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Synthesis of (±)-4′-ethynyl-5′,5′-difluoro-2′,3′-dehydro-3′-deoxy- carbocyclic thymidine: a difluoromethylidene analogue of promising anti-HIV agent Ed4T

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ABSTRACT

Synthesis of (±)-4′-ethynyl-5′,5′-difluoro-2′,3′-dehydro-3′-deoxy-carbocyclic-thymidine (**8**) was carried out. The difluoromethylylidene group of **8** was constructed by the electrophilic fluorination to the cyclopentenone **11** by using Selectfluor®. Introduction of thymine base was investigated based on the Mitsunobu reaction by employing cyclopentenyl allyl alcohols variously substituted at the 4-position. It was found the 4-methoxycarbonyl derivative **14** gave the highest selectivity both in terms of regio- and stereochemistry.

1. Introduction

The finding that thymidine derivatives having 4′-azido (**1**),[1] 4′-cyano (**2**),[2] and 4′-ethynyl (**3**)[3] substituents show significant inhibitory activity against HIV proliferation stimulated the synthesis of 4′-substituted thymidine analogues (Fig. 1). As a result of our studies carried out along this line, the 4′-ethynyl derivative (Ed4T, **5**)[4] of stavudine (d4T, **4**) was found to be a promising anti-HIV agent: more anti-HIV active than d4T; has a lower cellular and mitochondrial toxicity than d4T;[4a,b] active against many drug-resistant HIV-1 strains, in which the reverse transcriptase (RT) bears amino acid substitutions such as M184V (3TC-resistant) and A62V/V75I/F77L/F116Y/Q151M (multidrug-resistant);[4c] its 5′-triphosphate showed much less inhibitory effects toward major host DNA polymerases.[4d] This compound (**5**) has recently entered into Phase I clinical trial.

As a part of the structure–activity relationship studies of **5**, synthesis of the carbocyclic (**6**)[5] and the 4′-thio (**7**)[6] analogues has also been carried out. In the present study, we designed and synthesized **8**, in which the furanose ring oxygen of **5** is replaced with a geminal-difluoromethylidene (CF_2) group, because the CF_2 group has been suggested to work as an isopolar and isosteric substituent for oxygen.[7]

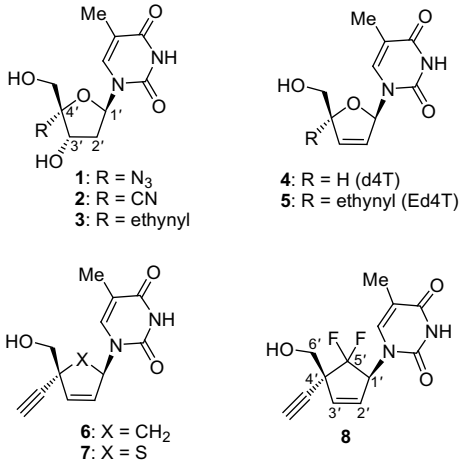

Figure 1. Compounds **1**–**8**.

2. Results and discussion

2.1. Preparation of allylalcohol (9)

For the preparation of the *gem*-difluoro carbocyclic unit **9**, the cyclopentenol **10** reported from our laboratory,[5] was selected (Scheme 1). Oxidation of **10** by using PDC gave the cyclopentenone

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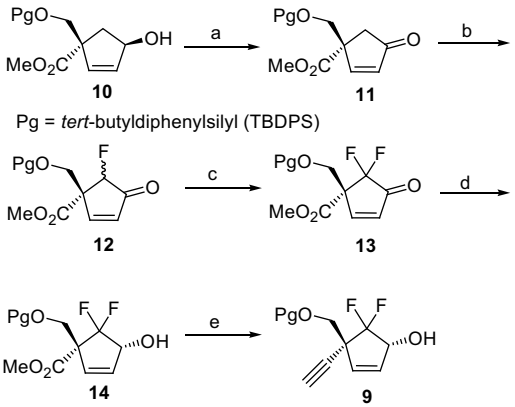
11. To introduce the fluorine atom, the ketone **10** was first converted to the corresponding silyl enol ether, and then reacted with Selectfluor®.[8] This procedure gave the monofluorinated ketone **12** in 82% yield. Simply by repeating this procedure for **12**, the difluorocyclopentenone **13** was obtained in moderate yield. It was fortunate that the Luche reduction[9] of **13** proceeded stereoselectively to give the alcohol **14** as the sole product. The stereochemistry of **14** was confirmed by NOE experiments.[10]



Scheme 1. Reagents and conditions: (a) PDC, CH_2Cl_2 (78%); (b) (i) TMSCl, Li/HMDS, THF, −78 °C, (ii) Selectfluor®, MeCN; (c) (i) TMSCl, Li/HMDS, THF, −78 °C, (ii) Selectfluor®, MeCN (76% from **11**); (d) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, THF, −78 °C (quant); (e) (i) DIBAL-H, CH_2Cl_2, −78 °C, (ii) $P(O)(OMe)_2C(N_2)COMe$ (**15**), K_2CO_3, MeOH (81% from **14**).

Conversion of the ester function of **14** to an ethynyl group was carried out by partial reduction with DIBAL-H, which was followed by treatment with the Ohira–Bestman reagent (**15**)[11] in the presence of K_2CO_3. This procedure gave the desired cyclopentenol **9** in 81% yield in two steps.

2.2. Introduction of thymine base through the Mitsunobu reaction

Introduction of thymine base was next examined (Scheme 2). Compound **9** was reacted with N^3-benzoylthymine under the conventional Mitsunobu conditions[12] (DIAD and Ph_3P in THF, at rt). After removal of the N^3-benzoyl group, there were formed three N^1-alkylated products: one was the desired **16** and others were **17α** and **17β**.[13] The depicted stereochemistry of these products was confirmed by NOE experiments.[14] The fact that **16** was formed through S_N2 process, while **17α** and **17β** resulted from S_N2' process came from their HMBC spectra: in the case of **16**, the correlation was observed between H-6′ protons (δ 3.90 and 3.94) and sp^2-hybridized carbon (C-3′, δ 136.6); in the cases of **17α** and **17β**, the correlation between H-6′ protons and sp^3-hybridized carbon (C-3′, δ 62.1 and 65.1, respectively) was apparent.

