Supporting Information

Enantioselective Total Synthesis of the Potent Anti-HIV Nucleoside EFdA

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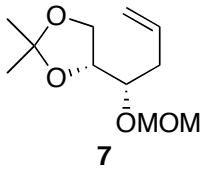
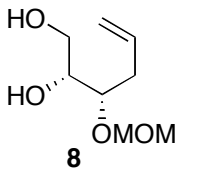
General Information

IR spectra were recorded by an FT/IR spectrometer using an ATR (ZnSe) attachment. ^{1}H NMR spectra were recorded at 400 or 600 MHz and ^{13}C NMR spectra were recorded at 100 MHz or 150 MHz with TMS as an internal standard in $CDCl_3$ unless otherwise stated. Optical rotation values were measured as solutions in $CHCl_3$ unless otherwise stated. High-resolution MS data were obtained by operating in the EI or FAB mode. Column chromatography was performed using 70–230 mesh silica gel. Solvents for reactions were distilled prior to use: THF from Na and benzophenone; MeOH from Mg and I_2; CH_2Cl_2, DMF and CH_3CN from CaH_2. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.



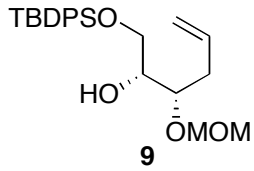
7

(*R*)-4-[(*S*)-1-Methoxymethoxy-3-butenyl]-2,2-dimethyl-1,3-dioxolane (7). Compound **7** was obtained by diastereoselective allylation of **6** followed by MOM-protection and chromatographic purification according to the procedure reported in Ref. 8. $[\alpha]^{21}_D$ +23.5 (*c* 1.10, $CHCl_3$); IR: ν_{max} 3080 (w), 1643 (w), 1213 (s), 1153 (s); ^{1}H NMR (400 MHz): δ 1.35 (3H, s), 1.41 (3H, s), 2.28–2.42 (2H, m), 3.38 (3H, s), 3.74 (1H, ddd, *J* = 5.5, 5.5, 5.5 Hz), 3.89 (1H, dd, *J* = 8.0, 6.4 Hz), 4.04 (1H, dd, *J* = 8.0, 6.4 Hz), 4.10 (1H, ddd, *J* = 6.4, 6.4, 5.5 Hz), 4.70 (1H, d, *J* = 7.2 Hz), 4.72 (1H, d, *J* = 7.2 Hz), 5.10 (1H, dm, *J* = 10.0 Hz), 5.13 (1H, dm, *J* = 17.1 Hz), 5.87 (1H, dddd, *J* = 17.1, 10.0, 7.1, 7.1 Hz); ^{13}C NMR (100 MHz): δ 25.3, 26.4, 36.0, 55.7, 66.0, 76.8, 77.1, 96.3, 109.0, 117.6, 134.1; HRMS (FAB): *m/z* calcd for $C_{11}H_{21}O_4$, 217.1440; found, 217.1444 ($[M+H]^+$).



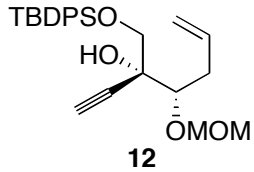
8

(2*R*,3*S*)-3-Methoxymethoxy-5-hexene-1,2-diol (8). To a stirred solution of **7** (3.87 g, 17.9 mmol) in MeOH/H_2O (100:1, 181.8 mL) was added PPTS (227 mg, 0.903 mmol) at room temperature. After 1.5 h, the mixture was stirred at 55 °C for 1.5 h, and at 60 °C for an additional 2 h. The mixture was quenched with solid $NaHCO_3$ and concentrated in vacuo. The residue was diluted with ether and the resulting ethereal solution was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20:1) to give 2.62 g (83%) of **8**. $[\alpha]^{23}_D$ +60.9 (*c* 1.13, $CHCl_3$); IR: ν_{max} 3400 (br s), 3077 (w), 1641 (w), 1098 (s); ^{1}H NMR (400 MHz): δ 2.30–2.45 (3H, m), 3.04 (1H, d, *J* = 7.4 Hz), 3.42 (3H, s), 3.62–3.82 (4H, m), 4.66 (1H, d, *J* = 6.6 Hz), 4.70 (1H, d, *J* = 6.6 Hz), 5.10 (1H, dm, *J* = 10.2 Hz), 5.14 (1H, dm, *J* = 17.2 Hz), 5.83 (1H, dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz); ^{13}C NMR (100 MHz): δ 36.1, 55.9, 62.9, 72.7, 81.0, 97.3, 117.8, 134.1; HRMS (FAB): *m/z* calcd for $C_8H_{17}O_4$, 177.1127; found, 177.1133 ($[M+H]^+$).



