9.1 Hz), 49.2 (t, J = 21.5 Hz) and 48.2 (t, J = 20.6 Hz), 28.5, 26.0, 25.7, 18.2, 18.1, −4.8, −5.0, −5.4, −5.6, rotamers; IR (thin film) 3463, 2956, 1704, 1474, 1369, 1257, 1170, 1133, 839, 779 cm^{-1}; MS (ESI) *m/z* 529.3 (M + NH_4^+); HRMS-ESI *m/z* 534.2849 (M + Na^+, $C_{23}H_{47}F_2NO_5NaSi_2$ required 534.2853).

(5*S*,4*R*,3*R*)-*N*-*tert*-Butyloxycarbonyl-5-*tert*-butyldimethylsilyloxymethyl-4-difluoromethyl-3-(*tert*-butyldimethylsilyloxy)pyrolidin-2-one (25) and (2*R*,3*S*,4*R*)-*N*-*tert*-Butyloxycarbonyl-4-*tert*-butyldimethylsiloxy-3-difluoromethyl-2-(*tert*-butyldimethylsiloxymethyl)-2-hydroxypyrrolidine (27). Compounds **25** (260 mg, less polar, 54%) and **27** (10 mg, more polar, 2%) were prepared as clear oils from compound **23** (465 mg, 0.94 mmol), using the same conditions as described for compounds **24** and **26**. Compound **25**: $[\alpha]^{20}_D$ −7.8 (*c* 0.74, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 6.24 (td, J = 55.3, 2.1 Hz, 1H), 4.91 (d, J = 9.3 Hz, 1H), 4.33 (br, 1H), 4.10 (dd, J = 2.7, 2.7 Hz, 1H), 3.79 (dd, J = 1.8, 2.1 Hz, 1H), 3.11−2.96 (m, 1H), 1.52 (s, 9H), 0.94, 0.90 (2s, 18H), 0.21−0.07 (m, 12H), rotamers; ^{19}F NMR (282 MHz, acetone-d_6) δ −126.03 to −127.26 (ddd, J = 284.3, 9.7, 7.8 Hz, 1F), −127.79 to −131.08 (ddd, J = 284.5, 26.6, 26.1 Hz, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 171.6, 150.6, 116.6 (t, J = 240.1 Hz), 83.5, 71.4 and 71.3, 64.6, 55.5 (t, J = 4.1 Hz), 44.5 (t, J = 19.3 Hz), 28.3, 26.3, 26.2, 19.0, −4.2, −5.1, −5.3, −5.4, rotamers; IR (thin film) 2957, 2932, 1801, 1772, 1720, 1473, 1370, 1311, 1258, 1158, 839, 781 cm^{-1}; MS (ESI) *m/z* 548.3 (M + K^+), 532.3 (M + Na^+); ESI-HRMS *m/z* 532.2687 (M + Na^+, $C_{23}H_{45}F_2NO_5NaSi_2$ required 532.2697). Compound **27**: $[\alpha]^{20}_D$ −25.1 (*c* 0.46, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 6.13 (td, J = 56.7, 6.9 Hz, 1H), 5.25−5.19 (m, 1H), 4.23−3.97 (m, 4H), 3.64 (dd, J = 11.4, 9.9 Hz, 1H), 3.01−2.87 (m, 1H), 1.46 (s, 9H), 0.92, 0.90 (2s, 18H), 0.16−0.10 (m, 12H); ^{19}F NMR (282 MHz, acetone-d_6) δ −114.80 to −116.91 (ddd, J = 297.93, 53.30, 56.96 Hz, 1F), −124.67 to −124.06 (ddd, J = 437.1, 43.71, 20.59 Hz, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 154.7 and 154.3, 118.9 (t, J = 236.2 Hz) and 118.7 (t, J = 238.0 Hz), 87.3, 80.5 and 80.4, 77.0 (d, J = 8.3 Hz) and 76.4 (d, J = 9.3 Hz), 63.3 and 62.0, 59.0 and 58.9, 47.0 (t, J = 23.1 Hz) and 46.0 (t, J = 21.5 Hz), 28.6, 26.4, 26.0, 19.0, 18.6, −4.7, −5.1, −5.3, −5.4, rotamers; IR (thin film) 3441, 2958, 1705, 1473, 1392, 1368, 1257, 1105, 1058, 838, 779 cm^{-1}; MS (ESI) *m/z* 550.2 (M + K^+), 534.3 (M + Na^+); HRMS-ESI *m/z* 534.2853 (M + Na^+, $C_{23}H_{47}F_2NO_5NaSi_2$ required 534.2853).

