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Catalytic enantioselective synthesis of the dopamine D1 antagonist ecopipam

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ABSTRACT

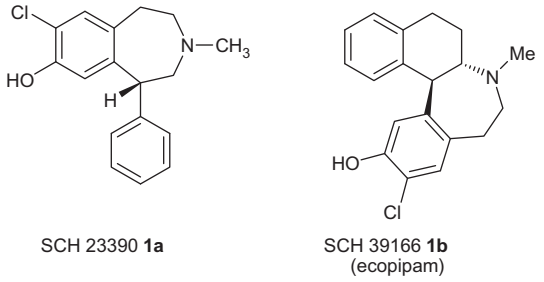
A concise asymmetric synthesis of the potent dopamine D1 antagonist, ecopipam, has been accomplished in six steps with 33% overall yield via catalytic enantioselective aziridination and subsequent one-pot Friedel–Crafts cyclization of an in situ generated tethered aziridine with high diastereo- and enantioselectivities.

1. Introduction

2,3,4,5-Tetrahydro-1*H*-3-benzazepines have been the subject of great interest over the last few decades because of their selective affinity for the D1 subpopulation of dopamine receptors in the central nervous system.[1] Benzazepine SCH 23390 **1a** was initially developed as a prototype dopamine D1 receptor antagonist (Fig. 1).[2] Ethylene bridged restricted benzazepine, *trans*-(−)-(6a*S*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth[2,l-*b*]azepin-l2-ol (SCH 39166) was later developed as a potent dopamine D1 antagonist to treat schizophrenia and other D1 dependent neurological disorders.[3] SCH 39166 **1b** (ecopipam) was shown to reduce the craving for addictive substances such as cocaine, nicotine, alcohol, and so on, in animal models.[4] Clinical trials showed that ecopipam **1b** reduced the euphoric effects of cocaine,[5] but was not effective in completely treating the addiction. It also shows sedative and antipsychotic effects, but it was not approved for medical prescription due to side effects such as depression and anxiety.[6] Ecopipam was further studied as a potential candidate to enhance and maintain weight loss in obese people.[7] It is currently under clinical trial for the treatment of Lesch–Nyhan syndrome[8] and Tourette syndrome.[9]

2. Results and discussion

Due to its importance, several syntheses of ecopipam **1b** are known in the literature.[10] The discovery synthesis[3a] described the construction of the tetracyclic core structure as a mixture of *cis*/*trans* isomers via Friedel–Crafts cyclization of 2{[2-(3,4-dimethoxyphenyl)-ethyl]-methylamino}-1-hydroxytetralin. Separation of the *trans*-isomer and late stage resolution provided the enantiomerically pure SCH 39166. Since these benzoazepine compounds display a high enantiospecificity toward the dopamine D1 receptor,



SCH 23390 **1a** SCH 39166 **1b** (ecopipam)

Figure 1. Benzoazepine dopamine D1 antagonists.

much effort has focused on the asymmetric synthesis. Wu et al. the first reported chiral-pool based asymmetric synthesis of ecopipam **1b** starting from (1*S*,2*S*)-2-amino-1-phenyl-1,3-diol in eleven steps, where one-carbon homologation, amide coupling, double reduction, and two Friedel–Crafts cyclization reactions were the key steps.[10b] A number of strategies starting from either L-homophenylalanine or *trans*-*N*-alkyl-1-amino-2-hydroxytetralin have already been reported in the literature.[10c,d] Among these, the regio- and stereoselective ring openings of the aziridinium ion, derived from enantiomerically pure *trans*-*N*,*N*-dialkyl-1-amino-2-hydroxytetralin, by a 3-chloro-4-methoxyphenyl Grignard reagent to form 2-amino-1-aryltetralin are one of the more efficient methods.[10c] *trans*-2-Amino-1-aryltetralin **2**, usually prepared in 4–6 steps, is thus found to be an advanced intermediate for the synthesis of ecopipam. One convenient and concise strategy for the asymmetric synthesis of aminotetralin **2** is the stereoselective intramolecular Friedel–Crafts type cyclization of tethered chiral aziridine **3** (Scheme 1). Herein, we report the asymmetric synthesis of ecopipam via a catalytic enantioselective one-pot aziridoarylation reaction, which proceeds with high diastereo- and enantioselectivities.

