Supplementary Material

An Expedient Enantioselective Route to Diaminotetralins: Application in the Preparation of Analgesic Compounds

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The following general experimental details apply to all following reactions.

All flasks were flame-dried under a stream of nitrogen or argon and cooled before use. Solvents and solutions were transferred with syringes and cannulae using standard inert atmosphere techniques.

¹H NMR spectra were recorded at 300 MHz using a Varian Gemini NMR spectrometer or at 400 MHz using a Varian XL400 spectrometer with CDCl₃ as reference standard (δ 7.24 ppm) or some other suitable solvent. Spectral features are tabulated in the following order: chemical shift (δ , ppm); number of protons; multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-complex multiplet, br-broad); coupling constants (*J*, Hz). ¹³C NMR spectra were recorded at 400 MHz with CDCl₃ as reference standard (δ = 77.0 ppm) or some other suitable solvent.

IR spectra were obtained using a Nicolet DX FT-JR spectrometer as a KBr pellet or neat film between KBr plates. High resolution mass spectra were obtained from a VG 70-250S (double focusing) mass spectrometer at 70 eV. Combustion analyses were submitted to Canadian Microanalytical Service Ltd., BC. Optical rotations were measured on a Perkin-Elmer Model 243 Polarimeter using the sodium D line with spectro-grade CHCl₃ in a 1 dm cell. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

HPLC analysis was performed on a Waters 600E with Chiralcel OD or OJ columns. Analytical TLC was performed using EM Separations precoated silica gel 0.2 mm layer UV 254 fluorescent sheets. Column chromatography was performed as "Flash Chromatography" as reported by Still¹ using (200-400 mesh) Merck grade silica gel.

Diethyl ether, THF, benzene and toluene were distilled from sodium benzophenone ketyl immediately prior to use. CH₂Cl₂ was distilled from calcium hydride. DME was distilled from sodium benzophenone ketyl and stored. DMF was dried and stored over activated molecular sieves. The (R, S)-PPF-P^tBu₂ ligand was donated by Solvias. (α S, α ¹S)-2,2¹-Bis(α -*N,N*-dimethylaminoethyl)-(R,R)-1,1¹-bis-(diphenylphosphino)-ferrocene (C₂-

¹ Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1989**, *54*, 5667.

Ferriphos) was prepared according to literature procedure² starting from (R)-2-Methyl-CBS-oxazaborolidine. All other reagents were obtained from Aldrich and used as received unless otherwise stated.

N-Boc 4

1,4-Dihydro-1,4-epiazano-naphthalene-9-carboxylic acid tert-butyl ester (N-Boc 4):

To *N*-Boc pyrrole (16.7 g, 100 mmol) in DME (40 mL) at 50°C in a flame dried 3-neck flask fitted with a reflux condenser and 2 addition funnels was simultaneously added a solution of anthranilic acid (13.8 g, 100 mmol) in DME (~100 mL) and a separate solution of isoamyl nitrite (16.8 mL, 125 mmol) in DME (50 mL). The addition took about 45 minutes. The reaction was allowed to stir at 50°C for 30 mm until no further gas was evolved. The crude red solution was reduced in volume by rotovap distillation to approximately half the original volume. The reaction mixture was then partitioned between Et₂O and saturated K₂CO₃ and the aqueous layer was extracted 3 times with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated. The resulting dark brown oil was further evaporated under reduce pressure to remove the iosamyalcohol byproduct. This crude mixture can be purified by repeated recrystallization from hexanes or the process can be sped up by performing column chromatography with a short plug of silica gel to remove most of the colored byproducts. Recrystallization gives **N-Boc 4** in 63% yield as an off white solid. Spectral data is identical to that reported in the literature.³

N-Tos 4

9-(Toluene-4-sulfonyl)-1,4-dihydro-1,4-epiazano-naphthalene (N-Tos 4): **N-Boc 4** (6 g, 23.6 mmol) was dissolved in 100 mL CH₂Cl₂ followed by the addition of Et₃N (4 mL) and heating to reflux. TMSI (3.7 mL, 25.9 mmol) was added dropwise over 10 minutes and the reaction was heated at reflux for an additional 15 minutes after which time TLC analysis showed complete consumption of **N-Boc 4**. The reaction mixture was cooled to 0°C then MeOH (1 mL, 30 mmol) was added dropwise. After 10 minutes at 0°C, Tosyl chloride (4.56g, 24 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was stirred at room temperature for an additional hour. Water (100 mL) and CH₂Cl₂ was added until all precipitates dissolved. The organic and

² Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, 4, No.5, 950.

³ Carpino, L.A.; Barr, D.E. *J. Org. Chem.* **1966**, 31, 764.

aqueous phases were separated and the aqueous phase was extracted twice with CH₂Cl₂. The organic fractions were combined, dried over MgSO₄ and concentrated. Recrystallization from ethylacetate gave **N-Tos 4** as a crystalline solid. Spectral data was identical to that reported in the literature.⁴

N-Nos 4

9-(4-Nitro-benzenesulfonyl)-1,4-dihydro-1,4-epiazano-naphthalene (N-Nos 4): **N-Boc 4** (6 g, 23.6 mmol) was dissolved in 100 mL CH₂Cl₂ followed by the addition of Et₃N (4 mL) and heating to reflux. TMSI (3.7 mL, 25.9 mmol) was added dropwise over 10 minutes and the reaction was heated at reflux for an additional 15 minutes after which time TLC analysis showed complete consumption of **N-Boc 4**. The reaction mixture was cooled to 0°C then MeOH (1 mL, 30 mmol) was added dropwise. After 10 minutes at 0°C, Nosyl chloride (5.5 g, 24 mmol) was added and the reaction was allowed to warm to room temperature. The formation of a white precipitate was observed at this point. The reaction was stirred at room temperature for an additional hour. Water (100 mL) and CH₂Cl₂ was added until all precipitates dissolved. The organic and aqueous phases were separated and the aqueous phase was extracted twice with CH₂Cl₂. The organic fractions were combined, dried over MgSO₄ and concentrated. Trituration in Et₂O gave 7.13 g of a white crystalline solid **N-Nos 4** (92% yield). R_f = 0.45 on silica gel (40% ethyl acetate:hexanes); mp 205-210°C (decomp) (Et₂O); IR (KBr, cm⁻¹) ¹H NMR (400MHz, d₆-DMSO) δ 8.15 (2H, d, J= 7.9Hz), 7.76 (2H, d, J= 7.9Hz), 7.12-7.05 (2H, m), 6.90 (2H, s), 6.73-6.66 (2H, m), 5.64 (2H, s); ¹³C NMR (400MHz, d₆-DMSO) δ 149.6, 147.1, 143.2, 142.9, 129.9, 124.9, 124.1, 121.7, 67.5. Anal. Calcd for C₁₆H₁₂N₂O₄S: C, 58.53; H, 3.68; N, 8.53. Found: C, 58.55; H, 7.10; N, 5.67.