9

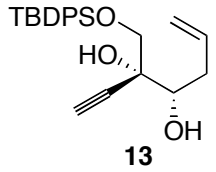
(2*R*,3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-methoxymethoxy-5-hexen-2-ol (9). To a stirred solution of **8** (4.03 g, 22.9 mmol) in DMF (110 mL) were successively added imidazole (3.89 g, 57.2 mmol) and TBDPSCl (6.2 mL, 23.8 mmol) at room temperature under a nitrogen atmosphere. After 2 h, the mixture was diluted with brine and extracted with ether. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give 9.12 g (96%) of **9**. $[\alpha]^{22}_{D}$ +8.9 (*c* 1.18, $CHCl_3$); IR: ν_{max} 3459 (w), 1641 (w), 1105 (vs), 1033 (vs), 770 (vs); ^{1}H NMR (400 MHz): δ 1.07 (9H, s), 2.26-2.42 (2H, m), 2.70 (1H, d, *J* = 4.3 Hz), 3.26 (3H, s), 3.62-3.82 (4H, m), 4.59 (1H, d, *J* = 6.9 Hz), 4.62 (1H, d, *J* = 6.9 Hz), 5.05 (1H, dm, *J* = 10.1 Hz), 5.08 (1H, dm, *J* = 17.2 Hz), 5.83 (1H, dddd, *J* = 17.2, 10.1, 7.1, 7.1 Hz), 7.34–7.48 (6H, m), 7.60–7.70 (4H, m); ^{13}C NMR (100 MHz): δ 19.2, 26.8 (3C), 35.3, 55.7, 64.6, 72.7, 78.6, 96.5, 117.3, 127.8 (4C), 129.8 (2C), 133.05, 133.08, 134.6, 135.5 (2C), 135.6 (2C); HRMS (FAB): *m*/*z* calcd for $C_{24}H_{35}O_4Si$, 415.2305; found, 415.2310 ($[M+H]^+$).



12

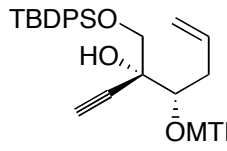
(3*R*,4*S*)-3-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-methoxymethoxy-6-hepten-1-yn-3-ol (12). To a stirred solution of **9** (4.42 g, 10.4 mmol) in CH_2Cl_2 (100 mL) were successively added solid $NaHCO_3$ (4.38 g, 52.2 mmol) and DMP (5.74 g, 13.5 mmol) at room temperature under a nitrogen atmosphere. After 25 min, additional $NaHCO_3$ (5.35 g, 63.6 mmol) and DMP (1.37 g, 3.23 mmol) were added, and the resulting mixture was stirred for 20 min. The mixture was quenched with a mixture of satd $NaHCO_3$ aq, satd $Na_2S_2O_3$ aq, and water (1:1:1), and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to give **10**, which was then taken up in THF (88 mL). A solution of bromo(trimethylsilylethynyl)magnesium was prepared by adding EtMgBr (1.0 M in THF, 14.0 mL, 14.0 mmol) to a solution of ethynyltrimethylsilane (2.00 mL, 1.36 mmol) in THF (14 mL) at 0 °C and subsequently stirring the resulting mixture at room temperature for 1 h. To the Grignard reagent was added the solution of **10** in THF obtained above at –78 °C under a nitrogen atmosphere, and the mixture was gradually warmed to 0 °C over 3 h and stirred for an additional 13 h. To the mixture containing **11** were successively added MeOH (100 mL) and K_2CO_3 (2.88 g, 20.8 mmol), and the mixture was stirred at reflux for 2 h. Since the desilylation was sluggish in the THF/MeOH solvent system, the solvents (THF and MeOH) was evaporated, and the residue was diluted with MeOH (100 mL) and mixed with additional K_2CO_3 (2.71 g, 19.6 mmol). The mixture was stirred at room temperature for 20 min, quenched with satd NH_4Cl aq, and extracted with EtOAc. The extract was washed with brine, dried

($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give 4.17 g (91%) of **12**. $[\alpha]^{23}_D$ –5.0 (*c* 1.04, $CHCl_3$); IR: ν_{max} 3462 (w), 3302 (m), 1641 (w), 1040 (vs), 701 (vs); ^{1}H NMR (400 MHz): δ 1.09 (9H, s), 2.43 (1H, dddm, *J* = 14.7, 8.8, 7.7 Hz), 2.49 (1H, s), 2.69 (1H, ddddd, *J* = 14.7, 6.5, 3.3, 1.6, 1.6), 3.22 (3H, s), 3.32 (1H, s), 3.73 (1H, dd, *J* = 8.8, 3.3 Hz), 3.80 (1H, d, *J* = 9.8 Hz), 3.85 (1H, d, *J* = 9.8 Hz), 4.62 (1H, d, *J* = 6.8 Hz), 4.69 (1H, d, *J* = 6.8 Hz), 5.05 (1H, dm, *J* = 10.2 Hz), 5.13 (1H, dddd, *J* = 17.0, 1.7, 1.7, 1.6 Hz), 5.91 (1H, dddd, *J* = 17.0, 10.2, 7.7, 6.5 Hz), 7.34–7.48 (6H, m), 7.64-7.76 (4H, m); ^{13}C NMR (100 MHz): δ 19.3, 26.8 (3C), 35.7, 56.0, 67.8, 73.4, 73.7, 80.9, 83.7, 97.6, 117.1, 127.76 (2C), 127.78 (2C), 129.9 (2C), 132.6, 132.7, 135.5, 135.6 (2C), 135.7 (2C); HRMS (FAB): *m*/*z* calcd for $C_{26}H_{35}O_4Si$, 439.2304; found, 439.2302 ($[M+H]^+$)