To begin the synthesis of ecopipam, styrene **4** was prepared by two routes. Wittig reaction of dihydrocinnamaldehyde **5** and phosphonium salt **6** provided as an *E*/*Z*-mixture of compound **4**

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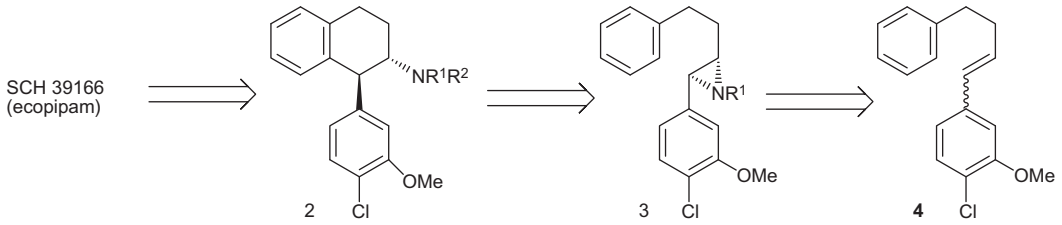
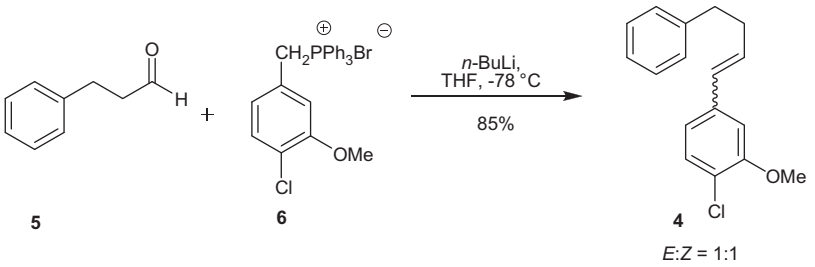


Scheme 1. Retrosynthesis of SCH 39166.

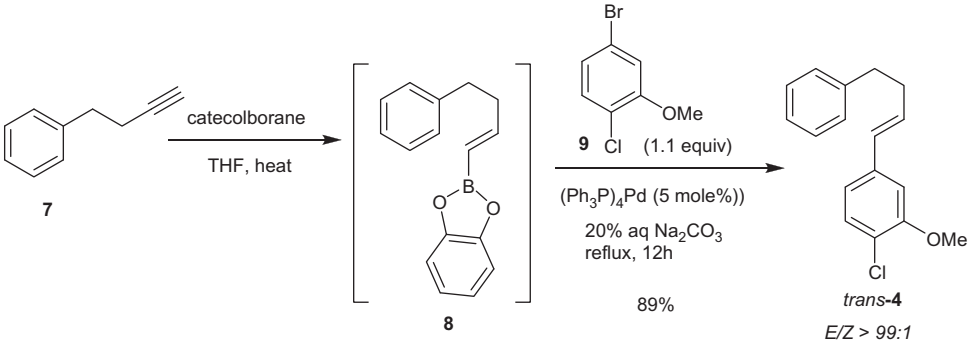


Scheme 2. Preparation of styrene **4** via a Wittig reaction.

(1:1) in an 85% yield (Scheme 2). Suzuki coupling[11] of the in situ generated vinylborane **8**, obtained by heating alkyne **7** with catecholborane, and 4-bromo-1-chloro-2-methoxybenzene **9** exclusively provided *trans*-alkene *trans*-**4** (Scheme 3).

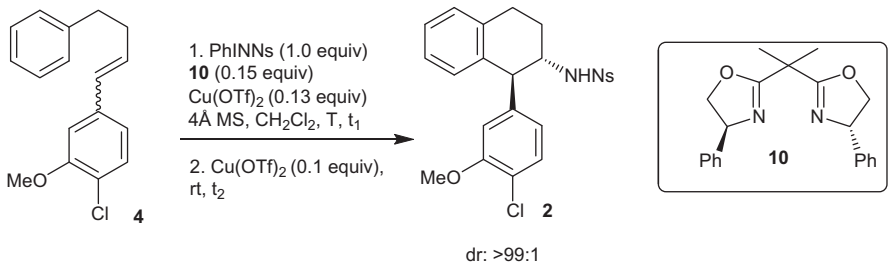
From our previous studies we found that the $Cu(OTf)_2$ catalyzed intramolecular Friedel–Crafts type cyclization of an in situ generated aziridine from the tethered alkene provided *trans*-2-amino-1-aryltetralins, where [*N*-(4-nitrobenzenesulfonyl)imino]-phenyliodinane, $PhINSO_2(4\text{-}NO_2C_6H_4)$ [PhINNs] was used as an efficient nitrenoid source for the aziridination of the tethered alkenes.[12] Chiral copper complexes prepared from $Cu(OTf)_2$ and the bis-oxazoline (Box) ligand derived from phenylglycinol was found to be the more efficient ones.[12b]