2-(3,4-Dichloro-phenyl)-1-(1,4 dihydro-1,4-epiazano-naphthalen-9yl)-ethanone : **N-Boc 4** (6 g, 23.6 mmol) was dissolved in 100 mL CH₂Cl₂ followed by the addition of Et₃N (4 mL) and heating to reflux. TMSI (3.7 mL, 25.9 mmol) was added dropwise over 10 minutes and the reaction was heated at reflux for an additional 15 minutes after which time TLC analysis showed complete consumption of **N-Boc 4**. The reaction mixture was cooled to 0°C then MeOH (1 mL, 30 mmol) was added dropwise. After 10 minutes at 0°C, 3,4-Dichlorophenyl acetyl chloride (5.3 g, 24 mmol) was added and the reaction was

⁴ Kaupp, G. *Chem. Ber.* **1970**, 2288.

allowed to warm to room temperature. The reaction was stirred at room temperature for an additional hour. Water (100 mL) and CH₂Cl₂ was added until all precipitates dissolved. The organic and aqueous phases were separated and the aqueous phase was extracted twice with CH₂Cl₂. The organic fractions were combined, dried over MgSO₄ and concentrated. Trituration in Et₂O gave 7.13 g of a white crystalline solid (92% yield). *R*_f = 0.45 on silica gel (20% ethyl acetate:hexanes); mp 124-125°C (Et₂O); IR (KBr, cm⁻¹) 3691(w), 3050(s), 2685(w), 2528(w), 2305(m), 2169(w), 2119(w), 1996(w), 1794(m), 1648(s), 1560(w), 1421(s), 1262(s), 1133(w), 1034(m), 906(s), 730(s); ¹H NMR (400MHz, CDCl₃) δ 7.30-7.22(3H, m), 7.12-7.02(2H, m), 6.97-6.88(4H, m), 5.89(1H, s), 5.52(1H, s), 3.55-3.47(2H, m); ¹³C NMR (400MHz, CDCl₃) δ 165.25, 147.98, 147.66, 144.19, 142.20, 134.24, 132.51, 131.12, 130.45, 128.61, 125.47, 125.20, 121.58, 120.34, 65.90, 63.65, 39.99. HRMS calcd for C₁₈H₁₃NOCl₂ (M⁺): 329.0374. Found: 329.0367.

General Procedure for the ARO Reactions with Amine Nucleophiles: To a flame dried round bottom flask were added **N-Boc 4** (100mg, 0.41mmol), [Rh(COD)Cl]₂ (2.5mol%), (*R,S*)-PPF-P^tBu₂ or C₂-Ferriphos (10mol%) followed by addition of THP and nucleophile (3 equivalents). The mixture was heated to 100°C until the reaction was complete as judged by thin layer chromatography. The solvents were removed *in vacuo* and the crude mixture was purified by flash chromatography.

(5b)

(1S, 2S)-(2-Pyrrolidin-1-yl-1,2-dihydro-naphthalen-1-yl)-carbamic acid *tert*-butyl ester [(+)-5b].

Following the general procedure, **5b** was obtained as a white solid (99mg, 77%). The ee was determined to be 86% using HPLC analysis on a CHIRALCEL AD column, λ = 486 nm. Retention times in 2% isopropanol in hexanes (0.5ml/min, 15°C) were 21.45 min (minor) and 23.04 min (major). *R*_f = 0.2 on silica gel (50% ethyl acetate:hexanes); mp 84-87°C (Et₂O); [α]_D²⁵ = +230.5 (c = 0.98, CCl₄); IR (KBr, cm⁻¹) 3450(w), 2809(m), 2360(s), 1716(s), 1653(w), 1557(s), 1251(m), 1169(m), 1005(m); ¹H NMR (400MHz, CDCl₃) δ 7.33-7.31(1H, m), 7.24-7.17(2H, m), 7.08-7.06(1H, m), 6.60(1H, d, J = 9.6Hz), 5.97(1H, dd, J = 9.8Hz, 5.2Hz), 4.93(1H, br s), 4.76(1H, br d, J = 6Hz), 3.34(1H, t, J = 4Hz), 2.69-2.59(4H, m), 1.68(4H, m), 1.42(9H, s); ¹³C NMR (400MHz, CDCl₃) δ 155.15, 134.86, 132.17, 129.18, 128.42, 128.14, 126.78, 126.23, 61.23, 50.12, 28.43, 23.48. HRMS calcd for C₁₉H₂₆N₂O₂ (M⁺): 314.1994. Found: 314.1991.

(+/-) **5a**

4-Methyl-N-(2-pyrrolidin-1-yl-1,2-dihydro-naphthalen-1-yl)-benzenesulfonamide

[(+/-) **5a]:** To round bottomed flask was added **N-Tos 4** (60 mg, 0.2 mmol), [Rh(COD)Cl]₂ (2.5 mg, 0.005 mmol), and DPPF (5.5 mg, 0.01 mmol). THF (2 ml) was then added followed by triethylamine hydrochloride (138 mg, 1.0 mmol) and pyrrolidine (83 μ l, 1.0 mmol). The resulting heterogeneous mixture was heated to reflux for 14 hours. Upon completion, the reaction mixture was concentrated and chromatographed (30% ethyl acetate:hexanes) to give **(+/-) 5a** (70 mg, 96%) a white solid. The regiochemistry and relative stereochemistry was proven by X-ray diffraction. R_f = 0.15 on silica gel (30% ethyl acetate:hexanes); mp 140-145°C; IR (KBr, cm^{-1}) 3496 (br), 3035 (m), 2967 (s), 1454 (m), 1193 (s), 1117 (m), 1048 (s). ¹H NMR (400MHz, CDCl₃) δ 7.74 (2H, d, J = 8.3Hz), 7.30 (2H, d, J = 8.2Hz), 7.22-7.17 (1H, m), 7.08-7.02 (2H, m), 6.84 (1H, d, J = 7.5Hz), 6.61 (1H, d, J = 9.7Hz), 5.93 (1H, dd, J = 4.9, 9.7Hz), 4.70 (1H, br s), 4.45 (1H, d, J = 3.7Hz), 3.89 (1H, dd, J = 4.2, 4.2Hz), 2.58-2.49 (2H, m), 2.45 (3H, s), 2.36-2.29 (2H, m), 1.63-1.58 (4H, m); ¹³C NMR (400MHz, CDCl₃) δ 143.46, 138.05, 133.63, 132.17, 129.72, 129.46, 128.55, 128.27, 128.16, 127.40, 126.91, 125.59, 61.24, 53.63, 49.97, 23.46, 21.65. Anal. Calcd for C₂₁H₂₄N₂O₂S: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.51; H, 6.62; N, 7.55.

