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3′-Fluoro-3′-deoxy-5′-noraristeromycin derivatives: Synthesis and antiviral analysis

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Abstract—The promising antiviral properties of 3′-fluoro-3′-deoxyadenosine and 4′,4′-difluoro-4′-deoxy-5′-noraristeromycin prompted the synthesis of the corresponding 3′-fluoro derivatives of 5′-noraristeromycin. These target compounds, which were prepared from the same readily accessible cyclopentenol, were found to be inactive when subjected to 31 viral assays. The results have some implications on the mechanism of antiviral action of 5′-noraristeromycin and provide guidance for future *geminal*-difluoro analog design.

1. Introduction

The biological properties of aristeromycin (**1**) and its unsaturated partner neplanocin A (**2**) (Fig. 1) have provided the framework for numerous analog studies.[1] Investigations in our own laboratories with 5′-noraristeromycin (**3**) provide representative examples.[2]

The well-established biological relationship for drug design purposes of a fluorine atom and a hydroxyl group[3] and the biological attributes of 3′-fluoro-3′-deoxyadenosine (**4**)[4] prompted us to extend studies with **3** and to seek 3′-fluoro-3′-deoxy-5′-noraristeromycin (**5** and **6**). This, in turn, represents part of a broader program that is exploring uncharted areas of fluorocarbocyclic nucleosides[5] that gave rise to the 4′,4′-difluoro derivative **7**.[6] The antiviral activity of **7** toward cytomegalovirus and orthopoxviruses[6] prompted interest in the 3′,3′-difluoro analog **8**. This derivative together with **5** and **6** provides the basis for this report.

2. Chemistry

Retrosynthetic consideration to **5** and **6** led us to begin with (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**9**),[7] which has been a common starting point for much of our work. Thus, a Pd (0) mediated coupling of **9** and the sodium salt of 6-chloropurine furnished **10**[8] (Scheme 1). Transformation of **10** into diol **12** required initial protection of the secondary hydroxyl of **10** as the *t*-butyldiphenylsilyl ether (**11**).[9] This was followed by dihydroxylation with osmium tetroxide and *N*-methylmorpholine *N*-oxide. Using stannylene methodology,[10] **12** was converted in moderate regioselectivity into the 4-methoxybenzyl ethers **13** and **14**, with the latter product as the major isomer (6:1) after flash chromatography separation.

Regioisomers **13** and **14** were distinguished unequivocally by homo- and hetero-nuclear two-dimensional NMR experiments (2D DQF-COSY and HMQC) on the Dess–Martin periodinane oxidation product of **14** (structure assigned in hindsight). In the ^{1}H–^{1}H DQF-COSY experiment, both H_{α}-5′ (δ 2.84, q, J = 11.68 Hz) and H_{β}-5′ (δ 2.32–2.38, m) coupled to a multiplet at δ 4.35–4.40 ppm and to doublet of doublets at δ 4.20 (J = 8.41, 8.48 Hz), but displayed no coupling to a doublet at δ 4.66 (J = 7.04 Hz), which was assigned either as H-2′ (in **15**) or H-3′ (in **16**) (structure placed in Scheme 1). The structure of **15** was confirmed in an HMQC experiment where the multiplet resonance of H-1′ at δ 4.35–4.40 ppm was cross-linked to C-1′ at δ 55.5 ppm and the doublet of doublets at δ 4.20 ppm for H-4′ was coupled to C-4′ at δ 73.6 ppm. Thus, the product from oxidation of **14** was **15**.

The availability of **14** made possible the synthesis of **5** and **6** (Scheme 2). Thus, treatment of **14** with DAST

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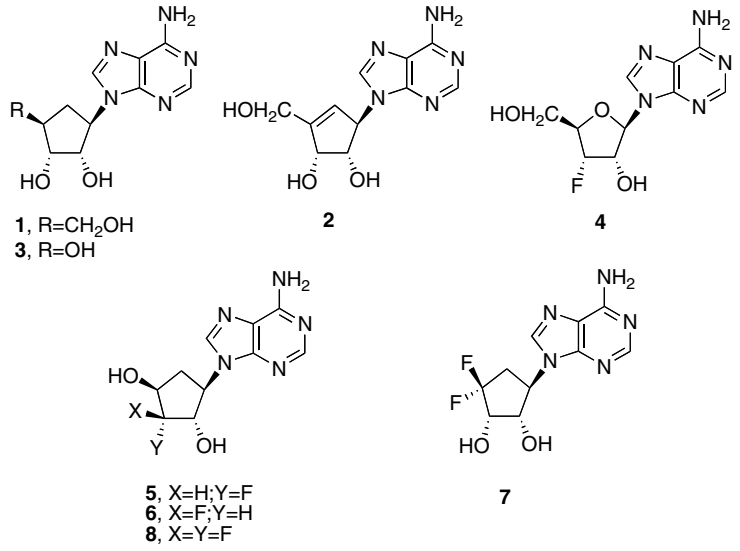
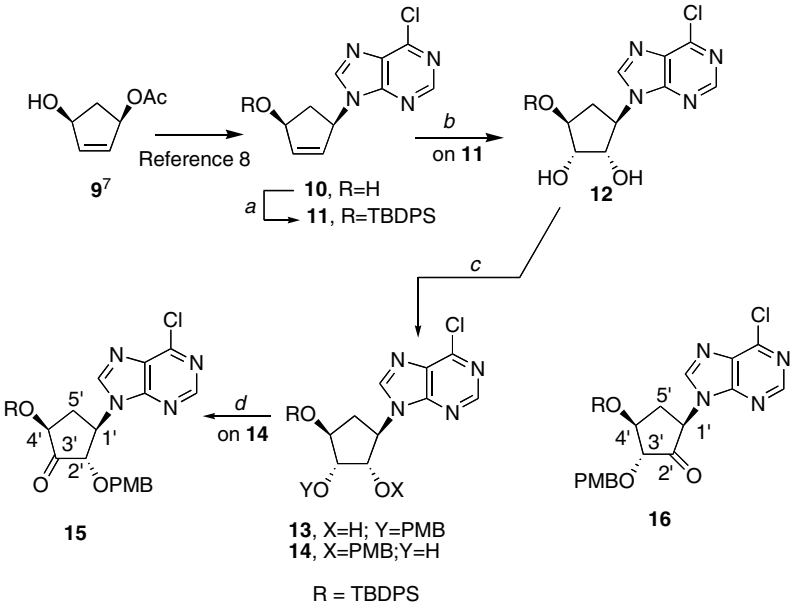


Figure 1.



