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Synthesis of the 5′-Fluoro-2′β-methyl Analogues of Neplanocin

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Synthesis of the 5′-fluoro-2′-β-methyl analogues of neplanocin was carried out. Key intermediate cyclopentenone **19** was prepared from methyl α-D-mannopyranoside by a new approach consisting of ring-closing metathesis, stereoselective introduction of the 2′-methyl group, and intramolecular oxyselenenylation of the double bond as representative steps. Subsequent introduction of a fluorine atom at the 5′-position of **19** was performed by electrophilic fluorination by using Selectfluor.

Introduction

2′-Methyl ribonucleosides **1** and **2** (Figure 1) have been reported to show significant inhibitory activity against proliferation of the hepatitis C virus (HCV).[1] The 3′-valine ester of 2′-methylcytidine (**2**, valopicitabine)[2] is currently in phase II clinical trials. Further chemical modifications of these compounds have also been executed to develop new anti-HCV drugs.[3]

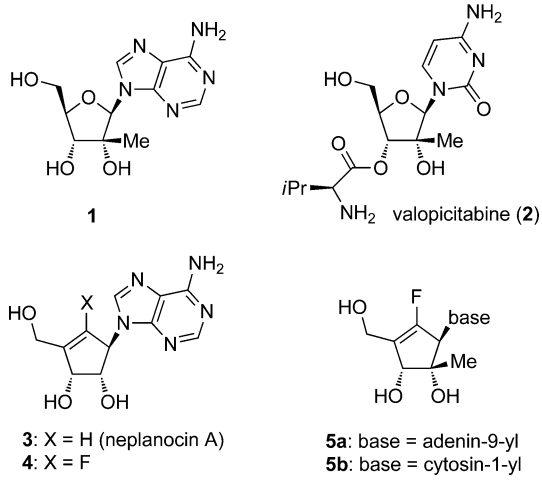

Figure 1. Compounds **1**–**5**.

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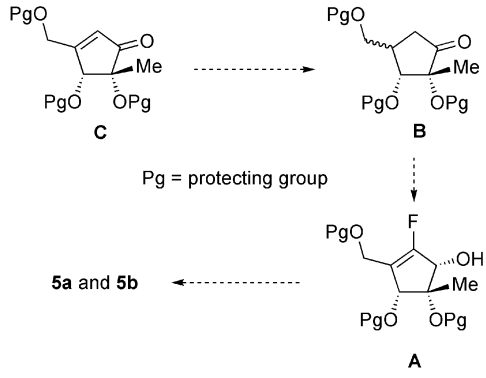
Carbocyclic nucleoside antibiotic neplanocin A (**3**) is known to be a potent inhibitor against (*S*)-adenosyl-L-homocysteine hydrolase (SAHase),[4a] which in turn leads to inhibition of the multiplication of a wide variety of RNA viruses.[4] Jeong et al. recently reported that compound **4**, which is the 5′-fluorinated analogue of **3**, shows a higher inhibitory activity against SAHase than mother compound **3**.[5] In the present study, we designed and synthesized **5**, which is a hybrid of **1** (or **2**) and **4**.

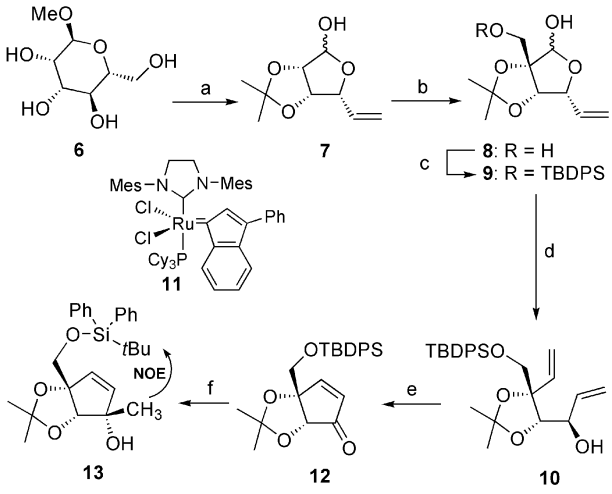
Results and Discussion

Our synthetic plan is depicted in Scheme 1. Title compounds **5a** and **5b** can be synthesized through an S_N2 reaction between the respective nucleobase and fluorinated allyl alcohol **A**, which can be prepared by electrophilic fluorination of ketone **B**. Compound **B** is the hydrogenation product of cyclopentenone **C**. Although there have been precedents[3b,3e] for the preparation of **C** via 2-β-*C*-methyl-ribonolactone, either from diacetone-D-glucose or from D-



Scheme 1. Synthetic plan for **5a** and **5b**.

fructose, we examined an original approach starting from commercially available methyl α-D-mannopyranoside (**6**; Scheme 2).

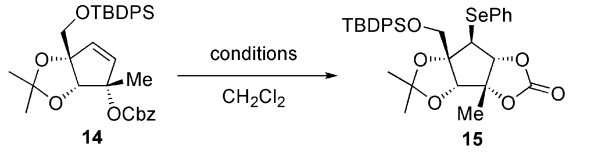


Scheme 2. Reagents and conditions: (a) see ref.[6]; (b) aq. HCHO, K_2CO_3, MeOH (80%); (c) TBDPSCl, DMAP, Et_3N, CH_2Cl_2 (96%); (d) CH_3Ph_3PBr, BuLi, THF (92%); (e) 1. Umicore M2 (**11**, 0.73 mol-%), CH_2Cl_2; 2. PDC, 4 Å MS (93% from **10**); (f) MeLi, THF, –78 °C (93%).

Compound **6** was converted into hemiacetal **7** in 86% yield by our reported method.[6] Aldol reaction between **7** and aqueous HCHO in the presence of K_2CO_3 gave **8**, the preparation of which was recently reported by Jeong et al. by using an epimer of **7**.[7] Regioselective silylation of **8** gave **9** in 96% yield. Wittig reaction of **9** led to the formation of diene **10** (92%).[7b–7d] Ring-closing metathesis of **10**[7b–7d] by using a catalytic amount of Umicore M2[8] (**11**, 0.73 mol-%) furnished the corresponding cyclopentenol, which was then oxidized with pyridinium dichromate (PDC) to give cyclopentenone **12** in almost quantitative yield. It is worth noting from a practical viewpoint that every step in the reaction sequence from **6** to **12** can be carried out on a multi-10 gram scale without decreasing the yield. Stereoselective 1,2-addition of MeLi to **12** gave allyl alcohol **13** in 93% yield, the stereochemistry of which was confirmed by an NOE experiment (1.9%, between Me and OSi*t*Bu).