(2*S*,3*R*,4*S*,5*S*)-*N*-*tert*-Butyloxycarbonyl-2-acetyloxy-3-*tert*-butyldimethylsilyloxyl-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidine (28). To a −78 °C solution of **24** (92 mg, 0.18 mmol) in THF (5 mL) was added $LiBEt_3H$ (0.45 mL, 1 M in THF, 0.45 mmol) dropwise. The mixture was then stirred at −78 °C for 1 h and the reaction was quenched with H_2O (2 mL) at −78 °C. After the mixture was warmed to room temperature, H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 20:1) to afford a clear oil (92 mg), which was solved in CH_2Cl_2 (9 mL). Then, to this resulting solution was added DMAP (17 mg, 0.14 mmol) and Et_3N (0.97 mL, 6.9 mmol), followed by Ac_2O (0.35 mL, 3.70 mmol) dropwise. The mixture was stirred at room temperature for 2 h and the reaction was quenched with H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 25:1) to afford **28** as a clear oil (95 mg, 95%). $[\alpha]^{20}_D$ −23.5 (*c* 1.5, acetone); ^{1}H NMR (300 MHz, MeOH-d_4) δ 6.27 (d, J = 2.7 Hz, 1H), 6.20 (td, J = 56.4, 7.4 Hz, 1H), 4.57−4.54 (m, 1H), 4.12−4.00 (m, 2H), 3.78−3.73 (m, 1H), 2.78−2.65 (m, 1H), 2.04 (s, 3H), 1.43 (s, 9H), 0.95, 0.87 (2s, 18H), 0.11, 0.10, 0.07, 0.05 (4s, 12H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −114.00 to −115.28 (ddd, J = 293.99, 11.28, 11.14 Hz, 1F), −117.32 to −118.55 (dd, J = 60.07, 57.25 Hz, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 171.0, 154.9, 117.4 (t, J = 239.3 Hz), 88.9 and 88.8, 82.6, 77.4, 61.6, 60.5 and 60.4, 54.4, 28.7, 26.5, 26.1, 21.5, 19.2, 18.7, −4.4, −4.9, −5.2, −5.5, rotamers; IR (thin film) 2957, 1759, 1710, 1473, 1369, 1257, 1116, 1019, 840 cm^{-1}; MS (ESI) *m/z* 576.3 (M + Na^+); ESI-HRMS *m/z* 576.2969 (M + Na^+, $C_{25}H_{49}F_2NO_6NaSi_2$ required 576.2959).