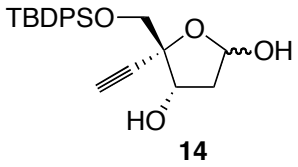


13

(3*R*,4*S*)-3-[(*tert*-Butyldiphenylsilyloxy)methyl]-6-hepten-1-yne-3,4-diol (13). To a stirred solution of **12** (1.23 g, 2.80 mmol) in CH_2Cl_2 (28 mL) were successively added $ZnBr_2$ (805 mg, 3.58 mmol) and 1-dodecanethiol (1.3 mL, 5.43 mmol) at room temperature. After 30 min, the mixture was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1) to give 1.06 g (96%) of **13**. $[\alpha]^{24}_D$ –2.4 (*c* 1.05, $CHCl_3$); IR: ν_{max} 3512 (m), 3303 (m), 1643 (w), 1111 (vs), 700 (vs); ^{1}H NMR (400 MHz): δ 1.09 (9H, s), 2.17 (1H, d, *J* = 5.7 Hz), 2.23 (1H, ddddd, *J* = 14.5, 10.3, 7.8, 1.0, 1.0 Hz), 2.48 (1H, s), 2.65 (1H, ddddd, *J* = 14.5, 6.2, 2.5, 1.3, 1.3 Hz), 3.30 (1H, s), 3.77 (1H, ddd, *J* = 10.3, 5.7, 2.5 Hz), 3.85 (1H, d, *J* = 10.0 Hz), 3.92 (1H, d, *J* = 10.0 Hz), 5.14 (1H, dm, *J* = 10.2 Hz), 5.17 (1H, dm, *J* = 17.2 Hz), 5.90 (1H, dddd, *J* = 17.2, 10.2, 7.8, 6.2 Hz), 7.36–7.48 (6H, m), 7.64–7.74 (4H, m); ^{13}C NMR (100 MHz): δ 19.3, 26.8 (3C), 36.1, 67.7, 73.2, 73.7, 74.3, 82.9, 117.8, 127.8 (2C), 127.9 (2C), 130.00, 130.01, 132.4, 132.5, 135.0, 135.56 (2C), 135.63 (2C); HRMS (FAB): *m*/*z* calcd for $C_{24}H_{31}O_3Si$, 395.2043; found, 395.2045 ($[M+H]^+$).

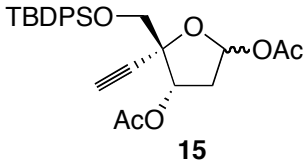


Determination of the enantiomeric excess of 13. The (*R*)- and (*S*)-mono-MTPA esters of **13** were prepared by treating **13** with 4.8 equiv of (*S*)- and (*R*)-MTPACl, respectively, in pyridine overnight at room temperature; the disappearance of the starting material **13** was checked by TLC. The TBDPSO-bearing methylene protons of the (*R*)-MTPA ester were observed as a singlet at δ 3.65 (2H, s) in ^{1}H NMR (600 MHz, $CDCl_3$), while those of the (*S*)-MTPA ester were detected at δ 3.73 (1H, d, *J* = 10.3 Hz) and δ 3.75 (1H, d, *J* = 10.3 Hz). Comparison of the two spectra indicated that the enantiomeric excess of **13** is more than 95%.



14

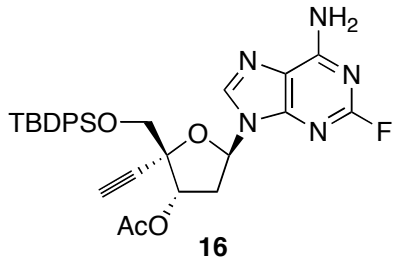
(2*R*/*S*,4*S*,5*R*)-5-[(*tert*-Butyldiphenylsilyloxy)methyl]-5-ethynyltetrahydrofuran-2,4-diol (14). Ozone was bubbled into a solution of **13** (3.21 g, 8.13 mmol) in CH_2Cl_2/MeOH (4:1, 100 mL) at –78 °C for 25 min. After removal of excess ozone by a stream of O_2 (for about 10 min), $NaHCO_3$ (3.33 g, 39.6 mmol) and Me_2S (6.0 mL, 81.7 mmol) were successively added, and the resulting mizture was gradually warmed to room temperature. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1–3:2) to give 2.71 g (84%) of **14** as an anomeric mixture (α-anomer/β-anomer = 2.8:1). $[\alpha]^{24}_{D}$ +5.7 (*c* 0.99, $CHCl_3$); IR: ν_{max} 3411(br s), 3291 (s), 1084 (vs), 701 (vs); ^{1}H NMR (400 MHz): δ 1.05 (0.74 × 9H, s), 1.09 (0.26 × 9H, s), 2.10 (0.26H, d, *J* = 6.9 Hz), 2.16 (0.74H, ddd, *J* = 13.6, 1.4, 0.8 Hz), 2.16–2.24 (0.26H, m), 2.31 (0.26H, ddd, *J* = 13.5, 6.5, 2.2 Hz), 2.36 (0.74H, ddd, *J* = 13.6, 5.3, 5.3 Hz), 2.65 (0.26H, s), 2.70 (0.74H, s), 2.80 (0.74H, d, *J* = 5.5 Hz), 3.00 (0.26H, d, *J* = 6.1 Hz), 3.57 (0.74H, d, *J* = 7.2 Hz), 3.63 (0.74H, d, *J* = 10.6 Hz), 3.76 (0.74H, d, *J* = 10.6 Hz), 3.81 (0.26H, d, *J* = 10.5 Hz), 3.85 (0.26H, d, *J* = 10.5Hz), 4.42 (0.74H, ddd, *J* = 5.5, 5.3, 1.4 Hz), 4.62 (0.26H, br q, *J* = 6.9 Hz), 5.51 (0.74H, br dd, *J* = 7.2, 5.0 Hz), 5.58 (0.26H, ddd, *J* = 6.1, 5.5, 5.2 Hz), 7.34–7.50 (6H, m), 7.60–7.74 (4H, m); ^{13}C NMR (100 MHz): δ 19.2, 26.7/26.8 (3C), 41.2/41.8, 67.1/67.5, 72.3/74.0, 77.7, 80.7, 84.3/85.9, 97.9/100.2, 127.8/127.9 (4C), 129.88/129.92/129.96/130.03 (2C), 132.61/132.64 (2C), 135.6/135.7 (4C); HRMS (FAB): *m*/*z* calcd for $C_{23}H_{28}O_4SiNa$, 419.1655; found, 419.1656 ([M+Na]$^+$).



