Supporting Information

Synthesis of 2',3'-Dideoxy-6',6' -difluorocarbocyclic Nucleosides

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General. All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions requiring anhydrous conditions were performed in vacuum heat-dried glassware under nitrogen atmosphere. Reaction mixtures were stirred magnetically. Tetrahydrofuran and toluene were distilled from sodium and benzophenone immediately before use. Dichloromethane and DMF were distilled from CaH_2 . ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM300 spectrometer. ^{19}F NMR was recorded on a Bruker AM300 spectrometer (FCCl_3 as outside standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d =doublet, t =triplet, q =quartet, m = multiplet.

Chlorodifluoroacetic acid (Z)-5-benzyloxy-pent-2-enyl ester (**3**).

A solution of (Z)-4-Benzyloxy-but-2-en-1-ol (5.3g, 29.8mmol) and chlorodifluoroacetic acid (4.2g, 32.2mmol) in 50ml of toluene was treated with 0.5ml of sulfonic acid. The mixture was heated and distilled slowly for 7h until the distillate became clear. Then the solvent was removed by distillation and the residue was purified by flash column chromatography (eluting with 20% EtOAc in petroleum spirit) to afford **3** (8.45g, 96%) as a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.29 (m, 5H), 5.98-5.90 (m, 1H), 5.78-5.69 (m, 1H), 4.90 (d, $J = 6.6$ Hz, 2H), 4.53 (s, 2H), 4.17-4.14 (m, 2H); ^{19}F NMR (282 MHz, CDCl_3) δ -63.8 (s); IR (thin film) 3034, 2861, 1781, 1455, 1367, 1302, 1171, 1134 cm^{-1} , MS m/z 290 (M^+ , 3), 181 (6), 105 (10), 91 (100). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{O}_3\text{F}_2\text{Cl}$: C, 53.71; H, 4.51. Found: C, 54.18; H, 4.53.

3-Benzyloxymethyl-2,2-difluoro-pent-4-enoic acid ethyl ester(**4**)

A mixture of **3** (4.56g, 15.7mmol), chlorotrimethyl silane (4ml, 31.8mmol), and freshly activated zinc dust (5.1g, 78.5mmol) was heated for 20h in 40ml of dry acetonitrile at 100 °C. Then the mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in 50ml of ethanol treated with 2ml of H_2SO_4 and the mixture was stirred at 50 °C for 24h. Then 40ml of the solvent was evaporated under reduced pressure. The residue was dissolved in 60ml of ethyl acetate, and washed with brine (50ml $\times$ 2), saturated aqueous Na_2HCO_3 (50ml), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by flash column chromatography (eluting with 5% EtOAc in petroleum spirit) to afford **4** (3.726g, 84%)

as a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 7.30-7.18 (m, 5H), 5.68 (ddd, $J = 8.7$ Hz, 10.8 Hz, 16.5 Hz, 1H), 5.26 (dd, $J = 10.5$ Hz, 0.9 Hz, 1H), 5.25 (d, $J = 17.7$ Hz, 1H), 4.39 (s, 2H), 4.06 (q, $J = 7.2$ Hz, 2H), 3.61 (dd, $J = 7.8$ Hz, 9.9 Hz, 1H), 3.50 (ddd, $J = 1.8$ Hz, 6.0 Hz, 8.1 Hz, 1H), 3.30-3.13 (m, 1H), 1.15 (t, $J = 7.2$ Hz, 3H); ^{19}F NMR (282 MHz, CDCl_3) δ -108.6 (dd, $J = 10.7$ Hz, 257.2 Hz, 1F), -114.9 (dd, $J = 18.0$ Hz, 258.6 Hz, 1F); IR (thin film) 2987, 2872, 1773, 1645, 1456, 1373, 1310, 1201, 1126 cm^{-1} , MS m/z 284 (M^+ , 5), 255 (6), 181 (10), 107 (10), 91 (100). Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{F}_2$: C, 63.37; H, 6.38. Found: C, 63.59; H, 6.25.