(2*S*,3*R*,4*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-2-acetyloxy-3-*tert*-butyldimethylsilyloxyl-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidine (29a) and (2*R*,3*R*,-4*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-2-acetyloxy-3-*tert*-butyldimethylsilyloxyl-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidine (29b). Compounds **29a** (151 mg, 55%) and **29b** (29 mg, 11%) were prepared as clear oils from compound **25** (253 mg, 0.50 mmol), using the same conditions as described for compound **28**. Compound **29a**: $[\alpha]^{20}_D$ −16.1 (*c* 0.78, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 6.39 (d, J = 4.2 Hz, 1H), 6.17 (td, J = 56.4, 6.1 Hz, 1H), 4.77−4.72 (m, 1H), 4.11−4.00 (m, 2H), 3.62−3.53 (m, 1H), 2.70−2.56 (m, 1H), 2.04 (s, 3H), 1.47, 1.42 (2s, 9H), 0.92, 0.88 (2s, 18H), 0.11−0.061 (m, 12H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −114.15 to −115.41 (m, 1F), −120.62 to −121.88 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 171.1, 154.5, 117.1 (t, J = 240.2 Hz), 82.6, 71.5, 65.2, 64.4, 59.1 (t, J = 5.1 Hz), 49.9 (t, J = 19.9 Hz), 28.6, 26.4, 26.2, 21.1, 19.2, 18.8, −5.0, −5.2; IR (thin film) 2958, 2932, 1753, 1716, 1473, 1392, 1369, 1259, 1149, 1113, 839 cm^{-1}; MS (ESI) *m/z* 592.3 (M + K^+), 576.3 (M + Na^+); ESI-HRMS *m/z* 576.2960 (M + Na^+, $C_{25}H_{49}F_2NO_6NaSi_2$ required 576.2959). Compound **29b**: $[\alpha]^{24}_D$ −42.5 (*c* 0.97, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 6.34 (dt, J = 57.2, 8.1 Hz, 1H), 5.53−5.52 (br, 1H), 5.22 (t, J = 5.4 Hz, 1H), 4.24−3.85 (m, 2H), 3.66−3.55 (m, 1H), 2.98−2.85 (m, 1H), 2.05 (s, 3H), 1.49 (s, 9H), 1.0 (s, 18H), 0.18, 0.16, 0.09, 0.07 (4s, 12H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −117.56 to −115.87 (m, 2F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 171.6, 154.6, 117.8 (t, J = 239.4 Hz), 82.2, 72.4, 64.9, 63.5, 58.8 (t, J = 5.8 Hz), 48.0 (t, J = 21.2 Hz), 28.8, 26.4, 26.4, 20.9, 19.2, 19.1, −4.4, −4.6, −4.8, −5.2; IR (thin film) 2958, 1755, 1713, 1473, 1397, 838 cm^{-1}; MS (ESI) *m/z* 554.2 (M + H^+); ESI-HRMS *m/z* 576.2963 (M + Na^+, $C_{25}H_{49}F_2NO_6NaSi_2$ required 576.2959).

1-[(2*R*,3*R*,4*S*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-*tert*-butyldimethylsilyloxy-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-2-yl]uracil (30a) and 1-[(2*S*,3*R*,4*S*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-*tert*-butyldimethylsilyloxy-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-2-yl]uracil (30b). To a stirred solution of **28** (95 mg, 0.17 mmol) and uracil (60 mg, 0.54 mmol) in anhydrous acetonitrile (8 mL) was added *N*,*O*-bis-(trimethylsilyl)acetamide (0.30 mL, 0.91 mmol). The reaction mixture was stirred under reflux for 30 min. After the mixture was cooled to 0 °C, TMSOTf (0.08 mL, 0.38 mmol) was added dropwise and the solution was stirred at room temperature for a further 30 min. The reaction was quenched with cold saturated aqueous $NaHCO_3$ (2 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 7:1) to give two compounds, the less polar compound **30a** (7 mg, 7%, white foam) and the more polar compound **30b** (70 mg, 67%, white foam). Compound **30a**: $[\alpha]^{25}_D$ −60.2 (*c* 0.30, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.09 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 6.24 (td, J = 55.4, 6.5 Hz, 1H), 5.99 (d, J

