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Highly Enantioselective Construction of A Chiral Tertiary Carbon Center *via* Alkynylation of Cyclic *N*-Acyl Ketimine: An Efficient Preparation of HIV Therapeutics

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General Procedure: Melting point was uncorrected. ^{1}H NMR spectra were recorded on 300 MHz spectrometers with TMS as an internal standard. ^{13}C NMR spectra were recorded on 75 MHz spectrometers with TMS as an internal standard and. Coupling constants, *J* values, were given in Hz. ^{19}F NMR spectra were obtained at 282 MHz with $CFCl_3$ as external standard, downfield shifts being designated as positive. IR spectra were taken on a Shimadzu 440-IR spectrophotometer. MS spectra were run respectively on a finnigan 4021 GC MS/DC and MAT 21 instrument with an ionizing voltage of 70 Ev. All reactions were performed using oven dried glassware under a argon atmosphere with magnetic stirring. Toluene was distilled from Na and Et_3N from CaH_2. $Zn(OTf)_2$ was purchased from TCI and dried in oven at 100 ^{o}C under vacuum (5 mmHg) before used.

(*1S, 2S*)-1-(*p*-nitrophenyl)-2-(*N,N*-dimethylamino)-3-trityloxy-propan-1-ol (5b):

To a solution of (*1S, 2S*)-2-*N,N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol (1.95 g, 8 mmol) in CH_2Cl_2 (50 mL) were added triphenylmethane chloride (3.34 g, 12 mmol) and Et_3N (2 mL) at 0 ^{o}C. The mixture was stirred for overnight at rt. and washed with water (20 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The resulting residue was recrystallized from cyclohexane/ethyl acetate to give **5b** (3.7 g, 95%). $[\alpha]_D^{20}$ =

-20.4 (c = 0.50, $CHCl_3$); FTIR (KBr) ν = 3315, 2870, 1601, 1525, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.09-8.06 (d, J = 8.4 Hz, 2H), 7.36-7.33 (d, J = 8.6 Hz, 2H), 7.25-7.17 (m, 15H), 4.28-4.25(d, J = 10.0 Hz, 1H), 3.28(dd, J = 10.2 Hz, 6.4 Hz 1H), 3.01(dd, J = 10.7 Hz, 3.9 Hz, 1H), 2.71 (m, 1H), 2.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ =150.1, 147.6, 143.6, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 127.3, 123.7, 87.7, 70.9, 70.6, 58.6, 41.6; MS (EI) *m/e* = 479(M+-3, 0.03), 330 (29), 243 (100).

(*1S, 2S*)-1-(*p*-nitrophenyl)-2-(*N,N*-dimethylamino)-3-(*t*-butyloxy)- propan-1-ol (5c):

Concentrated H_2SO_4 (0.8 g) was added dropwise to a solution of (*1S, 2S*)-2-*N, N*-dimethylamino-3-(*p*-nitrophenyl)propane-1,3-diol (1.8 g, 7.5 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC. Isobutene gas was bubbled for 1 h with the temperature maintained at 0-5 ^oC. An additional concentrated H_2SO_4 (0.2 g) was added. The mixture was allowed to warm to rt and stirred vigorously for 7 h with the isobutene bubbling into. Then the mixture was cooled to 0 ^oC and neutralized with saturated K_2CO_3 aqueous to pH = 7. The separated organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Hexane: EtOAc = 10:1) to afford **5c** (1.44 g, 65%). m.p. 100.0 – 101.3 ^oC; $[\alpha]_D^{20}$ = -23.5 (c = 1.0, $CHCl_3$); FTIR (KBr) ν = 3333, 2972, 1606, 1523, 1357, 1197 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.19 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 4.59 (d, J = 9.9 Hz, 1H), 3.34 (dd, J = 3.0 Hz, and 9.9 Hz, 1H), 3.21 (dd, J = 6.5 Hz, and 10 Hz, 1H), 2.56 (m, 1H), 2.47 (s, 6H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ =150.6, 147.6, 128.46, 123.49, 73.3, 70.3, 69.8, 56.0, 41.8, 27.4; MS (EI) *m/e* = 223(M^+-73, 3), 209 (21), 144 (68), 88 (100), 71(10), 57(31); Anal. calcd. for $C_{15}H_{24}N_2O_4$: C, 60.81; H, 8.11; N, 9.46. Found: C, 60.72; H, 8.26; N, 9.14.