With the standard reaction conditions in hand, we started the synthesis of ecopipam. First, alkene **4** was subjected to an aziridination reaction in the presence of $Cu(OTf)_2$ (0.13 equiv) and (*S*)-Box-ligand **10** (0.15 equiv) derived from L-phenylglycinol and molecular sieves in DCM. This gave aziridine **3** after 3 h at 32 °C as detected from the ^1H NMR of the crude reaction mixture. Without isolation of the aziridine, the reaction was continued with an additional 0.1 equiv of $Cu(OTf)_2$ at rt and in one-pot. This gave the desired (1*R*,2*S*)-*N*-nosyl-2-amino-1-aryltetralin **2** in a 79% yield with 89% ee (Table 1, entry 1). It was thought that the use of pure *trans*-alkene *trans*-**4** might give a better yield and selectivity than the *E*/*Z* mixture of alkene **4**. When *trans*-**4** was subjected to the aziridination reaction under similar reaction conditions, it underwent smooth aziridination in 1 h and upon further treatment with an additional 10 mol % $Cu(OTf)_2$ provided aminotetralin **2** within 1 h at rt (entry 2). The use of the *trans*-alkene provided an improved yield of the reaction (85% yield) with the same enantioselectivity (89% ee). Generally large excess of alkene was used to ensure complete consumption of the nitrene reagent.[12,13] Both the yield and ee decreased upon lowering the alkene loading (entry 3). Attempts to enrich the ee by crystallization from different solvents were unsuccessful. The reaction of *trans*-**4** under similar conditions using Box ligand *ent*-**10** derived from D-phenylglycinol produced aminotetralin *ent*-**2** in 92% ee with a high yield (85%) (entry 4). It should be noted that L- and D-phenylglycines were obtained from different sources; the former showed a slightly lower enantiomeric purity. Thus, the use of (*S*)-Box derived from better quality L-phenylglycine might provide aminotetralin **2** with up to 92% ee. It should be noted that the *E*/*Z* (1:1) mixture of styrene **4** upon aziridination and subsequent Friedel–Crafts cyclization exclusively provided *trans*-2-amino-1-aryltetralin **2** (dr >99:1) while the corresponding *cis*-cyclized product was not detected in the crude reaction mixture by ^1H NMR analysis. This is due to the dual chemoselectivity of the aziridination and Friedel–Crafts reactions.[12a,b] The *E*/*Z* ratio of the recovered styrene **4** attained to



Scheme 3. Synthesis of styrene *trans*-**4** via a Suzuki coupling.

Table 1
Catalytic and enantioselective one-pot synthesis of aminotetralin **2**[a]