= 6.9 Hz, 1H), 5.71 (d, J = 7.5 Hz, 1H), 4.65 (dd, J = 6.6, 6.9 Hz, 1H), 4.19 (t, J = 10.8 Hz, 2H), 3.87 (d, J = 10.8 Hz, 1H), 3.16−2.98 (m, 1H), 1.36 (s, 9H), 1.00 (s, 9H), 0.86 (s, 9H), 0.21, 0.05, −0.07 (3s, 12H); ^{19}F NMR (282 MHz, acetone-d_6) δ −114.75 to −116.14 (m, 1F), −117.48 to −118.79 (m, 1F); ^{13}C NMR (100.0 MHz, acetone-d_6) δ 163.2, 154.3, 151.8, 140.6, 117.1 (t, J = 239.68 Hz), 103.1, 81.6, 75.1, 73.6, 63.3, 58.7, 49.0 (t, J = 20.5 Hz), 28.3, 26.5, 25.9, 19.0, 18.2, −4.5, −4.9, −5.1, −5.7; IR (thin film) 3202, 3071, 2958, 1699, 1635, 1463, 1370, 1259, 1164, 839 cm^{-1}; MS (ESI) *m/z* 628.3 (M + Na$^+$), 606.3 (M + H$^+$); ESI-HRMS *m/z* 606.3199 (M + H$^+$, $C_{27}H_{50}F_2N_3O_6Si_2$ required 606.3201). Compound **30b**: $[\alpha]^{20}_D$ +7.2 (*c* 0.65, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.12 (s, 1H), 7.61 (d, J = 8.1 Hz, 1H), 6.40 (d, J = 6.6 Hz, 1H), 6.21 (td, J = 55.5, 6.6 Hz, 1H), 5.60 (d, J = 7.8 Hz, 1H), 4.95 (t, J = 8.6 Hz, 1H), 4.30 (d, J = 5.7 Hz, 1H), 4.20 (d, J = 11.4 Hz, 1H), 3.68 (d, J = 11.4 Hz, 1H), 3.11−2.95 (m, 1H), 1.37 (s, 9H), 0.97, 0.81 (2s, 18H), 0.13, 0.12, 0.10, 0.06 (4s, 12H); ^{19}F NMR (282 MHz, acetone-d_6) δ −113.70 to −115.00 (ddd, J = 298.2, 12.1, 11.7 Hz, 1F), −117.73 to −119.03 (ddd, J = 297.9, 13.0, 11.7 Hz, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 163.2, 153.0, 151.9, 142.4, 118.0 (t, J = 240.2 Hz), 102.1, 81.7, 71.6 and 71.5, 68.4, 60.3, 58.0 and 57.9, 50.5 (t, J = 20.3 Hz), 28.4, 26.3, 25.9, 18.7, 18.2, −4.5, −5.0, −5.3, −5.5, rotamers; IR (thin film) 3190, 2958, 1701, 1629, 1368, 1259, 1137, 838, 780 cm^{-1}; MS (ESI) *m/z* 628.3 (M + Na$^+$), 606.3 (M + H$^+$); ESI-HRMS *m/z* 628.3025 (M + Na$^+$, $C_{27}H_{49}F_2N_3O_6NaSi_2$ required 628.3020).

1-[(2*R*,3*R*,4*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-*tert*-butyldimethylsilyloxy-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-2-yl]uracil (31a) and 1-[(2*S*,3*R*,4*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-*tert*-butyldimethylsilyloxy-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-2-yl]uracil (31b). Compounds **31a** (49 mg, less polar, 77%) and **31b** (8 mg, more polar, 13%) were prepared as white foams from compound **29a** (58 mg, 0.10 mmol) and uracil (37 mg, 0.33 mmol), using the same conditions as described for compounds **30a** and **30b**. Compound **31a**: $[\alpha]^{20}_D$ −43.0 (*c* 0.83, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.15 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 6.14 (td, J = 55.8, 5.1 Hz, 1H), 5.87 (br, 1H), 5.56 (d, J = 7.2 Hz, 1H), 4.63−4.60 (m, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.23 (d, J = 7.5 Hz, 1H), 3.82 (d, J = 11.1 Hz, 1H), 2.95−2.82 (m, 1H), 1.42 (s, 9H), 0.97, 0.91 (2s, 18H), 0.22−0.15 (m, 12H); ^{19}F NMR (282 MHz, acetone-d_6) δ −117.05 to −120.02 (m, 1F), −124.25 to −126.31 (m, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 163.7, 155.0, 151.9, 140.9, 117.9 (t, J = 239.3 Hz), 102.1, 82.1, 76.9, 75.7, 63.1, 60.0, 46.0 (t, J = 20.5 Hz), 28.4, 26.5, 26.2, 19.3, 18.7, −4.4, −5.0, −5.1, −5.3; IR (thin film) 2933, 1712, 1676, 1373, 1334, 1257, 1148, 1111, 836 cm^{-1}; MS (ESI) *m/z* 628.3 (M + Na$^+$), 606.2 (M + H$^+$); ESI-MALDI *m/z* 628.3033 (M + Na$^+$, $C_{27}H_{49}F_2N_3O_6NaSi_2$ required 628.3020). Compound **31b**: $[\alpha]^{20}_D$ −48.7 (*c* 