3-Benzyloxymethyl-2,2-difluoro-pent-4-enoic acid methoxy-methyl-amide (5)

To a suspension of N,O-dimethyl-hydroxylamine in toluene (4ml) at -10 °C was added trimethyl-aluminum (2ml, 2M in toluene, 4mmol) dropwise (caution: vigorous evolution of gas occurred). After the addition, the cooling bath was removed. The clear solution was stirred at 10 °C for 30 min and then cooled to -10 °C. A solution of **4** (284mg, 1mmol) in toluene (6ml) was added. The reaction mixture was stirred at 10 °C for 2h and then quenched with HCl solution (2N, 2ml) slowly (caution: vigorous evolution of gas occurred) at -10 °C. The resulting mixture was extracted with CH_2Cl_2 (80ml $\times$ 3). The combined organic layer was washed with saturated Na_2HCO_3 solution (80ml) and dried over Na_2SO_4 . Concentration and column chromatography (eluting with 10% EtOAc in petroleum spirit) gave amide **5** (255mg, 85%) as a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.27 (m, 5H), 5.78 (ddd, $J = 8.7$ Hz, 10.5 Hz, 16.8 Hz, 1H), 5.33 (dd, $J = 10.5$ Hz, 1.5 Hz, 1H), 5.32 (d, $J = 18.0$ Hz, 1H), 4.48 (s, 2H), 3.76-3.54 (m, 6H), 3.05 (s, 3H); ^{19}F NMR (282 MHz, CDCl_3) δ -107.7 (dd, $J = 8.7$ Hz, 255.8 Hz, 1F), -110.6 (dd, $J = 19.4$ Hz, 256.3 Hz, 1F); IR (thin film) 2942, 2870, 1690, 1455, 1190, 1105, 982 cm^{-1} , MS m/z 268 ($\text{M}^+ - \text{OMe}$, 3), 208 (3), 192 (5), 162 (24), 91 (100). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3\text{F}_2$: C, 60.19; H, 6.40; N, 4.68. Found: C, 60.31; H,

6.62;N, 4.48.

6-Benzylloxymethyl-5,5-difluoro-octa-2,7-dien-4-one(6)

To a stirred solution of **5** (83mg, 0.33mmol) in THF (8ml) was added allylmagnesium bromide (8ml, 1mmol, 0.125M solution in THF) at 20 °C. After being stirred for 15min at the same temperature, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ether (20ml $\times$ 2) and the combined organic layers were washed with brine, and then dried over Na₂SO₄. After concentration in vacuo, the residue was purified by flash column chromatography(eluting with 5% EtOAc in petroleum spirit) to give **6** (71mg, 91%) as a colorless oil: ¹H NMR(300 MHz, CDCl₃) δ 7.37-7.25 (m, 5H), 7.08 (dq, J = 7.5 Hz, 15.0 Hz, 1H), 6.52 (dq, J = 1.5 Hz, 15.3 Hz, 1H), 5.78 (ddd, J = 9.0 Hz, 10.8 Hz, 17.1 Hz, 1H), 5.34 (dd, J = 0.9 Hz, 10.2 Hz, 1H), 5.32 (d, J = 17.4 Hz, 1H), 4.45 (s, 2H), 3.69 (dd, J = 9.6 Hz, 7.2 Hz, 1H), 3.58 (ddd, J = 1.5 Hz, 6.0 Hz, 7.8 Hz, 1H), 3.40-3.20 (m, 1H), 1.89 (dd, J = 6.9 Hz, 1.8 Hz, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ -109.4 (dd, J = 10.7 Hz, 262.0Hz, 1F), -116.6 (dd, J = 18.6 Hz, 263.1Hz, 1F); IR (thin film) 2872, 1711, 1631, 1455, 1365, 1118 cm⁻¹, MS m/z 281(M⁺ + H, <1), 225 (14), 154 (18), 91(100). Anal. Calcd for C₁₆H₁₈O₂F₂: C, 68.56; H, 6.47. Found: C, 68.56; H, 6.77.

