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Asymmetric total synthesis of (+)-indatraline via diastereoselective amination of chiral ethers using chlorosulfonyl isocyanate

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ABSTRACT

A concise asymmetric total synthesis of (+)-indatraline from readily available cinnamic acid is described. The key steps include Corey's oxazaborolidine-catalyzed asymmetric carbonyl reduction and a highly stereoselective amination of chiral benzylic ether with retention of stereochemistry using chlorosulfonyl isocyanate.

1. Introduction

The indane motif is a common scaffold found in several medical agents. In particular, compounds including the amine functionality on an indane framework have been used in drug candidates aiming at modulating a diverse group of target structures, such as dopamine,[1] serotonin[2] and neurokinin-2 receptors,[3] and monoamine transporters.[4] For example, (+)-indatraline (Lu-19005) is a non-selective monoamine transporter inhibitor to block the reuptake of dopamine, norepinephrine, and serotonin.[4] Rasagiline (Azilect) is a prescribed agent for the treatment of Parkinson's disease,[5] and irindalone displays antihypertensive properties via the selective blocking of 5-HT_2 receptor (Fig. 1).[6]

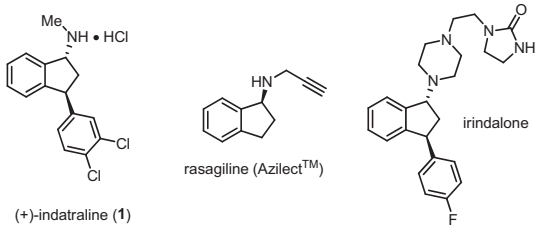

Fig. 1. Biologically active compounds containing 1-amino indane scaffold.

Cocaine is a non-selective monoamine reuptake inhibitor that blocks the reuptake of dopamine, norepinephrine and serotonin.[7] The illicit abuse of cocaine continues to be a serious public health problem throughout the world, but no uniformly effective medication for its treatment has been developed.[8] A possible treatment for cocaine dependence includes substitution medication that produces cocaine-like behavior, but with a slower onset and longer duration of action than cocaine.[9] (+)-Indatraline (**1**), is a potent long-acting monoamine reuptake inhibitor that has been investigated as a potential drug for the treatment of major depressive disorder and cocaine addiction. The (+)-enantiomer of indatraline is 20 times more potent than the (−)-enantiomer.[10,11a] Commercial production of (+)-indatraline relies on the chiral resolution of racemic indatraline. Due to its interesting pharmacological activity and unique structural features, several synthetic methods for indatraline have been developed. Most of these synthetic approaches rely on the preparation of 3-phenyl-1-indanone, which can be easily converted into *trans*-3-phenyl-1-indanamine through nucleophilic substitution reaction.[11,12] In a representative example of asymmetric synthesis, Davies reported an asymmetric total synthesis of (+)-indatraline based on rhodium-catalyzed enantioselective carbenoid C–H bond insertion into 1,4-cyclohexadiene.[12a] In another example, a diastereoselective total synthesis of (±)-indatraline was described via iodine-promoted oxidative ring contraction of 1,2-dihydronaphthalene followed by Hofmann rearrangement.[13] In a recent example, Juhl demonstrated a total synthesis of (+)-indatraline via enzymatic resolution of racemic *trans*-3-phenyl-1-indanol.[14]

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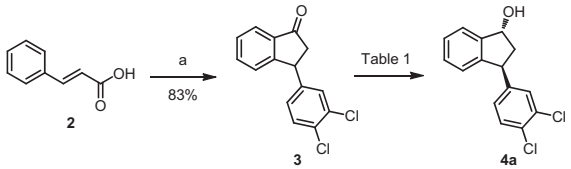
As part of an ongoing research program aimed at developing asymmetric total synthesis of biologically active compounds,[15] we recently described a facile strategy for the preparation of (+)-sertraline via stereoselective amination of various chiral benzylic ethers using chlorosulfonyl isocyanate (CSI).[16] In connection with our previous work on the regioselective and diastereoselective amination of cyclic benzylic ethers using CSI, we herein describe an asymmetric total synthesis of (+)-indatraline (**1**) starting from commercially available cinnamic acid (**2**) via highly stereoselective amination of chiral benzylic ether using chlorosulfonyl isocyanate as the key step.