0.35, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.03 (s, 1H), 7.42 (d, J = 5.7 Hz, 1H), 6.31−6.29 (br, 1H), 6.20 (t, J = 55.2 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 4.96 (t, J = 8.1 Hz, 1H), 4.35 (br, 2H), 3.58−3.52 (m, 1H), 3.06−2.88 (m, 1H), 1.36 (s, 9H), 0.93, 0.86 (2s, 18H), 0.16, 0.12, 0.11, 0.06 (4s, 12H); ^{19}F NMR (282 MHz, acetone-d_6) δ −116.88 to −118.10 (m, 1F), −122.99 to −124.31 (ddd, J = 290.9, 18.9, 17.8 Hz, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 163.4, 153.1, 151.8, 142.1, 116.7 (t, J = 238.6 Hz), 101.4, 81.6, 71.5, 70.5, 63.3, 58.6, 48.2, 28.3, 26.2, 26.0, 18.6, 18.4, −5.0, −5.4; IR (thin film) 3200, 3065, 2956, 2931, 2860, 1699, 1630, 1471, 1464, 1368, 1259, 1147, 839, 780 cm^{-1}; MS (ESI) *m/z* 628.3 (M + Na$^+$), 606.3 (M + H$^+$); ESI-HRMS *m/z* 606.3209 (M + H$^+$, $C_{27}H_{50}F_2N_3O_6Si_2$ required 606.3201).

1-[(2*R*,3*R*,4*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-*tert*-butyldimethylsilyloxy-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-2-yl]thymine (32a) and 1-[(2*S*,3*R*,4*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-*tert*-butyldimethylsilyloxy-4-difluoromethyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-2-yl]thymine (32b). Compounds **32a** (30 mg, less polar, 49%) and **32b** (19 mg, more polar, 31%) were prepared as white foams from compound **29a** (54 mg, 0.098 mmol) and thymine (38 mg, 0.30 mmol), using the same conditions as described for compounds **30a** and **30b**. Compound **32a**: $[\alpha]^{20}_D$ −56.1 (*c* 0.49, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ 10.06 (s, 1H), 7.64 (s, 1H), 6.27 (td, J = 56.0, 3.6 Hz, 1H), 5.85 (br, 1H), 4.73 (t, J = 5.4 Hz, 1H), 4.33 (d, J = 10.8 Hz, 1H), 4.25−4.22 (m, 1H), 3.83 (dd, J = 2.1, 2.4 Hz, 1H), 2.84−2.81 (m, 1H), 1.88 (s, 3H), 1.39 (s, 9H), 0.98, 0.90 (2s, 18H), 0.19, 0.13 (2s, 12H); ^{19}F NMR (282 MHz, acetone-d_6) δ −121.91 to −123.08 (dd, J = 33.0, 54.71 Hz, 1F), −126.64 to −127.89 (m, 1F); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 164.2, 155.0, 151.7, 136.2, 117.4 (t, J = 239.8 Hz), 110.4, 81.8, 76.2, 75.2, 64.2, 59.0, 46.0 (t, J = 20.6 Hz), 28.2, 26.5, 26.0, 19.2, 18.5, 12.9, −4.6, −4.8, −5.1, −5.2; IR (thin film) 3192, 3060, 2957, 2933, 1694, 1472, 1370, 1258, 1147, 1107, 838 cm^{-1}; MS (ESI) *m/z* 642.3 (M + Na$^+$), 620.3 (M + H$^+$); ESI-HRMS *m/z* 620.3363 (M + H$^+$, $C_{28}H_{52}F_2N_3O_6Si_2$ required 620.3357). Compound **32b**: $[\alpha]^{20}_D$ −42.2 (*c* 0.61, acetone); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.25 (s, 1H), 6.26 (d, J = 6.9 Hz, 1H), 6.12 (t, J = 55.8 Hz, 1H), 4.88 (t, J = 8.1 Hz, 1H), 4.56−4.30 (m, 2H), 3.48 (d, J = 9.9 Hz, 1H), 2.96−2.77 (m, 1H), 1.85 (s, 3H), 1.33 (s, 9H), 0.94, 0.83 (2s, 18H), 0.12, 0.10, 0.09, 0.01 (4s, 12H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −118.13 to −119.38 (ddd, J = 287.6, 9.3, 9.7 Hz, 1F), −124.4 to −125.7 (ddd, J = 287.2, 24.3, 22.0 Hz, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 116.3, 154.2, 152.8, 139.5, 117.0 (t, J = 239.7 Hz), 110.2, 82.8, 71.9, 71.1, 63.7, 59.1, 48.7 (t, J = 21.7 Hz), 28.5, 26.4, 26.1, 19.0, 18.7, 12.5, −5.0,−5.2, −5.3, −5.4; IR (thin film) 3194, 3060, 2957, 2932, 2860, 1693, 1473, 1369, 1259, 1148, 838, 780 cm^{-1}; MS (ESI) *m/z* 620.0 (M + H$^+$); ESI-HRMS *m/z* 642.3179 (M + Na$^+$, $C_{28}H_{51}F_2N_3O_6NaSi_2$ required 642.3177).