Konno,[15] Okano,[16] and Kim[7h] have independently reported that fluoroalkyl-substituted allylic alcohols undergo nucleophilic substitution exclusively at remote carbon atom from the electron-withdrawing fluoroalkyl group, presumably as a result of electronic effect of the fluorine atom. We assumed, however, that bulkiness of the substituent at the 4-position of **9** could have a significant influence on the regiochemical bias.

To inspect our assumption, two 4-substituted cyclopentenyl alcohols **18** and **19** (Fig. 2) were prepared from the 4-methoxycarbonyl derivative **14**. The 4,4-bis-(*tert*-butyldiphenylsilyloxy)-methyl derivative **18** was prepared by the following sequence of reactions: protection of the allyl alcohol, reduction of the ester group followed by protection of the resulting primary alcohol as TBDPS ether, and finally deprotection of the allyl alcohol. Compound **14** was also converted to the cyano derivative **19**: partial reduction of the ester to give the aldehyde, oxime formation, O-acetylation, and elimination.

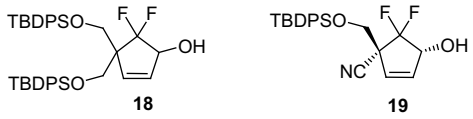
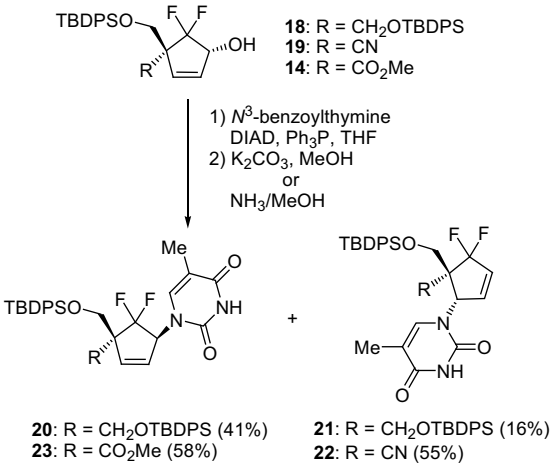


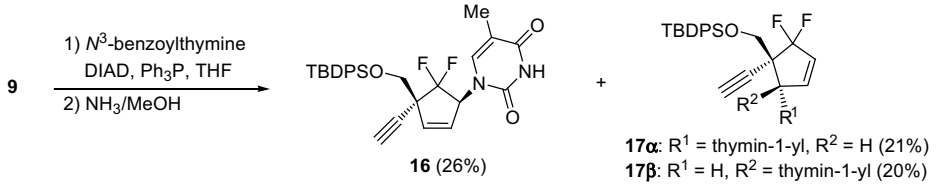
Figure 2. Compounds **18** and **19**.

As shown in Scheme 3, upon being reacted with N^3-benzoylthymine under similar conditions to the case of **9**, **18** gave a mixture of **20** and the S_N2' product (**21**) with a slightly improved S_N2-selectivity. In contrast, the cyano derivative (**19**) gave exclusively the S_N2' product (**22**).[17] The highest S_N2-selectivity was observed in the reaction of the 4-methoxycarbonyl derivative **14**, forming **23** as the sole product in 58% yield.



Scheme 3. Mitsunobu reaction of compounds **18**, **19** and **14**.

Since methoxycarbonyl group is not seemingly bulky enough, one may consider that the above observed exclusive formation of **23** from **14** is not a consequence of its bulkiness, but of its participation to an allyl cation intermediate as depicted in Figure 3, which could prevent the reaction taking place at the 3-position as well as from concave face. Although such participation is unlikely due to anticipated severe strain, we nevertheless carried out an additional reaction with a hope that some supportive evidence might be obtained for S_N2 mechanism for the formation of **23**.



Scheme 2. Mitsunobu reaction of compound **9**.

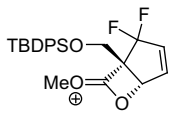


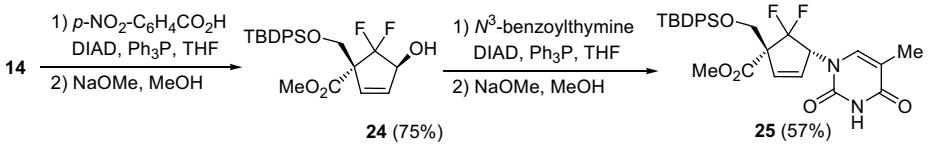
Figure 3.

Thus, the epimeric ally alcohol **24**[18] was prepared from **14** by reacting with *p*-nitrobenzoic acid under the Mitsunobu conditions followed by treating the product with NaOMe (Scheme 4). When **24** was reacted with N^3-benzoylthymine as described for the case of **9**, again only the S_N2 product **25** was isolated in 56% yield after debenzoylation.[19]

not to be inhibitory against HIV proliferation (data not shown) (Fig. 4).

3. Conclusion

The synthesis of racemic 5′,5′-difluoromethylidene analogue of a promising anti-HIV agent Ed4T has been carried out. Preparation of the difluoro carbocyclic unit **9** was initiated with repeating electrophilic fluorination with Selectfluor® to the enolate derived from **11**. The resulting difluoroenone **13** was stereoselectively reduced to the allyl alcohol **14** by employing the Luche reduction. Manipulation of the methoxycarbonyl group of **14** allowed to prepare **9**.



Scheme 4. Preparation and Mitsunobu reaction of compound **24**.

2.3. Synthesis of compound 8 and its brief conformational analysis based on X-ray structure

The 4′-methoxycarbonyl carbocyclic nucleoside **23** was reacted with DIBAL-H and then with $P(O)(OMe)_2C(N_2)COMe$ (**15**), by a similar manner described for the transformation of **14** to **9**, to give **16** in 80% yield. The title compound **8** was obtained in a good yield after desilylation with Bu_4NF/THF in the presence of AcOH. The depicted stereochemistry of **8** shown in Figure 4 came from its X-ray crystallographic analysis.