2. Results and discussion

Our initial investigations focused on the efficient construction of indanone **3** and the formation of chiral indanol **4a** based on the reported literature (Scheme 1). First, cinnamic acid (**2**) was coupled with 1,2-dichlorobenzene in the presence of an excess amount of trifluoromethanesulfonic acid (TfOH) to afford our desired product **3** in 83% yield.[17]



Scheme 1. Reagents and conditions: (a) 1,2-dichlorobenzene, CF_3SO_3H, rt, 72 h.

The enantioselective reduction of **3** was achieved by Corey's oxazaborolidine-catalyzed asymmetric carbonyl reduction methodology (Table 1).[18] Treatment of the ketone **3** with (*S*)-(−)-2-methyl-CBS-oxazaborolidine catalyst (**5**) and catecholborane afforded a separable mixture of (1*R*,3*S*)-*trans*-indanol **4a** and its diastereoisomer **4b** with high enantioselectivities (Table 1, entry 1). The relative stereochemistry of **4a** and **4b** was confirmed by NOESY NMR analysis (see Supplementary data for further details). After optimization of the reaction conditions, we found that prochiral ketone **3** was converted into our desired compound **4a** in 45% yield with excellent enantioselectivity (>99% ee) by the use of **5** and *N*,*N*-diethylaniline borane (Table 1, entry 4).[19] The absolute configuration of **4a** was determined by comparison with a reported data via chiral HPLC analysis.[12e]

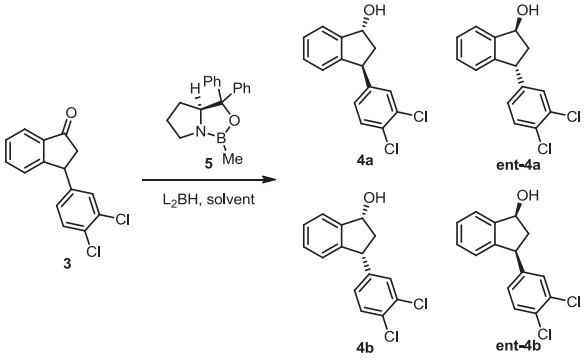
Benzylation of **4a** under standard conditions (benzyl bromide, NaH, THF/DMF) afforded benzyl ether **6** in 83% yield. Next, the diastereoselectivity of the reaction of **6** using chlorosulfonyl isocyanate (CSI) was examined under various reaction conditions, and the selected results are summarized in Table 2. As shown in entry 1, the reaction in methylene chloride at −40 °C gave the desired product **7** and its diastereomer with 92:8 of diastereomeric ratio. After screening of solvents under otherwise identical conditions, *n*-hexane was found to be most effective solvent in this reaction, affording exclusively compound **7** in 75% yield with an excellent diastereoselectivity (99>1). The observed stereochemistry can be explained by the competition between the S_Ni mechanism leading to retention of stereochemistry through a four-centered transition state and the S_N1 mechanism through carbocation intermediate.[20] This result is consistent with the formation of a tight ion pair in nonpolar *n*-hexane solvent, compared to relatively polar methylene chloride solvent.

Table 2
Selected optimization for the diastereoselective amination of **6**[a]

Entry	Solvent	Time (h)	Yield[b] (%)	dr[c]
1	CH_2Cl_2	14	61	92:8
2	Toluene	40	70	96:4
3	*n*-Hexane	40	75	99>1

[a] Reaction conditions: (i) compound **6** (1 equiv), chlorosulfonyl isocyanate (3 equiv), Na_2CO_3 (3 equiv), solvent (0.06 M), −40 °C (ii) 25% Na_2SO_3, rt, 12 h.
[b] Isolated yield by flash column chromatography.
[c] Diastereomeric ratio was determined by ^{1}H NMR analysis of a crude reaction mixture.

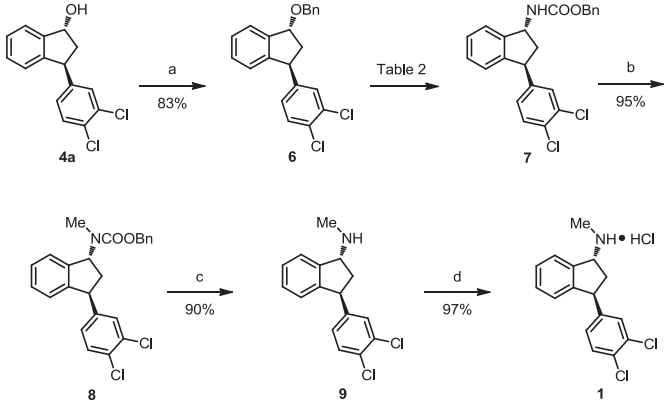
Table 1
Selected optimization for the asymmetric reduction of **3**[a]