Scheme 1. Reagents and conditions. (a) TBDPSCI, imidazole, DMF, rt, 90%; (b) OsO_4, NMO, THF/H_2O/acetone (8:1:1), 88%; (c) i—Bu_2SnO, benzene, reflux; ii—Bu_4NBr, PMBCI, 12% (for **13**), 74% (for **14**) for two steps; (d) Dess–Martin periodinane, CH_2Cl_2, 82%.

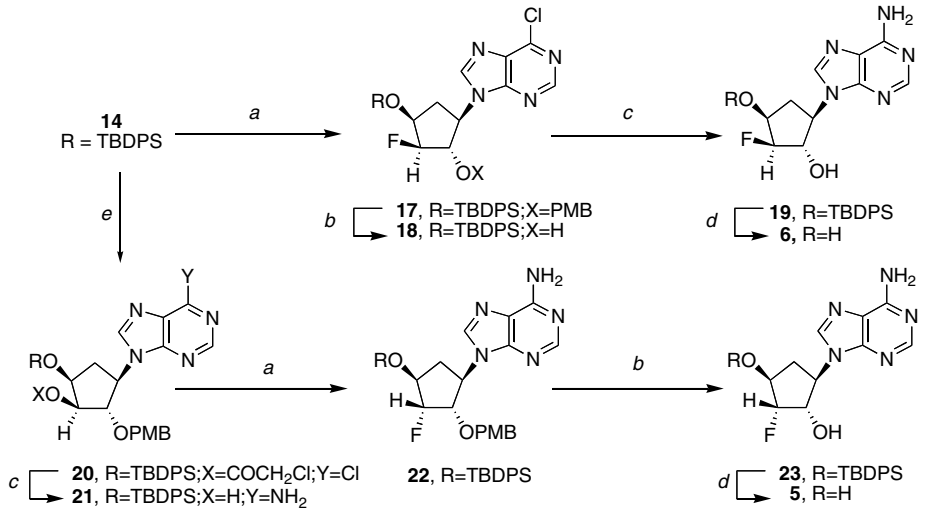
(diethylaminosulfur trifluoride)[11] to **17** (^{19}F NMR: δ −202.44, $J_{F,H}$ = 58 Hz) followed by removal of the 4-methoxybenzyl protecting group with ceric ammonium nitrate (CAN) gave **18**. Ammonolysis of **18** (to **19**) and subsequent fluoride promoted desilylation yielded the desired **6**.

Mitsunobu inversion of the C-4′ hydroxyl of **14** proceeded through **20** that became **21** upon ammonolysis. As before, DAST transformed **21** into **22** whose conversion to **5** followed the same deprotection sequence as used for obtaining **6**.

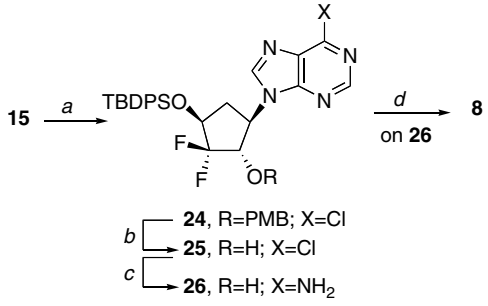
The introduction of the *gem*-difluoro moiety for achieving **8** was accomplished by, first, exposure of **15** to DAST to afford **24** (Scheme 3). The two diastereotopic fluorine atoms of **24** could be easily detected by ^{19}F NMR, which showed two signals at δ −117.93 and −120.48 with a diastereotopic *geminal* coupling constant $J_{F,F}$ = 253 Hz. The reaction of **24** with CAN resulted in the removal of the 4-methoxybenzyl group and subsequent ammonolysis followed by desilylation with ammonium fluoride furnished the target compound **8**.

3. Antiviral analysis

Viruses subjected to **5**, **6**, and **8** were respiratory syncytial virus, herpes simplex virus 1 and 2, herpes simplex 1 TK^-, human cytomegalovirus, varicella zoster virus,



Scheme 2. Reagents and conditions: (a) DAST, CH_2Cl_2, 73% (for **17**), 67% (for **22**); (b) CAN, MeCN/H_2O (9:1), 70% (for **18**), 71% (for **23**); (c) satd NH_3, MeOH 80 °C, 80% (for **19**), 74% (for **21**); (d) NH_4F, MeOH, 80 °C, 76% (for **6**), 78% (for **5**); (e) PPh_3, DIAD, $ClCH_2CO_2H$, THF, 51%.



Scheme 3. Reagents and conditions. (a) DAST, CH_2Cl_2, 76%; (b) i—CAN, MeCN/H_2O (9:1), 76%; (c) satd NH_3, MeOH, 75 °C, 81%; (d) NH_4F, MeOH, reflux, 83%.

Epstein–Barr virus, vaccinia virus, cowpox virus, adenovirus type 1, hepatitis B, Punta Toro virus, SARS, yellow fever, measles, parainfluenza-3, reovirus, Sindbis virus, Coxsackie virus B4, and vesicular stomatitis. In addition, **5** and **6** were evaluated against smallpox, HIV, PIV, and Tacaribe, while the effects of **8** toward influenza A (H1N1 and H3N2), influenza B, Venezuelan equine encephalitis, Dengue virus, hepatitis C, rhinovirus, and West Nile were tested.[12] No activity was found.