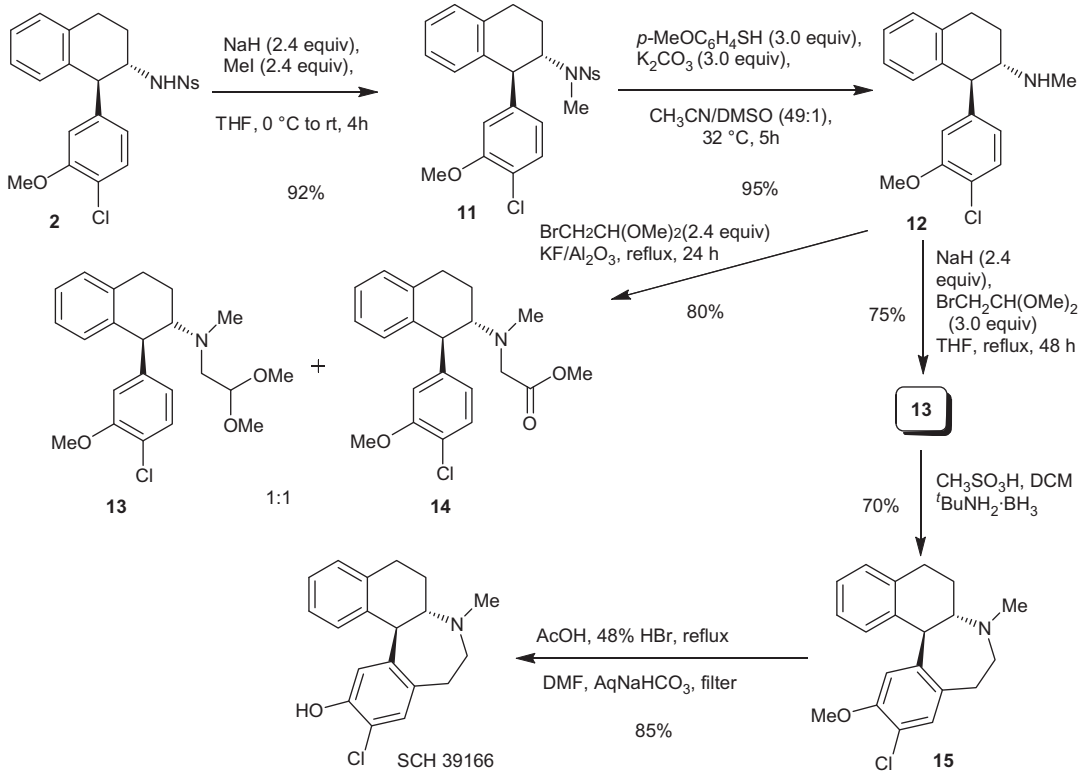


Entry	Alkene	*E*/*Z* ratio	Alkene loading (equiv)	*T* (°C)	t_1[b] (h)	t_2[c] (h)	Yield of **2**[d] (%)	ee[e] (%)
1	**4**	1:1	5	32	3	2	79	89
2	*trans*-**4**	>99:1	5	25	1	1	85	89
3	*trans*-**4**	>99:1	2.5	25	2	1	71	82
4[f]	*trans*-**4**	>99:1	5	25	1	1	85	92[g]

[a] To a solution of bis(oxazoline)–Cu(II) complex derived from 13 mol % $Cu(OTf)_2$ and 15 mol % bis(oxazoline) ligand **10** and styrene **4** (5 equiv) in CH_2Cl_2, PhINNs (1.0 equiv) was added. The suspension was stirred at the specified temperature. After dissolution of all of the nitrenoid reagents, an additional 10 mol % of $Cu(OTf)_2$ was added.
[b] Time required for the aziridination reaction.
[c] Time required for the Friedel–Crafts cyclization.
[d] Isolated yields of **2** after column chromatography.
[e] Enantiomeric excess (ee) was determined by HPLC using a chiral column.
[f] Reaction carried out using Box ligand *ent*-**10**.
[g] The opposite enantiomer *ent*-**2** was formed.

1:1.6 from 1:1 that might further support the chemoselectivity at aziridination step.

For the synthesis of ecopipam, N-methylation of aminotetralin **2** was carried out on the sodium salt of compound **2**, generated by the reaction of NaH, with MeI at 0 °C. Within 1 h, it provided compound **11** in good yield (92%) (Scheme 4). Denosylation of compound **11** with 4-methoxythiophenol (3.0 equiv) and K_2CO_3 (3 equiv) in CH_3CN/DMSO (49:1) at 32 °C afforded the *N*-methylaminotetralin **12** after 5 h with excellent yield. Compound **12** was refluxed with KF/Al_2O_3 and $BrCH_2CH(OMe)_2$ in acetonitrile,[10d] but produced a 1:1 mixture of the desired product **13** along with ester **14** as a by-product. The problem was resolved when the sodium salt of compound **12**, generated by the reaction of NaH (2.4 equiv) at 0 °C for 1 h in dry THF, was refluxed with $BrCH_2CH(OMe)_2$ (3.0 equiv) under an argon atmosphere. After 48 h, compound **13** was obtained in 75% yield. The specific rotation of **13** {$[\alpha]_D^{23} = +56.9$ (*c* 1.40, EtOH)} was found to be in good agreement with the literature data {$[\alpha]_D^{20} = +63.5$ (*c* 1.49, EtOH)}.[10d] Construc-



Scheme 4. Synthesis of SCH 39166.

tion of the azepine core and demethylation would complete the synthesis. For this purpose, an acid catalyzed cyclization using $MeSO_3H$ and subsequent one-pot reduction with t-$BuNH_2{\cdot}BH_3$ afforded tetracyclic compound **15** in a 70% yield.[10d] Finally, the HBr mediated demethylation of compound **15** in acetic acid at 130 °C accomplished the synthesis of ecopipam as an HBr salt. Neutralization with 5% aq $NaHCO_3$ gave ecopipam **1b** as a white solid in excellent yield. The specific rotation of the synthesized ecopipam was found to be $[\alpha]_D^{24} = -200.9$ (c 0.52, DMF), which was in good agreement with the literature value {$[\alpha]_D = -220.8$ (c 0.56, DMF)}.[3a] The overall yield of this catalytic and enantioselective synthesis of ecopipam (−)-SCH 39166 was 33% starting from alkene *trans*-**4** in six steps. Similarly, the other enantiomer of ecopipam was successfully synthesized from aminotetralin *ent*-**2**. The specific rotation of (+)-SCH 39166 {$[\alpha]_D^{24} = +202.8$ (c 0.29, DMF)} matched well with the literature data {$[\alpha]_D = +220.5$ (c 0.29, DMF)}.[3a]

3. Conclusion

In conclusion, we have achieved a concise asymmetric synthesis of aminotetralin **2** from alkene *trans*-**4** and also from **4** (E/Z = 1:1) with diastereo- (>99:1) and enantioselectivity (ee 89%) via catalytic and enantioselective aziridoarylation. Aminotetralin **2** was transformed to ecopipam in five steps. The overall yield of this synthesis from alkene *trans*-**4** was found to be 33%. We have also synthesized (+)-SCH 39166 from aminotetralin *ent*-**2** prepared via an aziridoarylation reaction using (*R*)-Box ligand *ent*-**10**.