Entry	L_2BH	Solvent (M)	Temp (°C)	Time (h)	**4a**+*ent*-**4a**		**4b**+*ent*-**4b**	
					Yield[b] (%)	ee (%)[c]	Yield[b] (%)	ee (%)[c]
1	Catecholborane	CH_2Cl_2 (0.5)	−78	12	31	95	50	85
2	*N*,*N*-DEAB	Toluene (0.15)	−20	24	No reaction			
3	*N*,*N*-DEAB	Toluene (0.15)	0	24	5	—	5	—
4	*N*,*N*-DEAB	Toluene (0.15)	rt	4	45	>99	46	91

[a] Reaction conditions: compound **3** (3.0 mmol), **5** (20 mol %), L_2BH (6.0 mmol), solvent, under N_2.
[b] Isolated yields by flash column chromatography.
[c] Enantiomeric excess (ee) was determined by chiral stationary phase HPLC analysis.

To complete the synthesis of (+)-indatraline, the carbamate **7** was treated with MeI and NaH to afford the compound **8**, which was hydrogenated using the Raney Ni catalyst to afford indatraline free amine (**9**) in 90% yield (Scheme 2). The spectral data (^{1}H NMR and ^{13}C NMR) and specific rotation of **8** were in full agreement with the reported values.[12e] Finally, indatraline free amine (**9**) was treated with HCl in diethyl ether to give (+)-indatraline hydrochloride salt in 97% yield.



Scheme 2. Reagents and conditions: (a) NaH, BnBr, THF/DMF (4:1), rt, 12 h; (b) NaH, MeI, THF/DMF (4:1), rt, 12 h; (c) Raney Ni, H_2, CH_2Cl_2/MeOH (1:4), rt, 6 h; (d) 1 M HCl, Et_2O, rt, 2 h.

3. Conclusion

We have described a concise total synthesis of (+)-indatraline starting from readily available cinnamic acid in seven linear steps (19.3% overall yield) via Corey's oxazaborolidine-catalyzed asymmetric carbonyl reduction and a stereoselective amination reaction into chiral cyclic benzylic ether using chlorosulfonyl isocyanate. It is believed that this synthetic strategy can be applied to the preparation of a broad range of biologically active compounds containing a chiral amine moiety.

4. Experimental

4.1. General

Commercially available reagents were used without additional purification, unless otherwise stated. All reactions were performed under an inert atmosphere of nitrogen or argon. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a Bruker Unity 300 MHz and Varian Unit 500 MHz spectrometers for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on Bruker Infrared spectrophotometer and are reported as cm^{-1}. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. LC-mass spectra (LC/MS) were recorded on a Waters 2767 LCMS system. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-600 spectrometer. Chiral HPLC separations were performed on an Shimadzu HPLC unit equipped with UV–VIS Diode-Array detector using Daicel Chiralcel OJ-RH and OD-RH columns (4.6×150 mm, 5 μm).

*4.1.1. 3-(3,4-Dichlorophenyl)-2,3-dihydro-1H-inden-1-one (**3**).*[17] To a stirred solution of cinnamic acid (**2**) (1.45 mg, 9.789 mmol) in 1,2-dichlorobenzene (7.25 mL) was added CF_3SO_3H (30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 72 h. The resulting mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (100 mL×2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=6:1) to afford 2.25 g (8.125 mmol, 83% yield) of **3** as a white solid. R_f=0.37 (*n*-hexane/EtOAc=5:1); mp 114–117 °C [lit.[11c] mp 113–115 °C]; IR (KBr) ν 3434, 2915, 1700, 1587, 1471, 1411, 1130, 898, 826, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (dd, J=19.1, 3.8 Hz, 1H), 3.22 (dd, J=19.1, 8.0 Hz, 1H), 4.54 (dd, J=8.0, 3.4 Hz, 1H), 6.94 (dd, J=8.0, 1.9 Hz, 1H), 7.21 (d, J=1.9 Hz, 1H), 7.25 (dd, J=7.6, 1.1 Hz, 1H), 7.38 (d, J=8.4 Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.61 (dt, J=7.6, 1.1 Hz, 1H), 7.82 (d, J=7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.5, 46.5, 123.7, 126.7, 127.0, 128.4, 129.6, 130.9, 131.1, 132.9, 135.4, 136.7, 143.9, 156.5, 204.9; LC/MS (ESI) m/z 277.06 $[M+H]^+$, 279.05 $[M+2+H]^+$; HRMS (EI) calcd for $C_{15}H_{10}OCl_2$ $[M]^+$ 276.0109, found 276.0109.