(1*S*, 2*S*)-1-(*p*-nitrophenyl)-2-(*N, N*-benzyl-methyl-amino)-3-trityloxy-propan-1-ol (5d):

A mixture of (*1S, 2S*)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol (2.12 g, 10 mmol), benzaldehyde (1.2 g, 10.5 mmol) and $CuSO_4$ (0.2 g) in methanol (10 mL) was refluxed for 7 h. The mixture was cooled to rt, and the solid was filtered. The filtrate was added THF (10 mL) and $NaBH_4$ (0.4 g). The resulting mixture was refluxed for 2 h and poured into 5% HCl (20 mL). The mixture was extracted with ether (20 mLx3). The combined extracts was washed with brine and concentrated. The residue in HCOOH (10 mL) was refluxed with 37% HCHO aqueous (10 mL) for 8 h. After cooling to 0 ^oC, the mixture was basified to pH = 11-12 with 20% NaOH and extracted with CH_2Cl_2 (15 mL x 3). The combined organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Hexane/EtOAc = 1:1) to afford 1.2 g (38% for two steps) product. FTIR (KBr) ν = 3543, 3208, 2943, 1516, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.15 (d, J = 10.7 Hz, 2H), 7.50 (d, J = 11.0 Hz, 2H), 7.40-7.26 (m, 5H), 4.63 (d, J = 9.6 Hz, 1H), 4.01 (d, J = 13.1 Hz, 1H), 3.82(d, J = 12.7 Hz, 1H), 3.63 (m, 2H), 2.78 (m, 1H) 2.43 (s, 3H); MS (EI) *m/e* = 317 (M+1, 0.8), 164 (51), 91 (100).

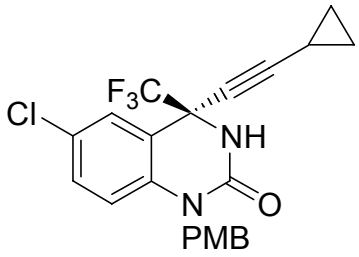
The above product (380 mg, 1.2 mmol) in CH_2Cl_2 (15 mL) was treated with triphenylmethane chloride (334 mg, 1.2 mmol) and Et_3N (0.2 mL) at 0 ^oC for overnight at rt. The mixture was washed with water (10 mL). The separated organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (Hexane/EtOAc = 15:1) to afford **5d** (500 mg, 75%). m.p. 58.0 – 59.3 ^oC; $[\alpha]_D^{20}$ = +47 (*c*, 0.25, $CHCl_3$); FTIR (KBr) ν = 3314, 2926, 1602, 1521,1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.07 (d, J = 8.8 Hz, 2H), 7.40-7.19 (m,

22H), 4.30 (d, *J* = 9.6 Hz, 1H), 3.94 (d, *J* = 13.0 Hz, 1H), 3.73(d, *J* = 6.8 Hz, 1H), 3.36 (m, 1H), 3.06 (m, 1H) 2.89 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ =150.6, 147.6, 143.46, 138.2, 129.3, 128.8, 128.7, 128.6 ,128.4, 128.0, 127.7 127.4, 123.7, 87.8, 70.5, 69.8, 60.1, 58.0, 37.0; MS (EI) *m/e* = 406(M+-152, 24.9), 243 (100); Anal. calcd. for $C_{15}H_{24}N_2O_4$: C, 77.42; H, 6.09; N, 5.02. Found: C, 77.26; H, 6.06; N, 4.65.