4. Conclusion

In conclusion, highly efficient and regioselective synthetic routes to the 3′-fluoro-3′-deoxy-5′-noraristeromycin epimers **5** and **6** and 3′-deoxy-3′,3′-difluoro-5′-noraristeromycin (**8**) have been accomplished but the antiviral properties reported for **4** and **7** did not extend to this new series. The results with **5** may be revealing as they relate to the proposed mechanism of antiviral action of **3** by inhibition of *S*-adenosylhomocysteine hydrolase as a co-factor depletion agent.[1b] This observation will form the basis of additional studies in the 5′-noraristeromycin series.

Furthermore, the lack of activity for **8** will direct our future attention on exploitation of the C-4′ center of **7** before proceeding with other *geminal*-difluoro isomers of **7**.

5. Experimental

5.1. Materials and methods

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer (operated at 400 or 250 MHz, respectively). All ^1H chemical shifts are reported in δ relative to internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-d_6 (center of septet, δ 39.51). ^{19}F chemical shifts are reported in δ relative to internal standard α,α,α-trifluorotoluene (δ −63.732). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad), and dd (doublet of doublet). Elemental analyses were performed by Atlantic Microlabs, Atlanta, Georgia. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineral light UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5–25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

5.2. (1*R*,4*S*)-9-[4-(*t*-Butyldiphenylsilanyloxy)cyclopent-2-enyl]-6-chloro-9*H*-purine (11)

To a stirred solution of **10**[8] (4.00 g, 16.9 mmol) in dry CH_2Cl_2 (100 mL) were added TBDPSCl (6.6 mL,

25.4 mmol) and imidazole (2.88 g, 42.25 mmol). The reaction mixture was stirred overnight at room temperature. Then it was treated with ice-cold H_2O and extracted with CH_2Cl_2 (3× 80 mL), the extracts dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified via column chromatography, eluting with hexanes/EtOAc (1:4) to give 7.23 g (90%) of **11** as a white solid, mp 116.8–117.3 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.10 (s, 9H), 1.97 (dt, 1H, J = 5.00, 14.96 Hz), 2.77–2.90 (m, 1H), 4.93 (t, 1H, J = 4.31 Hz), 5.65 (d, 1H, J = 7.50 Hz), 5.97 (dd, 1H, J = 1.82, 5.41 Hz), 6.16 (dd, 1H, J = 3.30, 5.42 Hz), 7.34–7.47 (m, 6H), 7.64–7.74 (m, 4H), 8.47 (s, 1H), 8.72 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.0, 26.9, 41.8, 57.4, 76.2, 127.8, 129.9, 130.0, 130.7, 131.7, 132.6, 133.4, 135.6, 139.8, 144.4, 150.7, 151.3, 151.7. Anal. Calcd for $C_{26}H_{27}ClN_4OSi$: C, 65.73; H, 5.73; N, 11.79. Found: C, 65.51; H, 5.70; N, 11.88.

5.3. (1*S*,2*S*,3*S*,5*R*)-3-(*t*-Butyldiphenylsilanyloxy)-5-(6-chloropurin-9-yl)-cyclopentane-1,2-diol (12)

To a solution of **11** (2.00 g, 4.21 mmol) in THF/H_2O/acetone (8:1:1, 80 mL) was added a 50% aqueous solution of *N*-methylmorpholine *N*-oxide (1.94 mL, 8.42 mmol) and OsO_4 (50 mg). Following stirring at room temperature for 24 h, rotary evaporation removed the solvent and the residue was co-evaporated with EtOH (3× 50 mL) to give a gummy material. This crude material was purified by flash chromatography (eluent EtOAc/hexanes, 3:2) to afford **12** (1.88 g, 88%) as a white solid, mp 121.2–122.8 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.17 (s, 9H), 2.07–2.14 (m, 1H), 2.69–2.82 (m, 1H), 3.95 (br s, 1H), 4.15 (d, 1H, J = 5.10 Hz), 4.32 (br s, 1H), 4.86–4.96 (m, 2H), 5.00 (d, 1H, J = 4.80 Hz), 7.24–7.41 (m, 6H), 7.65 (t, 4H, J = 7.80 Hz), 8.26 (s, 1H), 8.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.6, 27.5, 37.8, 60.8, 76.5, 77.9, 78.2, 127.5, 128.4, 130.6, 132.0, 133.6, 135.4, 136.2, 145.3, 151.2, 152.1, 152.3. Anal. Calcd for $C_{26}H_{29}ClN_4O_3Si$: C, 61.34; H, 5.74; N, 11.01. Found: C, 61.25; H, 5.72; N, 11.12.

5.4. (1*S*,2*S*,3*S*,5*R*)-3-(*t*-Butyldiphenylsilanyloxy)-5-(6-chloropurin-9-yl)-2-(4-methoxybenzyloxy)cyclopentanol (13) and (1*S*,2*S*,3*R*,5*S*)-5-(*t*-butyldiphenyl-silanyloxy)-3-(6-chloropurin-9-yl)-2-(4-methoxybenzyloxy)cyclopentanol (14)