The glycosyl tortional angle ($\chi=-94.9°$) of **8** showed its *anti* (−anticlinal) orientation, which is similar to that of the parent compound stavudine (**4**, $\chi=-100.8°$).[20] However, the orientation of the hydroxylmethyl group at the C-4′ position adopted *trans*,*gauche* (−synclinal, $\gamma=-144.8°$) conformation, which was completely different from that of **4** (+synclinal, $\gamma=52.8°$). Moreover, the cyclopentene ring of **8** has an envelope type puckering, due to sticking out of the CF_2 group from the cyclopentene plane toward the thymine base: the C-5′ of **8** deviates ca. 0.44 Å from the plane consisting of C1′, C2′, C3′ and C4′. It has been proposed that planarity of the furanose ring of **4** plays one important role for the recognition by cellular kinase.[21] Presumably due to these conformational differences, **8** was found

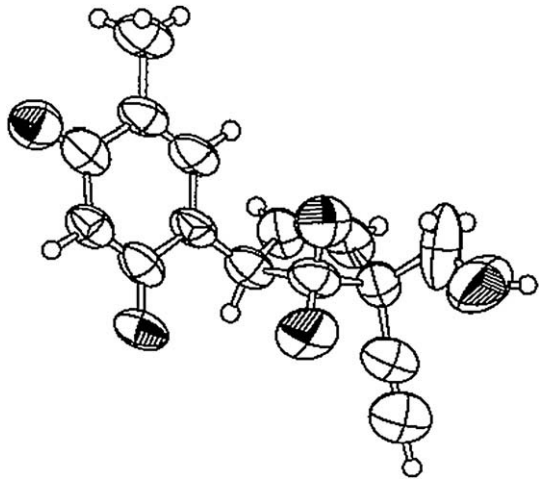


Figure 4. ORTEP drawing of compound **8**.

Introduction of thymine base to **9** under the Mitsunobu conditions resulted in the formation of the S_N2 product **16** and the two S_N2' products **17α** and **17β**. It was found that the methoxycarbonyl derivative **14** gave exclusively the S_N2 product **23** in good yield. The title compound **8** was finally prepared from **23** through a series of reactions. A brief conformational analysis of **8** was also carried out based on its X-ray crystallographic data.

4. Experimental

4.1. General

Melting points were determined on a Yanaco micro melting point apparatus, and are uncorrected. ^1H and ^{13}C NMR spectra were recorded either at JEOL JNM-GX 400 (400 MHz). Chemical sifts are reported relative to Me_4Si. ^{19}F NMR spectra were measured at 500 MHz with $CFCl_3$ as an internal standard. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix on a JEOL JMS-700. Infrared spectra (IR) were recorded on a JASCO FT/IR-410 spectrophotometer. Column chromatography was carried out on silica gel (Micro Bead Silica Gel PSQ 100B, Fuji Silysia Chemical Ltd). Thin-layer chromatography (TLC) was performed on precoated silica gel plate F_{254} (Merck). When necessary, analytical samples were purified by high performance liquid chromatography (HPLC). HPLC was carried out on a Shimadzu LC-6AD with a Shim-pack PREP-SIL (H)˙ KIT column (2×25 cm). THF was distilled from benzophenone ketyl.

4.2. (±)-1-(*tert*-Butyldiphenylsiloxymethyl)-4-oxo-cyclopent-2-enecarboxylic acid methyl ester (11)

To a CH_2Cl_2 (60 mL) solution of **10** (8.5 g, 20.7 mmol) were added MS 4 Å (8 g) and PDC (15.6 g, 41.4 mmol). The resulting mixture was stirred at rt for 40 h. The reaction mixture was then diluted by slow addition of EtOAc (100 mL) and stirred for further 0.5 h. After filtration by a Celite pad, the resulting filtrate was evaporated and the residue was purified by column chromatography (hexane/EtOAc=7/1). This gave **11** (6.6 g, 78%) as an oil. ^1H NMR ($CDCl_3$) δ 1.03 (9H, s, *t*-Bu), 2.44 (1H, d, J_{gem}=18.8, CH_2), 2.84 (1H, d, J_{gem}=18.8, CH_2), 3.73 (3H, s, OMe), 3.86 (1H, d, J_{gem}=9.6, $SiOCH_2$), 3.92 (1H, d, J_{gem}=9.6, $SiOCH_2$), 6.23 (1H, d, J=5.6, CH=CH), 7.37–7.47 (7H, m, Ph and CH=CH), 7.58–7.62 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.6, 41.1, 52.6, 58.3, 67.9, 127.8, 130.0, 132.5, 132.6,

134.9, 135.5, 135.6, 162.4, 172.2,206.9: HRFAB-MS *m*/*z* 409.1862 (M^++H), calcd for $C_{24}H_{29}O_4Si$ (M^++H) 409.1835.

4.3. (±)-1-(*tert*-Butyldiphenylsiloxymethyl)-5,5-difluori-4-oxo-cyclopent-2-enecarboxylic acid methyl ester (13)

A mixture of **11** (6.05 g, 14.8 mmol) and TMSCl (3.76 mL, 29.6 mmol) in THF (100 mL) was treated with dropwise addition of LHMDS (1.1 M solution of THF, 27.0 mL, 29.6 mmol) at −78 °C under positive pressure of dry Ar. After being stirred for 0.5 h at same temperature, the mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The resulting crude silyl enol ether was dissolved in MeCN (120 mL) and reacted with Selectfluor® (10.49.g, 29.6 mmol). After stirring for 24 h at rt, the reaction mixture was partitioned between EtOAc and 1 M HCl. Column chromatography (hexane/EtOAc=1/1) of the organic layer gave the crude monofluoride **12** (ca. 6.6 g) as an oil. The above procedure was repeated to **12** by using TMSCl (3.76 mL, 29.6 mmol), LHMDS (1.1 M solution of THF, 27.0 mL, 29.6 mmol) and Selectfluor® (10.49.g, 29.6 mmol). Column chromatography (hexane/EtOAc=9/1) of the organic layer gave the crude difluoride **13** (5.03 g, 76% from **11**) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.00 (9H, s, *t*-Bu), 3.79 (3H, s, OMe), 3.95 (1H, d, J_{gem}=9.6, $SiOCH_2$), 4.13 (1H, d, J_{gem}=9.6, $SiOCH_2$), 6.52–6.54 (1H, m, CH=CH), 7.38–7.46 (6H, m, Ph), 7.56–7.59 (4H, m, Ph), 7.88–7.91 (1H, m, CH∼CH); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.5, 53.1, 61.6 (t, $J_{C,F}$=19.2), 64.1 (d, $J_{C,F}$=9.6), 113.0 (dd, $J_{C,F}$=271.1 and 255.5), 127.9, 128.0, 130.2, 132.0, 135.5,161.2 (d, $J_{C,F}$=4.8), 166.8 (d, $J_{C,F}$=4.8), 191.6 (t, $J_{C,F}$=25.2); ^{19}F NMR ($CDCl_3$) δ −112.8 (d, $J_{F,F}$=283.4), −129.5 (d, $J_{F,F}$=283.4); HRFAB-MS *m*/*z* 445.1647 (M^++H), calcd for $C_{24}H_{27}F_2O_4Si$ (M^++H) 445.1640.