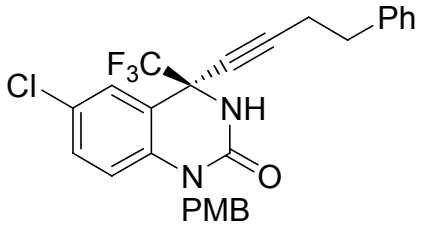
(*1R, 2R*)-1-(*p*-nitrophenyl)-2-(*N,N*-dimethylamino)-3-(*t*-butyloxy)-propan-1-ol (6): Compound **6** was prepared in 68% yield using the same procedure for preparing **5c**. $[\alpha]_D^{20}$ = +22.5 (*c*, 1.00, $CHCl_3$); FTIR (KBr) ν = 3333, 2972, 1606, 1523 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.19 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 4.59 (d, *J* = 9.9 Hz, 1H), 3.34 (dd, *J* = 3.0 Hz, and 9.9 Hz, 1H), 3.21 (dd, *J* = 6.5 Hz, and 10 Hz, 1H), 2.56 (m, 1H), 2.47 (s, 6H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.6, 147.6, 128.46, 123.49, 73.3, 70.3, 69.8, 56.0, 41.8, 27.4.

General procedure for the asymmetric alkynylation of the ketimine 2: To a solution of $Zn(OTf)_2$ (396 mg, 1.1 mmol) and (1*R*, 2*R*)-**6** (326 mg, 1.1 mmol), triethylamine (252 mg, 2.5 mmol) in dried toluene (1 mL) was added terminal acetylene (**2**) (1.1 mmol) under argon atmosphere for 2 h at 25 ^{o}C. Then ketimine **2** (369 mg, 1 mmol) was added. After 6-15 h, the mixture was cooled to 0 ^{o}C, and 6N HCl (5 mL) was added. The mixture was extracted with EtOAc (5 mL x 3). The combined organic layer was washed with 6N HCl (5 mL x 3), saturated Na_2CO_3 aqueous, brine and dried with Na_2SO_4. After removal of solvent in *vacuo*, the residue was purified by flash chromatography on silica gel (Hexane: EtOAc = 6:1) to afford **3**. The combined acidic water phases was cooled to 0-5 ^{o}C and basified to pH = 10-11 with 10% NaOH and extracted with EtOAc (5 mL x 3). The combined extracts was

dried with Na_2SO_4 and concentrated *in vacuo* to give ligand (1*R*, 2*R*)-**6** (294 mg, 90% recovery).

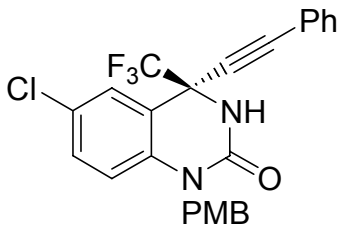


95% yield and 99.3% ee as determined by HPLC analysis (Chiralcel OD, *i*-PrOH/hexane = 10/90, 0.7 mL/min, 254 nm), t_r 19.9 (minor), 25.3 (major); $[\alpha]^{20}_D$ -74.1 (*c* = 0.6, MeOH); FTIR (KBr) ν = 3209, 2247, 1684, 1174 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 9.00 (s, 1H), 7.46 (bs, 1H), 7.41 (dd, *J* = 2.8 and 8.9 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.12 (d, *J* = 16.4 Hz, 1H), 4.93 (d, *J* = 16.5 Hz, 1H), 3.69 (s, 3H), 1.52 (m, 1H), 0.93 – 0.87 (m, 2H), 0.77 - 0.72 (m, 2H); ^{19}F NMR (282 MHz, DMSO-d_6) δ = -81.3 (s, 3F); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 158.3, 151.2, 136.6, 130.8, 128.4, 127.6, 127.5, 125.8, 123.8 (q, *J* = 289 Hz), 117.1, 116.5, 114.0, 91.8, 68.0, 57.7 (q, *J* = 32 Hz), 54.9, 43.9, 8.3, 8.2, -1.2; MS (EI) *m/e* 434(M^+, 6.6), 365(13.8), 121(100); HREIMS calcd for $C_{22}H_{18}ClF_3N_2O_2$ 434.1009, found 434.0967.