4. Experimental

4.1. General

All reactions were conducted using oven-dried glassware under an atmosphere of Argon (Ar). Commercial grade reagents were used without further purification. Solvents were dried and distilled following the usual protocols. Flash chromatography was carried out using silica gel (230–400 mesh). TLC was performed on aluminum-backed plates coated with Silica gel 60 with F_{254} indicator. The ^{1}H NMR spectra were recorded with a 200 and a 400 MHz instrument and the ^{13}C NMR spectra were recorded with a 50 and a 100 MHz instrument using $CDCl_3$. ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to $CDCl_3$ (δ = 7.26). ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the central $CDCl_3$ resonance (δ = 77.0). Mass spectra were obtained under positive electron spray ionization (m/z values are given). HPLC analyses were done by Chiralpak AD-H (0.46 cm × 15 cm). Melting points were uncorrected.

4.1.1. 1-Chloro-2-methoxy-4-(4-phenyl-but-1-enyl)-benzene 4

To a stirred suspension of substituted benzyl triphenylphosphonium bromide **6** (27.7 g, 55.90 mmol) in dry THF (100 mL) under a nitrogen atmosphere, *n*-BuLi in hexane (34.9 mL, 1.6 M in hexane) was injected dropwise at −78 °C via a glass syringe and the stirring was maintained for 30 min. 3-Phenylpropionaldehyde **5** (5.0 g, 37.26 mmol) in dry THF (25 mL) was then slowly added. The reaction mixture was allowed to reach room temperature over 1 h. The reaction was quenched with aqueous NH_4Cl solution and extracted with diethyl ether (three times). The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. Flash column chromatography of the crude mass over silica-gel yielded alkene **4** (8.6 g, 85%) as an E/Z-mixture (E/Z = 1:1). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.31–7.18 (m, 6H), 6.88 (d, J = 6.2 Hz, 1H), 6.76 (d, J = 6.2 Hz, 1H), 6.43–6.18 (m, 1.5H,), 5.80–5.67 (m, 0.5H,), 3.91 (s, 1.5H), 3.86 (s, 1.5H), 2.85–2.75 (m, 2H), 2.69–2.45 (m, 2H); ESI-MS m/z: 272 $[M]^+$; Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.86; H, 6.28. Found: C, 74.98; H, 6.13.

4.1.2. 1-Chloro-2-methoxy-4-(4-phenyl-but-1-enyl)-benzene *trans*-4

To a stirred solution of alkyne **7** (2.0 g, 15.38 mmol) in 25 mL of THF was added catecholborane (4.8 g, 38.46 mmol) slowly over a period of 5 min under ice cold conditions. Then the reaction mixture was refluxed for 3 h. The reaction mixture was again cooled to ice cold conditions and 4-bromo-1-chloro-2-methoxybenzene **9** (3.7 g, 16.9 mmol) was added slowly over 1 min, after which $(Ph_3P)_4Pd$ (0.93 g, 0.769 mmol) was added to the reaction mixture. The mixture was allowed to stir at rt for 25 min. The reaction mixture was recooled to 0 °C, at which point 15.38 mL of 20% aqueous Na_2CO_3 solution was added slowly over the reflux condenser. The reaction mixture was then allowed to reflux for 12 h. Upon completion of the reaction, it was cooled to rt, diluted with 50 mL of EtOAc and the organic portion was washed with brine and dried with Na_2SO_4. Solvent evaporation and column purification (EtOAc/hexane = 7/93) gave the title alkene *trans*-**4** (3.7 g, 89% yield) as a light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.18 (m, 6H), 6.89 (d, J = 7.2 Hz, 2H), 6.39 (d, J = 16.0 Hz, 1H), 6.31–6.24 (m, 1H), 3.90 (s, 3H), 2.85–2.80 (m, 2H), 2.59–2.53 (dd, J = 7.2, 15.7, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.8, 141.5, 137.7, 130.8, 130.0, 129.5, 128.5 (2C), 128.4 (2C), 125.9, 120.8, 118.9, 109.4, 56.0, 35.7, 34.8; ESI-MS m/z: 272 $[M]^+$; Anal. Calcd for $C_{17}H_{17}ClO$: C, 74.86; H, 6.28. Found: C, 74.96; H, 6.18.