To transform **13** into requisite cyclopentenone **C** (Scheme 1), introduction of an appropriate oxygen functionality at the vinylic carbon is necessary. However, several approaches (hydroboration, oxymercuration, *m*-CPBA epoxidation, and dihydroxylation) all met with failure, presumably due to the fact that the double bond of **13** is highly congested by the presence of the two tertiary carbinol carbon atoms. An intramolecular approach may be a promising to overcome this problem. We turned our attention to an intramolecular oxyselenenylation reported by Kim et al.[9] Benzyl carbonate **14** to be used for this reaction was prepared from **12** in 74% yield by treatment with MeLi followed by CbzCl. Results of the selenocyclization by utilizing **14** are summarized in Table 1.

Table 1. Intramolecular selenocyclization reaction of **14**.



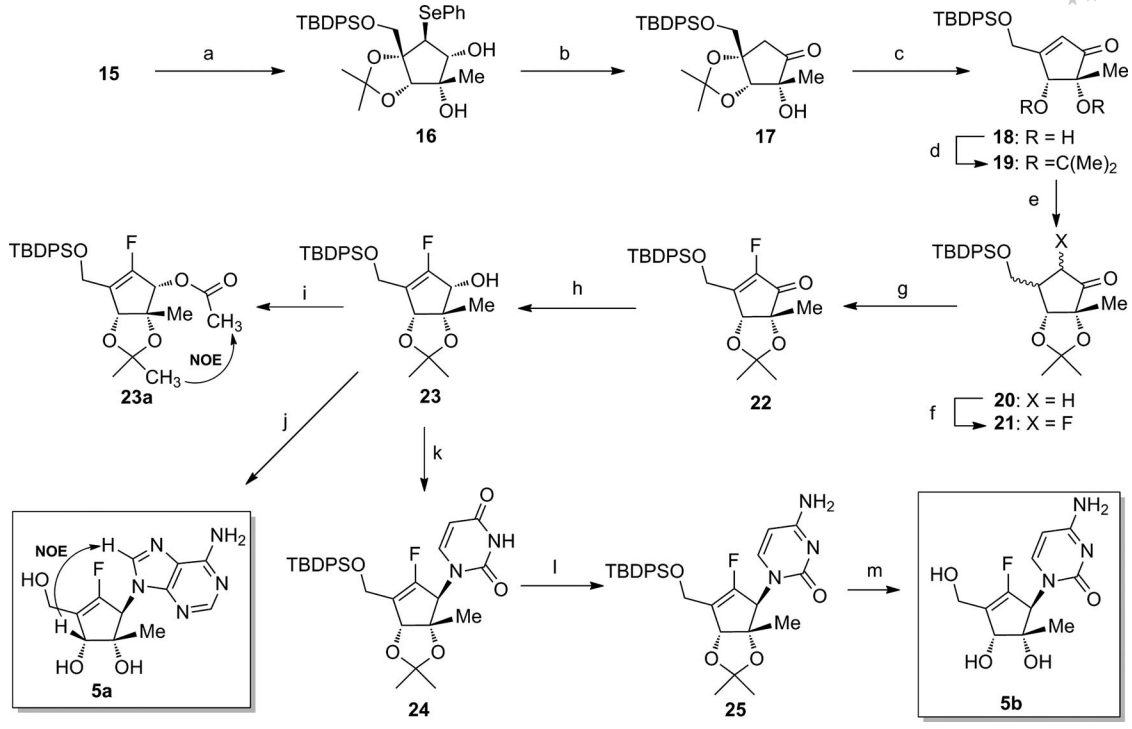
Entry	Conditions	*T* [°C]	Time [h]	Yield [%]
1	PhSeCl, AgOTf	–78 to r.t.	12	30
2	PhSeCl, AgOTf, $(PhSe)_2$	–78 to r.t.	12	48
3	PhSeCl, AgOTf, $(PhSe)_2$	–78 to –30	48	58[a]
4	$(PhSe)_2$, Br_2, AgOTf	–78 to –30	16	89

[a] Compound **14** was recovered in 29% yield.

Compound **14** was treated with PhSeCl and AgOTf in CH_2Cl_2 for 12 h (Table 1, Entry 1). Although disappearance of starting material **14** was confirmed by TLC, requisite tricyclic product **15** was obtained only in 30% yield. Addition of 1.5 equiv. of $(PhSe)_2$ gave a slight increase in the yield of **15** (Table 1, Entry 2). Further improvement was observed when the reaction temperature was kept at –30 °C to give **15** in 58% yield along with the recovery of a considerable amount of unreacted **14** (29%; Table 1, Entry 3). As shown in Entry 4, the best yield of **15** (89%) was obtained when PhSeBr, prepared in situ from Br_2 (1 equiv.) and an excess amount of $(PhSe)_2$ (2 equiv.), was employed instead of PhSeCl.

Although the actual role of $(PhSe)_2$ is not known, one possibility could be that it acts as a scavenger for the electrophilic benzyl halide or benzyl triflate that is generated during the reaction. In fact, when isolated **15** was treated with benzyl triflate in CH_2Cl_2 at room temperature, disappearance of **15** was observed by TLC within 1 h and several polar unknown products were obtained.

Preparation of cyclopentenone **19** that corresponds to **C** in Scheme 1 was carried out next (Scheme 3). Compound **15** was treated with K_2CO_3 in MeOH to give diol **16**. Conversion of **16** into ketone **17** was conducted by *m*-CPBA oxidation of the phenylseleno group followed by *syn* elimination of the resulting selenoxide. Treatment of **17** with NaOMe gave vicinal diol **18** as a result of the elimination of acetone. Compound **18** was converted into acetonide **19** (75%) in a conventional manner. ^1H and ^{13}C NMR spectroscopic data of **19** thus obtained are in full agreement with those reported.[3e] Transformation of **19** into fluorocyclopentenol **23** was carried out as follows: Compound **19** was hydrogenated in AcOEt in the presence of 10% Pd/C to give **20** as a single isomer (stereochemistry of **20** was not determined.). Prior to carrying out electrophilic fluorination at the α-position, **20** was first treated with lithium hexamethyldisilazane (LHMDS) in the presence of TMSCl in THF. Reaction of the resulting silyl enol ether with Selectfluor in MeCN was followed by simple extractive workup to give crude **21**.[10] Regeneration of the double bond was performed by LHMDS-mediated phenylselenation of **21** and subsequent *m*-CPBA oxidation, which ef-