1-[(2*R*,3*R*,4*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-hydroxy-4-difluoromethyl-5-(hydroxymethyl)pyrrolidin-2-yl]-uracil (33). To a 0 °C solution of **31a** (40 mg, 0.066 mmol) in THF (10 mL) was added TBAF (0.16 mL, 1 M in THF, 0.16 mmol) dropwise. The mixture was stirred at room temperature for 1.5 h and the reaction was quenched with H_2O (10 mL). Then, the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the resulting residue was purified by flash chromatography (hexane/ethyl acetate, 1:2.5) to give **33** as a white foam (20 mg, 80%). $[\alpha]^{20}_D$ −87.4 (*c* 0.46, H_2O); ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.35 (d, J = 8.4 Hz, 1H), 6.21 (td, J = 56.03, 3.3 Hz, 1H), 5.84 (br, 1H), 5.67 (d, J = 5.7 Hz, 1H), 4.50 (br, 1H), 4.21−4.13 (m, 2H), 3.63 (d, J = 11.1 Hz, 1H), 2.87−2.70 (m, 1H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −119.87 to −123.53 (m, 1F), −126.94 to −129.31 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 166.3, 155.8, 152.7, 142.7, 117.8 (t, J = 238.4 Hz), 102.3, 83.0, 77.2, 74.7, 62.2, 59.8, 46.3 (t, J = 20.8 Hz), 28.5; IR (thin film) 3398, 2925, 2854, 1704, 1472, 1396, 1371, 1085, 808 cm^{-1}; MS (ESI) *m/z* 777.3 (2M + Na$^+$), 755.2 (2M + H$^+$), 400.0 (M + Na$^+$); ESI-HRMS *m/z* 400.1282 (M + Na$^+$, $C_{15}H_{21}F_2N_3O_6Na$ required 400.1291).

1-[(2*R*,3*R*,4*R*,5*S*)-*N*-*tert*-butyloxycarbonyl-3-hydroxy-4-difluoromethyl-5-(hydroxymethyl)pyrrolidin-2-yl]-thymine (34a). Compound **34a** (14 mg, 74%) was prepared as a white foam from compound **32a** (30 mg, 0.049 mmol), using the same conditions as described for compound **33**. $[\alpha]^{20}_D$ −78.5 (*c* 0.43, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.26 (s, 1H), 6.20 (td, J = 55.9, 3.6 Hz, 1H), 5.83 (br, 1H), 4.50−4.47 (br, 1H), 4.23 (d, J = 11.7 Hz, 1H), 4.13−4.10 (m, 1H), 3.65 (d, J = 10.8 Hz, 1H), 2.87−2.72 (m, 1H), 1.86 (s, 3H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −119.73 to −123.38 (m, 1F), −126.87 to −129.15 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 166.6, 155.9, 152.8, 138.6, 117.8 (t, J = 239.5 Hz), 111.1, 83.1, 77.0, 74.6, 62.2, 59.9, 46.3 (t, J = 20.9 Hz), 28.5, 12.4; IR (thin film) 3459, 3061, 3000, 2940, 1712, 1678, 1660, 1636, 1475, 1385, 1226, 1088, 773 cm^{-1}; MS (ESI) *m/z* 430.3 (M + K$^+$), 414.2 (M + Na$^+$); ESI-HRMS *m/z* 414.1438 (M + Na$^+$, $C_{16}H_{23}F_2N_3O_6Na$ required 414.1447).