A solution of **12** (0.60 g, 1.2 mmol) in anhydrous benzene (70 mL) was heated under reflux with dibutyltin oxide (0.30 g, 1.2 mmol) in a Dean–Stark apparatus for 3 h; tetrabutylammonium bromide (0.387 g, 1.2 mmol) and 4-methoxybenzyl chloride (0.33 mL, 2.4 mmol) were added and refluxing continued for 3 h. Water was then added to the reaction mixture followed by extraction with EtOAc (3× 60 mL), drying the combined extracts (Na_2SO_4), and evaporation under vacuum. Chromatography (eluent EtOAc/hexanes, 3:2) of the residue afforded **13** (91.4 mg, 12%) followed by **14** (548.6 mg, 74%) as white solids. For **13**, mp 52.3–53.1 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.13 (s, 9H), 2.01–2.11 (m, 1H), 2.63–2.75 (m, 1H), 3.26 (d, 1H, J = 9.20 Hz), 3.77 (s, 3H), 4.05 (q, 2H, J = 11.4 Hz), 4.35 (s, 2H), 4.71–4.78 (m, 1H), 4.81–4.89 (m, 1H), 6.75 (d, 2H, J = 8.37 Hz), 6.87 (d, 2H, J = 8.35 Hz), 7.38–7.47 (m, 6H), 7.66–7.78 (m, 4H), 8.50 (s, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.2, 27.1, 37.8, 55.4, 60.5, 72.1, 73.4, 77.4, 84.3, 114.0, 128.1, 129.4, 129.7, 130.4, 132.0, 133.0, 135.8, 144.4, 151.0, 151.8, 152.1, 159.5. Anal. Calcd for $C_{34}H_{37}ClN_4O_4Si$: C, 64.90; H, 5.93; N, 8.90. Found: C, 64.79; H, 6.01; N, 8.61.

For **14**, mp 48.6–49.7 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.14 (s, 9H), 2.02–2.12 (m, 1H), 2.65–2.78 (m, 1H), 3.00 (br s, 1H), 3.74 (s, 3H), 4.08 (d, 1H, J = 4.20 Hz), 4.11 (d, 1H, J = 7.81 Hz), 4.31 (d, 1H, J = 5.20 Hz), 4.44 (d, 1H, J = 7.92 Hz), 4.63–4.67 (m, 1H), 4.97 (q, 1H, J = 9.98 Hz), 6.57 (d, 2H, J = 8.42 Hz), 6.85 (d, 2H, J = 8.41 Hz), 7.33–7.46 (m, 6H), 7.63–7.71 (m, 4H), 8.17 (s, 1H), 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.1, 26.9, 37.2, 55.1, 58.2, 72.2, 75.1, 75.6, 82.5, 113.5, 127.8, 128.5, 129.4, 130.0, 131.7, 133.1, 135.6, 144.7, 150.6, 151.4, 151.5, 159.4. Anal. Calcd for $C_{34}H_{37}ClN_4O_4Si$: C, 64.90; H, 5.93; N, 8.90. Found: C, 64.81; H, 5.92; N, 8.52.

5.5. (2*S*,3*R*,5*S*)-5-(*t*-Butyldiphenylsilanyloxy)-3-(6-chloropurin-9-yl)-2-(4-methoxybenzyloxy)cyclopentanone (15)

To a solution of **14** (500 mg, 0.8 mmol) in dry CH_2Cl_2 (80 mL) was added Dess–Martin periodinane reagent (848 mg, 2.0 mmol) in CH_2Cl_2 (40 mL) and the reaction mixture was stirred at room temperature for 24 h. Then it was diluted with Et_2O (100 mL), satd $NaHCO_3$ solution (70 mL) and H_2O (70 mL) added, and this mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted with Et_2O (3× 80 mL). The combined organic fractions were dried (Na_2SO_4), and evaporated under vacuum. The crude material was chromatographed (hexanes/EtOAc, 3:2) to afford 408.7 mg (82%) of **15** as a white solid, mp 59.8–60.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (s, 9H), 2.32–2.38 (m, 1H), 2.84 (q, 1H, J = 11.68 Hz), 3.71 (s, 3H), 4.20 (dd, 1H, J = 8.41, 8.48 Hz), 4.35–4.40 (m, 1H), 4.51 (d, 1H, J = 12.08 Hz), 4.66 (d, 1H, J = 7.04 Hz), 4.70 (d, 1H, J = 11.80 Hz), 6.41 (d, 2H, J = 8.70 Hz), 6.75 (d, 2H, J = 8.60 Hz), 7.35–7.44 (m, 6H), 7.66 (t, 2H, J = 8.08 Hz), 7.80 (t, 2H, J = 8.11 Hz), 7.85 (s, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 26.8, 31.8, 55.5, 55.8, 73.0, 73.6, 76.8, 113.3, 127.8, 128.0, 129.8, 130.3, 132.2, 132.4, 133.2, 135.8, 136.0, 145.0, 151.1, 151.2, 151.3, 159.5, 210.1. Anal. Calcd for $C_{34}H_{35}ClN_4O_4Si$: C, 65.1; H, 5.6; N, 8.9. Found: C, 64.8; H, 5.5; N, 8.7.

5.6. (1*R*,2*S*,3*R*,4*S*)-9-[4-(*t*-Butyldiphenylsilanyloxy)-3-fluoro-2-(4-methoxy-benzyloxy)cyclopentyl]-6-chloro-9*H*-purine (17)

DAST (0.9 mL, 6.66 mmol) was added to a solution of **14** (700 mg, 1.11 mmol) in CH_2Cl_2 (60 mL) at −78 °C. This solution was stirred for 2 h and then at room temperature for 16 h. After that period, the reaction mixture was quenched with a saturated solution of $NaHCO_3$.