Scheme 3. Reagents and conditions: (a) K_2CO_3, MeOH (quant.); (b) *m*-CPBA, 1,2-dichloroethane, reflux; (c) NaOMe, MeOH, –30 °C; (d) TsOH, $Me_2C(OMe)_2$, acetone (75% from **16**); (e) H_2, 10% Pd/C, AcOEt (quant.); (f) 1) TMSCl, LHMDS, THF, –78 °C; 2) Selectfluor, MeCN; (g) 1) TMSCl, LHMDS, PhSeCl, THF; 2) *m*-CPBA, $NaHCO_3$, CH_2Cl_2 (48% from **20**); (h) DIBALH, CH_2Cl_2, –78 °C (80%); (i) Ac_2O, pyridine (87%); (j) 1) bis(Boc)adenine, DIAD, Ph_3P, THF; 2) 2 M HCl (54% from **23**); (k) 1) N^3-benzoyluracil, DIAD, Ph_3P, THF; 2) NaOMe, MeOH (50% from **23**); (l) 1) TPSCl, DMAP, MeCN; 2) NH_4OH (48% from **24**); (m) 3 M HCl, MeOH (71%).

fected spontaneous selenoxide *syn* elimination to give fluorocyclopentenone **22** in 48% overall yield from **20**. According to the report by Moon et al.,[3e] diisobutylaluminum hydride (DIBALH) was employed for the stereoselective 1,2-reduction of **22** to give allyl alcohol **23** in 80% yield. The stereochemistry of **23** was confirmed by an NOE experiment of its acetate **23a** [1.9%, between Me (acetyl) and Me (acetonide)]. Finally, introduction of the nucleobase was carried out. Allyl alcohol **23** was exposed to conventional Mitsunobu conditions[11] [bis(Boc)adenine,[12] DIAD and Ph_3P in THF]. Title compound **5a** was obtained after removal of all the protecting groups. The regiochemistry of **5a** was confirmed by HMBC spectra, namely, correlations between 1′-H and C-8 and between 1′-H and C-4 of the adenine ring were observed. An NOE experiment indicated the stereochemistry of **5a** as depicted in Scheme 3 (8-H/3′-H, 1.0%). Cytosine analogue **5b** was also synthesized by a series of reactions: introduction of N^3-benzoyluracil followed by debenzoylation to give **24** (50%);[13] transformation of **24** into cytosine in a conventional manner [2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl), DMAP, and Et_3N then NH_4OH] to give **25** (48%); deprotection under the acidic conditions to form desired **5b** (71%).

Conclusions

The synthesis of 5′-fluoro-2′-β-methyl neplanocin analogues was carried out. Cyclopentenone **12**, a synthetic precursor to key intermediate **19**, was prepared in good overall yield (ca. 57%). Conversion into **19** was achieved by employing an intramolecular selenocyclization reaction. Electrophilic fluorination by using Selectfluor moderately proceeded to introduce a fluorine atom at the 5′-position. Although the anti-HIV, anti-HCV, and antitumor activities of products **5a** and **5b** were evaluated, no significant activity was observed.

Experimental Section

General Methods: NMR spectra were recorded with a Jeol JNM AL-400 or a Jeol JMN ECA-500 instrument spectrometer (^{1}H: 400 or 500 MHz, ^{13}C: 100 or 125 MHz, and ^{19}F: 470 MHz). Chemical sifts are reported relative to Me_4Si, except for fluorine-containing compounds where $CFCl_3$ was used as an internal standard. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix. Column chromatography was carried out on silica gel. Thin-layer chromatography (TLC) was performed on precoated silica gel plate F_{254}. When necessary, analytical samples were purified by high-performance liquid chromatography (HPLC). THF was distilled from benzophenone ketyl.

5,6-Dideoxy-2-hydroxymethyl-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranose (8): To a MeOH (150 mL) solution of **7** (20.7 g, 111 mmol) was added K_2CO_3 (7.68 g, 55.6 mmol) and 37% aq. HCHO (55 mL). The resulting mixture was heated at 70 °C for 12 h. After evaporation, the whole reaction mixture was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH, 15:1). Appropriate fractions were evaporated and dissolved in NH_3/

MeOH (ca. 150 mL) and kept at 4 °C for 12 h. After evaporation, crude **8** (19.2 g, 80%, anomeric mixture ca. 2:1) was obtained as an oil. This was used for the next step without further purification. ^{1}H NMR ($CDCl_3$ + D_2O): δ = 1.41 (s, 3 H, Me), 1.46 (s, 1.5 H, Me), 1.48 (s, 3 H, Me), 3.76 (d, J = 11.6 Hz, 0.5 H, CH_2OH), 3.80 (d, J = 11.6 Hz, 0.5 H, CH_2OH), 3.85 (d, J = 12.0 Hz, 1 H, CH_2OH), 3.97 (d, J = 12.0 Hz, 1 H, CH_2OH), 4.06 (dd, J = 7.2, 3.2 Hz, 0.5 H, 4-H), 4.55 (d, J = 3.2 Hz, 0.5 H, 3-H), 4.58 (d, J = 3.2 Hz, 1 H, 3-H), 4.63 (dd, J = 7.2, 3.2 Hz, 1 H, 4-H), 5.31–5.45 (m, 4.5 H, CH=CH_2 and 1-H), 5.92–6.04 (m, 1.5 H, CH=CH_2) ppm.

2-(*tert*-Butyldiphenylsiloxymethyl)-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranose (9): To a stirred mixture of **8** (19.1 g, 88.3 mmol), Et_3N (36.9 mL, 264.9 mmol), and DMAP (3.25 g, 26.5 mmol) in CH_2Cl_2 (200 mL) was added TBDPSCl (24.1 mL, 92.7 mmol) over 3 h at 0 °C. The resulting mixture was stirred for another 16 h at room temperature and partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Column chromatography (hexane/AcOEt, 3:1) of the organic layer gave **9** (38.7 g, 96%, anomeric mixture ca. 4:1) as an oil. $[\alpha]_D^{26}$ = –34.6 (c = 2.69, $CHCl_3$). ^{1}H NMR ($CDCl_3$ + D_2O): δ = 1.06 (s, 7.2 H, *t*Bu), 1.07 (s, 1.8 H, *t*Bu), 1.17 (s, 1.8 H, Me), 1.29 (s, 2.4 H, Me), 1.44 (s, 0.6 H, Me), 1.50 (s, 2.4 H, Me), 3.73–3.89 (m, 2.0 H, CH_2OSi), 4.06–4.09 (m, 0.8 H, 4-H), 0.45 (d, J = 3.2 Hz, 0.2 H, 3-H), 4.52 (d, J = 3.2 Hz, 0.8 H, 3-H), 4.58–4.60 (m, 0.2 H,4-H), 5.13 (s, 0.8 H, 1-H), 5.30–5.43 (m, 2.2 H, CH=CH_2 and 1-H), 5.91–6.02 (m, 1 H, CH=CH_2), 7.36–7.46 (m, 6 H, Ph), 7.63–7.71 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 19.2, 26.7, 26.8, 27.1, 27.2, 63.8, 65.0, 65.8, 81.8, 84.5, 89.0, 93.6, 97.0, 113.5, 113.8, 119.0, 119.2, 127.9, 130.0, 132.0, 132.2, 132.3, 132.6, 135.5, 135.6, 135.8 ppm. MS (FAB): m/z = 493 [M + K]$^+$. $C_{26}H_{34}O_5Si$ (454.64): calcd. C 68.69, H 7.54; found C 68.49, H 7.64.