4.4. (±)-*r*-1-(*tert*-Butyldiphenylsiloxymethyl)-5,5-difluori-*t*-4-hydroxy-cyclopent-2-enecarboxylic acid methyl ester (14)

To a mixture of **13** (380 mg, 0.85 mmol), $CeCl_3\cdot 7H_2O$ (317 mg, 0.85 mmol) and THF (3 mL) in MeOH (20 mL) was added $NaBH_4$ (76 mg, 1.7 mmol) at −78 °C. The mixture was stirred at same temperature for 16 h. After treatment with acetone (ca. 3 mL), the mixture was concentrated, partitioned between CH_2Cl_2 and 1 M HCl. Column chromatography (hexane/EtOAc=1/1) of the organic layer gave **14** (379 mg, quant.) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.03 (9H, s, *t*-Bu), 2.27 (1H, dd, *J*=11.2 and 2.8, OH), 3.75 (3H, s, OMe), 3.94 (1H, d, J_{gem}=9.6, $SiOCH_2$), 3.99 (1H, d, J_{gem}=9.6, $SiOCH_2$), 4.76.4.83 (1H, m, C*H*OH), 6.02–6.06 (1H, m, CH=CH), 6.16–6.19 (1H, m, CH=CH), 7.37–7.46 (6H, m, Ph), 7.60–7.63 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.7, 52.7, 64.0 (d, $J_{C,F}$=6.0), 64.6 (t, $J_{C,F}$=21.6), 78.0 (dd, $J_{C,F}$=30.0 and 20.4), 125.5 (dd, $J_{C,F}$=268.7 and 255.5), 127.8, 129.9, 130.0, 132.4, 132.6 (d, $J_{C,F}$=8.4), 133.1 (d, $J_{C,F}$=8.4), 135.5, 135.6, 169.1; ^{19}F NMR ($CDCl_3$) δ −116.9 (d, $J_{F,F}$=239.8), −120.0 (d, $J_{F,F}$=239.8); HRFAB-MS *m*/*z* 447.1788 (M^++H), calcd for $C_{24}H_{29}F_2O_4Si$ (M^++H) 447.1803.

4.5. (±)-*t*-4-(*tert*-Butyldiphenylsiloxymethyl)-*c*-4-ethynyl-5,5-difluoro-cyclopent-2-en-*r*-1-ol (9)

To a CH_2Cl_2 (100 mL) solution of **14** (3.5 g, 7.83 mmol) was added DIBAL-H (1.0 M solution in toluene, 23.5 mL, 23.5 mmol) dropwise over 1 h at −78 °C. The mixture was stirred for further 0.5 h at same temperature. The reaction mixture was partitioned between CH_2Cl_2 and 1 M HCl. The crude aldehyde was obtained after evaporation of the organic layer. A solution of this aldehyde in MeOH (90 mL) was treated with K_2CO_3 (3.25 g, 23.5 mmol) followed by $MeC(O)C(N_2)P(O)(OMe)_2$ (3.76 g, 19.6 mmol). The resulting mixture was stirred for 20 h at rt. Partition of the reaction mixture between CH_2Cl_2 and saturated aqueous NH_4Cl was followed by column chromatography (hexane/EtOAc=2/1) of the organic layer. This gave **9** (2.59 g, 81%) as an oil. IR (neat) 2090 cm^{-1} (C≡C); ^{1}H NMR ($CDCl_3$) δ 1.03 (9H, s, *t*-Bu), 2.15 (1H, dd, *J*=10.9 and 4.0, OH), 2.35 (1H, s, C≡C*H*), 3.65 (1H, dd, *J*=10.4 and 2.9, $SiOCH_2$), 3.98 (1H, d, *J*=10.4, $SiOCH_2$), 4.92–4.97 (1H, m, C*H*OH), 5.82–5.83 (1H, m, CH=CH), 6.01–8.02 (1H, m, CH=CH), 7.38–7.46 (6H, m, Ph), 7.62–7.66 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.7, 53.9 (dd, $J_{C,F}$=24.0 and 20.4), 64.9 (d, $J_{C,F}$=4.8), 74.7, 77.6 (dd, $J_{C,F}$=30.0 and 21.6), 78.3 (d, $J_{C,F}$=7.2), 125.3 (dd, $J_{C,F}$=269.9 and 256.7), 127.8, 129.8, 129.9, 132.3, 132.5, 133.2, 133.3, 135.5, 135.7; ^{19}F NMR ($CDCl_3$) δ −113.1 (d, $J_{F,F}$=228.9), −123.1 (d, $J_{F,F}$=228.9); HRFAB-MS *m*/*z* 413.1751 (M^++H), calcd for $C_{24}H_{27}F_2O_2Si$ (M^++H) 413.1748.

4.6. The Mitsunobu reaction of 9

To a THF (3 mL) solution of Ph_3P (291 mg, 1.11 mmol) was added DIAD (219 μL, 1.11 mmol) at 0 °C. After stirring for 10 min, a THF (5 mL) solution of **9** (150 mg, 0.37 mmol) and N^3-benzoylthymine (256 mg, 1.11 mmol) were added at −40 °C. The reaction mixture was allowed to warm to rt, and stirred for further 50 h at ambient temperature. The mixture was partitioned between Et_2O and H_2O. After evaporation of the organic layer, the residue was treated with NH_3/MeOH (30 mL) at −4 °C for 12 h. After evaporation, the residue was carefully purified by column chromatography (hexane/Et_2O=2/1 to 1/4). This gave **16** (50 mg, 26% as a solid), **17α** (40 mg, 21%, as a foam) and **17β** (39 mg, 20% as a foam).