1-[(2*S*,3*R*,4*R*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-hydroxy-4-difluoromethyl-5-(hydroxymethyl)pyrrolidin-2-yl]-thymine (34b). Compound **34b** (22 mg, 63%) was prepared as a white foam from compound **32b** (55 mg, 0.089 mmol), using the same conditions as described for compound **33**. $[\alpha]^{20}_{D}$ −28.6 (*c* 0.79, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.29 (s, 1H), 6.19−6.15 (br, 1H), 6.18 (td, J = 56.1, 5.4 Hz, 1H), 4.54 (br, 1H), 4.36−4.26 (m, 1H), 4.21 (d, J = 6.0 Hz, 1H), 3.48 (d, J = 11.7 Hz, 1H), 2.95−2.79 (m, 1H), 1.87 (s, 3H), 1.34 (s, 9H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −118.01 to −119.24 (dd, J = 15.3, 15.2 Hz, 1F), −124.54 to −125.84 (ddd, J = 292.22, 15.23, 15.79 Hz, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 166.5, 154.5, 152.9, 140.1, 118.1 (t, J = 238.4 Hz), 109.6, 82.6, 72.5, 70.0, 60.8, 60.2, 47.0, 28.5, 12.4; IR (thin film) 3396, 2928, 1691, 1477, 1370, 1264, 1145, 776 cm^{-1}; MS (ESI) *m/z* 430.2 (M + K^+), 414.3 (M + Na^+), 392.3 (M + H^+); ESI-HRMS *m/z* 414.1439 (M + Na^+, $C_{16}H_{23}F_2N_3O_6Na$ required 414.1447).

1-[(2*S*,3*R*,4*S*,5*S*)-*N*-*tert*-Butyloxycarbonyl-3-hydroxy-4-difluoromethyl-5-(hydroxymethyl)pyrrolidin-2-yl]-uracil (35). Compound **35** (36 mg, 85%) was prepared as a white foam from compound **30b** (68 mg, 0.11 mmol), using the same conditions as described for compound **33**. $[\alpha]^{25}_{D}$ +2.8 (*c* 0.97, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 7.56 (d, J = 7.5 Hz, 1H), 6.30 (d, J = 6.3 Hz, 1H), 6.19 (td, J = 55.9, 6.6 Hz, 1H), 5.70 (d, J = 8.1 Hz, 1H), 4.88−4.82 (m, 1H), 4.25−4.22 (m, 1H), 4.10−4.00 (m, 1H), 3.60−3.52 (m, 1H), 2.80−2.68 (m, 1H), 1.46, 1.36 (2s, 9H); ^{19}F NMR (282 MHz, MeOH-d_4) δ −113.74 to −115.36 (m, 1F), −120.49 to −122.04 (m, 1F); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 166.3, 154.0, 152.9, 143.1, 118.7 (t, J = 240.2 Hz), 102.2, 82.7, 70.9 and 70.8, 70.3, 60.3, 59.1, 50.2 (t, J = 18.3 Hz), 28.5, rotamers; IR (thin film) 3589, 3523, 3318, 3043, 1702, 1660, 1631, 1481, 1389, 1240 cm^{-1}; MS (ESI) *m/z* 777.3 (2M + Na^+), 755.3 (2M + H^+), 628.3 (M + Na^+), 400.2 (M + Na^+); ESI-HRMS *m/z* 400.1293 (M + Na^+, $C_{15}H_{21}F_2N_3O_6Na$ required 400.1291).

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Supporting Information Available: Crystallographic data (CIF) and ORTEP drawing for the compounds **21** and **30a**; copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **4**, **5**, and **8**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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