5

4-Nitro-N-(2-pyrrolidin-1-yl-1,2-dihydro-naphthalen-1-yl)-benzenesulfonamide (5**):**

To round bottomed flask was added **N-Nos 4** (66 mg, 0.2 mmol), [Rh(COD)Cl]₂ (2.5 mg, 0.005 mmol), and DPPF (5.5 mg, 0.01 mmol). THF (2 ml) was then added followed by triethylamine hydrochloride (138 mg, 1.0 mmol) and pyrrolidine (83 μ l, 1.0 mmol). The resulting heterogeneous mixture was heated to reflux for 16 hours. Upon completion, the reaction mixture was concentrated and chromatographed (30% ethyl acetate:hexanes) to give **5** (67 mg, 84%) a white solid. R_f = 0.12 on silica gel (30% ethyl acetate:hexanes); mp 142-145°C; IR (KBr, cm^{-1}) 3389 (br), 3026 (m), 2978 (s), 1497 (s), 1343 (s), 1117 (m), 1048 (s). ¹H NMR (400MHz, CDCl₃) δ 8.30 (2H, d, J = 8.8Hz), 7.99 (2H, d, J = 8.8Hz), 7.24-7.18 (1H, m), 7.10-7.04 (2H, m), 6.95-6.90 (1H, m), 6.63 (1H, d, J = 9.9Hz), 5.93 (1H, dd, J = 4.7, 9.7Hz), 5.20-4.80 (1H, br s), 4.60 (1H, d, J = 3.8Hz), 3.40-3.35 (1H, m), 2.58-2.50 (2H, m), 2.43-2.34 (2H, m), 1.64-1.57 (4H, m); ¹³C NMR (400MHz, CDCl₃) δ 149.8, 147.1, 132.8, 131.9, 129.7, 128.8, 128.2, 128.1, 128.0, 127.1, 125.0, 124.1, 61.4, 54.4, 50.0, 23.4. Anal. Calcd for C₂₀H₂₁N₃O₄S: C, 60.13; H, 5.30; N, 10.52. Found: C, 60.16; H, 5.33; N, 10.50.

(1S, 2S)-(2-Piperidin-1-yl-1,2-dihydro-naphthalen-1-yl)-carbamic acid *tert*-butyl ester (7)

Following the general procedure, **7** was obtained as a white solid (94mg, 70%). The ee was determined to be 84% using HPLC analysis on a CHIRALCEL OD column, $\lambda = 486$ nm. Retention times in 2% isopropanol in hexanes were 5.61min (minor) and 6.02min (major). $R_f = 0.3$ on silica gel (40% ethyl acetate:hexanes); mp 118-122°C (Et₂O); $[\alpha]_D^{25} = +200.5$ (c = 0.98, CCl₄); IR (KBr, cm⁻¹) 3448(m), 2978(m), 2288(m), 1713(s), 1549(s), 1251(s), 1170(m), 1005(m), 760(s); ¹H NMR (400MHz, CDCl₃) δ 7.36-7.34 (1H, m), 7.23-7.19 (2H, m), 7.09-7.06 (1H, m), 6.62 (1H, d, $J = 10$ Hz), 5.97 (1H, dd, $J = 9.8$ Hz, 4.4Hz), 5.03 (1H, br s), 4.60 (1H, br s), 3.37 (1H, t, $J = 4.4$ Hz), 2.61-2.56 (2H, m), 2.44-2.42 (2H, m), 1.50-1.37 (6H, m), 1.45 (9H, s); ¹³C NMR (400MHz, CDCl₃) δ 155.32, 135.83, 132.57, 129.36, 128.23, 128.04, 127.80, 126.78, 126.39, 64.92, 50.08, 48.15, 29.82, 28.57, 26.55, 24.69. HRMS calcd for C₂₀H₂₈N₂O₂ (M⁺): 328.2150. Found: 328.2145.

4-Methyl-N-(2-piperidin-1-yl-1,2-dihydro-naphthalen-1-yl)-benzenesulfonamide (8):

To round bottomed flask was added **N-Tos 4** (60 mg, 0.2 mmol), [Rh(COD)Cl]₂ (2.5 mg, 0.005 mmol), and DPPF (5.5 mg, 0.01 mmol). THF (2 ml) was then added followed by triethylamine (140 μ l, 1.0 mmol) and piperidine hydrochloride (121 mg, 1.0 mmol). The resulting heterogeneous mixture was heated to reflux for 14 hours. Upon completion, the reaction mixture was concentrated and chromatographed (30% ethyl acetate:hexanes) to give **8** (72 mg, 94%) a white solid. $R_f = 0.17$ on silica gel (30% ethyl acetate:hexanes); mp 116-117°C; IR (KBr, cm⁻¹) 3496 (br), 3034 (m), 2975 (s), 1455 (m), 1193 (s), 1048 (s). ¹H NMR (400MHz, CDCl₃) δ 7.75 (2H, d, $J = 8.2$ Hz), 7.30 (2H, d, $J = 7.8$ Hz), 7.21-7.18 (1H, m), 7.10-7.05 (1H, m), 7.04 (1H, d, $J = 7.5$ Hz), 6.94 (1H, d, $J = 7.5$ Hz), 6.61 (1H, dd, $J = 1.0, 9.7$ Hz), 5.91 (1H, dd, $J = 4.8, 9.7$ Hz), 4.82 (1H, s (br)), 4.53 (1H, d, $J = 4.4$ Hz), 3.38-3.35 (1H, m), 2.44 (3H, s), 2.41-2.34 (2H, m), 2.16-2.09 (2H, m), 1.40-1.26 (6H, m); ¹³C NMR (400MHz, CDCl₃) δ 143.3, 137.7, 134.2, 132.2, 129.6, 129.4, 128.2, 128.0, 127.7, 127.2, 126.6, 125.0, 64.2, 50.9, 49.6, 26.2, 24.3, 21.5. HRMS calcd for C₂₂H₂₆N₂O₂S (M⁺): 382.1715. Found: 382.1713.