*4.1.2. (1R,3S)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1H-inden-1-ol (**4a**).* To a stirred solution of (*S*)-(+)-2-methyl-CBS-oxazaborolidine (0.6 mL, 0.60 mmol) in anhydrous toluene (10 mL) was added *N*,*N*-diethylaniline borane (1.1 mL, 5.98 mmol) at room temperature. The indanone **3** (0.828 g, 2.988 mmol) in anhydrous toluene (10 mL) was slowly added dropwise with the aid of a syringe pump over 3 h period. The reaction mixture was stirred at room temperature for 1 h under N_2. The reaction mixture was carefully quenched with MeOH (1 mL), followed by addition of 1 M HCl (1 mL) and stirred for 10 min. The organic layer was extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=5:1) to afford **4a** (0.375 g, 1.344 mmol, 45% yield, >99% ee) as a colorless oil and **4b** (0.384 g, 1.374 mmol, 46% yield, 91% ee) as a white solid, respectively. R_f=0.17 (*n*-hexane/EtOAc=4:1); $[\alpha]_D^{25}$ −24.8 (*c* 1.0, $CHCl_3$); IR (neat) ν 3317, 2917, 2849, 1470, 1399, 1326, 1177, 945, 879, 821 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (d, J=4.6 Hz, 1H), 2.28–2.37 (m, 1H), 2.52–2.60 (m, 1H), 4.60 (t, J=7.6 Hz, 1H), 5.36–5.41 (m, 1H), 6.96 (d, J=8.2 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 7.22 (s, 1H), 7.22–7.38 (m, 3H), 7.48 (d, J=6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.2, 48.2, 75.1, 124.6, 125.3, 127.3, 127.8, 129.3, 129.8, 130.5, 132.6, 144.9, 145.0, 145.1, 145.6; HRMS (EI) calcd for $C_{15}H_{12}OCl_2$ $[M]^+$ 278.0265, found 278.0269; HPLC (Chiralcel OJ-RH column, CH_3CN/H_2O (0.1% TFA)=10:90 to 100:0, 1.0 mL/min, 265 nm): t_R (minor)=15.26 min (1*S*,3*R*), t_R (major)=18.43 min (1*R*,3*S*).

*4.1.3. (1R,3R)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1H-inden-1-ol (**4b**).* R_f=0.26 (*n*-hexane/EtOAc=4:1); $[\alpha]_D^{25}$ −16.7 (*c* 1.0, $CHCl_3$); mp 95–98 °C; IR (KBr) ν 3432, 3231, 1467, 1400, 1030, 1028, 818, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83–1.96 (m, 2H), 2.97–3.06 (m, 1H), 4.15 (t, J=8.4 Hz, 1H), 5.26–5.33 (m, 1H), 6.93 (d, J=8.0 Hz, 1H), 7.07 (dd, J=8.4, 1.9 Hz, 1H), 7.24–7.35 (m, 3H), 7.38 (d, J=8.0 Hz, 1H), 7.48 (d, J=7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.7, 47.5, 74.8, 123.9, 124.9, 127.6, 127.7, 128.6, 130.2, 130.5, 132.5, 144.4, 144.6, 145.1; HRMS (EI) calcd for $C_{15}H_{12}OCl_2$ $[M]^+$ 278.0265, found 278.0270; (Chiralcel OD-RH column, CH_3CN/H_2O (0.1% TFA)= 10:90 to 100:0, 1.0 mL/min, 265 nm): t_R (minor)=18.07 min (1*S*,3*S*), t_R (major)=18.74 min (1*R*,3*R*).