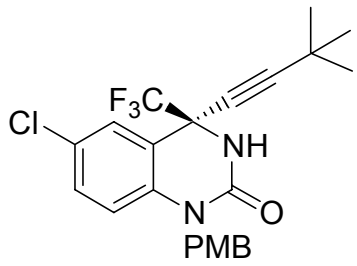


73% yield and 98.2% ee as determined by HPLC analysis (Chiralcel AD, *i*-PrOH/hexane = 10/90, 0.7 mL/min, 254 nm), t_r 23.8 (major), 27.5 (minor); m.p. 158.2 – 159.4 C; $[\alpha]^{20}_D$ -19.0 (*c* = 2.0, MeOH); FTIR (KBr) ν = 3211, 2252, 1684, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.43 (s, 1H), 7.35-7.30 (m, 2H), 7.27-7.17 (m, 4H),

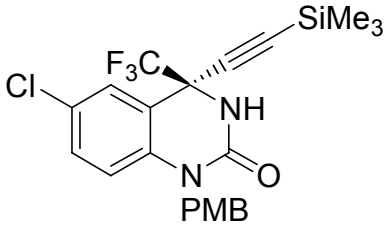
7.14 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 9.2 Hz, 1H), 5.95 (s, 1H), 5.13 (d, J = 16.5 Hz, 1H), 4.99 (d, J = 16.4 Hz, 1H), 3.76 (s, 3H), 2.88 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -82.3 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 152.2, 139.9, 136.6, 130.9, 128.9, 128.8, 128.7, 128.6, 128.3, 127.9, 127.8, 126.9, 123.9 (q, J = 287 Hz), 117.6, 114.4, 88.5, 74.5, 58.9, 55.4, 45.8, 34.3, 31.1 (q, J = 44 Hz), 21.1; MS (EI) m/e = 498(M^+, 4.9), 429(8.7), 121(100); HREIMS calcd for $C_{27}H_{22}ClF_3N_2O_2$ 498.1349, found 498.1335.



88% yield and 98.2% ee as determined by HPLC analysis (Chiralcel AD, *i*-PrOH/hexane = 20/80, 0.7 mL/min, 254 nm), t_r 13.2 (major), 15.9 (minor); m.p. 190.5 – 191.1 ^oC; $[\alpha]^{20}_D$ -64.2 (c = 1.1, MeOH); FTIR (KBr) ν = 3213, 2235, 1675, 1187 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.26 (s, 1H), 7.63-7.60 (m, 3H), 7.52-7.44 (m, 4H), 7.17 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 9.1 Hz, 1H), 6.89 (d, J = 11.4 Hz, 2H), 5.17 (d, J = 16.7 Hz, 1H), 4.93 (d, J = 17.0 Hz, 1H), 3.70 (s, 3H); ^{19}F NMR (282 MHz, DMSO-d_6) δ = -76.2 (s, 3F); ^{13}C NMR (75 MHz, DMSO-d_6) δ =159.0, 151.8, 137.4, 132.6, 131.7, 130.8, 129.6, 129.0, 128.4, 128.2, 126.8, 120.6, 117.4, 117.2, 114.7, 87.6, 82.5, 58.9 (q, J = 32 Hz), 55.6, 44.7; MS (EI) m/e = 470(M^+, 6.8), 401(12.8), 121(100); HREIMS calcd for $C_{25}H_{18}ClF_3N_2O_2$ 470.1009, found 470.0997.