(1*R*,4′*S*,5′*S*)-1-(5′-*tert*-Butyldiphenylsiloxymethyl)-(2′,2′-dimethyl-5′-vinyl[1′,3′]dioxol-4′-yl)prop-2-en-1-ol (10): To a suspension of Ph_3PCH_3Br (88.7 g, 248.2 mmol) in THF (300 mL) was added BuLi (2.63 M in hexane, 88 mL, 231.6 mmol) dropwise at 0 °C. After stirring for 1.5 h at 0 °C, a THF (100 mL) solution of **9** (37.6 g, 82.7 mmol) was added. The reaction mixture was stirred for another 48 h at room temperature and partitioned between H_2O and AcOEt. Column chromatography (hexane/AcOEt, 1:1) of the organic layer gave **10** (34.4 g, 92%) as an oil. $[\alpha]_D^{27}$ = –26.9 (c = 1.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.07 (s, 9 H, *t*Bu), 1.47 (s, 3 H, Me), 1.66 (s, 3 H, Me), 2.39 (d, J = 3.6 Hz, 1 H, OH), 3.52 (d, J = 10.4 Hz, 1 H, CH_2OSi), 3.63 (d, J = 10.4 Hz, 1 H, CH_2OSi), 4.19–4.23 (m, 1 H, 1-H), 4.35 (d, J = 6.4 Hz, 1 H,1-H), 5.19–5.20 (m, 1 H, CH=CH_2), 5.22 (dd, J = 11.2, 2.0 Hz, 1 H, CH=CH_2), 5.37–5.42 (m, 1 H, CH=CH_2), 5.46 (dd, J = 16.6, 2.0 Hz, 1 H, CH=CH_2), 5.79 (ddd, J = 16.8, 10.4, 6.4 Hz, 1 H, 2-H), 5.88 (dd, J = 16.8, 11.2 Hz, 1 H, CH=CH_2), 7.36–7.45 (m, 6 H, Ph), 7.65–7.70 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 26.8, 27.0, 28.0, 67.0, 71.4, 81.2, 84.4, 108.4, 116.5, 118.3, 127.7, 129.7, 129.8, 132.7, 132.8, 135.6, 135.7, 136.1, 136.2 ppm. MS (FAB): m/z = 453 [M + H]$^+$. $C_{27}H_{36}O_4Si$ (452.66): calcd. C 71.64, H 8.02; found C 71.90, H 8.06.

(3a*R*,6a*S*)-6a-(*tert*-Butyldiphenylsiloxymethyl)-2,2-dimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (12): A mixture of **10** (33.0 g, 72.9 mmol) and Umicore M2 (**11**; 500 mg, 0.53 mmol) in CH_2Cl_2 (500 mL) was stirred for 70 h at room temperature under positive pressure of dry Ar in the dark. The resulting mixture was further treated with PDC (54.9 g, 145.8 mmol) in the presence of 4 Å MS (ca. 33 g) for 72 h. The reaction mixture was diluted with AcOEt (ca. 100 mL) and filtered through a pad of silica gel. Column chromatography (hexane/AcOEt, 3:1) of the filtrate gave **12** (28.5 g, 93%) as an oil. $[\alpha]_D^{27}$ = +43.0 (c = 2.33, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.02 (s, 9 H, *t*Bu), 1.34 (s, 3 H, Me), 1.38 (s, 3 H, Me), 3.85 (d, J = 10.6 Hz, 1 H, CH_2OSi), 3.90 (d, J = 10.6 Hz, 1 H, CH_2OSi), 4.36 (s, 1 H, 3a-H), 6.24 (d, J = 6.0 Hz, 1 H, 6-H), 7.36–7.47 (m, 7 H, 6-H and Ph), 7.61–7.66 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 26.5, 26.7, 28.1, 65.6, 79.5, 89.2, 127.7, 127.8, 127.9, 132.5, 132.6, 134.1, 134.8,135.6, 135.7, 161.6, 203.7 ppm. MS (FAB): m/z = 423 [M + H]$^+$. $C_{25}H_{30}O_4Si$ (422.60): calcd. C 71.05, H 7.16; found C 71.32, H 7.21.

(3a*R*,4*S*,6a*S*)-6a-(*tert*-Butyldiphenylsiloxymethyl)-3a,6a-dihydro-2,2,4-trimethylcyclopenta[1,3]dioxol-4-ol (13): To a stirred solution of **12** (2.9 g, 6.86 mmol) in THF (50 mL) was added MeLi (1.09 M in THF, 12.6 mL, 13.7 mmol) dropwise at –78 °C. The reaction mixture was stirred for 1 h at room temperature and partitioned between saturated aqueous NH_4Cl and AcOEt. Column chromatography (hexane/AcOEt, 4:1) of the organic layer gave **13** (2.8 g, 93%) as an oil. $[\alpha]_D^{27}$ = +29.3 (c = 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.06 (s, 9 H, *t*Bu), 1.27 (s, 3 H, Me), 1.44 (s, 3 H, Me), 1.45 (s, 3 H, Me), 3.20 (s, 1 H, OH), 3.55 (d, J = 11.2 Hz, 1 H, CH_2OSi), 3.85 (d, J = 11.2 Hz, 1 H, CH_2OSi), 4.26 (s, 1 H, 3a-H), 5.57 (d, J = 5.6 Hz, 1 H, CH=CH), 5.74 (d, J = 5.6 Hz, 1 H, CH=CH), 7.35–7.46 (m, 6 H, Ph), 7.66–7.73 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 25.3, 26.8, 27.9, 28.2, 65.8, 77.3, 79.4, 85.1, 95.2, 112.3, 127.7, 129.7, 129.9, 131.1, 132.8,132.9, 135.6, 135.7, 140.4 ppm. MS (FAB): m/z = 439 [M + H]$^+$. $C_{26}H_{34}O_4Si$ (438.64): calcd. C 71.19, H 7.81; found C 71.23, H 7.75.