The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were washed with H_2O (75 mL), dried (anhydrous Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed (hexanes/EtOAc, 3:2) to produce **17** (513 mg, 73%) as a gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 2.10–2.28 (m, 1H), 2.42–2.51 (m, 1H), 3.81 (s, 3H), 4.13 (d, 1H, J = 12.32 Hz), 4.31 (d, 1H, J = 13.8 Hz), 4.33–4.37 (m, 1H), 4.65 (dt, 1H, J = 5.14, 51.64 Hz), 4.72–4.80 (m, 2H), 6.62 (d, 2H, J = 8.68 Hz), 6.90 (d, 2H, J = 8.68 Hz), 7.38–7.46 (m, 6H), 7.64–7.72 (m, 4H), 8.18 (s, 1H), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 27.1, 36.2 (d, $^3J_{C,F}$ = 2.1 Hz), 55.3, 55.7 (d, $^3J_{C,F}$ = 7.8 Hz), 70.1 (d, $^2J_{C,F}$ = 16.2 Hz), 72.5, 84.2 (d, $^2J_{C,F}$ = 23.7 Hz), 95.3 (d, $^1J_{C,F}$ = 192.1 Hz), 113.7, 128.0, 128.6, 129.4, 129.7, 130.3, 132.8, 133.3, 135.8, 136.1, 144.1, 151.1, 151.6, 152.0, 159.4; ^{19}F NMR ($CDCl_3$, 250 MHz) δ −201.73 (dt, J = 15.0, 55.75 Hz). Anal. Calcd for $C_{34}H_{36}ClFN_4O_3Si$: C, 64.70; H, 5.75; N, 8.88. Found: C, 64.81; H, 5.72; N, 8.74.

5.7. (1*S*,2*R*,3*S*,5*R*)-3-(*t*-Butyldiphenylsilanyloxy)-5-(6-chloropurin-9-yl)-2-fluoro-cyclopentanol (18)

A solution of **17** (500 mg, 0.79 mmol) and ceric ammonium nitrate (1.74 g, 3.16 mmol) in MeCN–H_2O (9:1, 40 mL) was stirred for 20 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (25 mL), and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, concentrated, and subjected to silica gel column chromatography using EtOAc/hexanes (1:1) as eluent to give **18** (284 mg, 70%) as a white solid, mp 151.3–152.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (s, 9H), 2.22–2.30 (m, 1H), 2.51–2.58 (m, 1H), 4.41–4.47 (m, 1H), 4.65 (q, 1H, J = 6.71 Hz), 4.66 (dt, 1H, J = 4.6, 51.42 Hz), 4.76 (t, 1H, J = 5.4 Hz), 4.81 (t, 1H, J = 5.3 Hz), 7.37–7.46 (m, 6H), 7.68–7.73 (m, 4H), 8.22 (s, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 27.0, 35.4 (d, $^3J_{C,F}$ = 2.0 Hz), 58.4 (d, $^3J_{C,F}$ = 8.0 Hz), 70.8 (d, $^2J_{C,F}$ = 16.5 Hz), 79.8 (d, $^2J_{C,F}$ = 24.9 Hz), 95.8 (d, $^1J_{C,F}$ = 191.4 Hz), 128.0, 128.1, 130.2, 131.6, 133.3, 135.7, 136.0, 144.0, 151.2, 151.8, 152.0; ^{19}F NMR ($CDCl_3$, 250 MHz) δ −202.50 (dt, J = 32.75, 57.50 Hz). Anal. Calcd for $C_{26}H_{28}ClFN_4O_2Si$: C, 61.10; H, 5.52; N, 10.96. Found: C, 61.24; H, 5.50; N, 10.83.

5.8. (1*S*,2*R*,3*S*,5*R*)-5-(6-Aminopurin-9-yl)-3-(*t*-butyldiphenylsilanyloxy)-2-fluoro-cyclopentanol (19)

A solution of **18** (300 mg, 0.58 mmol) in dry MeOH (40 mL) was saturated with NH_3. This mixture was heated in a Parr stainless steel sealed reaction vessel at 75 °C for 24 h. After being cooled to room temperature, the reaction mixture was evaporated to dryness and the residue purified by flash chromatography using EtOAc/MeOH (5:1) to afford **19** (231 mg, 80%) as a white solid, mp 173.3–174.2 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.05 (s, 9H), 2.21–2.27 (m, 1H), 2.41–2.50 (m, 1H), 4.00–4.10 (m, 1H), 4.28–4.32 (m, 1H), 4.61 (dt, 1H, J = 5.2, 52.4 Hz), 4.63 (t, 1H, J = 5.13 Hz), 5.80 (br s, 1H), 7.28 (br s, 2H), 7.40–7.48 (m, 6H), 7.61–7.67 (m, 4H), 8.13 (s, 1H), 8.14 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 19.0, 26.7, 35.8 (d, $^3J_{C,F}$ = 2.3 Hz), 56.0 (d, $^3J_{C,F}$ = 10.5 Hz), 69.6 (d, $^2J_{C,F}$ = 15.9 Hz), 77.2 (d, $^2J_{C,F}$ = 23.2 Hz), 95.8 (d, $^1J_{C,F}$ = 190.5 Hz), 119.1, 128.0, 130.5, 132.8, 133.0, 135.2, 135.8, 139.5, 149.6, 152.1, 156.1; ^{19}F NMR (DMSO-d_6, 250 MHz) δ −201.33 (ddd, J = 10.25, 22.0, 55.0 Hz). Anal. Calcd for $C_{26}H_{30}FN_5O_2Si$: C, 63.52; H, 6.15; N, 14.25. Found: C, 63.45; H, 6.14; N, 14.31.

5.9. (1*S*,2*S*,3*S*,4*R*)-4-(6-Aminopurin-9-yl)-2-fluorocyclopentane-1,3-diol (6)

Ammonium fluoride (378 mg, 10.2 mmol) was added to a solution of **19** (250 mg, 0.51 mmol) in MeOH (80 mL) and this refluxed for 24 h under a N_2 atmosphere. The MeOH was evaporated to dryness, and chromatography of the residue using EtOAc/MeOH (4:1) afforded **6** as a white solid (98 mg, 76%), mp 245.6 °C; $[\alpha]_D^{25.8}$ −28.7 (*c*, 0.17 in DMSO); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.02–2.06 (m, 1H), 2.52–2.60 (m, 1H), 4.11–4.16 (m, 1H), 4.58–4.63 (m, 2H), 4.72 (t, 1H, J = 5.28 Hz), 5.64 (d, 1H, J = 5.67 Hz), 5.77 (d, 1H, J = 4.76) 7.31 (br s, 2H), 8.14 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 35.4 (d, $^3J_{C,F}$ = 2.0), 56.4 (d, $^3J_{C,F}$ = 10.8), 67.3 (d, $^2J_{C,F}$ = 16.6), 77.6 (d, $^2J_{C,F}$ = 22.5), 96.7 (d, $^1J_{C,F}$ = 188.2), 119.1, 139.8, 149.3, 152.2, 156.1; ^{19}F NMR (DMSO-d_6, 250 MHz) δ −198.98 (dt, J = 12.5, 66.0). Anal. Calcd for $C_{10}H_{12}FN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.34; H, 4.74; N, 27.44.