4.7. Physical data for 16

IR (neat) 2080 cm^{-1} (C≡C); ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s, *t*-Bu), 1.83 (3H, s, Me), 2.44 (1H, s, C≡C*H*), 3.90 (1H, d, *J*=10.4, $SiOCH_2$), 3.94 (1H, d, *J*=10.4, $SiOCH_2$), 5.81–5.83 (1H, m, CH=CH), 6.08–6.13 (1H, m, NC*H*), 6.16–6.19 (1H, m, CH=CH), 6.81 (1H, m, H-6), 7.36–7.47 (6H, m, Ph), 7.67–7.70 (4H, m, Ph), 8.39 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.3, 19.4, 26.6, 54.0 (dd, $J_{C,F}$=26.4 and 21.6), 62.7 (dd, $J_{C,F}$=30.0 and 19.2), 64.1 (d, $J_{C,F}$=9.6), 74.9, 78.1 (d, $J_{C,F}$=4.8), 110.9, 125.4 (dd, $J_{C,F}$=272.3 and 264.0), 126.9 (d, $J_{C,F}$=7.2), 127.8, 129.9, 132.7, 132.8, 135.6, 136.6, 137.0, 150.6, 163.2; ^{19}F NMR ($CDCl_3$) δ −106.3 (d, $J_{F,F}$=228.9), −119.2 (d, $J_{F,F}$=228.9); HRFAB-MS *m*/*z* 521.2022 (M^++H), calcd for $C_{29}H_{31}F_2N_2O_3Si$ (M^++H) 521.2072.

4.8. Physical data for 17α

IR (neat) 2090 cm^{-1} (C≡C); ^{1}H NMR ($CDCl_3$) δ 1.03 (9H, s, *t*-Bu), 1.91 (3H, d, *J*=1.6, Me), 2.32 (1H, s, C≡C*H*), 4.03 (2H, s, $SiOCH_2$), 6.11–6.13 (1H, m, NC*H*), 6.30–6.31 (1H, m, CH=CH), 6.39–6.41 (1H, m, CH=CH), 6.89 (1H, q, *J*=1.6, H-6), 7.37–7.48 (6H, m, Ph), 7.65–7.72 (4H, m, Ph), 9.21 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.5, 19.3, 26.6, 53.5 (dd, $J_{C,F}$=22.8 and 19.2), 62.1 (d, $J_{C,F}$=4.8), 65.6 (d, $J_{C,F}$=7.2), 75.5 (d, $J_{C,F}$=6.0), 78.5, 110.4, 127.4 (dd, $J_{C,F}$=255.5 and 249.5), 127.7, 127.8, 129.8, 129.9, 132.3, 132.4, 133.7 (t, $J_{C,F}$=27.6), 135.6, 137.1, 137.2 (t, $J_{C,F}$=8.4), 151.1, 163.9; ^{19}F NMR ($CDCl_3$) δ −78.2 (d, $J_{F,F}$=261.6), −110.2 (d, $J_{F,F}$=261.6); HRFAB-MS *m*/*z* 521.2048 (M^++H), calcd for $C_{29}H_{31}F_2N_2O_3Si$ (M^++H) 521.2072.

4.9. Physical data for 17β

IR (neat) 2070 cm^{-1} (C≡C); ^{1}H NMR ($CDCl_3$) δ 1.04 (9H, s, *t*-Bu), 1.68 (3H, d, *J*=1.2, Me), 2.45 (1H, s, C≡C*H*), 3.75 (2H, s, $SiOCH_2$), 6.00–6.07 (1H, m, NC*H*), 6.28–6.30 (1H, m, CH=CH), 6.33–6.35 (1H, m, CH=CH), 6.79 (1H, q, *J*=1.2, H-6), 7.33–7.36 (4H, m, Ph), 7.39–7.43 (2H, m, Ph), 7.54–7.57 (2H, m, Ph), 7.61–7.63 (2H, m, Ph), 8.82 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.3, 19.2, 26.7, 52.4 (t, $J_{C,F}$=22.8), 61.7 (d, $J_{C,F}$=7.2), 65.1, 74.3, 79.9, 110.8, 127.6, 127.7 (dd, $J_{C,F}$=279.5 and 223.1), 127.8, 129.8, 129.9, 132.3, 132.4, 132.6 (t, $J_{C,F}$=26.4), 135.5, 135.7, 136.5, 137.4 (t, $J_{C,F}$=9.6), 150.7, 163.1; ^{19}F NMR ($CDCl_3$) δ −106.3 (d, $J_{F,F}$=228.9), −119.3 (d, $J_{F,F}$=228.9);

HRFAB-MS *m*/*z* 521.2081 (M^++H), calcd for $C_{29}H_{31}F_2N_2O_3Si$ (M^++H) 521.2072.

4.10. (±)-4,4-Bis-(*tert*-Butyldiphenylsiloxymethyl)-5,5-difluoro-cyclopent-2-en-1-ol (18)

To a mixture of **14** (350 mg, 0.78 mmol) and PPTS (20 mg, 0.08 ooml) in CH_2Cl_2 (3 mL) was added 2,3-dihydrofuran (77 μL, 1.02 mmol). The resulting mixture was stirred for 0.5 h at rt. The mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was evaporated and the residue was dissolved in THF (5 mL). The resulting THF solution was treated with $LiAlH_4$ (30 mg, 0.78 mmol) at 0 °C for 0.5 h with stirring. The reaction mixture was quenched by adding EtOAc and H_2O, and then filtered through a Celite pad. The filtrate was evaporated and dissolved in MeCN (5 mL). A mixture of this solution, imidazole (106 mg, 1.56 mmol) and TBDPSCl (244 μL, 0.94 mmol) was stirred for 1 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer separated was evaporated, and the residue was treated with PPTS (20 mg, 0.08 mmol) in MeOH (8 mL) at rt for 3 h. After quenching with Et_3N (2 mL), the mixture was evaporated and purified by column chromatography (hexane/EtOAc=2/1). This gave **18** (206 mg, 40% from **14**) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (9H, s, *t*-Bu), 1.03 (9H, s, *t*-Bu), 3.17 (1H, d, *J*=10.4, OH), 3.68–3.76 (3H, m, SiOCH_2×3), 3.93 (1H, d, *J*=10.4, SiOCH_2), 4.50–4.57 (1H, m, H-4), 5.84–5.86 (1H, m, CH=CH), 6.05–6.15 (1H, m, CH=CH), 7.28–7.32 (4H, m, Ph), 7.36–7.46 (8H, m, Ph), 7.50–7.53 (4H, m, Ph), 7.62–7.66 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.2, 26.6, 26.8, 58.5 (t, $J_{C,F}$=21.6), 62.5 (d, $J_{C,F}$=12.0), 63.4 (d, $J_{C,F}$=6.0), 77.5 (dd, $J_{C,F}$=35.2 and 21.2), 127.7, 126.4 (dd, $J_{C,F}$=265.1 and 259.1), 127.9, 129.6, 129.7, 129.9, 130.0, 132.1, 132.3, 132.9, 134.9 (d, $J_{C,F}$=5.8), 135.4, 135.5, 135.6, 135.7; ^{19}F NMR ($CDCl_3$) δ −117.0 (d, $J_{F,F}$=239.8), −124.4 (d, $J_{F,F}$=239.8); HRFAB-MS *m*/*z* 657.3032 (M^++H), calcd for $C_{39}H_{47}F_2O_3Si_2$ (M^++H) 657.3032.