Benzyl [(3a*R*,4*S*,6a*S*)-6a-(*tert*-Butyldiphenylsiloxymethyl)-3a,6a-dihydro-2,2,4-trimethylcyclopenta[1,3]dioxol-4-yl] Carbonate (14): To a THF (200 nL) solution of **12** (10.0 g, 23.7 mmol) was added MeLi (0.96 M in THF, 37.0 mL, 35.5 mmol) dropwise at –78 °C. After stirring for 0.5 h at –78 °C, CbzCl (6.77 mL, 47.4 mmol) was added. The reaction mixture was stirred for 2 h at room temperature and partitioned between saturated aqueous $NaHCO_3$ and AcOEt. Column chromatography (hexane/AcOEt, 9:1) of the organic layer gave **14** (9.8 g, 74%) as an oil. $[\alpha]_D^{26}$ = +15.8 (c = 0.47, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.04 (s, 9 H, *t*Bu), 1.31 (s, 3 H, Me), 1.36 (s, 3 H, Me), 1.59 (s, 3 H, Me), 3.62 (d, J = 10.8 Hz, 1 H, CH_2OSi), 3.82 (dd, J = 10.8, 1.6 Hz, 1 H, CH_2OSi), 4.62 (s, 1 H, 3a-H), 5.10 (d, J = 11.6 Hz, 1 H, OCH_2Ph), 5.25 (d, J = 11.6 Hz, 1 H, OCH_2Ph), 5.75 (d, J = 5.6 Hz, 1 H, CH=CH), 5.91 (d, J = 5.6 Hz, 1 H, CH=CH), 7.31–7.42 (m, 11 H, Ph), 7.64–7.67 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 23.1, 26.8, 27.6, 28.3, 66.1, 69.0, 85.3, 88.6, 95.0, 112.5, 127.7, 128.1, 128.2, 128.4, 129.7, 129.8, 132.8, 132.9, 133.5, 135.6, 135.7, 136.7, 153.5 ppm. MS (FAB): m/z = 573 [M + H]$^+$. $C_{34}H_{40}O_6Si$ (572.77): calcd. C 71.30, H 7.04; found C 71.28, H 7.09.

Intramolecular Oxyselenenylation of 14 To Form 15: To a solution of $(PhSe)_2$ (8.24 g, 26.3 mmol) in CH_2Cl_2 (90 mL) was added Br_2 (676 μL, 13.2 mmol) dropwise. After stirring for 2 h at room temperature, AgOTf (6.76 g, 26.4 mmol) was added and stirring was continued for another 20 min. After cooling the mixture to –78 °C, a solution of **14** (7.4 g, 13.2 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was gradually warmed to –30 °C with vigorous stirring for 16 h. Partition of the reaction mixture between saturated aqueous $NaHCO_3$ and CH_2Cl_2 was followed by column chromatography (hexane/AcOEt, 2:1) of the organic layer. This gave **15** (7.36 g, 89%) as a foam. $[\alpha]_D^{28}$ = –0.9 (c = 0.91, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.13 (s, 9 H, *t*Bu), 1.22 (s, 3 H, Me), 1.45 (s, 3 H, Me), 1.55 (s, 3 H, Me), 3.84 (d, J = 10.8 Hz, 1 H, CH_2OSi), 3.86 (d, J = 4.4 Hz, 1 H, CHSePh), 3.99 (d, J = 10.8 Hz, 1 H, CH_2OSi), 4.31 (s, 1 H, O-CH-), 4.71 (dd, J = 4.4, 0.8 Hz, 1 H, O-

C*H*-), 7.26–7.30 (m, 3 H, Ph), 7.40–7.48 (m, 6 H, Ph), 7.53–7.55 (2 H, m Ph), 7.66–7.68 (m, 2 H, Ph), 7.72–7.75 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 22.3, 26.1, 27.2, 27.5, 55.1, 66.2, 86.3, 86.4, 113.5, 127.9, 128.0, 129.4, 129.5, 130.2, 130.3, 131.7, 132.2, 133.6, 135.6, 136.0, 153.5 ppm. MS (FAB): *m*/*z* = 877 $[M + H]^+$. $C_{33}H_{38}O_6SeSi$ (637.71): calcd. C 62.15, H 6.01; found C 62.24, H 5.95.

(3a*S*,4*S*,5*R*,6*S*,6a*S*)-6a-(*tert*-Butyldiphenylsiloxymethyl)-6-phenylseleno-5,6,3a,6a-tetrahydro-2,2,4-trimethylcyclopenta[1,3]dioxole-4,5-diol (16): To a mixture of **15** (1.67 g, 2.67 mmol), THF (5 mL), and MeOH (25 mL) was added K_2CO_3 (1.84 g, 13.3 mmol). The resulting mixture was stirred for 12 h at room temperature. The reaction mixture was partitioned between 0.5 M HCl and $CHCl_3$. Compound **16** (1.60 g, quant.) was obtained as a foam after evaporation of the organic layer. $[\alpha]_D^{29}$ = –10.6 (*c* = 0.34, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.11 (s, 9 H, *t*Bu), 1.23 (s, 3 H, Me), 1.33 (s, 3 H, Me), 1.47 (s, 3 H, Me), 2.62 (d, *J* = 11.2 Hz, 1 H, OH), 3.20 (s, 1 H, OH), 3.50 (d, *J* = 11.2 Hz, 1 H, 6-H), 3.74 (d, *J* = 10.0 Hz, 1 H, C*H*$_2$OSi), 3.82 (t, *J* = 11.2 Hz, 1 H, 5-H), 4.06 (d, *J* = 10.0 Hz, 1 H, C*H*$_2$OSi), 4.22 (s, 1 H, 3a-H), 7.19–7.27 (m, 3 H, Ph), 7.40–7.47 (m, 6 H, Ph), 7.61–7.74 (m, 6 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1, 24.8, 27.0, 27.5, 28.1, 60.3, 67.2, 72.9, 81.9, 86.0, 88.0, 114.3, 126.8, 127.8, 127.9, 128.8, 130.0, 130.1, 131.3, 132.0, 132.6, 133.4, 135.7, 136.0 ppm. MS (FAB): *m*/*z* = 613 $[M + H]^+$. $C_{32}H_{40}O_5SeSi$ (611.71): calcd. C 62.83, H 6.59; found C 62.97, H 6.58.