N-[2-(3,4-Dihydro-1H-isoquinolin-2-yl)-1,2-dihydro-naphthalen-1-yl]-4-methyl-benzenesulfonamide (9): To round bottomed flask was added **N-Tos 4** (60 mg, 0.2 mmol), [Rh(COD)Cl]₂ (2.5 mg, 0.005 mmol), and DPPF (5.5 mg, 0.01 mmol). THF (2 ml) was then added followed by triethylamine hydrochloride (138 mg, 1.0 mmol) and tetrahydroisoquinoline (125 μ l, 1.0 mmol). The resulting heterogeneous mixture was heated to reflux for 15 hours. Upon completion, the reaction mixture was concentrated and chromatographed (30% ethyl acetate:hexanes) to give **9** (70 mg, 81%) as a white solid. R_f = 0.22 on silica gel (30% ethyl acetate:hexanes); mp 142-146°C; IR (KBr, cm^{-1}) 3482 (br), 3036 (w), 2937 (s), 2853 (m), 1453 (s), 1193 (s), 1109 (s), 1046 (s). ¹H NMR (400MHz, CDCl₃) δ 7.73 (2H, d, J = 8.2Hz), 7.26-7.18 (3H, m), 7.12-6.98 (5H, m), 6.90 (1H, d, J = 8.1Hz), 6.80 (1H, d, J = 6.8Hz), 6.67 (1H, d, J = 9.7Hz), 5.95 (1H, dd, J = 4.7, 9.7Hz), 4.80 (1H, s), 4.62 (1H, s), 3.68 (1H, AB, d, J = 15.0Hz), 3.63 (1H, dd, J = 4.5, 4.5Hz), 3.40 (1H, AB, d, J = 15.0Hz), 2.68-2.56 (4H, m), 2.40 (3H, s); ¹³C NMR (400MHz, CDCl₃) δ 143.4, 137.7, 137.7, 134.1, 133.8, 132.2, 129.9, 129.6, 128.6, 128.5, 128.3, 127.9, 127.2, 126.8, 126.5, 125.9, 125.4, 124.6. Anal. Calcd for C₂₆H₂₆N₂O₂S: C, 72.53; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.12; N, 6.50.

(1S, 2S)-[2-(4-Phenyl-piperazin-1-yl)-1,2-dihydro-naphthalen-1-yl]-carbamic acid *tert*-butyl ester (10).

Following the general procedure, **10** was obtained as a white solid (126mg, 76%). The ee was determined to be 96% using HPLC analysis on a CHIRALCEL AD column, λ = 486 nm. Retention times in 10% isopropanol in hexanes were 7.13min (minor) and 8.46 min (major). R_f = 0.2 on silica gel (10% ethyl acetate:hexanes); mp 166-167°C (Et₂O); [α]_D²⁵ = +314.8 (c = 0.99, CCl₄); IR (KBr, cm^{-1}) 3453(m), 2979(m), 2328(m), 1711(s), 1562(m), 1483(m), 1367(m), 1169(s); ¹H NMR (400MHz, CDCl₃) δ 7.37(1H, m), 7.25(4H, m), 7.11-7.09(1H, m), 6.86 (2H, d, J = 8.4Hz), 6.82(1H, t, J = 7.2Hz), 6.66(1H, d, J = 10Hz), 6.00(1H, dd, J = 9.6Hz, 4.4Hz), 5.06(1H, br s), 4.60(1H, br d, J = 6.4Hz), 3.47(1H, t, J = 4.4Hz), 3.10(4H, t, J = 5.2Hz), 2.82-2.76(2H, m), 2.70-2.68(2H, m), 1.44(9H, s); ¹³C NMR (400MHz, CDCl₃) δ 155.38, 151.57, 135.37, 132.53, 129.82, 129.17, 128.42, 128.27, 127.95, 126.90, 125.48, 119.68, 116.22, 64.03, 49.76, 48.81, 48.64, 29.83, 28.61. HRMS calcd for C₂₅H₃₁N₃O₂ (M⁺): 405.2416. Found: 405.2411.

(11)

(1S, 2S)-(2-Morpholin-4-yl-1,2-dihydro-naphthalen-1-yl)-carbamic acid *tert*-butyl ester (11)

Following the general procedure, **11** was obtained as a white solid (90mg, 67%). The ee was determined to be 80% using HPLC analysis on a CHIRALCEL AD column, $\lambda = 486$ nm. Retention times in 10% isopropanol in hexanes (0.5ml/min, 15C) were 15.27min (minor) and 16.72 min (major). $R_f = 0.3$ on silica gel (40% ethyl acetate:hexanes); mp 113-116°C (Et₂O); $[\alpha]_D^{25} = +210.3$ ($c = 1.04$, CCl₄); IR (KBr, cm⁻¹) 3448(m), 2978(m), 2281(w), 1714(s), 1550(s), 1367(w), 1250(s), 1170(s), 1005(s), 757(s); ¹H NMR (400MHz, CDCl₃) δ 7.37-7.35(1H, m), 7.2-7.21(2H, m), 7.10-7.08(1H, m), 6.65(1H, d, $J = 9.6$ Hz), 5.97(1H, dd, $J = 9.4$ Hz, 4.4Hz), 5.02(1H, br s), 4.59(1H, br d, $J = 7.2$ Hz), 3.62-3.61(4H, m), 3.36(1H, t, $J = 4$ Hz), 2.65-2.62(2H, m), 2.54-2.52(2H, m), 1.45(9H, s); ¹³C NMR (400MHz, CDCl₃) δ 155.37, 135.27, 132.50, 129.88, 128.44, 128.29, 127.89, 126.90, 125.29, 67.52, 64.35, 49.33, 48.64, 28.58. HRMS calcd for C₁₉H₂₆N₂O₃ (M⁺): 330.1943. Found: 330.1945.

