Synthesis and Preparation of P7C3 Analogs

3,6-Dibromo-9-(oxiran-2-ylmethyl)-9H-carbazole (I)

Following established procedures (Asso et al., 2008), powdered KOH (0.103 g, 1.85 mmol) was added to a solution of 3,6-dibromocarbazole (0.500 g, 1.54 mmol) in DMF (1.5 mL) at ambient temperature and stirred for 30 min until dissolved. Epibromohydrin (0.32 mL, 3.8 mmol) was added via syringe and the reaction was stirred at room temperature overnight. Upon completion, the solution was partitioned between EtOAc and H$_2$O. The aqueous layer was washed 3× with EtOAc, and the combined organics were washed with saturated aqueous NaCl, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude residue was recrystallized from EtOAc/Hexane to afford the desired product (389 mg, 66%).

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 8.10 (d, 2H, $J$ = 2.0 Hz), 7.54 (dd, 2H, $J$ = 2.0, 8.5 Hz), 7.31 (d, 2H, $J$ = 8.5 Hz), 4.62 (dd, 1H, $J$ = 2.5, 16.0 Hz), 4.25 (dd, 1H, $J$ = 5.5, 16.0 Hz), 3.29 (m, 1H), 2.79 (dd, 1H, $J$ = 4.0, 4.5 Hz), 2.46 (dd, 1H, $J$ = 2.5, 5.0 Hz).

1-(3,6-dibromo-9H-carbazol-9-yl)-3-(3-methoxyphenylamino)propan-2-ol (II, P7C3-OMe)

Following established procedures (Asso et al., 2008), m-anisidine (1.0 mL, 8.95 mmol) was added to a suspension of epoxide I (3.02 g, 7.92 mmol) in cyclohexane (73 mL). BiCl$_3$ (0.657 g, 2.08 mmol) was added and the mixture was heated at reflux overnight. Upon completion, the reaction was partitioned between EtOAc and H$_2$O. The aqueous layer was washed 3× with EtOAc, and the combined organics were washed with saturated aqueous NaCl, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude residue was purified by chromatography (SiO$_2$, 0–50% EtOAc/Hexane) to afford the desired alcohol as an opaque yellow solid (998 mg, 25%).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 8.12 (d, 2H, $J$ = 1.6 Hz), 7.52 (dd, 2H, $J$ = 2.0, 8.8 Hz), 7.32 (d, 2H, $J$ = 8.8 Hz), 7.07 (dd, 1H, $J$ = 8.0 Hz), 6.31 (dd, 1H, $J$ = 2.4, 8.0 Hz), 6.21 (dd, 1H, $J$ = 2.0, 8.0 Hz), 6.12 (dd, 1H, $J$ = 2.0, 2.4 Hz), 4.34–4.39 (m, 3H), 4.00 (br s, 1H), 3.71 (s, 3H), 3.30 (dd, 1H, $J$ = 3.6, 13.2 Hz), 3.16 (dd, 1H, $J$ = 6.4, 13.2 Hz), 2.16 (br s, 1H).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 161.0, 149.2, 139.9 (2C), 130.4 (2C), 129.5 (2C), 123.8 (2C), 123.5 (2C), 112.8, 111.0 (2C), 106.7, 103.8, 99.8, 69.5, 55.3, 48.0, 47.4. ESI m/z 502.9 ([M+H]+; C$_2$H$_5$Br$_2$N$_2$O$_4$: requires 503.0).

1-(3,6-Dibromo-9H-carbazol-9-yl)-3-(3-methoxyphenylamino)propan-2-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (III)

Alcohol II (0.150 g, 0.298 mmol) was dissolved in anhydrous dichloromethane (6 mL) and cooled to 0 °C. Pyridine (0.053 mL, 0.655 mmol) was added, followed by S- (+)-$\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetyl chloride (5-Mosher’s acid chloride, 0.083 mL, 0.446 mmol) and dimethylaminopyridine (0.004 g, 0.030 mmol). The reaction was allowed to warm to room temperature over 4 hours, after which it was quenched by addition of saturated aqueous NaHCO$_3$. The mixture was extracted 3× with EtOAc, and the combined organics were washed with saturated aqueous NaCl, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude residue was purified by chromatography (SiO$_2$, 0–50% EtOAc/Hexane) to afford a mixture of both possible esters and both possible amides (~5:1 ester:amide ratio by $^1$H NMR, 132 mg, 64%). Separation of the mixture was achieved using HPLC (Phenomenex SiO$_2$: Luna, 21×250 mm, 15% EtOAc/Hexane, 16 mL/min; HPLC Retention time: 25.6 min (ester 1) and 41.2 min (ester 2)).