4.11. (±)-*t*-4-(*tert*-Butyldiphenylsiloxymethyl)-*c*-4-cyano-5,5-difluoro-cyclopent-2-en-*r*-1-ol (19)

A CH_2Cl_2 (16 mL) solution of **14** (500 g, 1.12 mmol) was treated with DIBAL-H (1.0 M solution in toluene, 3.36 mL, 3.36 mmol) dropwise over 1 h at −78 °C and then stirred for 0.5 h at same temperature. The resulting aldehyde obtained by partition (CH_2Cl_2/1 M HCl) of the reaction mixture was dissolved in pyridine (15 mL) and reacted with NH_2OH·HCl (1.56 g, 22.4 mmol) at rt for 12 h. The oxime obtained by partition (CH_2Cl_2/0.5 M HCl) of the reaction mixture was acetylated with Ac_2O (317 μL, 3.36 mmol) in MeCN (20 mL) in the presence of DMAP (343 mg, 2.8 mmol) and *i*-Pr_2NEt (585 μL, 3.36 mmol) for 1 h. The diacetate obtained by partition (CH_2Cl_2/1 M HCl) was subjected to elimination by reacting with NaOAc (82 mg, 1.0 mmol) in AcOH (18 mL) at 100 °C for 3 h. The resulting product obtained by partition (CH_2Cl_2/saturated aqueous $NaHCO_3$) was treated with NH_3/MeOH (10 mL) below 0 °C overnight. The requisite cyano derivative (**19**) was isolated from the reaction mixture by column chromatography (hexane/EtOAc=3/1). This gave **19** (244 mg, 53% from **14**) as an oil. IR (neat) 2080 cm^{-1} (C≡N); ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s, *t*-Bu), 3.84 (1H, d, J_{gem}=10.4, $SiOCH_2$), 3.94 (1H, dd, *J*=10.4 and 0.8, $SiOCH_2$), 4.83–4.87 (1H, m, H-4), 5.91–5.94 (1H, m, CH=CH), 6.13–6.17 (1H, m, CH=CH), 7.39–7.49 (6H, m, Ph), 7.60–7.65 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.6, 54.6 (dd, $J_{C,F}$=25.2 and 20.4), 63.3 (d, $J_{C,F}$=6.0), 77.0 (dd, $J_{C,F}$=31.2 and 20.4), 115.2 (d, $J_{C,F}$=4.8), 123.9 (dd, $J_{C,F}$=269.9 and 260.3), 128.1, 129.5, 130.2, 130.3, 131.6, 131.8, 135.5, 135.6, 135.7; ^{19}F NMR ($CDCl_3$) δ −111.9 (d, $J_{F,F}$=239.8), −120.2 (d, $J_{F,F}$=239.8); HRFAB-MS *m*/*z* 414.1679 (M^++H), calcd for $C_{23}H_{26}F_2NO_2Si$ (M^++H) 414.1701.

4.12. The Mitsunobu reaction of 18: formation to 20 and 21

Compound **18** (360 mg, 0.55 mmol) was reacted as described above for **9**. After purification by a preparative TLC ($CHCl_3$ three times elution), compound **20** (172 mg, 41%, foam) and **21** (66 mg, 16%, foam) were obtained.

*4.12.1. Physical data for **20***

^{1}H NMR ($CDCl_3$) δ 0.96 (9H, s, *t*-Bu), 1.06 (9H, s, *t*-Bu), 1.86 (3H, d, *J*=0.4, 5-Me), 3.77 (2H, s, $SiOCH_2$), 3.83 (1H, d, J_{gem}=10.0, $SiOCH_2$), 3.99 (1H, d, J_{gem}=10.0, $SiOCH_2$), 5.79–5.80 (1H, m, CH=CH), 6.04–6.07 (1H, m, CH=CH), 6.07–6.13 (1H, m, C*H*-N), 6.83 (1H, q, *J*=0.4, H-6), 7.26–7.45 (12H, m, Ph), 7.54–7.57 (4H, m, Ph), 7.61–7.67 (4H, m, Ph), 8.45 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.4, 19.1, 19.2, 26.6, 59.5 (t, $J_{C,F}$=20.2), 61.5 (d, $J_{C,F}$=10.8), 63.4 (d, $J_{C,F}$=9.6), 63.9 (dd, $J_{C,F}$=30.0 and 20.4), 110.3, 127.3 (d, $J_{C,F}$=8.4), 127.6 (dd, $J_{C,F}$=267.5 and 261.5), 127.7, 127.8, 129.7, 129.8, 129.9, 132.5, 132. 6, 132.7, 132.8, 135.5, 135.6, 135.7, 137.4, 137.6, 150.8, 163.6; ^{19}F NMR ($CDCl_3$) δ −114.9 (d, $J_{F,F}$=239.8), −116.1 (d, $J_{F,F}$=239.8); HRFAB-MS *m*/*z* 765.3368 (M^++H), calcd for $C_{44}H_{51}F_2N_2O_4Si_2$ (M^++H) 765.3355.