15

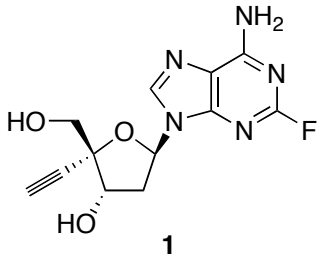
(2*R*,3*S*,5*R*/*S*)-5-Acetoxy-2-[(*tert*-butyldiphenylsilyloxy)methyl]-2-ethynyltetrahydrofuran-3-yl acetate (15). To a stirred solution of **14** (135 mg, 0.340 mmol) and DMAP (25.8 mg, 0.211 mmol) in CH_2Cl_2 (3.5 mL) were successively added Et_3N (210 μL, 1.51 mmol) and Ac_2O (130 μL, 1.38 mmol) at room temperature. After 1.5 h, the mixture was quenched with satd NH_4Cl aq and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to give 153 mg (94%) of **15** as an anomeric mixture (α-anomer/β-anomer = 1:1.4). $[\alpha]^{24}_{D}$ –11.4 (*c* 0.97, $CHCl_3$); IR: ν_{max} 3281 (w), 1744 (vs), 1227 (s), 702 (s); ^{1}H NMR (400 MHz): δ 1.05 (0.42 × 9H, s), 1.09 (0.58 × 9H, s), 1.86 (0.58 × 3H, s), 2.11 (0.42 × 3H, s), 2.12 (0.58 × 3H, s), 2.15 (0.42 × 3H, s), 2.24 (0.42H, dm, *J* = 14.5 Hz), 2.40–2.56 (0.58 × 2H, m), 2.51 (0.42H, s), 2.53 (0.58H, s), 2.70 (0.42H, ddd, *J* = 14.5, 7.8, 5.4 Hz), 3.82 (0.58H, d, *J* = 10.8 Hz), 3.83 (0.42H, d, *J* = 10.8 Hz), 3.86 (0.58H, d, *J* = 10.8Hz), 3.90 (0.42H, d, *J* = 10.8 Hz), 5.65 (0.42H, dd, *J* = 7.8, 1.6 Hz), 5.73 (0.58H, dd, *J* = 7.1, 7.0 Hz), 6.40–6.45 (1H, m), 7.34–7.48 (6H, m), 7.64–7.74 (4H, m); ^{13}C NMR (100 MHz): δ 19.2/19.3, 21.0, 21.2/21.3, 26.68/26.71 (3C),

37.3/38.9, 66.5/67.9, 72.0/73.5, 76.40/76.43, 79.0/79.2, 84.1/85.9, 96.5/98.6, 127.72/127.76 (2C), 127.82/127.83 (2C), 129.7/129.8/129.9 (2C), 132.4/132.6, 132.7/132.9, 135.5 (2C), 135.6/135.7 (2C), 169.96/169.97, 170.35/170.38; HRMS (FAB): *m/z* calcd for $C_{27}H_{32}O_6SiNa$, 503.1866; found, 503.1864 ($[M+Na]^+$).