5.10. (1*R*,2*S*,3*R*,5*S*)-Chloroacetic acid 5-(*t*-butyldiphenylsilanyloxy)-3-(6-chloro-purin-9-yl)-2-(4-methoxybenzyloxy)cyclopentyl ester (20)

A solution of triphenylphosphine (294 mg, 1.12 mmol) in dry THF (20 mL) was cooled to −20 °C and di*iso*propyl azodicarboxylate (0.22 mL, 1.12 mmol) added over a period of 10 min. This mixture was stirred at −20 °C for 20 min to yield a white precipitate of the triphenylphosphine–di*iso*propyl azodicarboxylate complex. To this latter complex as a suspension were added a solution of **14** (500 mg, 0.8 mmol) in dry THF (10 mL) and chloroacetic acid (106 mg, 1.12 mmol). The cooling bath was removed, and the reaction mixture was refluxed at 80 °C for 18 h. After evaporation of the reaction mixture to dryness, the residue was purified via flash chromatography (hexanes/EtOAc, 4:1) to afford 286 mg of **20** (51%) as a gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12 (s, 9H), 2.04–2.10 (m, 1H), 2.68–2.74 (m, 1H), 3.76 (s, 3H), 4.04 (d, 1H, J = 4.6 Hz), 4.10 (s, 2H), 4.25 (d, 1H, J = 11.87 Hz), 4.30 (d, 1H, J = 4.1 Hz), 4.43 (d, 1H, J = 11.86 Hz), 4.60–4.63 (m, 1H), 4.95–5.00 (m, 1H), 6.58 (d, 2H, J = 8.66 Hz), 6.86 (d, 2H, J = 8.46 Hz), 7.37–7.45 (m, 6H), 7.63–7.70 (m, 4H), 8.17 (s, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 27.0, 37.4, 40.0, 55.2, 58.3, 72.4, 75.3, 75.6, 82.8, 113.6, 128.0, 128.6, 129.6, 130.2, 133.2, 135.7, 135.8, 144.7, 150.8, 151.6, 151.7, 159.6, 167.1. Anal. Calcd for $C_{36}H_{38}Cl_2N_4O_5Si$: C, 61.27; H, 5.43; N, 7.94. Found: C, 61.15; H, 5.41; N, 8.08.

5.11. (1*R*,2*S*,3*R*,5*S*)-3-(6-Aminopurin-9-yl)-5-(*t*-butyldiphenylsilanyloxy)-2-(4-methoxybenzyloxy)cyclopentanol (21)

As for the preparation of **19**, ammonolysis of **20** (350 mg, 0.5 mmol) provided **21** (224 mg, 74%) as a white solid, mp 182.5–183.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12 (s, 9H), 2.00–2.10 (m, 1H), 2.68–2.75 (m, 1H), 3.71 (s, 3H), 4.08–4.13 (m, 2H), 4.31 (d, 1H, J = 11.67 Hz), 4.32–4.36 (m, 1H), 4.42 (d, 1H, J = 11.44 Hz), 4.60–4.64 (m, 1H), 5.01–5.05 (m, 1H), 6.65 (d, 2H, J = 8.16 Hz), 6.85 (br s, 2H), 6.91 (d, 2H, J = 8.20 Hz), 7.34–7.43 (m, 6H), 7.63–7.70 (m, 4H), 7.85 (s, 1H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 26.9, 37.7, 55.1, 60.4, 72.0, 75.4, 76.0, 83.2, 113.6, 119.4, 127.8, 128.8, 130.0, 133.2, 135.6, 135.7, 139.4, 149.8, 152.5, 155.8, 159.4. Anal. Calcd. for $C_{34}H_{39}N_5O_4Si$: C, 66.97; H, 6.45; N, 11.48. Found: C, 67.15; H, 6.46; N, 11.35.

5.12. (1*R*,2*S*,3*S*,4*S*)-9-[4-(*t*-Butyldiphenylsilanyloxy)-3-fluoro-2-(4-methoxy-benzyloxy)cyclopentyl]-9*H*-purine-6-ylamine (22)

Following the same procedure used in the preparation of **17**, **21** (400 mg, 0.66 mmol) and DAST (0.6 mL, 4.44 mmol) led to **22** (270 mg, 67%) as a gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (s, 9H), 2.19–2.22 (m, 1H), 2.46–2.51 (m, 1H), 3.72 (s, 3H), 4.01 (q, 1H, J = 5.61 Hz), 4.11–4.18 (m, 1H), 4.36 (s 2H), 4.63 (dt, 1H, J = 7.7, 56.12 Hz), 4.78–4.82 (m, 1H), 6.43 (br s, 2H), 6.68 (d, 2H, J = 8.50 Hz), 6.85 (d, 2H, J = 8.46 Hz), 7.37–7.46 (m, 6H), 7.62–7.72 (m, 4H), 7.91 (s, 1H), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 27.0, 36.6, 54.9 (d, $^3J_{C,F}$ = 6.8 Hz), 55.3, 71.4 (d, $^2J_{C,F}$ = 16.4 Hz), 72.0, 84.8 (d, $^2J_{C,F}$ = 23.4 Hz), 95.5 (d, $^1J_{C,F}$ = 190.1 Hz), 113.8, 119.4, 128.0, 128.8, 129.4, 130.2, 133.0, 133.3, 135.7, 136.0, 139.0, 150.0, 153.0, 155.8, 159.5; ^{19}F NMR ($CDCl_3$, 250 MHz) δ −201.82 (dt, J = 17.25, 54.50 Hz). Anal. Calcd for $C_{34}H_{38}FN_5O_3Si$: C, 66.75; H, 6.26; N, 11.45. Found: C, 66.81; H, 6.23; N, 11.33.