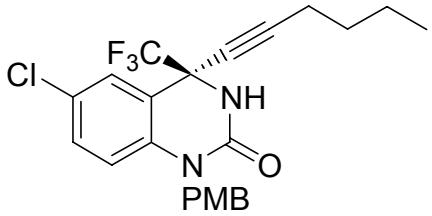


63% yield and 98.5% ee as determined by HPLC analysis (Chiralcel AD, *i*-PrOH/hexane = 20/80, 0.7 mL/min, 254 nm), t_r 7.2 (major), 8.4 (minor); mp 175.1 – 176.2 ^oC; $[\alpha]^{20}_D$ -46.4 (*c* = 1.0, MeOH); FTIR (KBr) ν= 3206, 2256, 1687, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ= 7.53 (d, *J* = 1.5 Hz 1H), 7.22-7.15 (m, 3H), 6.86-6.83 (m, 2H), 6.77 (d, *J* = 8.9 Hz, 1H), 6.42 (s, 1H), 5.14 (d, *J* = 16.4 Hz, 1H), 5.01 (d, *J* = 16.4 Hz, 1H), 3.76 (s, 3H), 1.27 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -82.6 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ=159.0, 152.3, 136.6, 130.8, 128.7, 127.9, 123.9 (q, *J* = 285 Hz), 117.9, 116.2, 114.4, 97.4, 72.2, 58.6 (q, *J* = 32 Hz), 55.5, 45.8, 30.6, 30.5, 29.9, 27.8; MS (EI) *m/e* = 450(M^+, 6.6), 381(10.7), 121(100); HREIMS calcd for $C_{23}H_{22}ClF_3N_2O_2$ 450.1322, found 450.1301.

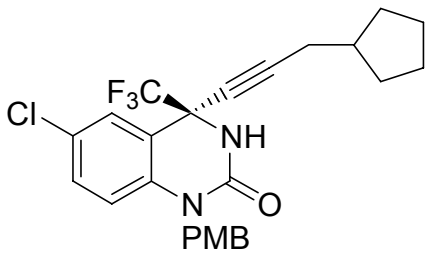


87% yield and >99.5% ee as determined by HPLC analysis (Chiralcel AD, *i*-PrOH/hexane = 20/80, 0.7 mL/min, 254 nm), t_r 8.3 (major), 9.1 (minor); mp 105.5 – 107.1 ^oC; $[\alpha]^{20}_D$ -43.5 (*c* = 1.1, MeOH); FTIR (KBr) ν= 3207, 1683, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ= 7.56 (d, *J* = 1.9 Hz 1H), 7.23 (dd, *J* = 8.8 and 2.4 Hz, 1H), 7.17-7.14 (m, 2H), 6.87-6.83 (m, 2H), 6.78 (d, *J* = 8.9 Hz), 5.83 (s, 1H), 5.13 (d, *J* = 16.8 Hz, 1H), 5.02 (d, *J* = 16.4 Hz, 1H), 3.78 (s, 3H), 0.26 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ= -82.2 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ=158.8, 151.6, 136.3, 130.8, 128.5, 127.9, 127.8, 116.8, 116.0,

114.2, 96.8, 94.2, 58.9, 55.2, 45.6, 29.9, -0.7; MS (EI) *m/e* = 466(M^+, 8.4), 397(12.0),121(100); HREIMS calcd for $C_{22}H_{22}ClF_3N_2O_2Si$ 466.1091, found 466.1081.