16

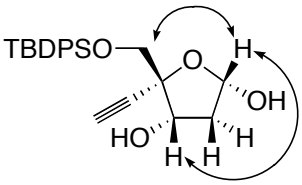
(2*R*,3*S*,5*R*)-5-(6-Amino-2-fluoropurin-9-yl)-2-[(*tert*-butyldiphenylsilyloxy)methyl]-2-ethynyltetrahydrofuran-3-yl acetate (16). To compound **3** (188 mg, 1.23 mmol) were added a solution of **16** (387 mg, 0.805 mmol) in CH_3CN (8.0 mL) and *N*,*O*-bis(trimethylsilyl)acetamide (1.10 mL, 4.50 mmol) at room temperature. The mixture was stirred at reflux for 2.5 h, and then cooled to 0 °C. To the mixture was added TMSOTf (0.300 mL, 1.66 mmol), and the resulting mixture was stirred at room temperature for 15 min and at reflux for an additional 17 h. The mixture was quenched with satd $NaHCO_3$ aq and filtered through a pad of Celite. The filtrate was diluted with water and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100:1) to give 213 mg (46%) of **16** and 115 mg (25%) of the corresponding α-anomer. **16**: mp: 182.6–183.3 °C; $[\alpha]^{26}_D$ +24.3 (*c* 1.13, $CHCl_3$); IR: ν_{max} 1747 (m), 1635 (s), 1362 (s), 702 (vs); ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.96 (9H, s), 2.13 (3H, s), 2.61 (1H, ddd, *J* = 14.0, 6.8, 4.7 Hz), 3.20 (1H, ddd, *J* = 14.0, 6.8, 6.8 Hz), 3.74 (1H, s), 3.78 (1H, d, *J* = 10.6 Hz), 3.95 (1H, d, *J* = 10.6 Hz), 5.82 (1H, dd, *J* = 6.8, 4.7 Hz), 6.37 (1H, dd, *J* = 6.8, 6.8 Hz), 7.32-7.38 (4H, m), 7.42–7.48 (2H, m), 7.54–7.64 (4H, m), 7.78–7.85 (1H, br s), 7.85–8.04 (1H, br s), 8.27 (1H, s); ^{13}C NMR (150 MHz): δ 19.1, 21.1, 26.7 (3C), 34.6, 66.7, 72.9, 79.6, 79.8, 83.0, 83.3, 118.0, 128.03 (2C), 128.05 (2C), 130.16, 130.18, 132.5, 132.7, 135.3 (2C), 135.4 (2C), 140.3, 150.5 (d, J_{CF} = 20.2 Hz), 157.9 (d, J_{CF} = 21.3 Hz), 158.7 (d, J_{CF} = 204.4 Hz), 169.6; HRMS (FAB): *m/z* calcd for $C_{30}H_{33}FN_5O_4Si$, 574.2286; found, 574.2290 ($[M+H]^+$). α-Anomer of **16**: mp: 221.0-221.7 °C; $[\alpha]^{25}_D$ +16.7 (*c* 1.03, $CHCl_3$); IR: ν_{max} 3330 (w), 3276 (w), 1759 (m), 1372 (s), 700 (vs); ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.05 (9H, s), 2.08 (3H, s), 2.81 (1H, ddd, *J* = 14.4, 3.8, 3.5 Hz), 3.05 (1H, ddd, *J* = 14.4, 7.3, 7.3 Hz), 3.75 (1H, d, *J* = 10.6 Hz), 3.77 (1H, s), 3.79 (1H, d, *J* = 10.6 Hz), 5.71 (1H, dd, *J* = 7.3, 3.5 Hz), 6.37 (1H, dd, *J* = 7.3, 3.8 Hz), 7.44–7.54 (6H, m), 7.66–7.74 (4H, m), 7.80–7.98 (2H, br m), 8.29 (1H, s); ^{13}C NMR (150 MHz): δ 19.1, 21.1, 26.8 (3C), 36.6, 67.5, 73.3, 79.2, 80.5, 83.4, 84.8, 117.4, 128.26 (2C), 128.27 (2C), 130.3, 130.4, 132.3, 132.4, 135.4 (2C), 135.5 (2C), 139.1, 150.9 (d, J_{CF} = 20.2 Hz), 157.9 (d, J_{CF} = 21.3Hz), 159.0 (d, J_{CF} = 203.6 Hz), 169.5; HRMS (FAB): *m/z* calcd for $C_{30}H_{33}FN_5O_4Si$, 574.2286; found, 574.2285 ($[M+H]^+$).



1

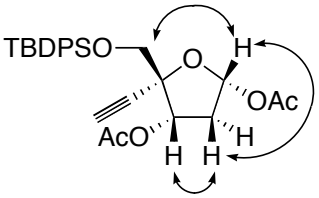
(2*R*,3*S*,5*R*)-5-(6-Amino-2-fluoropurin-9-yl)-2-ethynyl-2-(hydroxymethyl)-tetrahydrofuran-3-ol (1). To a stirred solution of **16** (66.2 mg, 0.115 mmol) in MeOH/CH_2Cl_2 (2:1, 1.5 mL) was added NH_4F (85.1 mg, 2.30 mmol) at room temperature. After 16 h, MeOH (0.5 mL) was added, and the resulting mixture was stirred for an additional 27 h. To the mixture was added 10% NaOH in MeOH (1.5 mL) to adjust the pH of the mixture to ca. 10. After 10 min, Dowex 50W×8 (200–400 mesh (H)) was added until the pH of the mixture reached ca. 4. To the resulting mixture was added $CaCO_3$ (259 mg, 2.59 mmol), and the mixture was stirred for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give 29.3 mg (87%) of **1**. Mp: 220.0–221.4 °C (dec.); $[\alpha]^{25}_D$ +12.4 (*c* 0.97, MeOH); IR: ν_{max} 3315 (br m), 3179 (br m), 1690 (vs), 1356 (vs); ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.43 (1H, ddd, *J* = 13.2, 7.3, 7.3 Hz), 2.70 (1H, ddd, *J* = 13.2, 6.8, 5.1 Hz), 3.52 (1H, s), 3.54 (1H, dd, *J* = 11.7, 6.4 Hz), 3.65 (1H, dd, *J* = 11.7, 5.0 Hz), 4.57 (1H, m), 5.32 (1H, m), 5.60 (1H, m), 6.24 (1H, dd, *J* = 7.2, 5.1 Hz), 7.82 (1H, br s), 7.92 (1H, br s), 8.31 (1H, s); ^{13}C NMR (150 MHz): δ 38.3, 64.4, 70.3, 79.2, 81.7, 82.2, 85.4, 117.6, 140.0, 150.4 (d, J_{CF} = 20.7 Hz), 157.8 (d, J_{CF} = 21.2 Hz), 158.8 (d, J_{CF} = 203.4 Hz); HRMS (FAB): *m/z* calcd for $C_{12}H_{13}FN_5O_3$, 294.1002; found, 294.1000 ($[M+H]^+$).

*Diagnostic NOE correlations in the anomers of **14** and **15**.*

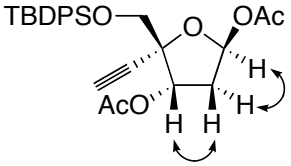


14α

As for **14β**, the two NOE correlations observed in **14α** were not detected.