(12)

N-(2-Morpholin-4-yl-1,2-dihydro-naphthalen-1-yl)-4-nitro-benzenesulfonamide (12):

To round bottomed flask was added **N-Nos 4** (5 g, 15.2 mmol), [Rh(COD)Cl]₂ (1 mol%), and DPPF (3 mol%). THF (60 ml) was then added and the mixture was stirred for approximately 5 minutes. It was then heated to reflux. At first sign of reflux, NH₄I (3.3 g, 22.8 mmol) was added followed by morpholine (4 mL, 46 mmol). The resulting heterogeneous mixture was heated to reflux for 15 hours. Upon completion, the reaction mixture was poured into an aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic fractions were combined and concentrated. The resulting crude residue was purified by chromatography (30% ethyl acetate:hexanes) to give **12** (5.8 g, 92%) an off white solid. $R_f = 0.33$ on silica gel (40% ethyl acetate:hexanes); mp 152-155°C; IR (KBr, cm⁻¹) 3482 (br), 3036 (w), 2937 (s), 2853 (m), 1453 (s), 1193 (s), 1109 (s), 1046 (s). ¹H NMR (400MHz, CDCl₃) δ 8.31 (2H, d, $J = 8.8$ Hz), 7.98 (2H, d, $J = 8.8$ Hz), 7.23-7.15 (1H, m), 7.08-6.99 (2H, m), 7.75 (1H, d, $J = 7.3$ Hz), 7.66 (1H, d, $J = 9.8$ Hz), 5.90 (1H, dd, $J = 5.1, 9.8$ Hz), 5.18 (1H, s), 4.65 (1H, s), 3.54-3.44 (4H, m), 3.42-3.37 (1H, m), 2.54-2.44 (2H, m), 2.34-2.24 (2H, m); ¹³C NMR (400MHz, CDCl₃) δ

149.6, 146.8, 132.5, 131.9, 129.9, 129.8, 128.2, 128.0, 127.5, 127.0, 124.1, 123.7, 67.1, 63.9, 51.9, 49.0. HRMS calcd for C₂₀H₂₁N₃O₅S (M⁺): 415.1202. Found: 415.1203.

(13)

N-(2-Diethylamino-1,2-dihydro-naphthalen-1-yl)-4-nitro-benzenesulfonamide (13):

To round bottomed flask was added **N-Nos 4** (5 g, 15.2 mmol), [Rh(COD)Cl]₂ (1 mol%), and DPPF (3 mol%). THF (60 ml) was then added and the mixture was stirred for approximately 5 minutes. It was then heated to reflux. At first sign of reflux, NH₄I (3.3 g, 22.8 mmol) was added followed by diethylamine (3.4 mL, 46 mmol). The resulting heterogeneous mixture was heated to reflux for 15 hours. Upon completion, the reaction mixture was poured into an aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic fractions were combined and concentrated. The resulting crude residue was purified by chromatography (30% ethyl acetate:hexanes) to give **13** (5.5 g, 91%) an off white solid. R_f = 0.22 on silica gel (40% ethyl acetate:hexanes); mp 92-95°C; IR (KBr, cm⁻¹) 3482 (br), 3036 (w), 2937 (s), 2853 (m), 1453 (s), 1193 (s), 1109 (s), 1046 (s). ¹H NMR (400MHz, CDCl₃) δ 8.32 (2H, d, J = 8.8 Hz), 7.98 (2H, d, J = 8.8 Hz), 7.24-7.18 (1H, m), 7.08-7.00 (2H, m), 6.75 (1H, d, J = 7.5 Hz), 6.67 (1H, d, J = 9.8 Hz), 5.90 (1H, dd, J = 5.1, 9.8 Hz), 5.88 (1H, s), 4.66 (1H, s), 3.58-3.44 (4H, m), 3.43-3.38 (1H, m), 2.54-2.45 (2H, m), 2.34-2.28 (2H, m); ¹³C NMR (400MHz, CDCl₃) δ 149.7, 146.8, 132.6, 131.9, 129.9, 128.8, 128.3, 128.1, 127.6, 127.1, 124.1, 123.7, 67.1, 63.9, 51.9, 49.0. HRMS calcd for C₂₀H₂₃N₃O₄S (M⁺): 401.1409. Found: 401.1407.

(14)

(1S, 2S)-(2-Dibenzylamino-1,2-dihydro-naphthalen-1-yl)-carbamic acid *tert*-butyl ester (14).

Following the general procedure, **14** was obtained as an oil (140mg, 78%). The ee was determined to be 89% using HPLC analysis on a CHIRALCEL OD column, λ = 486 nm. Retention times in 1% isopropanol in hexanes were 5.76 min (major) and 6.29 min. R_f = 0.4 on silica gel (10% ethyl acetate:hexanes); [α]_D²⁵ = +96.1 (c = 1.06, CCl₄); IR (KBr, cm⁻¹) 3447(m), 2280(w), 2000(w), 1954(w), 1712(s), 1549(s), 1366(m), 1251(s), 1170(s), 1005(s), 801(s); ¹H NMR (400MHz, CDCl₃) δ 7.37-7.32(5H, m), 7.27-7.24(4H, m), 7.20-7.17(4H, m), 7.03-7.00(1H, m), 6.57(1H, dd, J = 9.8 Hz, 1.6 Hz), 6.03(1H, dd, J = 9.8 Hz, 3.2 Hz), 5.25(1H, t, J = 5.6 Hz), 4.47(1H, br d, J = 8.8 Hz), 3.74(2H, d, J = 13.6 Hz), 3.54(2H, d, J = 13.6 Hz), 3.47-3.45(1H, m), 1.52(9H, s); ¹³C NMR (400MHz, CDCl₃) δ

155.67, 140.06, 135.75, 132.58, 129.50, 129.19, 129.10, 128.25, 128.16, 127.85, 127.35, 127.02, 126.91, 126.67, 79.47, 59.46, 54.04, 49.38, 28.64, 28.49. HRMS calcd for $C_{29}H_{32}N_2O_2$ (M^+): 440.2463. Found: 440.2455.

15

N-(2-Dibenzylamino-1,2-dihydro-naphthalen-1-yl)-4-nitro-benzenesulfonamide (15):

To round bottomed flask was added **N-Nos 4** (500 mg, 1.52 mmol), $[Rh(COD)Cl]_2$ (1 mol%), and DPPF (3 mol%). THF (8 ml) was then added and the mixture was stirred for approximately 5 minutes. It was then heated to reflux. At first sign of reflux, NH_4I (330 mg, 2.28 mmol) was added followed by dibenzylamine (900 mL, 4.6 mmol). The resulting heterogeneous mixture was heated to reflux for 15 hours. Upon completion, the reaction mixture was poured into an aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic fractions were combined and concentrated. The resulting crude residue was purified by chromatography (30% ethyl acetate:hexanes) to give **15** (710 mg, 89%) an off white solid. $R_f = 0.16$ on silica gel (15% ethyl acetate:hexanes); mp 192-194°C; IR (KBr, cm^{-1}) 3482 (br), 3036 (w), 2937 (s), 2853 (m), 1453 (s), 1363 (s), 1109 (s), 1046 (s). 1H NMR (400MHz, $CDCl_3$) δ 8.08 (2H, d, $J = 8.8$ Hz), 7.67 (2H, d, $J = 8.8$ Hz), 7.25-7.14 (13H, m), 7.06-7.00 (2H, m), 6.92 (1H, d, $J = 7.2$ Hz), 6.68 (1H, d, $J = 9.7$ Hz), 5.90 (1H, dd, $J = 5.1, 9.7$ Hz), 4.94-4.88 (1H, m), 4.81-4.75 (1H, m), 3.51-3.47 (1H, m), 3.44 (4H, d, $J = 4.6$ Hz); ^{13}C NMR (400MHz, $CDCl_3$) δ 149.4, 147.0, 139.4, 132.7, 132.0, 129.8, 128.8, 128.3, 128.1, 128.0, 127.6, 127.1, 126.9, 124.9, 123.9, 57.7, 53.3, 52.7. HRMS calcd for $C_{30}H_{27}N_3O_4S$ (M^+): 525.1722. Found: 525.1725.