4.1.3. (+)-*trans*-(1*R*,2*S*)-*N*-[1-(4-Chloro-3-methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-nitro-benzenesulfonamide 2

A 10 mL two-necked round bottom flask was charged with (*S*)-bis-oxazoline ligand **10** (0.012 g, 0.037 mmol, 0.15 equiv) and $Cu(OTf)_2$ (0.011 g, 0.032 mmol, 0.13 equiv). Anhydrous DCM (1.2 mL) was injected and the resulting mixture was stirred for 30 min. To this solution, alkene *trans*-**4** (0.320 g, 1.23 mmol, 5.0 equiv) in 1.2 mL of DCM, PhINNs (0.1 g, 0.247 mmol, 1.0 equiv), and 0.2 g of powdered molecular sieves (4 Å) were added and the reaction mixture was allowed to stir at rt under an argon atmosphere for 1 h. Upon dissolution of PhINNs, an additional 0.009 g of $Cu(OTf)_2$ (0.0247 mmol, 0.10 equiv) was added to the reaction mixture and it was allowed to stir for another 1 h at rt. The reaction was quenched by diluting with ethyl acetate (10 mL) and filtering through a short plug of silica gel. The silica gel was washed with an additional 10 mL of ethyl acetate. The filtrate was concentrated by rotary evaporation under reduced pressure. The crude mass was subjected to purification by flash column chromatography using 20% EtOAc in hexane as an eluent, which provided aminotetralin **2** (0.085 g, 85%). White solid, mp: 180–182 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.16 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.12–7.15 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 7.01–6.97 (m, 1H), 6.60 (d, J = 7.6 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 6.27 (s, 1H), 5.02 (d, J = 7.2 Hz, 1H), 3.83 (d, J = 9.2 Hz, 1H), 3.61 (s, 3H), 3.55–3.58 (m, 1H), 3.03–3.06 (m, 1H), 2.91–2.96 (m, 1H), 2.42–2.38 (m, 1H), 1.88–1.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.8, 149.6, 145.5, 142.7, 135.9, 135.2, 130.6, 129.9, 128.6, 127.6 (2C), 126.9, 126.3, 123.8 (2C), 122.1, 121.6, 112.0, 57.5, 55.7, 52.2, 29.9, 27.6; ESI-MS m/z: 473 $[M+H]^+$; Anal. Calcd for $C_{23}H_{21}ClN_2O_5S$: C, 58.41; H, 4.41; N, 5.92. Found: C, 58.30; H, 4.52; N, 5.84; $[\alpha]_D^{23} = +64.2$ (c 0.3, DCM) for 89% ee (HPLC, Daicel Chiralpak AD-H, hexane/*i*-propanol = 90/10, 1.0 mL/min, 220 nm, minor 15.1 min and major 18.4 min).

4.1.4. (−)-*trans*-(1*S*,2*R*)-*N*-[1-(4-Chloro-3-methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-nitro-benzenesulfonamide *ent*-2

$[\alpha]_D^{23} = -66.0$ (*c* 0.3, DCM) for 92% ee (HPLC, Daicel Chiralpak AD-H, hexane/*i*-propanol = 90/10, 1.0 mL/min, 220 nm, minor 14.0 min and major 16.7 min).

4.1.5. (+)-*trans*-(1*R*,2*S*)-*N*-[1-(4-Chloro-3-methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-nitro-benzenesulfonamide 11

To a stirred solution of aminotetralin **2** (0.10 g, 0.21 mmol) in 4 mL of THF, NaH (0.012 g, 0.50 mmol) was added at 0 °C and stirred at the same temp for 30 min. Next, MeI (0.072 g, 0.50 mmol) was added dropwise and the reaction mixture allowed to stir at rt. After 4 h, upon completion it was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated. It was then purified by column chromatography using EtOAc/hexane (1:4) as eluent to give compound **11** (0.094 g, 92%). White solid, mp: 205 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.14 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.16–7.12 (m, 3H), 7.04–6.95 (m, 1H), 6.62–6.57 (m, 2H), 6.44 (d, J = 1.6 Hz, 1H), 4.48–4.35 (m, 1H), 4.07 (d, J = 11.4 Hz, 1H), 3.69 (s, 3H), 3.21–3.12 (m, 1H), 3.06–3.02 (m, 1H), 2.93 (s, 3H), 2.17–2.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.9, 149.3, 145.5, 143.2, 137.7, 135.2, 130.0, 129.9, 128.4, 127.6 (2C), 126.6, 126.2, 123.8 (2C), 122.3, 121.4, 112.3, 61.2, 55.8, 48.9, 29.5, 28.5, 28.0; ESI-MS *m*/*z*: 487 $[M+H]^+$; Anal. Calcd for $C_{24}H_{23}ClN_2O_5S$: C, 59.19; H, 4.76; N, 5.75. Found: C, 58.98; H, 4.80; N, 5.62; $[\alpha]_D^{23} = +24.6$ (c 0.3, DCM).