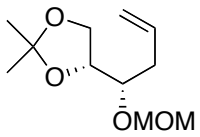


15α



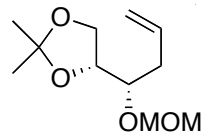
15β

^{1}H NMR (400 MHz, $CDCl_3$)

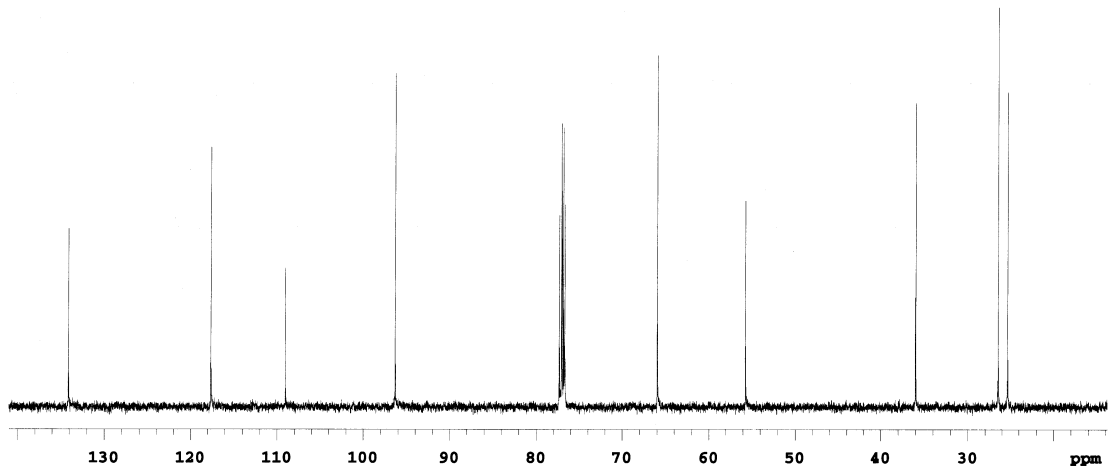


7

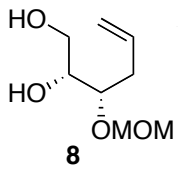
^{13}C NMR (100 MHz, $CDCl_3$)



7

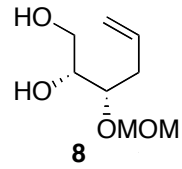


^{1}H NMR (400 MHz, $CDCl_3$)



8

^{13}C NMR (100 MHz, $CDCl_3$)



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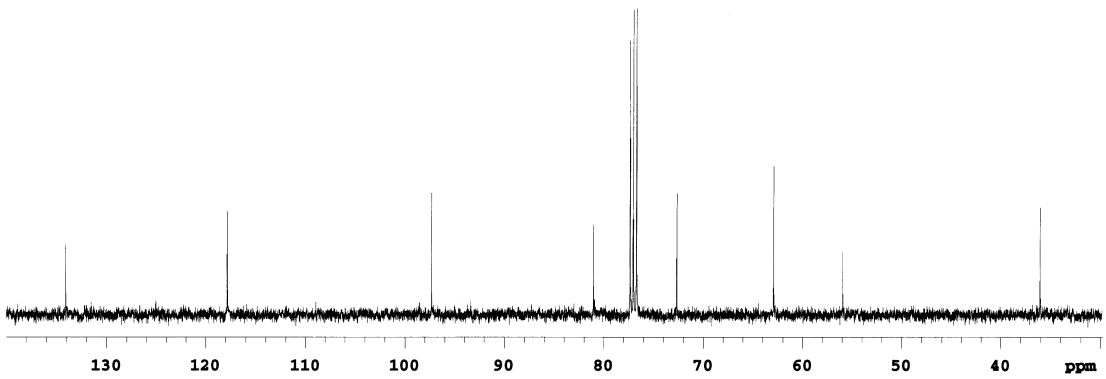
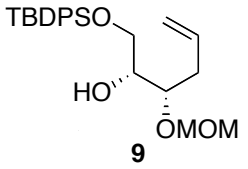
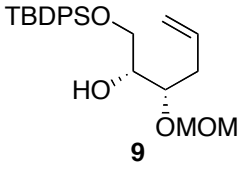


^{1}H NMR (400 MHz, $CDCl_3$)

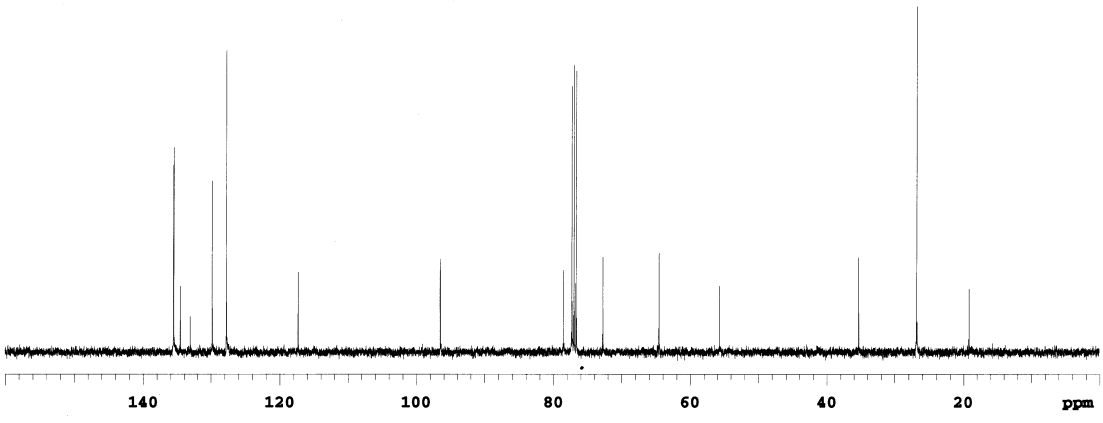


9

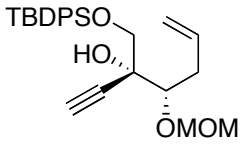
^{13}C NMR (100 MHz, $CDCl_3$)