*4.1.4. (1R,3S)-1-(Benzyloxy)-3-(3,4-dichlorophenyl)-2,3-dihydro-1H-indene (**6**).* To a stirred solution of **4a** (0.364 g, 1.304 mmol) in anhydrous THF (13 mL) and DMF (3.3 mL) were added NaH (78 mg, 1.96 mmol, 60% in mineral oil) and BnBr (0.465 mL, 3.91 mmol) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was carefully quenched with H_2O (10 mL) and extracted with EtOAc (100 mL×2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=30:1) to afford 0.399 g (1.080 mmol, 83% yield) of **6** as a colorless oil. R_f=0.26 (*n*-hexane/EtOAc=20:1); $[\alpha]_D^{25}$ −0.7 (*c* 1.0, $CHCl_3$); IR (neat) ν 3065, 3029, 2930, 2861, 1469, 1399, 1341, 1103, 1072, 1030, 821, 746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17–2.26 (m, 1H), 2.68–2.78 (m, 1H), 4.62 (t, J=7.6 Hz, 1H), 4.62 (s, 2H), 5.10 (dd, J=6.1, 2.3 Hz, 1H), 6.97–7.02 (m, 2H), 7.22 (d, J=1.9 Hz, 1H), 7.28–7.40 (m, 8H), 7.48 (dd, J=5.3, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.6, 48.5, 70.7, 81.3, 125.2, 125.5, 127.2, 127.5, 127.6, 127.8, 128.4, 129.2, 130.0, 130.4, 130.5, 132.5, 138.4, 142.7, 145.1, 146.6; LC/MS (ESI) m/z 369.05 $[M+H]^+$, 371.00 $[M+2+H]^+$; HRMS (EI) calcd for $C_{22}H_{18}OCl_2$ $[M]^+$ 368.0735, found 368.0726.

*4.1.5. Benzyl (1R,3S)-3-(3,4-dichlorophenyl)-2,3-dihydro-1H-inden-1-yl carbamate (**7**).* To a stirred solution of **6** (0.183 g, 0.496 mmol) in anhydrous *n*-hexane (8.3 mL) were added Na_2CO_3 (0.158 g, 1.48 mmol) and chlorosulfonyl isocyanate (0.130 mL, 1.49 mmol) at −40 °C under N_2. The reaction mixture was stirred at −40 °C for 40 h. The resulting mixture was carefully quenched with H_2O (10 mL) and extracted with EtOAc (60 mL). The organic layer was added to an aqueous solution of 25% sodium sulfite (20 mL) and the reaction mixture was stirred for 12 h at room temperature. The organic layer was washed with H_2O and brine, dried over

anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=6:1) to afford 0.153 g (0.371 mmol, 75% yield) of **7** a white solid. R_f=0.30 (*n*-hexane/EtOAc=5:1); $[\alpha]_D^{25}$ +41.1 (*c* 1.0, $CHCl_3$); mp 103–108 °C; IR (KBr) ν 3320, 3027, 1679, 1524, 1260, 1237, 1028, 754, 659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (t, *J*=6.1 Hz, 2H), 4.46 (t, *J*=6.9 Hz, 1H), 4.92–5.10 (m, 1H), 5.15 (s, 2H), 5.29–5.39 (m, 1H), 6.92 (dd, *J*=8.0, 1.9 Hz, 1H), 7.02 (d, *J*=5.7 Hz, 1H), 7.18 (s, 1H), 7.22–7.46 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.7, 44.1, 48.1, 67.0, 124.8, 125.3, 127.1, 128.0, 128.2, 128.3, 128.6, 129.0, 129.7, 130.6, 132.6, 136.4, 144.8, 145.0, 156.0; LC/MS (ESI) *m*/*z* 412.02 $[M+H]^+$, 414.19 $[M+2+H]^+$; HRMS (EI) calcd for $C_{23}H_{19}NO_2Cl_2$ $[M]^+$ 411.0793, found 411.0799.