5.13. (1*S*,2*S*,3*S*,5*R*)-5-(6-Aminopurin-9-yl)-3-[4-(*t*-butyldiphenylsilanyloxy)-2-fluorocyclopentanol (23)

Employing the same procedure used to produce **18**, compound **23** was obtained in 71% yield (172 mg) as a white solid from 300 mg (0.49 mmol) of **22**, mp 190.5–191.8 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.14 (s, 9H), 2.20–2.28 (m, 1H), 2.41–2.51 (m, 1H), 4.01–4.08 (m, 1H), 4.27–4.32 (m, 1H), 4.63 (dt, 1H, J = 4.8, 51.80 Hz), 4.62 (t, 1H, J = 5.8 Hz), 5.90 (br s, 1H), 7.32 (br s, 2H), 7.50–7.58 (m, 6H), 7.71–7.75 (m, 4H), 8.22 (s, 1H), 8.23 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 19.0, 26.8, 36.0 (d, $^3J_{C,F}$ = 2.5 Hz),, 56.1 (d, $^3J_{C,F}$ = 8.8 Hz), 69.8 (d, $^2J_{C,F}$ = 16.1 Hz), 77.3 (d, $^2J_{C,F}$ = 20.4 Hz), 96.0 (d, $^1J_{C,F}$ = 192.2 Hz), 119.3, 128.2, 129.1, 130.5, 133.4, 135.4, 135.7, 139.6, 149.6, 152.2, 156.2; ^{19}F NMR (DMSO-d_6, 250 MHz) δ −202.4 (dt, J = 16.5, 54.7 Hz). Anal. Calcd for $C_{26}H_{30}FN_5O_2Si$: C, 63.52; H, 6.15; N, 14.25. Found: C, 63.78; H, 6.18; N, 14.13.

5.14. (1*S*,2*R*,3*S*,4*R*)-4-(6-Aminopurin-9-yl)-2-fluorocyclopentane-1,3-diol (5)

Following the same procedure used in the preparation of **6**, **23** (280 mg, 0.57 mmol) led to **5** (113 mg, 78%) as a white solid, mp 251.2 °C; $[\alpha]_D^{25.8}$ −19.4 (c, 0.13 in DMSO); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.01–2.07 (m, 1H), 2.50–2.58 (m, 1H), 4.13–4.16 (m, 1H), 4.56–4.62 (m, 2H), 4.71 (t, 1H, J = 5.20), 5.72 (d, 1H, J = 5.70), 5.85 (d, 1H, J = 4.90) 7.40 (br s, 2H), 8.22 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 35.4 (d, $^3J_{C,F}$ = 2.5), 56.5 (d, $^3J_{C,F}$ = 11.0), 67.4 (d, $^2J_{C,F}$ = 15.6), 77.7 (d, $^2J_{C,F}$ = 22.7), 97.6 (d, $^1J_{C,F}$ = 188.5), 119.2, 140.0, 149.4, 152.3, 156.3; ^{19}F NMR (DMSO-d_6, 250 MHz) δ −201.8 (dt, J = 16.0, 71.4). Anal. Calcd for $C_{10}H_{12}FN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.31; H, 4.76; N, 27.78.

5.15. (1*R*,2*S*,4*S*)-9-[4-(*t*-Butyldiphenylsilanyloxy)-3,3-difluoro-2-(4-methoxy-benzyloxy)cyclopentyl]-6-chloro-9*H*-purine (24)

DAST (0.64 mL, 4.8 mmol) was added to a solution of **15** (500 mg, 0.8 mmol) in CH_2Cl_2 (70 mL) at room temperature and the mixture was refluxed for 24 h. The reaction mixture was cooled to room temperature and quenched with a saturated solution of $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3× 60 mL). The combined organic layers were washed with H_2O (75 mL), dried (anhydrous Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed (hexanes/EtOAc, 3:2) to produce **24** (394 mg, 76%) as a gum; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.15 (s, 9H), 2.38 (t, 2H, J = 6.47 Hz), 3.73 (s, 3H), 4.16–4.20 (m, 1H), 4.34 (d, 1H, J = 11.96 Hz), 4.50 (q, 1H, J = 8.96 Hz), 4.62 (d, 1H, J = 10.88 Hz), 4.70–4.84 (m, 1H), 6.50 (d, 2H, J = 8.36 Hz), 6.81 (d, 2H, J = 8.45 Hz), 7.26–7.43 (m, 6H), 7.65–7.72 (m, 4H), 7.93 (s, 1H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.4, 26.8, 33.8, 55.2 (d, $^3J_{C,F}$ = 9.2 Hz), 55.3, 71.7 (dd, $^2J_{C,F}$ = 19.4, 32.4 Hz), 72.7, 76.7 (dd, $^2J_{C,F}$ = 19.3, 27.2 Hz), 113.4, 124.1 (dd, $^1J_{C,F}$ = 251.0, 256.4 Hz), 127.8, 128.0, 128.6, 129.8, 130.2, 132.1, 133.0, 135.7, 136.0, 144.8, 150.9, 151.2, 151.4, 159.5; ^{19}F NMR ($CDCl_3$, 250 MHz) δ-122.36 (dt, J = 13.55, 251.75 Hz), −119.30 (dd, J = 7.00, 250.55 Hz). Anal. Calcd for $C_{34}H_{35}ClF_2N_4O_3Si$: C, 62.90; H, 5.43; N, 8.63. Found: C, 63.00; H, 5.41; N, 8.58.