4-Benzylloxymethyl-5,5-difluoro-cyclopent-2-enone (7)

To a solution of compound **6** (60mg, 0.214 mmol) in 20 ml toluene under N₂ atmosphere was added Grubbs-II catalyst (10mg, 0.01mmol) in toluene (5ml) under N₂

atmosphere. The reaction mixture was refluxed for 24h and then cooled to room temperature. After removing solvent in vacuo, the residue was purified by column chromatography on silica gel (eluting with 10% EtOAc in petroleum spirit) to afford the desired product **7** (47mg, 98%) as a brown oil: ^1H NMR (300 MHz, CDCl_3) δ 7.81-7.76 (m, 1H), 7.41-7.27 (m, 5H), 6.43-6.39 (m, 1H), 4.57 (s, 2H), 3.82 (dd, J = 9.6 Hz, 5.7Hz, 1H) , 3.65-3.59 (m, 1H) , 3.44-3.35 (m, 1H); ^{19}F NMR (282 MHz, CDCl_3) δ -111.8 (dd, J = 16.9Hz, 285.9 Hz, 1F), -127.2 (d, J = 285.7Hz, 1F); IR (thin film) 2871,1744, 1582, 1455,1203,1127 cm^{-1} , MS(ESI) m/z 261.0($\text{M} + \text{Na}^+$), 256.1 ($\text{M} + \text{NH}_4^+$). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{F}_2$: C, 65.55; H, 5.04. Found: C, 65.82; H, 5.13.

4-Benzyloxymethyl-5,5-difluoro-cyclopent-2-enol (**8a** and **8b**)

A solution of **7** (1.2g, 5.04 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (2.81 g, 7.54 mmol) in 10 ml of methanol was cooled to 0 °C, and NaBH_4 (282 mg, 7.83mmol) was added in portions. The solution was remained at the temperature for 1h and quenched with aqueous ammonium chloride, water was added, and the mixture was extracted with ethyl acetate. Chromatography on silica gel (eluting with 10% EtOAc in petroleum spirit) gave 767mg(63.4%) of **8a** (R_f 0.42, petroleum/EtOAc = 5/1) and 263mg(21.7%) of **8b** (R_f 0.60, petroleum/EtOAc = 5/1); total yield 1.03g(85%).

Data for **8a**.

^1H NMR (300 MHz, CDCl_3) δ 7.38-7.25 (m, 5H), 6.07-6.04 (m, 1H), 5.97-5.92 (m, 1H), 4.58 (s, 2H), 4.37-4.29 (m, 1H) , 3.69-3.65 (m, 1H), 3.53-3.48 (m, 1H), 3.15-3.11 (m, 1H), 3.02-2.96(m, 1H); ^{19}F NMR (282 MHz, CDCl_3) δ -102.5 (ddd, J = 13.5Hz, 16.6Hz, 239.1Hz, 1F), -126.5 (dt, J = 4.5Hz, 237.9Hz, 1F); IR (thin film) 3438, 2872, 1455, 1347, 1173, 1108, 1058, 823, 749, 699 cm^{-1} , MS m/z 241(2, $\text{M} + \text{H}^+$), 222(23), 192(4), 181(6), 116(3), 105(6), 91(100). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{F}_2$: C, 65.00; H, 5.83. Found: C, 64.89; H, 5.86.

Data for **8b**.

^1H NMR (300 MHz, CDCl_3) δ 7.39-7.28 (m, 5H), 6.01-5.99 (m, 1H), 5.93-5.89 (m, 1H), 4.72 (dd, $J = 5.1\text{Hz}$, 12.0Hz , 1H), 4.54 (s, 2H), 3.68 (dd, $J = 5.1\text{Hz}$, 9.3Hz , 1H), 3.56 (dd, $J = 6.0\text{Hz}$, 9.0Hz , 1H), 3.29-3.22 (m, 1H), 2.05(br, 1H); ^{19}F NMR (282 MHz, CDCl_3) δ -113.0 (ddt, $J = 2.5\text{Hz}$, 15.5Hz , 238.8Hz , 1F), -119.1 (ddd, $J = 6.8\text{Hz}$, 9.3Hz , 239.1Hz , 1F); IR (thin film) 3435, 2872, 1455, 1347, 1173, 1108, 1058, 823, 749, 699 cm^{-1} ; MS m/z 240(2, M^+), 223(1), 200(1), 172(1), 149(1), 120(1), 91(100). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{F}_2$: C, 65.00; H, 5.83. Found: C, 64.97; H, 5.94.