(1S, 2S)-2-(3,4-Dichloro-phenyl)-N-(2-pyrrolidin-1-yl-1,2-dihydro-naphthalen-1-yl)-acetamide:

To round bottomed flask was added **2-(3,4-Dichloro-phenyl)-1-(1,4-dihydro-1,4-epizano-naphthalen-9yl)-ethanone** (66 mg, 0.2 mmol), $[Rh(COD)Cl]_2$ (2.5 mg, 0.005 mmol), and C_2 -Ferriphos (5.5 mg, 0.01 mmol). THF (2 ml) was then added followed by triethylamine hydrochloride (138 mg, 1.0 mmol) and pyrrolidine (125 μ l, 1.0 mmol). The resulting heterogeneous mixture was heated to reflux for 15 hours. Upon completion, the reaction mixture was concentrated and chromatographed (50% ethyl acetate:hexanes with 5% Et_3N) to give the product as a tan solid (78 mg, 98%). The ee was determined to be 99% using HPLC analysis on a CHIRALCEL OD column, $\lambda = 486$

nm. Retention times in 10% isopropanol in hexanes were 13.8 min (major) and 18.68min. $R_f = 0.1$ on silica gel (50% ethyl acetate:hexanes); mp 78-84°C; $[\alpha]_D^{25} = +59.4$ (c= 0.98, CHCl₃); IR (KBr, cm⁻¹) 3683(m), 3014(s), 2400(s), 2246(w), 1968(w), 1883(w), 1670(s), 1518(s), 1423(s), 1220(s), 1033(s), 929(s), 805(s). ¹H NMR (400MHz, CDCl₃) δ 7.36-7.31(1H, m), 7.26-7.19(4H, m), 7.11-7.04(2H, m), 6.61(1H, d, J=12.8Hz), 5.97(1H, dd, J=13.2Hz, 6.4Hz), 5.76(1H, d, J=10.8Hz), 5.28-5.23(1H, m), 3.41(2H, s), 3.31(1H, t, J=6Hz), 2.67-2.55(4H, m), 2.02(1H, br s), 1.69-1.65(4H, m); ¹³C NMR (400MHz, CDCl₃) δ 168.95, 135.02, 134.03, 132.52, 132.22, 131.18, 131.06, 130.45, 129.24, 128.52, 128.30, 128.20, 128.03, 126.82, 126.13, 60.54, 49.82, 49.59, 42.41, 23.46. HRMS calcd for C₁₈H₁₄NOCl₂ [(M-C₄H₉N)⁺]: 329.0374. Found: 329.0366

Preparation of Analgesic Compound 3.

(+/-) **16a**

4,N-Dimethyl-N-(2-pyrrolidin-1-yl-1,2-dihydro-naphthalen-1-yl)-benzenesulfonamide [(+/-) 16a]: To a round bottomed flask was added (+/-) **5a** (100 mg, 0.27 mmol) and potassium carbonate (112 mg, 0.81 mmol). Acetone (3 ml) was then added followed by iodomethane (18 µl, 0.28 mmol). The mixture was stirred at room temperature for 4 hours then quenched with water. Extraction with ethylacetate, combining of the organic fractions and concentration gave a light yellow solid. Chromatography (30% ethyl acetate:hexanes) gave pure (+/-) **16a** (101 mg, 98%) a white crystalline solid. $R_f = 0.18$ on silica gel (30% ethyl acetate:hexanes); mp 109-111°C; IR (KBr, cm⁻¹) 3386 (br), 3016 (m), 2984 (s), 1497 (s), 1343 (s), 1117 (m), 1048 (s). ¹H NMR (400MHz, CDCl₃) δ 7.86 (2H, d, J= 8.0Hz), 7.31 (2H, d, J= 8.0Hz), 7.26-7.12 (3H, m), 7.06 (1H, d, J= 6.9Hz), 6.58 (1H, d, J= 9.7Hz), 5.95 (1H, dd, J= 4.6, 9.9Hz), 5.35 (1H, d, J= 4.5Hz), 3.42 (1H, dd, J= 4.5, 4.5Hz), 2.62-2.48 (4H, m), 2.50 (3H, s), 2.45 (3H, s), 1.70-1.63 (4H, m); ¹³C NMR (400MHz, CDCl₃) δ 143.0, 137.7, 133.6, 132.1, 129.5, 129.1, 128.9, 128.2, 128.1, 127.4, 126.5, 125.9, 58.2, 56.5, 48.6, 29.6, 23.5, 21.5. Anal. Calcd for C₂₂H₂₆N₂O₂S: C, 69.08; H, 6.85; N, 7.32. Found: C, 69.14; H, 6.91; N, 7.30.

(+/-) **17a**

4,N-Dimethyl-N-(2-pyrrolidin-1-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-benzenesulfonamide [(+/-) 17a]: To a round bottomed flask was added (+/-) **16a** (100

mg, 0.26 mmol), ethylacetate (2 ml) and palladium on carbon (5mg). Hydrogen was added over this heterogeneous mixture via balloon for 15 hours. Upon completion, the mixture was filtered through celite and concentrated to give (+/-) **17a** as a white solid. Crude ^1H NMR showed that this crude product was >95% pure. Further purification could be obtained by chromatography (30% ethyl acetate:hexanes) giving pure (+/-) **17a** (98 mg, 98%). R_f = 0.15 on silica gel (30% ethyl acetate:hexanes); mp 109-110°C; IR (KBr, cm^{-1}) 3384 (br), 3009 (m), 2978 (s), 1338 (s), 1115 (m), 1052 (s). ^1H NMR (400MHz, CDCl_3) δ 7.99 (2H, d, J = 8.1Hz), 7.30 (2H, d, J = 8.3Hz), 7.15-7.02 (4H, m), 5.29 (1H, d, J = 8.1Hz), 3.03-2.67 (5H, m), 2.65-2.52 (2H, m), 2.44 (3H, s), 2.43 (3H, s), 2.05-1.96 (1H, m), 1.90-1.80 (1H, m), 1.72-1.64 (4H, m); ^{13}C NMR (400MHz, CDCl_3) δ 142.8, 138.5, 137.5, 133.9, 129.2, 128.5, 127.7, 127.1, 126.4, 60.0, 59.3, 48.7, 30.3, 27.9, 23.6, 21.5, 21.4. Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.79; H, 7.37; N, 7.22.