Ester 1: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 8.11 (d, 2H, $J$ = 2.0 Hz), 7.45 (dd, 2H, $J$ = 8.5 Hz), 7.24 (m, 2H), 7.22 (m, 4H), 7.05 (t, 1H, $J$ = 8.0 Hz), 6.32 (dd, 1H, $J$ = 2.0, 8.0 Hz), 6.12 (dd, 1H, $J$ = 2.0, 8.0 Hz), 6.05 (dd, 1H, $J$ =
2.0, 2.5 Hz), 5.59 (m, 1H), 4.54 (d, 2H, J = 6.5 Hz), 3.71 (br s, 1H), 3.69 (s, 3H), 3.43 (m, 1H), 3.29 (ddd, 1H, $J = 5.5, 13.5$ Hz), 3.19 (s, 3H).

Ester 2: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 8.08 (d, 2H, $J = 2.0$ Hz), 7.42 (dd, 2H, $J = 2.0, 9.0$ Hz), 7.28 (m, 2H), 7.24 (m, 4H), 7.04 (t, 1H, $J = 8.0$ Hz), 6.31 (dd, 1H, $J = 2.0, 8.0$ Hz), 6.11 (dd, 1H, $J = 2.0, 8.0$ Hz), 6.01 (dd, 1H, $J = 2.0, 2.5$ Hz), 5.63 (m, 1H), 4.49 (d, 2H, $J = 6.5$ Hz), 3.82 (dd, 1H, $J = 5.5, 6.0$ Hz), 3.66 (s, 3H), 3.42 (s, 3H), 3.39 (m, 1H), 3.28 (dd, 1H, $J = 5.0, 13.5$ Hz).

R- or S-1-(3,6-Dibromo-9H-carbazol-9-yl)-3-(3-methoxyphenylamino)propan-2-ol ( (+)- and (-)-P7C3-OMe) Following established procedures (Abad et al., 1996) ester III (0.011 g, 0.015 mmol) was dissolved in degassed Et$_2$O (0.150 mL) and cooled to 0 °C. Lithium aluminum hydride (1M in THF, 0.018 mL, 0.018 mmol) was added via syringe and the reaction was stirred for 20 min. Upon completion by TLC the reaction was quenched by the addition of MeOH and stirred for 45 min. The mixture was partitioned between EtOAc and H$_2$O. The aqueous layer was extracted 3× with EtOAc, and the combined organics were washed with saturated aqueous NaCl, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude residue was purified by chromatography (SiO$_2$, 0–30% EtOAc/Hexanes) to afford the desired alcohol (4.7 mg, 64%).

Optical purity was determined by HPLC (ChiralCel OD-H; 20% iPrOH/Hexane; 1ml/min. (R)-(+) configuration ret. time = 87 min. (S)-(−) configuration ret. time = 46 min

(R)-(+)P7C3-A17 (From Ester 1): $[\alpha]_D = +10^0$ (c = 0.1, CH$_2$Cl$_2$) >95% ee

(S)-(−)P7C3-A17 (From Ester 2): $[\alpha]_D = −14^0$ (c = 0.1, CH$_2$Cl$_2$) >95% ee

N-(3-(3,6-dibromo-9H-carbazol-9-yl)-2-fluoropropyl)-3-methoxyaniline (P7C3A20) DAST [(Et$_2$NSF$_3$) 0.12 ml, 0.916 mmol ] was added dropwise to a solution of alcohol II (0.102 g, 0.203 mmol) in 6.0 ml of anhydrous DCM at -78 °C. The reaction was stirred at -78 °C for one hour before being slowly warmed to 0 °C over 5 hours. The reaction was quenched by addition of phosphate buffer (pH=8) and extracted with CH$_2$Cl$_2$. The aqueous phase was extracted twice with 10 ml CH$_2$Cl$_2$. The combined organics were dried over Na$_2$SO$_4$, filtered and concentrated. The crude reaction material was purified by flash chromatography on SiO$_2$ (20% EtOAc/hexanes/0.2%TEA). Fractions containing the desired fluorinated product were further purified with 40% EtOAc/hexanes (+ 0.1%TEA) to provide 5.7 mg desired product.