3-Benzyloxymethyl-2,2-difluoro-cyclopentanol (**9a**)

9a

In 30ml of benzene, the benzyl ester **8a** (1.0g, 4.2mmol) and Pd-black (45mg) was hydrogenated for 24h at room temperature. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (eluting with 10% EtOAc in petroleum spirit) to give **9a** (844 mg, 84%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.41-7.28 (m, 5H), 4.58 (s, 2H), 4.07-4.01 (m, 1H), 3.62 (dd, $J = 4.8\text{Hz}$, 5.7Hz , 1H), 2.58-2.46 (m, 2H), 2.04-1.73 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3) δ -100.0 (dm, $J = 240.5\text{Hz}$, 1F), -127.0(dm, $J = 234.9\text{Hz}$, 1F); IR (thin film) 3412, 2878, 1455, 1367, 1207, 1104, 1047, 740, 699 cm^{-1} ; MS m/z 242(8, M^+), 210(2), 200(2), 181(6), 107(48), 91(100). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{F}_2$: C, 64.45; H, 6.65. Found: C, 64.58; H, 6.64.

3-Benzyloxymethyl-2,2-difluoro-cyclopentylamine(**10a**)

10a

Ti_2O (2.18ml, 12.9mmol) was added to alcohol **9a** (844mg, 3.49mmol) and pyridine

(5ml) in CH₂Cl₂ (20ml) at -60 °C over 10 min. After 2h at -40 °C, DMF (5ml) and NaN₃ (860mg, 13.2 mmol) were added. The mixture was allowed to warm to room temperature over 20 h. The resulting yellow solution was diluted in water, and extracted with petroleum (40ml × 3), dried (Na₂SO₄), concentrated, and chromatographed (eluting with 5% EtOAc in petroleum spirit) to give azide compound as a colorless oil. The product couldn't be separated from the side product, so we used it directly in the following step. The crude azide compound was dissolved in benzene (10ml), and hydrogenated for 23h at the presence of Pd black (37mg). The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (eluting with 75% EtOAc in petroleum spirit) gave **10a** (467mg, 1.94mmol, 56% for 3 steps) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.29 (m, 5H), 4.54 (s, 2H), 3.62 (dd, *J* = 5.7Hz, 9.3Hz, 1H), 3.49 (dd, *J* = 6.3Hz, 9.3Hz, 1H), 3.33-3.25 (m, 1H), 2.60-2.43 (m, 1H), 2.12-1.93 (m, 2H), 1.58-1.36 (m, 4H); ¹⁹F NMR (282 MHz, CDCl₃) δ -109.2 (ddd, *J* = 10.4Hz, 18.0Hz, 229.3Hz, 1F), -116.7(dt, *J* = 10.2Hz, 230.1Hz, 1F); ¹³C NMR (75MHz, CDCl₃) δ 138.0, 128.5(dd, *J* = 250.5Hz, 255.6 Hz), 128.2, 127.4, 127.3, 73.0, 68.2(dd, *J* = 4.9Hz, 7.8Hz), 57.1(dd, *J* = 21.7Hz, 25.6Hz), 43.4(dd, *J* = 20.6Hz, 23.2Hz), 29.3(d, *J* = 6.3Hz), 22.5(dd, *J* = 2.5Hz, 5.1Hz); IR (thin film) 3385, 2873, 1743, 1455, 1367, 1199, 1103, 1027, 739, 699 cm⁻¹; HRMS Found 222.1326 (-HF), C₁₃H₁₇NOF₂ requires 222.1294 (-HF).

1-(2,2-Difluoro-3-hydroxymethyl-cyclopentyl)-1H-pyrimidine-2,4-dione(2a)

Silver cyanate (488mg, 3.25mmol, previously dried over phosphorus pentoxide at 100 °C for 3h) was refluxed in dry benzene (10ml) for 2h, and a solution of

