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Ethyl (2-methoxyphenyl)-2-oxo-3-carbethoxypentanoate (7). Potassium t-butoxide (179 g,.1.51 mol, 1.2 eq.) and 600 mL ether were cooled to 10°C. Diethyl oxalate (257 ml, 1.89 mol, 1.5 eq.) and ethyl 2-methoxyphenyl butyrate (280 g, 1.26 mol) were dissolved in 600 mL ether and added to the cold potassium t-butoxide slurry at such a rate as to maintain the reaction temperature below 25 °C. The ice bath was removed and the reaction was allowed to stir at ambient temperature for 19 h. The reaction was quenched onto 1 kg ice, and extracted with diethyl ether. The combined organic extracts were washed with 1 N NaOH, and the aqueous layers combined. The aqueous layer was acidified with conc. HCl to pH 1, and extracted with diethyl ether. The ether extract was washed with brine, dried ($MgSO_4$), and concentrated to yield 384 g (95%) of crude product, which was used in the next step without purification, . ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H), 1.37 (t, 3H), 2.10-2.35 (m, 2H), 2.6-2.8 (m, 2H), 4.0 (dd, 1H), 4.18 (q, 2H), 4.32 (q, 2H), 6.80-6.92 (m, 2H), 7.10-7.22 (m, 3H).

5-methoxy-1,2,3,4-tetrahydronaphthalene-1,2-carboxylic anhydride (8). The keto diester **7** (384 g, 1.20 mol) was added to an ice cold solution of 80% H_2SO_4 (3.1 L). The ice bath was removed and the reaction was stirred at ambient temperature for 6 h. The reaction was then poured onto 3 kg of ice with vigorous stirring, and the resulting yellow solid was collected by filtration, washed with 1.5 L H_2O, and dried. The dried product was recrystallized from 1:1 ethyl acetate:acetonitrile to yield 140 g (51%) of the intermediate dihydronaphthalene. The product was dissolved in 1500 mL ethyl acetate and 14 g 10% Pd/C was added. The reaction was hydrogenated at 4 atm H_2 for 20 h, filtered, and the solvent evaporated. Recrystallization from ethyl acetate yielded 135 g (49%) of the title compound, m.p. 138-140 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (m, 1H), 2.28 (m, 1H), 2.47 (m, 1H), 2.95 (m, 1H), 3.55 (m, 1H), 3.83 (s, 3H), 4.32 (d, 1H), 6.83 (d, 1H), 7.17 (d, 1H), 7.27 (t, 1H).

(3aR,9bR)-6-Methoxy-((S)-α-methylbenzyl)-2,3,3a,4,5,9b-[1H]-hexahydrobenz[e]isoindole-1,3-dione (9). The anhydride **8** (48.8 g, 210 mmol) was combined with (S)-(-)-α-methylbenzyl amine (28.1 g, 0.230 mmol) in xylene (200 mL), and the reaction was heated to reflux with water removal (Dean Stark trap) until the theoretical amount of water was removed. The reaction was then cooled and diluted with ethyl acetate (300 mL). The resulting solution was washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to dryness. The resulting oily solid was triturated with diethyl ether, and the resulting crystalline (3aR, 9bR) product was collected (28.14 g, 40%), m.p. 148-150 °C. The diasetereomeric purity of the imide

was determined by HPLC (Chiracel OD column; 95:5 hexane:isopropanol; 1.0 mL/min.) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (d, 3H), 1.80 (m, 1H), 2.20 (m, 2H), 2.89 (m, 1H), 3.20 (m, 1H), 3.80 (s, 3H), 3.95 (d, 1H), 5.49 (q, 1H), 6.79 (d, 1H), 7.17 - 7.45 (m, 7H).

(3aR,9bR)-6-Methoxy-2,3,3a,4,5,9b-[1H]-hexahydrobenz[e]isoindole hydrochloride (10). The imide **9** (28.0 g, 83.5 mmol) was dissolved in THF (100 mL) and added over 5 min to a 1.0 M solution of BH_3 in THF. The reaction mixture was heated at reflux for 2 h, and then cooled to 25 °C. Methanol (100 mL) was added cautiously, and after the evolution of H_2 ceased, solvent was evaporated at reduced pressure. The resulting oil was dissolved in 2:1 methanol:isopropyl alcohol saturated with HCl (g), and the resulting solution was heated at reflux for 3 h. The solvent was removed *in vacuo*, and the resulting solid was triturated with 1:1 ethanol:diethyl ether, and the title compound (25.8 g, 90%) was collected by filtration. m.p. 229 -231 °C. The diastereomeric purity of the amine was determined by HPLC (Chiracel OD column; 99:1 hexane:isopropanol, 0.1% diethylamine; 0.5 mL/min). Absolute stereochemistry was determined by single crystal X-Ray of the amine hydrochloride salt. ^{1}H NMR (free base) (300 MHz, $CDCl_3$) δ 1.38 (d, 3H), 1.49 (m, 1H), 1.57 (m, 1H), 2.07 (dd, 1H), 2.15 (m, 1H), 2.40 - 2.72 (m, 3H), 2.97 (dd, 1H), 3.21 (q, 1H), 3.49 (m, 2H), 3.81 (s, 3H), 6.68 (d, 1H), 6.77 (d, 1H), 7.11 (t, 1H), 7.19 - 7.38 (m, 5H).