(3a*R*,6a*R*)-6-(*tert*-Butyldiphenylsiloxymethyl)-2,2,3a-trimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (19): To a solution of **16** (12.0 g, 19.6 mmol) in 1,2-dichloroethane (150 mL) was added *m*-CPBA (>65%, 5.47 g, 20.6 mmol) at –30 °C. After stirring for 20 min at room temperature, *i*Pr$_2$NEt (11.9 mL, 68.6 mmol) was added, and then the reaction mixture was heated at reflux for 2 h. Partition of the reaction mixture between saturated aqueous $NaHCO_3$ and CH_2Cl_2 followed by flash column chromatography (hexane/AcOEt, 1:3) of the organic layer gave crude ketone **17**. Crude **17** was dissolved in MeOH (100 mL) and treated with 1 M NaOMe in MeOH (58.8 mL) at –30 °C. After stirring for 15 min at 0 °C, the mixture was partitioned between saturated aqueous NH_4Cl and CH_2Cl_2. Crude enone **18** was obtained by evaporation of the organic layer. Crude **18** thus obtained was treated with a mixture of acetone (100 mL) and acetone dimethyl acetal (100 mL) in the presence of TsOH·H_2O (373 mg, 1.96 mmol) for 13 h at room temperature. The reaction was quenched by adding Et_3N (ca. 2 mL). Evaporation of the reaction mixture followed by column chromatography (hexane/AcOEt, 5:1) of the residue gave **19** (6.39 g, 75% from **16**) as an oil. ^{1}HNMR and ^{13}C NMR of **19** were in full agreement with the reported data.[3e] $[\alpha]_D^{24}$ = +8.3 (*c* = 1.20, $CHCl_3$) {ref.[3e] $[\alpha]_D^{25}$ = +4.8 (*c* = 1.06, $CHCl_3$)}. MS (FAB): *m*/*z* = 437 $[M + H]^+$. $C_{26}H_{32}O_4Si$ (436.62): calcd. C 71.52, H 7.39; found C 71.61, H 7.42.

Hydrogenation of 19 To Form 20: A mixture of **19** (6.04 g, 13.8 mmol) and 10% Pd/C (3.0 g) in AcOEt (70 mL) was stirred under positive pressure (1 atm) of H_2 for 20 h. Filtration of the reaction mixture through a pad of Celite followed by evaporation of the filtrate gave **20** (6.05 g, quant.) as an oil. $[\alpha]_D^{28}$ = –71.2 (*c* = 1.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.08 (s, 9 H, *t*Bu), 1.32 (s, 3 H, Me), 1.33 (s, 3 H, Me), 1.37 (s, 3 H, Me), 2.24 (dd, *J* = 17.2, 12.4 Hz, 1 H, -C*H*$_2$CO), 2.33 (dd, *J* = 17.2, 8.0 Hz, 1 H, -C*H*$_2$CO), 2.38–2.45 (m, 1 H, -CH$_2$C*H*-), 3.82 (dd, *J* = 10.0, 6.4 Hz, 1 H, C*H*$_2$OSi), 3.94 (dd, *J* = 10.0, 8.0 Hz, 1 H, C*H*$_2$OSi), 4.44 (d, *J* = 3.2 Hz, 1 H, O-C*H*), 7.36–7.45 (m, 6 H, Ph), 7.66–7.72 (4 H, m. Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.0, 19.2, 26.5, 26.8, 27.1, 36.6, 37.1, 63.5, 82.2, 85.5, 111.4, 127.6, 127.7, 129.7, 133.4, 133.6, 134.8, 135.5, 135.6, 216.1 ppm. MS (FAB): *m*/*z* = 439 $[M + H]^+$. HRMS (FAB): calcd. for $C_{26}H_{35}O_4Si$ $[M + H]^+$ 439.2305; found 439.2343.

(3a*R*,6a*R*)-6-(*tert*-Butyldiphenylsiloxymethyl)-5-fluoro-2,2,3a-trimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-one (22): To a stirred mixture of **20** (782 mg, 1.78 mmol) and TMSCl (453 µL, 3.57 mmol) in THF (15 mL) was added LHMDS (1.55 M in THF, 1.38 mL, 2.14 mmol) dropwise at –78 °C. The reaction mixture was stirred for 15 min at –78 °C and then partitioned between saturated aqueous $NaHCO_3$ and AcOEt. The organic layer was evaporated, and the residue was dissolved in MeCN (10 mL). To this was added Selectfluor (758 mg, 2.14 mmol) and $NaHCO_3$ (300 mg, 3.57 mmol). The resulting suspension was stirred for 1 h at room temperature. The mixture was partitioned between saturated aqueous $NaHCO_3$ and AcOEt. The organic layer was filtered through a pad of silica gel. Evaporation of the filtrate gave crude fluoride **21**, which was used for the next reaction without further purification. To a THF (18 mL) solution of above **21** was added LHMDS (1.55 M in THF, 1.38 mL, 2.14 mmol) dropwise at –78 °C. The mixture was stirred for 5 min at –78 °C and then at 0 °C for 1 h. After cooling the mixture to –78 °C, TMSCl (272 µL, 2.14 mmol) and a THF (5 mL) solution of PhSeCl (511 mg, 2.67 mmol) were sequentially added. The whole reaction mixture was stirred for 15 min at 0 °C and then partitioned between saturated aqueous $NaHCO_3$ and AcOEt. The organic layer was evaporated and dissolved in CH_2Cl_2 (20 mL), and the resulting solution was treated with *m*-CPBA (>65%, 1.19 g, 4.45 mmol) and $NaHCO_3$ (1.5 g, 17.8 mmol) at 0 °C for 0.5 h. Partition of the reaction mixture between saturated aqueous $NaHCO_3$ and CH_2Cl_2 was followed by column chromatography (hexane/AcOEt, 6:1) of the organic layer. This gave **22** (387 mg, 48% from **20**) as an oil. $[\alpha]_D^{28}$ = +9.8 (*c* = 0.49, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.09 (s, 9 H, *t*Bu), 1.28 (s, 3 H, Me), 1.45 (s, 6 H, Me×2), 4.53 (dd, *J* = 16.0, 3.2 Hz, 1 H, C*H*$_2$OSi), 4.76 (dd, *J* = 16.0, 2.0 Hz, 1 H, C*H*$_2$OSi), 4.91 (d, *J* = 6.4 Hz, 1 H, 6a-H), 7.35–7.48 (m, 6 H, Ph), 7.66–7.72 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 19.5, 26.8, 28.5, 28.6, 57.7, 79.7 (d, $J_{C,F}$ = 6.0 Hz), 80.7 (d, $J_{C,F}$ = 6.0 Hz), 114.9, 127.8, 127.9, 130.0, 130.1, 132.3, 132.5, 135.5, 135.6, 146.2, 151.9 (d, $J_{C,F}$ = 292.7 Hz), 194.6 (d, $J_{C,F}$ = 15.6 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ = –138.3 ppm. MS (FAB): *m*/*z* = 455 $[M + H]^+$. $C_{26}H_{31}FO_4Si$ (454.61): calcd. C 68.69, H 6.87; found C 68.62, H 6.99.