3-Ethoxy-2-propenoyl Chloride 270mg, 2.0mmol) in dry benzene (10ml) was then added dropwise. After addition of 3-Ethoxy-2-propenoyl Chloride was complete, the mixture was stirred under reflux for 40min before allowing the solid to settle out. The supernatant was then decanted and added slowly enough to cause no rise in temperature to a solution of **10a** (247mg, 1.02mmol) in DMF (10ml) under N₂ at -40 °C, following which the reaction mixture was stirred overnight at r.t.. The solvent was evaporated under reduced pressure while the temperature was maintained below 40 °C, and the residue was dissolved in 3ml of 2N H₂SO₄ in water, 4ml of dioxane and 4ml of CH₂Cl₂, and refluxed for 4h at 90°C. The mixture was filtered through a column of basic Al₂O₃, and the solvent was evaporated under reduced pressure. The resulting solid was dissolved in 40ml of methanol with 0.4ml of acetic acid, and hydrogenated under H₂ catalyzed by Pd on carbon (100mg) for 30min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (CH₂Cl₂: methanol = 15:1), afforded 146mg crude product, which was recrystallized to give colorless crystal **2a** (146mg, 58% yield for 3 steps), mp 205 °C: ¹H NMR (300 MHz, CD₃OD) δ 7.68 (dd, *J* = 2.4Hz, 8.1Hz, 1H), 5.71 (d, *J* = 8.1Hz, 1H), 5.23-5.11 (m, 1H), 3.76-3.63 (m, 2H), 2.55-2.45 (m, 1H), 2.18-2.08 (m, 3H), 1.71-1.64 (m, 1H); ¹⁹F NMR (282 MHz, CD₃OD) δ -107.9 (ddd, *J* = 10.4Hz, 13.5Hz, 236.0Hz, 1F), -118.5 (ddd, *J* = 13.8Hz, 22.3Hz, 235.8Hz, 1F); ¹³C NMR (75MHz, CD₃OD) δ 165.9, 152.9, 144.7 (d, *J* = 3.4Hz), 129.2 (dd, *J* = 253.0Hz, 256.4Hz), 102.6, 60.7 (dd, *J* = 11.0Hz, 18.2Hz), 60.2, 47.9, 26.0 (d, *J* = 6.8Hz), 23.5 (d, *J* = 5.0Hz); IR (thin film) 3352, 2949, 1637, 1578, 1418, 1031cm⁻¹; HRMS Found 246.0860, C₁₀H₁₂N₂O₃F₂ requires 246.0816.

3-Benzyloxymethyl-2,2-difluoro-cyclopentanol(9b)

In 15 ml of benzene, the benzyl ester **8b** (270mg, 1.12mmol) and Pd-black (14mg) was

hydrogenated for 17h at room temperature. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (eluting with 10% EtOAc in petroleum spirit) to give **9b** (260mg, 96%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.27 (m, 5H), 4.54 (s, 2H), 3.62 (dd, $J = 5.4\text{Hz}$, 9.6Hz , 1H), 3.49 (m, 1H), 3.32-3.22 (m, 1H), 2.63-2.44 (m, 1H), 2.12-1.93 (m, 2H), 1.58-1.27 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3) δ -109.2 (ddd, $J = 11.6\text{Hz}$, 19.4Hz , 229.8Hz , 1F), -116.7 (dt, $J = 9.9\text{Hz}$, 229.0Hz , 1F); ^{13}C NMR (75MHz, CD_3OD) δ 138.2, 128.5(dd, $J = 251.8\text{Hz}$, 257.1Hz), 128.3, 127.6, 127.5, 74.3(dd, $J = 21.0\text{Hz}$, 32.0Hz), 73.2, 67.9(d, $J = 8.3\text{Hz}$), 42.3(t, $J = 21.3\text{Hz}$), 28.8(d, $J = 2.6\text{Hz}$), 22.5(d, $J = 7.2\text{Hz}$) IR (thin film) 3387, 2873, 1455, 1367, 1199, 1104, 1028, 739, 699 cm^{-1} , HRMS Found 242.1158, $\text{C}_{13}\text{H}_{16}\text{O}_2\text{F}_2$ requires 242.1118.

3-Benzyloxymethyl-2,2-difluoro-cyclopentylamine(10b)

Tf₂O (0.9ml, 4.3mmol) was added to alcohol **9b** (210mg, 0.87mmol) and pyridine (1ml) in CH₂Cl₂ (10 ml) at -60 °C over 10 min. After 2h at -40 °C, DMF (5ml) and NaN₃ (565mg, 8.7 mmol) were added. The mixture was allowed to warm to room temperature over night, and was warmed to 55°C for 1h. The resulting yellow solution was diluted in CH₂Cl₂, and washed with water, filtered through celite. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography (eluting with 5% EtOAc in petroleum spirit) to give azide compound as a colorless oil. The product was difficult to be separated from the side product, so we used it directly in the following step. The crude azide compound was dissolved in benzene (30ml), and hydrogenated for 23h at the presence of Pd black (50mg). The mixture was filtered, and the solvent was evaporated under reduced pressure. Chromatography (eluting with 75% EtOAc in petroleum spirit) gave **10b** (69mg, 0.28mmol, 33% for 3 steps) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.27 (m, 5H), 4.54 (s, 2H), 3.71 (dd, *J* = 6.3Hz, 9.6Hz, 1H), 3.48 (dd, *J* = 7.8Hz, 8.4Hz, 1H), 3.37-3.24 (m, 1H), 2.64-2.43