$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ = 8.16 (2H, $J = 2.0$ Hz), 7.56 (dd, 2H, $J = 1.9, 8.7$ Hz), 7.31 (d, 2H, $J = 8.6$ Hz), 7.11 (t, 1H, $J = 8.1$ Hz), 6.36 (dd, 1H, $J = 2.2, 8.1$ Hz), 6.23 (dd, 1H, $J = 2.0, 8.0$ Hz), 6.15 (t, 1H, $J = 2.3$ Hz), 5.11 (ddddd, 1H, $J = 4.6, 5.8, 10.4, 47.7$ Hz ), 4.60 (m, 2H), 4.39 (dm, 2H), 3.95 (t, 1H, $J = 6.3$ Hz), 3.75 (s, 3H).

MS (ESI), m/z: 504.9 [M+1$^+$]. ([M+1$^+$] for C$_{22}$H$_{19}$Br$_2$FN$_2$O calculated 505.0).

3,6-dibromo-9-(2-(oxiran-2-yl)ethyl)-9H-carbazole (VI) Crushed KOH (0.0054 g, 0.0954 mmol, 1.2 equiv) was added to 3,6-dibromocarbazole (0.028 g, 0.0795 mmol, 1 equiv) in 0.5 mL DMF, and the mixture was stirred for 30 min. 1-Bromo-3,4-epoxybutane (0.0300 g, 0.199 mmol) in 0.5 mL DMF was added dropwise
into the mixture, and it was stirred at room temperature overnight. The crude reaction was diluted with
20 mL EtOAc and washed with water 5 × 10 mL. The organic layer was dried over anhydrous Na2SO4 and
evaporated to afford 31.2 mg white solid as product, yield 97.9%.

1H NMR (CDCl3, 400 MHz) δ = 1.65 - 1.81 (m, 1H), 2.13 - 2.27 (m, 1H), 2.34 (dd, J = 4.88, 2.64 Hz, 1H), 2.64
(dd, J = 4.78, 4.05 Hz, 1H), 2.69 - 2.80 (m, 1H), 4.26 - 4.54 (m, 2H), 7.27 (d, J = 8.69 Hz, 2H), 7.50 (dd, J = 8.69,
1.90 Hz, 2H), 8.08 (d, J = 1.90 Hz, 2H).

**4-(3,6-dibromo-9H-carbazol-9-yl)-1-(phenylamino)butan-2-ol (P7C3A35)**

Following the procedure outlined for the synthesis of P7C3-OMe, P7C3A35 was
isolated as a white solid in 31% yield.

1H NMR (CDCl3, 400 MHz) δ = 1.87 - 1.98 (m, 1H), 2.05 - 2.14 (m, 1H), 2.99 - 3.07 (dd, J
= 13.24, 3.43 Hz, 1H), 3.09 - 3.17 (dd, J = 13.24, 8.27 Hz, 1H), 3.60 - 3.74 (m, 1H), 4.39 - 4.48
(m, 1H), 4.51 - 4.60 (m, 1H), 6.57 (d, J = 7.71 Hz, 2H), 6.74 (t, J = 7.34 Hz, 1H), 7.15 (dd, J = 8.27, 7.59 Hz,
2H), 7.38 (d, J = 8.69 Hz, 2H), 7.56 (dd, J = 8.69, 1.90 Hz, 2H), 8.14 (d, J = 1.85 Hz, 2H)

m/z (ESI): 486.9 (M + H⁺) ([M+1] for C22H20Br2N2O requires 467.0)

**1-(3,6-dibromo-9H-carbazol-9-yl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)propan-2-ol (P7C3A29)**

A solution of 1-(3,6-dibromo-9H-carbazol-9-yl)-3-hydrazinylpropan-2-ol (56 mg, 0.136 mmol, derived
from opening epoxide I with hydrazine) and acetylacetone (13.7mg, 0.136mmol)
in 1 ml of EtOH was heated at 70 °C for 1 hour. The reaction mixture was cooled to
room temperature and concentrated under reduced pressure. The crude residue was purified by chromatography (SiO2, 0-50% EtOAc/Hexane) to afford
the desired alcohol as an off-white solid (29 mg, 45%).

1H NMR (400 MHz, CDCl3) δ = 8.12 (d, J = 1.9, 2H), 7.51 (dd, J = 1.9, 8.7, 2H), 7.14
(d, J = 8.7, 2H), 5.79 (s, 1H), 5.19-5.10 (br s, 1H), 4.51 (m, 1H), 4.38 (s, 1H), 4.36 (s,
1H), 3.92 (dd, J = 3.0, 13.8, 1H), 3.69 (dd, J = 6.4, 13.8, 1H), 2.21 (s, 3H), 1.85 (s, 3H).

ESI m/z 475.9 ([M+H]+), C37H26BrN4O requires 476.