*4.12.2. Physical data for **21***

^{1}H NMR ($CDCl_3$) δ 0.91 (9H, s, *t*-Bu), 1.05 (9H, s, *t*-Bu), 1.72 (3H, d, *J*=0.8, 5-Me), 3.41 (1H, d, J_{gem}=10.8, $SiOCH_2$), 3.67 (1H, d, J_{gem}=10.8, $SiOCH_2$), 3.75 (1H, d, J_{gem}=10.4, $SiOCH_2$), 4.23 (1H, d, J_{gem}=10.4, $SiOCH_2$), 6.07–6.09 (1H, m, C*H*–N), 6.18–6.19 (1H, m, CH=CH), 6.29–6.31 (1H, m, CH=CH), 6.74 (1H, q, *J*=0.8, H-6), 7.21–7.33 (4H, m, Ph), 7.35–7.52 (12H, m, Ph), 7.65–7.74 (4H, m, Ph), 8.03 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.4, 19.0, 19.3, 26.6, 26.7, 54.2 (t, $J_{C,F}$=19.2), 59.6 (d, $J_{C,F}$=9.6), 61.2, 63.9 (d, $J_{C,F}$=9.6), 110.3, 127.5, 127.7, 127.8, 129.7, 129.8, 130.3 (dd, $J_{C,F}$=249.9 and 240.5), 132.1, 132.5, 132.7, 134.2 (t, $J_{C,F}$=28.8), 135.4, 135.5, 135.6, 135.7, 136.9, 137.7 (t, $J_{C,F}$=9.6), 150.5, 162.9; ^{19}F NMR ($CDCl_3$) δ −90.1 (d, $J_{F,F}$=272.5), −110.2 (d, $J_{F,F}$=272.5); HRFAB-MS *m*/*z* 765.3368 (M^++H), calcd for $C_{44}H_{51}F_2N_2O_4Si_2$ (M^++H) 765.3355.

4.13. The Mitsunobu reaction of 19: formation to 22

Compound **19** (194 mg, 0.48 mmol) was reacted as described above for **9**. After purification by a preparative TLC (CH_2Cl_2/AcOEt=3/1), compound **22** (138 mg, 55%) was obtained as a foam.

*4.13.1. Physical data for **22***

IR (neat) 2250 cm^{-1} (C≡N); ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s, *t*-Bu), 1.94 (3H, d, *J*=1.2, 5-Me), 4.06 (1H, d, J_{gem}=10.0, $SiOCH_2$), 4.13 (1H, d, J_{gem}=10.0, $SiOCH_2$), 6.00–6.02 (1H, m, C*H*–N), 6.32–6.33 (1H, m, CH=CH), 6.39–6.40 (1H, m, CH=CH), 6.90 (1H, q, *J*=1.2, H-6), 7.41–7.46 (6H, m, Ph), 7.65–7.70 (4H, m, Ph), 8.73 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.6, 19.2, 26.5, 55.6 (dd, $J_{C,F}$=26.4 and 18.0), 61.1, 63.2 (d, $J_{C,F}$=8.4), 112.2, 113.7 (d, $J_{C,F}$=4.8), 126.2 (t, $J_{C,F}$=256.7), 127.9, 130.1, 131.7, 131.8, 132.7 (t, $J_{C,F}$=26.4), 135.6, 137.2 (t, $J_{C,F}$=9.6), 150.6, 163.0. ^{19}F NMR ($CDCl_3$) δ −78.7 (d, $J_{F,F}$=261.6), −105.5 (d, $J_{F,F}$=261.6); HRFAB-MS *m*/*z* 522.2049 (M^++H), calcd for $C_{28}H_{30}F_2N_3O_3Si$ (M^++H) 522.2025.

4.14. The Mitsunobu reaction of 14: formation to 23

To a THF (7 mL) solution of Ph_3P (583 mg, 2.22 mmol) was added DIAD (440 μL, 2.22 mmol) at 0 °C. After stirring for 10 min, a THF (15 mL) solution of **14** (330 mg, 0.74 mmol) and N^3-benzoylthymine (511 mg, 2.22 mmol) was added dropwise at −40 °C to the above mixture. The whole mixture was allowed to warm to rt, and stirred for 50 h at rt. The reaction mixture was partitioned between Et_2O and H_2O. After evaporation of the organic layer, the residue was treated with NaOMe (1.0 M solution of MeOH, 7.4 mL) at rt for 2 h. The resulting mixture was partitioned between CH_2Cl_2

and 1 M HCl. Column chromatography (hexane/EtOAc=1/1) of the organic layer gave **23** (239 mg, 58% from **14**) as a solid.

*4.14.1. Physical data for **23***

Mp 207–211 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, *t*-Bu), 1.75 (3H, d, J=0.8, 5-Me), 3.79 (1H, d, J_{gem}=10.0, $SiOCH_2$), 3.80 (3H, s, OMe), 4.30 (1H, d, J_{gem}=10.0, $SiOCH_2$), 5.94–5.99 (2H, m, CH=CH and C*H*–N), 6.45–6.47 (1 h, m, CH=CH), 6.72 (1H, q, J=0.8, H-6), 7.39–7.48 (6H, m, Ph), 7.63–7.67 (4H, m, Ph), 8.05 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.4, 19.3, 26.6, 53.0, 63.5 (d, $J_{C,F}$=12.0), 64.1 (dd, $J_{C,F}$=34.8 and 19.2), 65 8 (dd, $J_{C,F}$=34.8 and 21.5), 111.0, 124.8 (t, $J_{C,F}$=267.5), 127.6 (d, $J_{C,F}$=7.2), 127.9, 130.1, 132.3, 132.7, 135.5, 136.2, 137.2, 150.5, 162.9, 168.0; ^{19}F NMR ($CDCl_3$) δ −102.0 (d, $J_{F,F}$=239.8), −115.7 (d, $J_{F,F}$=239.8); HRFAB-MS m/z 555.2137 (M^++H), calcd for $C_{29}H_{33}F_2N_2O_5Si$ (M^++H) 555.2127.