DIBALH Reduction of 22 To Form 23: To a CH_2Cl_2 (28 mL) solution of **22** (1.27 g, 2.79 mmol) was added DIBALH (1.0 M in toluene, 5.59 mL, 5.59 mmol) dropwise at –78 °C. After stirring for 1 h at –78 °C, the reaction mixture was partitioned between 0.5 M HCl and CH_2Cl_2. HPLC separation (hexane/AcOEt, 4:1) of the organic layer gave **23** (t_R = 9.3 min, 1.02 g, 80%) as an oil. $[\alpha]_D^{26}$ = +43.5 (*c* = 1.29, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.06 (s, 9 H, *t*Bu), 1.31 (s, 3 H, Me), 1.48 (s, 3 H, Me), 1.49 (s, 3 H, Me), 2.80 (d, *J* = 9.0 Hz, 1 H, OH), 4.01 (dd, *J* = 9.0, 1.6 Hz, 1 H, C*H*-OH), 4.22 (dd, *J* = 12.8, 2.8 Hz, 1 H, C*H*$_2$OSi), 4.48 (d, *J* = 12.8 Hz, 1 H, C*H*$_2$OSi), 4.76 (d, *J* = 7.6 Hz, 1 H, O-C*H*), 7.36–7.46 (m, 6 H, Ph), 7.66–7.71 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 24.1, 28.9, 29.1, 55.5, 74.8 ($J_{C,F}$ = 20.4 Hz), 83.0 ($J_{C,F}$ = 6.0 Hz), 84.0 ($J_{C,F}$ = 7.2 Hz), 112.7, 117.2, 127.6, 127.7, 129.7, 129.8, 133.0, 133.2, 135.6, 135.7, 156.7 ($J_{C,F}$ = 290.3 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ = –128.3 ppm. MS (FAB): *m*/*z* = 457 $[M + H]^+$. $C_{26}H_{33}FO_4Si$ (456.63): calcd. C 68.39, H 7.28; found C 768.04, H 7.28.

Acetylation of 23 To Form 23a: To a pyridine (3 mL) solution of **23** (34 mg, 0.075 mmol) was added Ac_2O (35 µL, 0.37 mmol). The resulting mixture was stirred for 4 h at room temperature. After evaporation of all of volatiles, the residue was purified by preparative TLC (hexane/AcOEt, 4:1). This gave **23a** (32 mg, 87%) as an

oil. ^{1}H NMR ($CDCl_3$): δ = 1.07 (s, 9 H, *t*Bu), 1.38 (s, 3 H, Me_2C), 1.42 (s, 3 H, Me_2C), 1.53 (s, 3 H, Me), 2.11 (s, 3 H, Ac), 4.30 (dd, J = 13.2, 2.8 Hz, 1 H, CH_2OSi), 4.53 (d, J = 13.2 Hz, 1 H, CH_2OSi), 4.69 (d, J = 7.4 Hz, 1 H, CH-O), 4.99 (s, 1 H, CHOAc), 7.37–7.45 (m, 6 H, Ph), 7.67–7.70 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 20.8, 25.3, 26.7, 27.7, 27.9, 56.0, 76.6 (d, $J_{C,F}$ = 18.0 Hz), 81.7 (d, $J_{C,F}$ = 7.2 Hz), 84.9 (d, $J_{C,F}$ = 7.2 Hz), 113.3, 121.0 (d, $J_{C,F}$ = 3.6 Hz), 127.6, 127.7, 129.7, 129.8, 133.0, 133.1, 135.5, 135.6, 153.0 (d, $J_{C,F}$ = 287.9 Hz), 170.3 ppm. MS (FAB): m/z = 499 [M + H]$^+$.

9-[(1*S*,2*S*,3*R*)-2,3-Dihydroxy-5-fluoro-4-hydroxymethyl-2-methyl-4-cyclopenten-1-yl]adenine (5a): To a mixture of **23** (228 mg, 0.5 mmol), Ph_3P (197 mg, 0.75 mmol), and N^6-bis(Boc)adenine (252 mg, 0.75 mmol) in THF (10 mL) was added DIAD (148 μL, 0.75 mmol) dropwise at 0 °C. After stirring for 70 h at room temperature, the reaction mixture was evaporated, and the resulting residue was purified by column chromatography on silica gel (hexane/AcOEt, 3:1). Appropriate fractions were combined, and the solvents were evaporated. The residue was dissolved in a mixture of THF (5 mL) and 2 M HCl (5 mL). The resulting mixture was heated at 50 °C for 24 h and neutralized with NH_4OH (26%, ca. 10 mL), and the solvents were evaporated. Column chromatography (AcOEt/MeOH, 7:1) of the residue gave **5a** (80 mg, 54% from **23**) as a foam. $[\alpha]_D^{29}$ = –142.0 (c = 0.29, MeOH). ^{1}H NMR ([D$_6$]DMSO + D_2O): δ = 0.80 (s, 3 H, Me), 3.97 (d, J = 13.2 Hz, 1 H, CH_2OH), 4.27 (d, J = 13.2 Hz, 1 H, CH_2OH), 4.46 (d, J = 6.4 Hz, 1 H, 3′-H), 5.37 (s, 1 H, 1′-H), 8.08 (s, 1 H, 8-H), 8.17 (s, 1 H, 2-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 21.5, 52.5, 64.1 (d, $J_{C,F}$ = 16.8 Hz), 75.1 (d, $J_{C,F}$ = 7.2 Hz), 76.1 (d, $J_{C,F}$ = 4.8 Hz), 118.8, 123.5, 139.0, 149.9, 150.6 (d, $J_{C,F}$ = 281.9 Hz), 152.8, 156.0 ppm. ^{19}F NMR ([D$_6$]DMSO): δ = –131.7 ppm. MS (FAB): m/z = 296 [M + H]$^+$. $C_{12}H_{14}FN_5O_3 \cdot 1/2H_2O$ (304.28): calcd. C 47.37, H 4.97, N 23.01; found C 47.72, H 5.14, N 22.66.