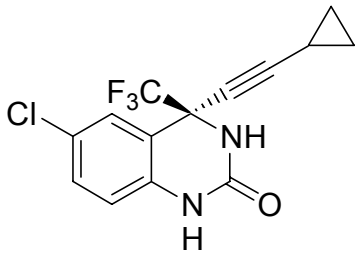


92% yield and >99.5% ee as determined by HPLC analysis (Chiralcel AD, *i*-PrOH/hexane = 20/80, 0.7 mL/min, 254 nm), t_r 9.4 (major), 10.5 (minor); m.p. 139.9 – 140.8 ^oC; $[\alpha]^{20}_D$ –51.1 (*c* = 1.9, MeOH); FTIR (KBr) ν = 3212, 2250, 1687, 1194 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 1.9 Hz 1H), 7.22-7.15 (m, 3H), 6.87-6.82 (m, 2H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.39 (s, 1H), 5.15 (d, *J* = 16.4 Hz, 1H), 5.01 (d, *J* = 16.4 Hz, 1H), 3.77 (s, 3H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.60-1.49 (m, 2H), 1.46-1.39 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -82.4 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 152.6, 136.6, 130.9, 128.8, 128.4, 127.9, 124.0 (q, *J* = 285 Hz), 117.9, 116.2, 114.4, 89.5, 73.6, 58.6 (q, *J* = 30 Hz), 55.4, 45.8, 30.2, 22.1, 18.5, 13.7; MS (EI) *m/e* = 450(M^+, 5.7), 381(9.3), 121(100); HREIMS calcd for $C_{23}H_{22}ClF_3N_2O_2$ 450.1322, found 450.1355.



86% yield and >99.5% ee as determined by HPLC analysis (Chiralcel AD, *i*-PrOH/ hexane = 5/95, 0.7 mL/min, 254 nm), t_r 25.5 (major), 27.8 (minor); m.p. 154.6 – 155.2 ^oC; $[\alpha]^{20}_D$ –50.1 (*c* = 1.1, MeOH); FTIR (KBr) ν = 3207, 2251, 1685, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 1.7 Hz 1H), 7.22-7.14 (m, 3H), 6.86-6.83 (m, 2H), 6.76 (d, *J* = 8.9

Hz, 1H), 6.27 (s, 1H), 5.14 (d, J = 16.5 Hz, 1H), 5.00 (d, J = 16.6 Hz, 1H), 3.77 (s, 3H), 2.32 (d, J = 6.7 Hz, 2H), 2.09 (m, 1H), 1.84-1.76 (m, 2H), 1.67-1.51 (m, 4H), 1.31-1.22 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -82.4 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 152.5, 136.6, 130.9, 128.8, 128.3, 127.9, 124.0 (q, J = 285 Hz), 117.9, 116.2, 114.4, 89.1, 73.6, 58.6 (q, J = 30 Hz), 55.5, 45.8, 38.7, 32.1, 30.5, 29.9, 25.5, 24.5; MS (EI) *m/e* = 476(M^+, 4.9), 407(10.9), 121(100); HREIMS calcd for $C_{25}H_{24}ClF_3N_2O_2$ 476.1478, found 476.1463.



DPC 961

Compound (-)-**3a** (868 mg, 2 mmol) in 10% aqueous CH_3CN (10 mL) was treated with ceric ammonium nitrate (4.4 g, 8 mmol) for 4 h at 25 ^{o}C. The reaction was diluted with water (10 mL) and extracted with EtOAc (10 mLx3). The combined organic layers was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to afford DPC 961 (502 mg, 80% yield). $[\alpha]^{20}_{D}$ -63.0 (c = 0.275, MeOH); FTIR (KBr) ν = 3219, 2249, 1701 cm^{-1}; ^{1}H NMR (300 MHz, Acetone-d_6) δ = 9.04 (s, 1H), 7.53 (s, 1H), 7.51 (s, 1H), 7.42 (dd, J = 8.9 and 2.3 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 1.50-1.43 (m, 1H), 0.95-0.89 (m, 2H), 0.80-0.75 (m, 2H); ^{19}F NMR (282 MHz, Acetone-d_6) δ = -82.9 (s, 3F); ^{13}C NMR (75 MHz, Acetone-d_6) δ =152.6, 137.8, 132.2, 129.0, 127.5, 125.4 (q, J = 285 Hz), 117.5, 116.8, 93.1, 69.2, 60.2 (q, J = 30 Hz), 9.2, 9.1, -0.003; MS (EI) *m/e* = 314(M^+, 7.4), 245(100).