The intermediate tertiary amine (25.7 g, 74.7 mmol) was dissolved in methanol (700 mL) and 10% Pd/C (5.9 g) was added. The reaction was hydrogentated at 4 atm of hydrogen at room temperature for 24 h. The catalyst was removed by filtration, and the solvent was evaporated to yield 15.9 g (89%) of the title compound as a white solid. m.p. 223-225 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 1.60 (m, 1H), 1.93 (m, 1H), 2.54 (m, 1H), 2.67 (m, 1H), 2.93 (m, 1H), 3.09 (dd, 1H), 3.13 (dd, 1H), 3.53 (m, 1H), 3.58 (dd, 1H), 3.67 (dd, 1H), 3.80 (s, 3H), 6.78 (d, 1H), 6.81 (d, 1H), 7.16 (t, 1H). $[\alpha]_D^{20}$ = -22.0° (c=1.39, MeOH, free base).

(3aR,9bR)-2-Aminoethyl-6-methoxy-2,3,3a,4,5,9b-[1H]-hexahydro-benz[e]isoindole (11). The isoindole hydrochloride salt **10** (2.39 g, 10.0 mmol) was dissolved in H_2O, basified to pH 12 with aqueous NaOH solution and extracted 3x CH_2Cl_2. The organic extracts were dried (K_2CO_3), and evaporated to yield 1.96 g (9.64 mmol) of the free base. To the free base dissolved in CH_3CN (10 mL) and diisopropylethylamine (5 mL) was added 0.67 mL (10.6 mmol) of chloroacetonitrile. The reaction was heated at 70 °C for 1 h, quenched in 5% $NaHCO_3$, and extracted with ethyl

acetate (2x). The organic extracts were washed with water (2x) and brine (1x), dried (Na_2SO_4) and evaporated to yield 2.20 g of the intermediate nitrile as an off white solid (90.5%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (m, 2H), 1.80 (m, 1H), 2.58 (m, 3H), 2.77 (m, 1H), 3.23 (m, 2H), 3.48 (q, 1H), 3.64 (s, 2H), 3.81 (s, 3H), 6.70 (d, 1H), 6.74 (d, 1H), 7.12 (t, 1H).

$LiAlH_4$ (0.82 g, 21.5 mmol) was suspended in THF (30 mL) and cooled to 0 °C. The nitrile (0.80 g, 3.30 mmol) was dissolved in THF (5 mL) and added dropwise to the above $LiAlH_4$ suspension. The reaction was then stirred at room temperature for 1.5 h, quenched by addition of H_2O (0.8 mL), 15% NaOH (0.8 mL) and H_2O (2.4 mL), filtered through celite, washing with several hot portions of THF, and the solvent evaporated to yield the title compound (0.75 g, 93%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 3H), 1.72 (m, 1H), 2.19 (m, 2H), 2.52 (m, 3H), 2.70 (m, 1H), 2.80 (t, 1H), 3.21 (dd, 1H), 3.28 (t, 1H, 3.40 (m, 1H), 3.80 (s, 3H), 6.67 (d, 1H), 6.75 (d, 1H), 7.11 (t, 1H).

3-[2-((3aR,9bR)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-[1H]benz[e]iso-indol-1-yl)ethyl]-pyrido[4',3':4,5]thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione dihydrochloride (1)

3-Amino-2-carbomethoxythieno[3,2-c]pyridine (**12**) (.61 g, 2.9 mmol), prepared by the procedure described by Dunn and Norrie[9], and Et_3N (0.88 mL, 6.3 mmol) were dissloved in anhydrous methylene chloride under nitrogen and cooled to -78° C. Phosgene (1.5 mL of a 1.93 M solution in toluene, 2.9 mmol) was added, and the reaction was stirred at -78 °C for 45 min and room temperature for 1.5 h. The amine **11** (0.60 g, 2.4 mmol) in CH_2Cl_2 was added, and the reaction mixture was stirred for 2 hours. The reaction mixture was partitioned between 1 N NaOH and CH_2Cl_2. The CH_2Cl_2 layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue obtained was dissolved in THF and treated with 1 M potassium t-butoxide in THF. The reaction was stirred for 1 h at room temperature, concentrated under reduced pressure and chromatographed on silica gel eluting with 5% EtOH in CH_2Cl_2 saturated with NH_3, increasing the EtOH concentration to 10%, to provide 0.68 g (75 %) of the title compound which was subsequently converted to its HCl salt: m.p. 261-262 °C. ^1H NMR (300 MHz, $CDCl_3$) of the free base δ 1.48-1.63 (m, 1H), 1.70-1.83 (m, 1H), 2.44-2.76 (m, 5H), 2.93-3.05 (m, 1H), 3.09-3.21 (m, 1H), 3.41-3.55 (m, 1H), 3.59-3.71 (m, 2H), 3.79 (s, 3H), 4.29-4.45 (m, 2H), 6.62 (d, 1H), 6.70 (d, 1H), 7.01 (t, 1H), 7.76 (d, 1H), 8.62 (d, 1H), 9.45 (s, 1H). MS (DCI/NH_3) m/e 449 $(M+H)^+$. Anal calcd for

$C_{24}H_{24}N_4O_3S \cdot 2$ HCl: C, 55.28; H, 5.03; N, 10.74. Found: C, 55.36; H, 5.04; N, 10.69.