5.16. (1*S*,3*S*,5*R*)-3-(*t*-Butyldiphenylsilanyloxy)-5-(6-chloropurin-9-yl)-2,2-difluoro- cyclopentanol (25)

A solution of **24** (390 mg, 0.6 mmol) and CAN (1.32 g, 2.4 mmol) in MeCN/H_2O (9:1, 40 mL) was stirred for 20 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (25 mL), and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, concentrated, and subjected to silica gel column chromatography using EtOAc/hexanes (1:1) as eluent to give **25** (228.8 mg, 72%) as a white solid, mp 170.3–171.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (s, 9H), 2.31–2.39 (m,

1H), 2.44–2.51 (m, 1H), 4.23–4.30 (m, 1H), 4.56–4.63 (m, 1H), 4.95–5.07 (m, 1H), 5.40 (br s, 1H), 7.35–7.44 (m, 6H), 7.70 (t, 4H, $J = 6.20$ Hz), 8.12 (s, 1H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 26.8, 34.0, 57.1 (d, $^3J_{C,F} = 9.9$ Hz), 71.4 (dd, $^2J_{C,F} = 19.5$, 32.4 Hz), 74.7 (dd, $^2J_{C,F} = 20.1$, 26.5 Hz), 122.5 (dd, $^1J_{C,F} = 250.2$, 262.4 Hz), 128.0, 130.2, 131.6, 132.1, 133.0, 135.8, 136.0, 145.0, 151.0, 151.5, 152.0; ^{19}F NMR ($CDCl_3$, 250 MHz) δ −121.78 (dt, $J = 13.45$, 250.75 Hz), −117.80 (dd, $J = 8.00$, 249.85 Hz). Anal. Calcd for $C_{26}H_{27}ClF_2N_4O_2Si$: C, 59.03; H, 5.14; N, 10.59. Found: C, 58.86; H, 5.18; N, 10.61.

5.17. (1*S*,3*S*,5*R*)-5-(6-Aminopurin-9-yl)-3-(*tert*-butyldiphenylsilanyloxy)-2,2-difluorocyclopentanol (26)

A solution of **25** (200 mg, 0.38 mmol) in dry MeOH (40 mL) was saturated with NH_3. This mixture was heated in a Parr stainless steel sealed reaction vessel at 75 °C for 24 h. After being cooled to room temperature, the reaction mixture was evaporated to dryness and the residue purified by flash chromatography using EtOAc/MeOH (5:1) to afford **26** (156 mg, 81%) as a white solid, mp 185.3–185.8 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.07 (s, 9H), 2.38 (t, 2H, $J = 8.22$ Hz), 4.10–4.20 (m, 1H), 4.46 (d, 1H, $J = 9.33$ Hz), 4.83–4.93 (m, 1H), 6.12 (d, 1H, $J = 6.66$ Hz), 7.26 (br s, 2H), 7.40–7.52 (m, 6H), 7.63 (t, 4H, $J = 6.50$ Hz), 8.13 (s, 1H), 8.14 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.9, 26.5, 33.5, 54.5 (d, $^3J_{C,F} = 8.7$ Hz), 71.2 (dd, $^2J_{C,F} = 18.2$, 31.5 Hz), 73.1 (dd, $^2J_{C,F} = 19.8$, 27.2 Hz), 119.4, 123.0 (dd, $^1J_{C,F} = 251.1$, 257.5 Hz), 128.0, 130.1, 130.2, 132.6, 135.2, 135.3, 140.5, 149.4, 152.2, 156.1; ^{19}F NMR (DMSO-d_6, 250 MHz) δ −120.18 (dt, $J = 14.74$, 251.67 Hz), −118.71 (dd, $J = 7.80$, 250.73 Hz). Anal. Calcd for $C_{26}H_{29}F_2N_5O_2Si$: C, 61.28; H, 5.74; N, 13.74. Found: C, 61.10; H, 5.71; N, 13.55.

5.18. (1*S*,3*S*,5*R*)-4-(6-Aminopurin-9-yl)-2,2-difluorocyclopentane-1,3-diol (8)

Ammonium fluoride (300 mg, 8.1 mmol) was added to a solution of **26** (0.20 g, 0.4 mmol) in MeOH (80 mL) and this mixture refluxed for 24 h under a N_2 atmosphere. The MeOH was evaporated to dryness and the residue subjected to chromatography (EtOAc/MeOH, 4:1) to afford **8** as a white solid (88.4 mg, 83%), mp 267 °C; $[\alpha]_D^{24.3}$ −45.7 (*c*, 0.18 in DMSO); ^1H NMR (DMSO-d_6, 400 MHz) δ 2.15–2.22 (m, 1H), 2.54–2.62 (m, 1H), 4.02–4.11 (m, 1H), 4.55 (q, 1H, $J = 8.98$ Hz), 4.67–4.77 (m, 1H), 6.07 (d, 2H, $J = 5.46$ Hz), 7.29 (br s, 2H), 8.14 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.1 (d, $^3J_{C,F} = 4.1$ Hz), 54.9 (d, $^3J_{C,F} = 11.6$ Hz), 69.1 (dd, $^2J_{C,F} = 19.9$, 30.5 Hz), 73.5 (dd, $^2J_{C,F} = 19.7$, 26.9 Hz), 119.4, 123.2 (dd, $^1J_{C,F} = 250.8$, 258.7 Hz), 140.3, 149.3, 152.2, 156.1; ^{19}F NMR (DMSO-d_6, 250 MHz) δ-120.48 (dt, $J = 14.75$, 253.75 Hz), −118.00 (dd, $J = 7.00$, 251.25 Hz). Anal. Calcd for $C_{10}H_{11}F_2N_5O_2 \cdot 0.2M\ H_2O$: C, 43.56; H, 4.20; N, 25.40. Found: C, 43.78; H, 4.21; N, 25.13.

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