9

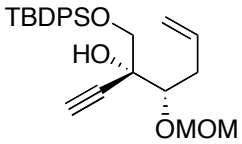


^{1}H NMR (400 MHz, $CDCl_3$)

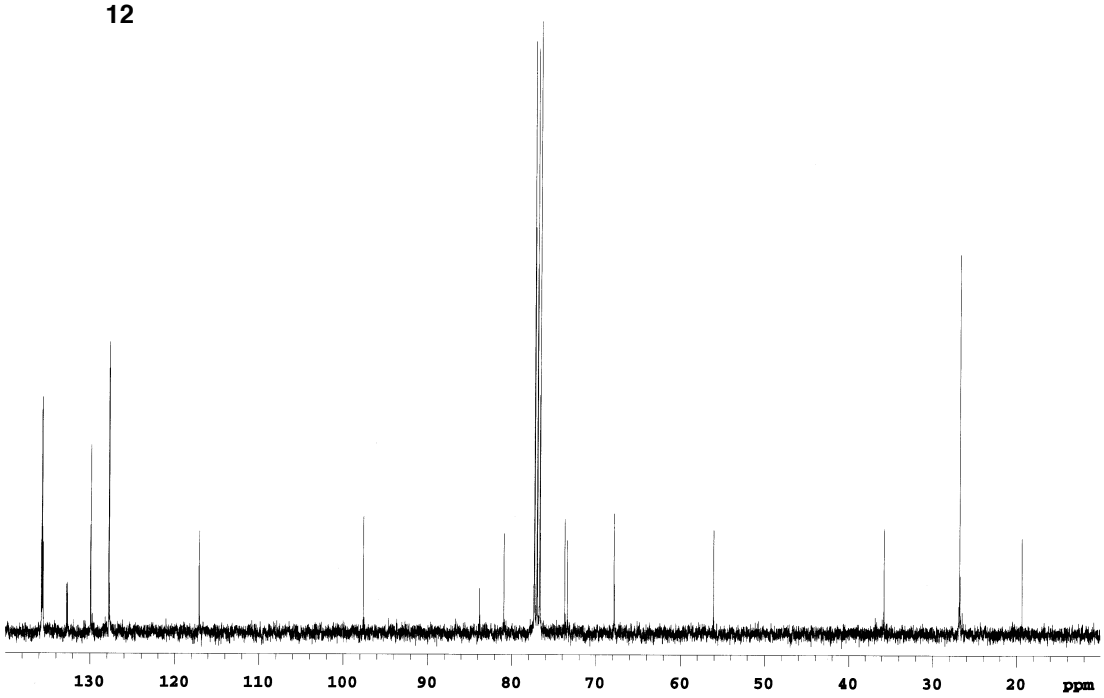


12

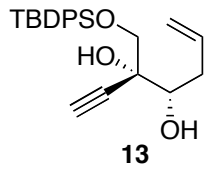
^{13}C NMR (100 MHz, $CDCl_3$)



12

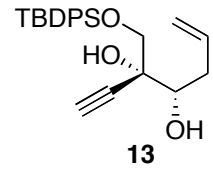


^{1}H NMR (400 MHz, $CDCl_3$)

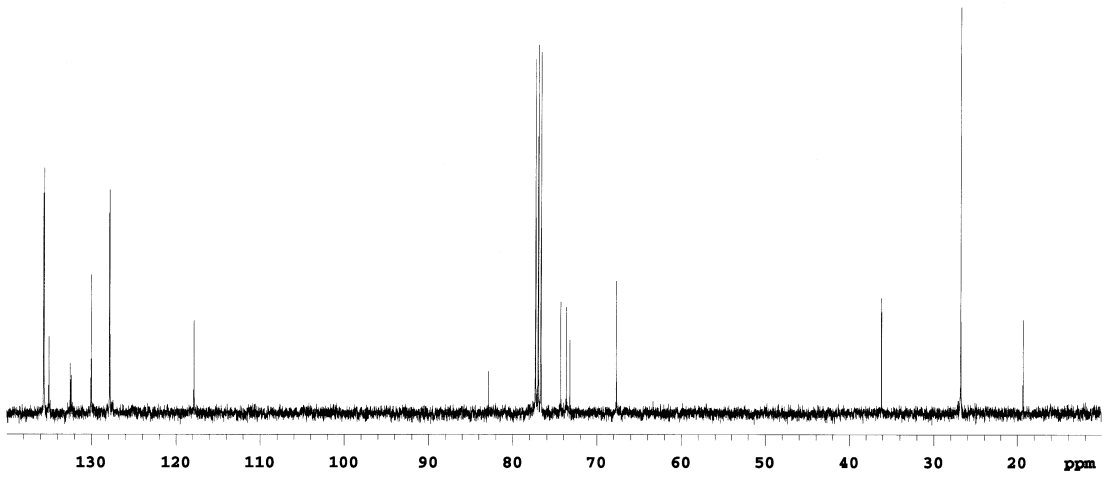


13

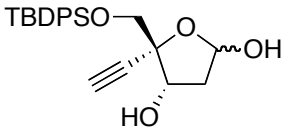
^{13}C NMR (100 MHz, $CDCl_3$)