(+/-) **18**

Methyl-(2-pyrrolidin-1-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amine [(+/-) **18]**: To a quartz tube was added (+/-) **17a** (80 mg, 0.2 mmol), 1,4-dimethoxybenzene (110 mg, 0.8 mmol) and sodium borohydride (76 mg, 2.0 mmol) followed by 90% aqueous ethanol solution (3 ml). The mixture was irradiated at 254 nm in a rayonet reactor for 2.5 hours. The crude mixture was concentrated azeotropically with ethanol and then chromatographed (90% acetone, 9% MeOH, 1% triethylamine) to give (+/-) **18** (42 mg, 91%). Spectral data was identical to the literature data.⁵ This compound was then converted to the analgesic compound **3** by the literature procedure.

(**16b**)

(1S, 2S)-Methyl-(2-pyrrolidin-1-yl-1,2-dihydro-naphthalen-1-yl)-carbamic acid tert-butyl ester [(+)-16b**]**.

KH(35% dispersion in mineral oil, 1.0g, 2 eq.) was washed three times with pentane, dried under a stream of nitrogen, and suspended in THF(20ml). A solution of (+)-**5b** (1.4g, 4.45mmol) in THF (10ml) was added dropwise via cannula. After 15 minutes at room temperature, iodomethane (292 μl , 4.68mmol) is added dropwise and the resulting solution is stirred at room temperature for 1 hour. The mixture was quenched by dropwise addition of water (25ml) and then extracted with CH_2Cl_2 (3x30ml). The

⁵ Freeman, J.P.; Michalson, E.T.; D'Andrea, S.V.; Baczynskyj, L.; Von Voigtlander, P.F.; Lahti, R.A.; Smith, M.W.; Lawson, C.F.; Scahill, T.A.; Mizesak, S.A.; Szmuszkovicz, J. *J. Med. Chem* **1991**, 34, 1891.

organic layers are combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Flash chromatography (30% EtOAc/hexanes→50%EtOAc/hexanes) provides the product as an oil (1.38g, 95%). *R*_f = 0.29 on silica gel (40 % ethyl acetate:hexanes); [α]²⁵_D = +17.90 (c = 0.98, CCl₄); *R*_f = on silica (% ethyl acetate:hexanes). IR (KBr, cm⁻¹) 3683(m), 1964(w), 1929(w), 1887(w), 3448(m), 1677(s), 1518(s), 1426(m), 1228(s), 1046(s), 928(s), 796(s); ¹H NMR (400MHz, CDCl₃) corresponding to a 1:1 mixture of rotamers : δ 7.19-7.17(3H, m), 7.07(1H, t, *J*=4.4Hz), 6.53(1H, t, *J*=7.6Hz), 6.05(1H, dd, *J*=9.8Hz, 4Hz), 5.65(0.5H, d, *J*=7.2Hz), 5.46(0.5H, d, *J*=8.4Hz), 3.69(0.5H, d, *J*=7.6Hz), 3.59(0.5H, s), 2.73-2.65(4H, m), 2.65(1.5H, s), 2.56(1.5H, s), 1.75-.173(4H, m), 1.49(9H, s); ¹³C NMR (400MHz, CDCl₃) corresponding to a 1:1 mixture of rotamers: δ 155.97, 134.32, 133.91, 133.78, 128.74, 128.04, 127.92, 127.81, 127.67, 127.56, 126.85, 126.68, 126.57, 79.88, 79.51, 58.83, 55.95, 54.12, 48.88, 29.61, 29.34, 28.63, 28.55, 23.76. HRMS calcd for C₂₀H₂₇N₂O₂ (M⁺): 327.2072. Found: 327.2080.

(17b)

(1S, 2S)-Methyl-(2-pyrrolidin-1-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-carbamic acid *tert*-butyl ester [(+)-17b].

To a mixture of (+)-**16b** (1.2g, 3.65mmol) and hydrazine monohydrate (7.1ml, 146.32mmol) in 95% EtOH:THF (30ml:10ml) at 0°C was added slowly a solution of NaIO₄ (7.8g, 36.58mmol) in H₂O (10ml). The resulting slurry was heated with stirring at 70°C for 4 hours (with reflux condenser left open to the atmosphere), over which time the mixture turned to a clear, homogeneous solution. The solution was cooled to room temperature, diluted with CH₂Cl₂, and washed with 1N NaOH, H₂O, and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated under reduced pressure to afford (+)-**17b** as an oil (1.1g, 93%). *R*_f = 0.29 on silica gel (40% ethyl acetate:hexanes); [α]²⁵_D = +23.3 (c = 1.03, CCl₄); IR (KBr, cm⁻¹) 2294(m), 1717(s), 1690(s), 1549(s), 1438(w), 1365(w), 1253(s), 1217(s), 1136(s), 1005(s), 764(s); ¹H NMR (400MHz, CDCl₃) corresponding to a 1:1 mixture of rotamers: δ 7.15-7.07(4H, m), 5.48(0.5H, d, *J*=9.2Hz), 5.29-5.26(0.5H, m), 3.02-2.76(5H, m), 2.65-2.63(2H, m), 2.58(1.5H, s), 2.51(1.5H, s), 2.10-2.05(1H, m), 1.85-1.72(5H, m), 1.51(4.5H, s), 1.49(4.5H, s); ¹³C NMR (400MHz, CDCl₃) corresponding to a 1:1 mixture of rotamers: δ 156.98, 156.74, 138.03, 137.96, 136.41, 136.12, 128.61, 128.57, 128.07, 127.78, 126.86, 126.76, 126.41, 126.27, 79.68, 79.28, 58.62, 57.34, 48.75, 48.58, 30.03, 29.09, 28.97, 28.70, 28.64, 25.44, 23.86, 23.74, 23.28, 23.15. HRMS calcd for C₂₀H₃₀N₂O₂ (M⁺): 330.2307. Found: 330.2316.

(18)

(1S, 2S)-Methyl-(2-pyrrolidin-1-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-amine [(+)-18].