4.1.6. (−)-*trans*-(1*S*,2*R*)-*N*-[1-(4-Chloro-3-methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-nitro-benzenesulfonamide *ent*-11

$[\alpha]_D^{23} = -24.9$ (*c* 0.3, DCM).

4.1.7. (+)-*trans*-(1*R*,2*S*)-[1-(4-Chloro-3-methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-methylamine 12

To a stirred solution of methyl protected aminotetralin **11** (0.1 g, 0.205 mmol) in 8 mL of CH_3CN/DMSO (49:1) were added K_2CO_3 (0.085 g, 0.62 mmol) and *p*-methoxythiophenol (0.086 g, 0.62 mmol). The reaction mixture was then stirred at rt for 5 h. Upon completion of the reaction, the mixture was concentrated under reduced pressure. The crude mass was subjected to column purification by using 3% methanol in DCM as eluent to give amine **12** (0.059 g, 95%). White solid, mp: 120–122 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.29 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 4.2 Hz, 2H), 7.08–6.98 (m, 1H), 6.75–6.65 (m, 3H), 3.97 (d, J = 8.4 Hz, 1H), 3.84 (s, 3H), 3.01–2.86 (m, 3H), 2.41 (s, 3H), 2.30–2.21 (m, 1H), 1.87 (br s, 1H), 1.79–1.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.0, 144.2, 137.4, 136.1, 130.2, 130.1, 128.5, 126.2, 126.0, 122.1, 120.7, 113.2, 62.2, 56.1, 51.9, 33.5, 27.3, 25.6; ESI-MS *m*/*z*: 302 $[M+H]^+$; Anal. Calcd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.49; H, 6.61; N, 4.54; $[\alpha]_D^{23} = +46.6$ (*c* 1.00, DCM).

4.1.8. (−)-*trans*-(1*S*,2*R*)-[1-(4-Chloro-3-methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-methylamine *ent*-12

$[\alpha]_D^{23} = -47.1$ (*c* 1.00, DCM).

4.1.9. (+)-*trans*-(1*R*,2*S*)-1-(4-Chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2- naphthalenamine 13

The Na salt of amine **12** (0.1 g, 0.33 mmol) was generated by treatment with NaH (0.019 g, 0.79 mmol) in 6 mL of THF at 0 °C over a period of 1 h. Then 3-bromo-1,1-dimethoxypropane (0.180 g, 0.99 mmol) was added to the reaction mixture at 0 °C and slowly warmed to rt. The mixture was left for 48 h at reflux, after which it was quenched with a saturated NH_4Cl solution and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. It was then purified by flash column chromatography using EtOAc/hexane (1:4) as eluent to give compound **13** (0.096 g, 75%) as a light yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.20 (d, J = 7.8 Hz, 1H), 7.07–6.93 (m, 3H), 6.74–6.61 (m, 3H), 4.11–4.01 (m, 2H), 3.81 (s, 3H), 3.18 (s, 3H), 3.10 (s, 3H), 2.94–2.90 (m, 3H), 2.58–2.50 (m, 2H), 2.29 (s, 3H), 2.06–1.98 (m, 1H), 1.76–1.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5, 146.4, 139.4, 136.7, 130.4, 129.4, 128.2, 125.5, 122.4, 119.7, 113.5, 103.9, 67.3, 56.5, 56.1 (2C), 54.1, 53.0, 49.3, 37.9, 29.7, 22.5; ESI-MS *m*/*z*: 390 $[M+H]^+$; Anal. Calcd for $C_{22}H_{28}ClNO_3$: C, 67.77; H, 7.24; N, 3.59. Found: C, 67.56; H, 7.36; N, 4.31; $[\alpha]_D^{23} = +56.9$ (*c* 1.40, EtOH).

4.1.10. (−)-*trans*-(1*S*,2*R*)-1-(4-Chloro-3-methoxyphenyl)-*N*-(2,2-dimethoxyethyl)-1,2,3,4-tetrahydro-*N*-methyl-2-naphthalenamine *ent*-13

$[\alpha]_D^{23} = -57.2$ (*c* 1.40, DCM).