13

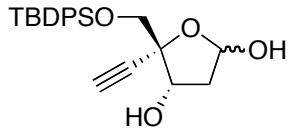


^{1}H NMR (400 MHz, $CDCl_3$)



14

^{13}C NMR (100 MHz, $CDCl_3$)



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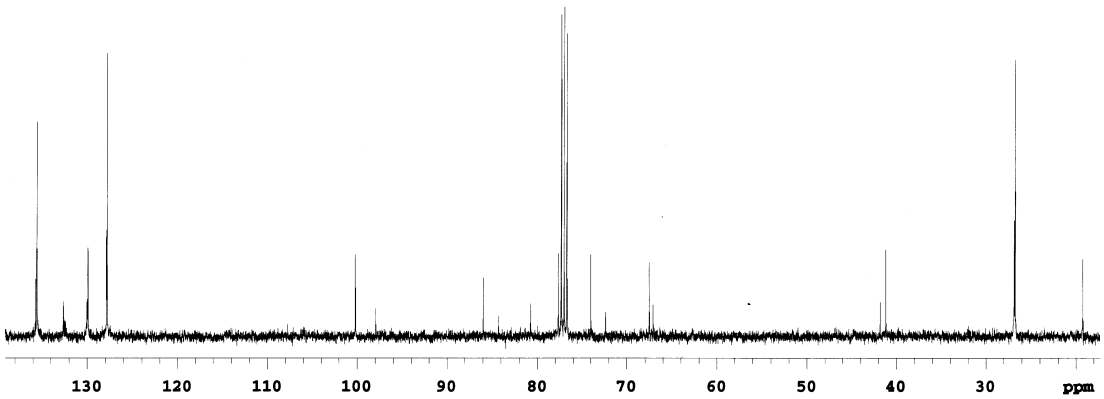
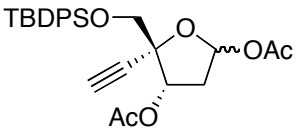
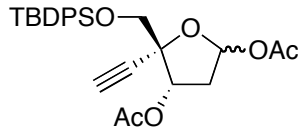


^{1}H NMR (400 MHz, $CDCl_3$)



15

^{13}C NMR (100 MHz, $CDCl_3$)



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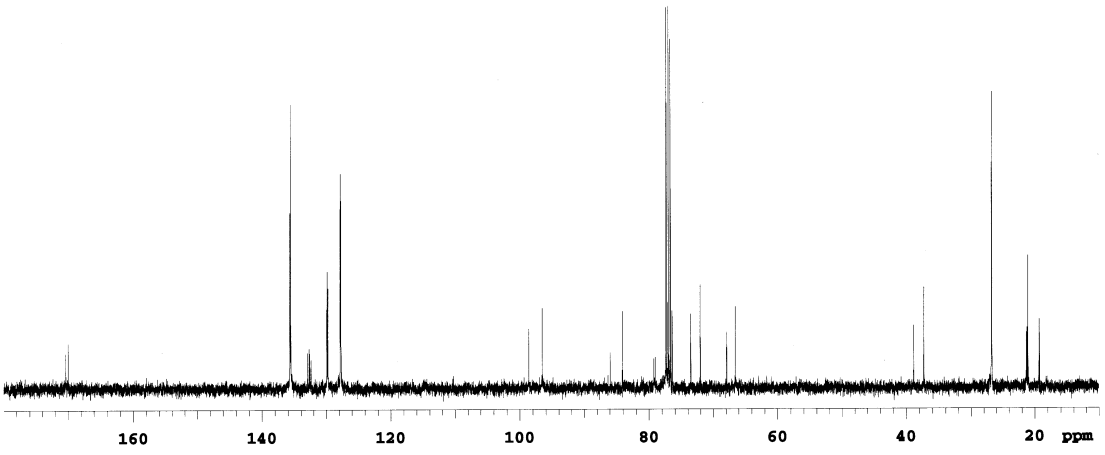
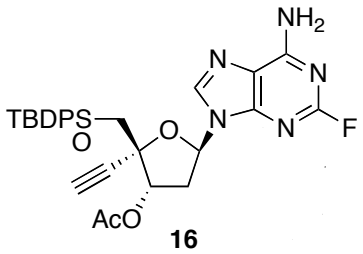
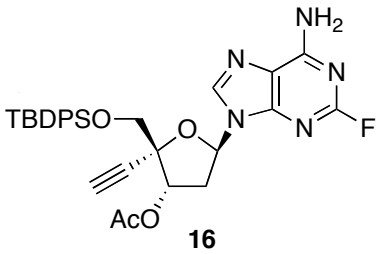


^{1}H NMR (600 MHz, DMSO-d_6)



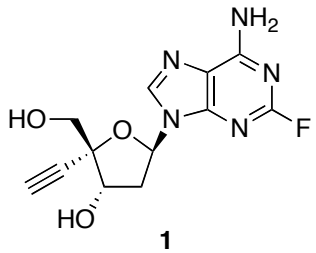
16

^{13}C NMR (150 MHz, DMSO-d_6)



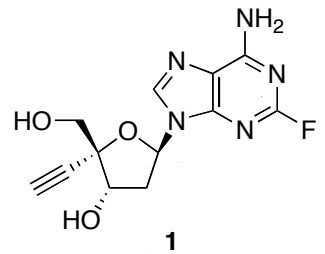
16

^{1}H NMR (600 MHz, DMSO-d_6)



1

^{13}C NMR (150 MHz, DMSO-d_6)



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