(m, 1H), 2.10-1.91 (m, 2H), 1.62-1.42 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3) δ -110.3 (dt, $J = 8.7\text{Hz}$, 224.2Hz, 1F), -129.3(dt, $J = 18.3\text{Hz}$, 226.7Hz, 1F); IR (thin film) 3387, 2876, 1606, 1455, 1367, 1209, 1106, 1031, 739, 699 cm^{-1} ; MS m/z 242(37, $\text{M} + \text{H}^+$), 221(1), 150(15), 100(41), 91(100). Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NOF}_2$: C, 64.71; H, 7.10; N, 5.81. Found: C, 64.40; H, 7.15; N, 5.96

1-(2,2-Difluoro-3-hydroxymethyl-cyclopentyl)-1H-pyrimidine-2,4-dione(2b)

Silver cyanate (250mg, 1.66mmol, previously dried over phosphorus pentoxide at 100 °C for 3h) was refluxed in dry benzene (5ml) for 2h, and a solution of 3-Ethoxy-2-propenoyl Chloride (100mg, 0.74mmol) in dry benzene (1ml) was then added dropwise. After addition of 3-Ethoxy-2-propenoyl Chloride was complete, the mixture was stirred under reflux for 40min before allowing the solid to settle out. The supernatant was then decanted and added slowly enough to cause no rise in temperature to a solution of **10b** (95mg, 0.39mmol) in DMF (5ml) under N_2 at -40 °C, following which the reaction mixture was stirred overnight at r.t.. The solvent was evaporated under reduced pressure while the temperature was maintained below 40 °C, and the residue was dissolved in 10ml of 2N H_2SO_4 in water, 3ml of acetone and 1ml of CH_2Cl_2 , and refluxed for 10h at 90 °C. The mixture was filtered through a column of basic Al_2O_3 , and the solvent was evaporated under reduced pressure. The resulting solid was dissolved in 30ml of methanol with 1ml of acetic acid, and hydrogenated under H_2 catalyzed by Pd on carbon (170mg) for 30min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2 : methanol = 15:1), and the crude product was further purified by recrystallization to give colorless crystal **2b** (49mg, 49% yield for 3 steps), mp 220 °C: ^1H NMR (300 MHz, CD_3OD) δ 7.67 (dd, $J = 2.7\text{Hz}$, 8.4Hz, 1H), 5.69 (d, $J = 8.1\text{Hz}$,

1H), 5.40-5.31 (m, 1H) , 3.82 (dd, $J = 6.6\text{Hz}$, 11.7Hz , 1H), 3.63 (dd, $J = 7.5\text{Hz}$, 11.7Hz , 1H), 2.64-2.53 (m, 1H), 2.24-2.05 (m, 3H), 1.80-1.71 (m, 1H); ^{19}F NMR (282 MHz, CD_3OD) δ -109.3(dt, $J = 9.6\text{Hz}$, 228.7Hz , 1F), -124.3(dt, $J = 19.4\text{Hz}$, 228.1Hz , 1F); ^{13}C NMR (75MHz, CD_3OD) δ 164.4, 151.5, 142.5(d, $J = 5.3\text{Hz}$), 127.6(dd, $J = 251.2\text{Hz}$, 259.0Hz), 101.0, 59.0(d, $J = 9.8\text{Hz}$), 57.3(dd, $J = 17.2\text{Hz}$, 23.8Hz), 44.9(t, $J = 20.6\text{Hz}$), 23.6(d, $J = 6.4\text{Hz}$), 21.7(d, $J = 7.1\text{Hz}$); IR (thin film) 3352, 2949, 1637, 1578, 1418, 1031cm^{-1} ; HRMS Found 246.0824 , $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_3\text{F}_2$ requires 246.0816.