4.1.11. {[1-(4-Chloro-3-methoxy-phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-methyl-amino}-acetic acid methyl ester 14

Gummy liquid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.20 (d, J = 7.8 Hz, 1H), 7.09–6.90 (m, 3H), 6.70–6.78 (m, 2H), 6.54 (dd, J = 1.6, 8.0 Hz, 1H), 4.09 (d, J = 8.2 Hz, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 3.26 (d, J = 6.2 Hz, 2H), 3.01–3.10 (m, 1H), 2.94–2.80 (m, 2H), 2.40 (s, 3H), 2.04–1.98 (m, 1H), 1.82–1.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9, 154.5, 146.1, 138.3, 136.7, 130.4, 129.5, 128.7, 126.1, 125.9, 122.1, 119.9, 113.4, 65.6, 56.0, 55.4, 51.4, 48.8, 38.5, 28.5, 23.1; ESI-MS *m*/*z*: 374 $[M+H]^+$; Anal. Calcd for $C_{21}H_{24}ClNO_3$: C, 67.46; H, 6.47; N, 3.75. Found: C, 67.56; H, 6.36; N, 3.61.

4.1.12. *trans*-(–)-(6a*S*,13b*R*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]-azepine 15

A solution of CH_3SO_3H (1.5 g, 15.62 mmol) and 2 mL of DCM was cooled to −15 °C, and then a solution of amine **13** (0.10 g, 0.251 mmol) in 4 mL of DCM was added over a 5 min period. After stirring at 25 °C for 24 h, *t*-$BuNH_2{\cdot}BH_3$ (0.034 g, 0.37 mmol) was added, and then after 1 h, a saturated solution of $NaHCO_3$ was added to neutralize the reaction mixture. The layers were separated, and the aqueous layer was extracted twice with 50 mL of DCM. The combined organic layers were washed with 20 mL of H_2O, dried over anhydrous Na_2SO_4, and concentrated. Column purification using 2% methanol in DCM provided the title compound (0.057 g, 70%). White solid, mp: 103–105 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15–7.08 (m, 4H), 6.98–6.95 (m, 1H), 5.85 (s, 1H), 4.74 (d, J = 7.2 Hz, 1H), 3.62–3.50 (m, 1H), 3.45 (s, 3H), 3.23–3.11 (m, 1H), 2.85–2.64 (m, 4H), 2.50 (s, 3H), 2.44–2.36 (m, 1H), 2.01–1.99 (m, 1H), 1.80–1.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2, 148.3, 139.6, 137.5, 135.0, 131.3, 130.3, 128.3, 126.3 (2C), 118.9, 111.3, 66.7, 58.3, 56.0, 45.1, 37.6, 32.1, 29.9 (2C); ESI-MS *m*/*z*: 328 $[M+H]^+$; Anal. Calcd for $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.45; H, 6.81; N, 4.19; $[\alpha]_D^{23} = -170.9$ (*c* 1.00, EtOH).

4.1.13. *trans*-(+)-(6a*R*,13b*S*)-11-Chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-12-methoxy-5*H*-benzo[*d*]naphth[2,1-*b*]-azepine *ent*-15

$[\alpha]_D^{23} = +172.5$ (*c* 1.00, EtOH).

4.1.14. *trans*-(−)-(6a*S*,13b*R*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth-[2,l-*b*]azepin-l2-ol SCH 39166

A mixture of **7** (0.10 g, 0.305 mmol) in 3 mL of 48% HBr and 3 mL of AcOH was heated at 130 °C for 7 h. The volatile materials

were removed from the reaction mixture until the mixture was concentrated to about 1 mL. The residue was chilled, and the precipitated solids were filtered and washed with a small amount of ice-water. The wet solids were dissolved in 1 mL of DMF by heating on a water bath. The hot solution was poured slowly into 5 mL of 5% $NaHCO_3$, with stirring. The precipitated solids were filtered and washed with water and cold ether. After drying under reduced pressure, the desired product was obtained in an 89% yield (0.085 g).White solid, mp: 217–219 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15–6.98 (m, 5H), 5.98 (s, 1H), 4.73 (d, J = 7.2 Hz, 1H), 3.61–3.48 (m, 1H), 3.22–3.13 (m, 1H), 2.95–2.65 (m, 4H), 2.49 (s, 3H), 2.43–2.33 (m, 1H), 2.04–1.96 (m, 1H), 1.75–1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.5, 149.0, 139.5, 137.3, 134.8, 131.0, 128.7, 128.0, 126.3, 126.1, 116.1, 114.5, 66.5, 58.2, 44.6, 37.2, 31.9, 29.7 (2C).;ESI-MS m/z: 314 $[M+H]^+$; $\{[\alpha]_D^{23} = -200.9$ (c 0.52, DMF)}.

4.1.15. *trans*-(+)-(6a*R*,13b*S*)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5*H*-benzo[*d*]naphth-[2,l-*b*]azepin-l2-ol (+)-SCH 39166

$\{[\alpha]_D^{23} = +202.8$ (c 0.29, DMF)}.

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