In a 25ml round bottom flask was added (+)-**17b** (300mg, 0.91mmol), CH₂Cl₂, and dropwise addition of trifluoroacetic acid (1ml). The solution is stirred at room temperature for 45 minutes. 10ml of KOH(10% aqueous solution) was added and the mixture was washed with CH₂Cl₂ (3x20ml). The organic layers are combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield the product as an oil (198mg, 95%). R_f = 0.1 on silica gel (100% ethyl acetate); mp °C (Et₂O); [α]_D²⁵ = +65.0 (c = 1.6, CCl₄); IR (KBr, cm⁻¹) 3459(s), 2305(m), 1550(s), 1422(m), 1264(s), 1122(m), 1003(m), 895(w); ¹H NMR (400MHz, CDCl₃) δ 7.28-7.24(1H, m), 7.15-7.05(3H, m), 3.66(1H, d, J=4Hz), 2.91-2.83(1H, m), 2.69-2.59(6H, m), 2.46(3H, s), 2.10-2.02(1H, m), 1.88-1.81(1H, m), 1.73-1.70(4H, m), 1.54(1H, br s); ¹³C NMR (400MHz, CDCl₃) δ 137.73, 137.62, 129.57, 128.73, 126.63, 125.70, 61.65, 60.87, 51.15, 34.65, 26.02, 23.50, 22.14. HRMS calcd for C₁₅H₂₂N₂ (M⁺): 230.1782. Found: 230.1792.

(3)

(1S, 2S)-2-(3,4-Dichloro-phenyl)-N-methyl-N-(2-pyrrolidin-1-yl-1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide (3) : In a 50ml round bottom flask was added (+)-**21** (200mg, 0.86mmol), CH₂Cl₂ (10ml), and then 3,4-dichlorophenylacetic acid (178mg, 0.86mmol). To this solution is added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (217mg, 1.13mmol) and dimethylaminopyridine (10mg). The solution is stirred at room temperature for 16hours. Water (20ml) is added and the mixture washed with CH₂Cl₂ (3x30ml). The organic layers are dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Flash chromatography (50% EtOAc/ hexanes with 5% Et₃N) yields the product as an oil (320mg, 90%). Spectral data was identical to the literature data.⁶ R_f = 0.1 on silica gel (50% ethyl acetate/hexanes); [α]_D²⁵ = +34.6 (c = 1.1, CHCl₃). HRMS calcd for C₁₅H₂₂N₂ (MH⁺): 417.1500. Found: 417.1516.

⁶ Freeman, J.P.; Michalson, E.T.; D'Andrea, S.V.; Baczynskyj, L.; Von Voigtlander, P.F.; Lahti, R.A.; Smith, M.W.; Lawson, C.F.; Scahill, T.A.; Mizesak, S.A.; Szmuszkovicz, J. *J. Med. Chem* **1991**, *34*, 1891.

(1S, 2S)-2-(4-Phenyl-piperazin-1-yl)-1,2-dihydro-naphthalen-1-ylamine : In a 25ml round bottom flask was added **10** (300mg, 0.91mmol), CH₂Cl₂, and dropwise addition of trifluoroacetic acid (1ml). The solution is stirred at room temperature for 45 minutes. 10ml of KOH(10% aqueous solution) was added and the mixture was washed with CH₂Cl₂ (3x20ml). The organic layers are combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield the product as a white solid (274mg, 99%). R_f = 0.1 on silica gel (100% ethyl acetate); mp 120-123°C (Et₂O); [α]_D²⁵ = +404 (c = 1.16, CHCl₃); IR (KBr, cm⁻¹) 3620(m), 3022(s), 2400(s), 1599(m), 1522(s), 1423(s), 1333(w), 1233(s), 1046(s), 928(m), 720(s); ¹H NMR (400MHz, CDCl₃) δ 7.40-7.37(1H, m), 7.24(4H, m), 7.08-7.05(1H, m), 6.88-6.78(3H, m), 6.59(1H, dd, J=13.2Hz, 2.4Hz), 6.03(1H, dd, J=13Hz, 4.8Hz), 4.12(1H, d, J=10Hz), 3.33-3.29(1H, m), 3.19-3.07(4H, m), 2.78-2.63(4H, m), 1.66(2H, s); ¹³C NMR (400MHz, CDCl₃) δ 151.11, 138.86, 131.68, 129.24, 128.91, 127.85, 127.08, 126.50, 125.73, 124.71, 119.59, 116.00, 66.96, 50.08, 49.86, 48.81. HRMS calcd for C₂₀H₂₃N₃ (M⁺): 305.1891. Found: 305.1899.

(1S, 2S)-4-Bromo-N-[2-(4-phenyl-piperazin-1-yl)-1,2-dihydro-naphthalen-1-yl]-benzenesulfonamide : In a 25ml round bottom flask was added **2-(4-Phenyl-piperazin-1-yl)-1,2-dihydro-naphthalen-1-ylamine** (300mg, 0.91mmol), CH₂Cl₂, Et₃N, and 4-bromobenzenesulfonyl chloride. The solution is stirred at room temperature for 16 hours. 10ml of KOH(10% aqueous solution) was added and the mixture was washed with CH₂Cl₂ (3x20ml). The organic layers are combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield the product as a white solid (274mg, 99%). R_f = 0.4 on silica gel (20% ethyl acetate/hexanes); mp 188-190°C (EtOAc); [α]_D²⁵ = +224.2 (c = 0.85, CHCl₃); IR (KBr, cm⁻¹) 3387(w), 3014(s), 2400(m), 2046(w), 1968(w), 1912(w), 1600(w), 1522(s), 1422(s), 1331(m), 1202(s), 1045(s), 929(s), 795(s); ¹H NMR (400MHz, CDCl₃) δ 7.74-7.72(4H, m), 7.26-7.21(4H, m), 7.11-7.07(2H, m), 6.85-6.82(3H, m), 6.78(1H, d, J=8Hz), 6.69(1H, d, J=10Hz), 5.95(1H, dd, J=9.8Hz, 5.2Hz), 4.68-4.66(1H, m), 4.62(1H, s), 3.55-3.53(1H, m), 3.04-2.97(4H, m), 2.68-2.63(2H, m), 2.47-2.42(2H, m); ¹³C NMR (400MHz, CDCl₃) δ 151.38, 140.15, 133.41, 132.58, 132.26, 130.07, 129.23, 128.95, 128.63, 127.98, 122.82, 127.82, 127.25, 124.47, 120.06, 116.38, 63.78, 51.44, 49.76, 48.65. HRMS calcd for C₂₅H₂₆N₃O₂SBr (M⁺): 523.0929. Found: 523.0908.