1-{(3a*S*,4*S*,6a*R*)-6-(*tert*-Butyldiphenylsiloxymethyl)-5-fluoro-2,2,3a-trimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-yl}uracil (24): To a stirred solution of Ph_3P (572 mg, 2.18 mmol) in THF (5 mL) was added DIAD (430 μL, 2.18 mmol) at 0 °C. After stirring for 10 min, N^3-benzoyluracil (471 mg, 2.18 mmol) in THF (10 mL) and **23** (397 mg, 9.87 mmol) in THF (5 mL) were sequentially added at –40 °C. The reaction mixture was stirred for 66 h at room temperature and then partitioned between brine and Et_2O. After evaporation of the organic layer, the residue was treated with NaOMe (470 mg, 7.7 mmol) in MeOH (30 mL) at room temperature for 24 h. Partition of the reaction mixture between 0.5 M HCl and CH_2Cl_2 followed by column chromatography (hexane/Et_2O, 1:3) of the organic layer gave **24** (239 mg, 50% from **23**) as a foam. $[\alpha]_D^{26}$ = +36.0 (c = 0.67, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.09 (s, 9 H, *t*Bu), 1.20 (s, 3 H, Me), 1.34 (s, 3 H, Me), 1.45 (s, 3 H, Me), 4.32 (d, J = 13.2 Hz, 1 H, CH_2OSi), 4.61 (d, J = 13.2 Hz, 1 H, CH_2OSi), 4.88 (d, J = 6.4 Hz, 1 H, 3′-H), 5.60 (s, 1 H, 1′-H), 5.68 (d, J = 8.0 Hz, 1 H, 5-H), 6.58 (d, J = 8.0 Hz, 1 H, 6-H), 7.40–7.49 (m, 6 H, Ph), 7.68–7.70 (m, 4 H, Ph), 8.74 (br., 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.1, 21.9, 26.8, 28.6, 29.0, 55.9, 66.9 (d, $J_{C,F}$ = 18.0 Hz), 85.1 (d, $J_{C,F}$ = 7.2 Hz), 85.9 (d, $J_{C,F}$ = 4.8 Hz), 103.0, 112.8, 124.7, 127.8, 130.0, 132.7, 133.1, 135.5, 135.7, 139.7, 148.8 (d, $J_{C,F}$ = 287.9 Hz), 161.0, 162.5 ppm. ^{19}F NMR ($CDCl_3$): δ = –124.8 ppm. MS (FAB): m/z = 551 [M + H]$^+$. $C_{30}H_{35}FN_2O_5Si \cdot 3/4H_2O$ (564.20): calcd. C 63.87, H 6.52, N 4.97; found C 63.67, H 6.35, N 5.35.

1-{(3a*S*,4*S*,6a*R*)-6-(*tert*-Butyldiphenylsiloxymethyl)-5-fluoro-2,2,3a-trimethyl-3a,6a-dihydrocyclopenta[1,3]dioxol-4-yl}cytosine (25): A stirred MeCN (4 mL) solution containing **24** (229 mg, 0.42 mmol), DMAP (103 mg, 0.84 mmol), and Et_3N (117 μL, 0.84 mmol) was treated with TPSCl (254 mg, 0.84 mmol) for 0.5 h at room temperature. The reaction mixture was then treated with NH_4OH (26%, ca. 10 mL) for 20 h at room temperature with stirring. After evaporation, the residue was purified by column chromatography (AcOEt/MeOH, 7:1) to give **25** (111 mg, 48%) as a foam. $[\alpha]_D^{26}$ = +60.5 (c = 0.46, $CHCl_3$). ^{1}H NMR ($CDCl_3$ + D_2O): δ = 1.08 (s, 9 H, *t*Bu), 1.16 (s, 3 H, Me), 1.32 (s, 3 H, Me), 1.43 (s, 3 H, Me), 4.31 (d, J = 13.2 Hz, 1 H, CH_2OSi), 4.58 (d, J = 13.2 Hz, 1 H, CH_2OSi), 4.86 (d, J = 6.4 Hz, 1 H, 3′-H), 5.76 (s, 1 H, 1′-H), 5.86 (d, J = 6.4 Hz, 1 H, 5-H), 6.68 (d, J = 6.4 Hz, 1 H, 6-H), 7.38–7.44 (m, 4 H, Ph), 7.45–7.47 (m, 2 H, Ph), 7.68–7.71 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.2, 21.2, 26.8, 28.7, 29.0, 55.9, 66.4 (d, $J_{C,F}$ = 18.0 Hz), 85.3 (d, $J_{C,F}$ = 8.4 Hz), 86.4 (d, $J_{C,F}$ = 6.0 Hz), 95.7, 112.4, 123.7, 127.7, 127.8, 129.8, 129.9, 132.8, 133.1, 135.5, 135.7, 140.6, 150.2 (d, $J_{C,F}$ = 287.9 Hz), 156.7, 165.6 ppm. ^{19}F NMR ($CDCl_3$): δ = –124.6 ppm. MS (FAB): m/z = 550 [M + H]$^+$. $C_{30}H_{36}FN_3O_4Si \cdot 1/5H_2O$ (553.31): calcd. C 65.07, H 6.63, N 7.59; found C 64.88, H 6.56, N 7.54.

1-[(1*S*,2*S*,3*R*)-2,3-Dihydroxy-5-fluoro-4-hydroxymethyl-2-methyl-4-cyclopenten-1-yl]cytosine (5b): A mixture of **25** (103 mg, 187 μmol) and 3 M HCl (6 mL) in MeOH (6 mL) was stirred at room temperature for 48 h. After neutralization with NH_4OH (26%, ca. 10 mL), the mixture was evaporated. Preparative TLC ($CHCl_3$/MeOH, 3:1, developed 6×) of the residue gave **5b** (36 mg, 71%) as a solid. M.p. 140–142 °C. $[\alpha]_D^{14}$ = –43.5 (c = 0.42, MeOH). ^{1}H NMR (CD_3OD): δ = 1.09 (s, 3 H, Me), 4.12 (d, J = 12.6 Hz, 1 H, CH_2OH), 4.39–4.41 (m, 2 H, CH_2OH and 3′-H), 5.55 (br., 1 H, 1′-H), 5.93 (d, J = 7.4 Hz, 1 H, 5-H), 7.40 (d, J = 7.4 Hz, 1 H, 6-H) ppm. ^{13}C NMR (CD_3OD): δ = 22.4, 54.4, 68.5, (d, $J_{C,F}$ = 19.2 Hz), 77.7, 96.9, 126.4, 129.8, 143.5, 153.9 (d, $J_{C,F}$ = 283.1 Hz), 159.5, 167.6 ppm. ^{19}F NMR (CD_3OD): δ = –130.1 ppm. MS (FAB): m/z = 272 [M + H]$^+$. HRMS (FAB): calcd. for $C_{11}H_{15}FO_4$ 272.1047 [M + H]$^+$; found 272.1047.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H, ^{13}C, and ^{19}F NMR spectra for all described compounds.

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