4.15. (±)-*r*-1-(*tert*-Butyldiphenylsiloxymethyl)-5,5-difluori-*c*-4-hydroxy-cyclopent-2-enecarboxylic acid methyl ester (24)

To a mixture of **14** (780 mg, 1.77 nnol), Ph_3P (698 mg, 2.66 mmol) and 4-nitrobenzoic acid (444 mg, 2.66 mmol) in THF (15 mL) was dropwise added DIAD (524 μL, 2.66 mmol) at 0 °C. After 24 h stirring at ambient temperature of the mixture, this was partitioned between aq $NaHCO_3$ and CH_2Cl_2. Short column chromatography (hexane/AcOEt=7/1) of the organic layer gave the crude benzoate (ca. 978 mg). The benzoate was dissolved in MeOH (40 mL) and treated with NaOMe (478 mg, 8.85 mmol). After 6 h stirring of the resulting mixture, this was partitioned between 0.5 N HCl and CH_2Cl_2. Column chromatography (hexane/AcOEt=1/1) of the organic layer gave **24** (587 mg, 75%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s, *t*-Bu), 2.97 (1H, d, J=10.0, OH), 3.69 (3H, s, OMe), 3.78 (1H, d, J_{gem}=10.0, $SiOCH_2$), 4.09 (1H, d, J_{gem}=10.0, $SiOCH_2$), 4.50–4.54 (1H, m, C*H*OH), 6.15–6.23 (2H, m, CH=CH), 7.38–7.45 (6H, m, Ph), 7.61–7.64 (4H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.7, 52.7, 63.9, 64.7 (t, $J_{C,F}$=24.0), 76.6 (dd, $J_{C,F}$=37.2 and 20.4), 124.2 (dd, $J_{C,F}$=271.1 and 254.3), 128.0, 130.1, 130.2, 131.7, 131.9, 132.9, 134.4 (d, $J_{C,F}$=4.8), 135.5, 135.7, 168.4; ^{19}F NMR ($CDCl_3$) δ −107.2 (d, $J_{F,F}$=239.8), −124.7 (d, $J_{F,F}$=239.8); HRFAB-MS m/z 447.1778 (M^++H), calcd for $C_{24}H_{29}F_2O_4Si$ (M^++H) 447.1803.

4.16. The Mitsunobu reaction of 24: formation to 25

Compound **24** (249 mg, 0.57 mmol) was reacted as described above for **9**. After purification by a preparative TLC (CH_2Cl_2/AcOEt=1/1), compound **25** (180 mg, 57%) was obtained as a foam.

*4.16.1. Physical data for **25***

^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, *t*-Bu), 1.91 (4H, d, J=1.2, Me), 3.76 (3H, s, OMe), 3.99 (1H, d, J_{gem}=10.0, $SiOCH_2$), 4.07 (1H, d, J_{gem}=10.0, $SiOCH_2$), 5.85–5.95 (1H, m, CH=CH), 6.00–6.05 (1H, m, C*H*–N), 6.45–6.47 (1H, m, CH=CH), 6.91 (1H, q, J=1.2, H-6), 7.39–7.49 (6H, m, Ph), 7.60–7.63 (4H, m, Ph), 8.48 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ 12.4, 19.2, 26.6, 52.8, 62.9 (dd, $J_{C,F}$=28.8 and 18.0), 64.5 (dd, $J_{C,F}$=9.6 and 3.6), 65.2 (t, $J_{C,F}$=21.6), 110.9, 125.5 (dd, $J_{C,F}$=273.5 and 259.1), 127.5 (d, $J_{C,F}$=8.4),127.8, 127.9, 130.0, 132.2, 135.5, 135.6, 136.2, 137.2 (d, $J_{C,F}$=3.6), 150.8, 163.6, 168.0 (d, $J_{C,F}$=6.0); ^{19}F NMR ($CDCl_3$) δ −108.7 (d, $J_{F,F}$=239.8), −115.4 (d, $J_{F,F}$=239.8); HRFAB-MS m/z 555.2120 (M^++H), calcd for $C_{29}H_{33}F_2N_2O_5Si$ (M^++H) 555.2127.

4.17. Conversion of 23 to 16

Compound **23** (555 mg, 1.0 mmol) was converted to **16** by the similar procedure described for the conversion of **14** to **9**. After purification of the reaction mixture by column chromatography (hexane/EtOAc=2/3), **16** (415 mg, 80% from **23**) was obtained as a solid.

4.18. (±)-1-(*t*-4-Ethynyl-5,5-difluoro-*c*-4-hydroxymethyl-cyclopent-2-en-*r*-1-yl)-thymine (8)

To a stirred solution of **23** (415 mg, 0.8 mmol) in THF (8 mL) containing AcOH (57 μL, 0.8 mmol) was added Bu_4NF (1.0 M solution in THF, 800 μL, 0.8 mmol) at 0 °C. The resulting mixture was stirred for 17 h at rt, and then evaporated. Column chromatography (CH_2Cl_2/EtOH=20/1) of the residue gave **8** (192 mg, 85%) as a solid, which was recrystallized from acetone/1,2-dichloroethane: mp >224 °C (dec); IR (KBr) 2120 cm^{-1} (C≡C); ^{1}H NMR (CD_3OD) δ 1.83 (3H, d, J=1.2, 5-Me), 2.89 (1H, d, $J_{C,F}$=1.2, C≡C*H*), 3.78 (1H, dd, J_{gem}=11.5, $J_{C,F}$=1.2, C*H*$_2$OH), 3.84 (1H, dd, J_{gem}=11.5, $J_{C,F}$=1.7, C*H*$_2$OH) 5.80–5.83 (1H, m, H-1′), 5.98–6.01 (1H, m, CH=CH), 6.17–6.20 (1H, m, CH=CH), 7.29 (1H, q, J=1.2, H-6); ^{13}C NMR (CD_3OD) δ 12.3, 56.2 (dd, $J_{C,F}$=26.4 and 21.2), 64.4 (d, $J_{C,F}$=8.4), 65.2 (dd, $J_{C,F}$=40.0 and 20.4), 76.6, 78.7 (d, $J_{C,F}$=6.0), 110.6, 126.0 (t, $J_{C,F}$=265.1), 128.2 (d, $J_{C,F}$=7.2), 138.7, 139.9, 153.0, 166.4; ^{19}F NMR (DMSO-d_6) δ −117.4 (d, $J_{F,F}$=239.8), −96.6 (d, $J_{F,F}$=239.8); HRFAB-MS m/z 283.0879 (M^++H), calcd for $C_{13}H_{13}F_2N_2O_3$ (M^++H) 283.0894. Anal. Calcd for $C_{13}H_{12}F_2N_2O_3$: C, 55.32; H, 4.29; N, 9.93. Found: C, 55.18; H, 4.12; N, 9.80.

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