*4.1.6. Benzyl (1R,3S)-3-(3,4-dichlorophenyl)-2,3-dihydro-1H-inden-1-yl methylcarbamate (**8**).* To a stirred solution of **7** (0.144 g, 0.393 mmol) in anhydrous THF (7 mL) and DMF (1.7 mL) were added NaH (28 mg, 0.70 mmol, 60% in mineral oil) and MeI (0.087 mL, 1.40 mmol) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was quenched with H_2O (20 mL) and extracted with EtOAc (100 mL×2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=10:1) to afford 0.159 g (0.373 mmol, 95% yield) of **8** as a colorless oil. R_f=0.27 (*n*-hexane/EtOAc=6:1); $[\alpha]_D^{25}$ +76.0 (*c* 1.0, $CHCl_3$); IR (neat) ν 2925, 2854, 1700, 1469, 1401, 1323, 1138, 1029, 760, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.32–2.55 (m, 4H), 2.66 (s, 3H), 4.49 (dd, *J*=8.8, 5.3 Hz, 1H), 5.21 (s, 2H), 5.87–6.19 (m, 1H), 6.89 (dd, *J*=8.4, 1.9 Hz, 1H), 7.04 (d, *J*=5.7 Hz, 1H), 7.16 (s, 1H), 7.24–7.39 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.7, 39.1, 48.7, 60.2, 67.3, 124.9, 125.4, 127.0, 127.8, 127.9, 128.0, 128.5, 128.8, 129.5, 130.4, 130.6, 132.6, 136.8, 141.3, 145.2, 145.7, 156.7; LC/MS (ESI) *m*/*z* 426.07 $[M+H]^+$, 428.05 $[M+2+H]^+$; HRMS (EI) calcd for $C_{24}H_{21}NO_2Cl_2$ $[M]^+$ 425.0949, found 425.0954.

*4.1.7. (1R,3S)-3-(3,4-Dichlorophenyl)-N-methyl-2,3-dihydro-1H-inden-1-amine (**9**).* To a stirred solution of **8** (0.100 g, 0.235 mmol) in CH_2Cl_2 (2 mL) and MeOH (8 mL) was added Raney Nickel (30 mg). The reaction mixture was stirred for 6 h under H_2 balloon at room temperature. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by column chromatography (CH_2Cl_2/MeOH=15:1) to afford 62 mg (0.212 mmol, 90% yield) of **1** as a colorless oil. R_f=0.29 (CH_2Cl_2/MeOH=9:1); $[\alpha]_D^{25}$ −17.9 (*c* 1.0, $CHCl_3$) [lit.[12e] $[\alpha]_D^{23}$ −18.9 (*c* 1.1, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (br, 1H), 2.20–2.29 (m, 1H), 2.41–2.49 (m, 1H), 2.52 (s, 3H), 4.26 (dd, *J*=6.9, 3.1 Hz, 1H), 4.51 (t, *J*=7.6 Hz, 1H), 6.97 (dd, *J*=8.0, 1.9 Hz, 2H), 7.22–7.30 (m, 3H), 7.36 (d, *J*=8.0 Hz, 1H), 7.39–7.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.3, 43.4, 48.5, 63.7, 124.7, 125.3, 127.2, 127.5, 128.3, 129.9, 130.3, 130.4, 132.4, 145.0, 145.5, 145.6; LC/MS (ESI) *m*/*z* 292.00 $[M+H]^+$, 293.99 $[M+2+H]^+$; HRMS (FAB) calcd for $C_{16}H_{16}Cl_2N$ $[M+H]^+$ 292.0660, found 292.0649.

*4.1.8. (+)-Indatraline (**1**).* To a stirred solution of indatraline free amine (**9**) (30 mg, 0.103 mmol) in diethyl ether (0.5 mL) was added a solution of 1 M HCl (0.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered and washed with diethyl ether. The resulting solid was dried in vacuo to afford 33 mg (0.100 mmol, 97% yield) of (+)-indatraline as a white solid. R_f=0.35 (CH_2Cl_2/MeOH/NH_4OH=9:1:0.1); $[\alpha]_D^{25}$ +30.1 (*c* 1.0, MeOH); mp 182–184 °C; IR (MeOH) ν 3359, 2946, 2833, 1451, 1406, 1032, 820, 630 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.46–2.57 (m, 1H), 2.78 (s, 3H), 2.75–2.84 (m, 1H), 4.70 (t, *J*=7.8 Hz, 1H), 4.89–4.92 (m, 1H), 7.07–7.08 (m, 1H), 7.11 (dd, *J*=8.0, 2.2 Hz, 1H), 7.35 (d, *J*=2.2 Hz, 1H), 7.43–7.51 (m, 3H), 7.63–7.66 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 31.4, 39.9, 49.4, 64.2, 127.0, 127.1, 129.0, 129.4, 131.2, 132.0, 132.1, 132.2, 133.7, 138.3, 145.8, 148.7; LC/MS (ESI) *m*/*z* 292.00 $[M+H]^+$, 293.99 $[M+2+H]^+$.

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Supplementary data

HPLC analysis data of compounds **4a** and **4b** and ^1H NMR and ^{13}C NMR copies of all compounds. Supplementary data related to this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.044.

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