**Iodine(III)-Mediated Ring Contraction of 1,2-Dihydronaphthalenes: A
Diastereoselective Total Synthesis of (±)-Indatraline**

Supporting Information

Luiz F. Silva, Jr.,^{†, *} Fernanda A. Siqueira,[†] Eliane C. Pedrozo,[†] Fabiana Y. M. Vieira[‡] and Antônio
C. Doriguetto[‡]

[†]*Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748, CP 26077, CEP
05513-970 São Paulo SP, Brazil and*

[‡]*Departamento de Ciências Exatas, Universidade Federal de Alfenas, Rua Gabriel Monteiro da
Silva, 714, CEP 37130-000 Alfenas MG, Brazil*

e-mail: luizfsjr@iq.usp.br

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1. Experimental Procedures

General Information

Tetralone **5** was prepared from 1-naphthol and 1,2-dichlorobenzene¹ which were used as received. The olefin **6** was prepared by reduction followed by dehydration of 1-tetralone.² HTIB and PIFA were used as received. Toluene and hexanes were distilled from sodium wire and storage in a bottle also containing sodium wire. MeOH, acetone, CH₃CN, AcOEt, were distilled from magnesium turnings, KMnO₄, CaH₂, CaH₂, respectively. DMF were distilled from toluene. These solvents were storage in a bottle containing molecular sieves 4A. THF and CH₂Cl₂ were freshly distilled from sodium/benzophenone and CaH₂, respectively. Column chromatography was performed using silica gel 200-400 Mesh. TLC analysis were performed using silica gel plates, using phosphomolibdic acid, vaniline or *p*-anisaldehyde solution for visualization. ¹H and ¹³C NMR spectra were recorded on Bruker or Varian spectrometers. IR spectra were measured on a Perkin-Elmer 1750-FT. Gas chromatography analysis were performed in a HP-6890 series II and/or Shimadzu-2010. Melting points are uncorrected. HRMS analysis were performed on a Bruker Daltonics Microtof Eletrospray.

1,2-Dihydro-1-methylnaphthalene (**9**)

NaBH₄ (0.378 g, 10.0 mmol) was added to a solution of 4-methyl-1-tetralone (3.20 g, 20.0 mmol) in MeOH. The mixture was stirred. The MeOH was removed under reduced pressure and the organic layer was extracted with Et₂O, washed with H₂O, brine, and dried over anhyd MgSO₄. The solvent was removed under reduced pressure giving a yellow oil that was dried in vacuum, affording the crude 4-methyl-1-tetralol. To a stirred solution of this crude product in THF (8.0 mL) was added H₃PO₄ 85% (20 mL). The mixture was stirred at rt. After 1 h the organic layer was extracted with AcOEt, washed with H₂O, brine, and dried over anhyd MgSO₄. The solvent was removed under

reduced pressure. The crude product was purified using flash column chromatography (hexanes) affording **9**³ (1.71 g, 11.9 mmol), as yellow oil.

4-Methyl-1,2-dihydronaphthalene (**15**)

A solution of 1-tetralone (2.10 mL, 2.31 g, 15.8 mmol) in Et₂O (9 mL) was added to a solution of MeMgI [prepared from MeI (2.70 mL, 42.6 mmol), Mg (1.06 g, 43.8 mmol) and I₂ (some crystals) in anhyd Et₂O (9 mL)]. The mixture was stirred for 6 h at rt. After that, a 10% aqueous solution of HCl at 0 °C was dropwise (dropwise, until pH acid). The solution was stirred for 1 h. The organic layer was extracted with Et₂O (100 mL), washed with Na₂S₂O₃ (2 x 25 mL), brine (2 x 25 mL) and dried over anhyd MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes) affording **15**⁴ (1.40 g, 9.68 mmol, 61%), as a colorless oil.

1,4-Dimethyl-1,2-dihydronaphthalene (**23**)

The reaction was performed as indicated for **15**. A mixture of 4-methyl-1-tetralone (2.00 mL, 2.16 g, 13.5 mmol), MeMgI [prepared from MeI (2.40 mL, 37.9 mmol), Mg (0.920 g, 37.9 mmol) and I₂ (some crystals) in anhyd Et₂O (9 mL)] was stirred for 6 h at rt. The crude product was purified by flash column chromatography (hexanes) affording **23**⁵ (1.29 g, 8.16 mmol, 60%), as a colorless oil.

Reaction of the 1,2-dihydronaphthalene (**6**) with HTIB in MeOH

HTIB (0.409 g, 1.04 mmol) was added to a stirred solution of **6** (0.133 g, 1.02 mmol) in MeOH (3 mL), at rt. After 30 min, the solution was washed with NaHCO₃ (10 mL) and the organic layer was extracted with AcOEt (50 mL), washed with brine (10 mL) and dried over anhyd MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/AcOEt 10:1) affording **7**⁶ (0.0825 g, 0.368 mmol, 36%), *trans*-**8**⁶ (0.0641 g, 0.286 mmol, 28%) and *cis*-**8**⁶ (0.0321 g, 0.143 mmol, 14%), as a colorless oil.

Reaction of **9** with HTIB

HTIB (1.18 g, 3.00 mmol) was added to a stirred solution of **9** (0.361 g, 2.50 mmol) in MeOH (12.5 mL). After 30 min, complete consumption of the starting material was observed. The organic layer was extracted with AcOEt, washed with H₂O, brine, and dried over anhyd MgSO₄. The solvent was removed under reduced pressure. The crude product was purified using flash column chromatography (gradient elution 5–10% AcOEt in hexanes) affording **10**⁶ (0.284 g, 1.38 mmol, 55%), as a colorless oil and a 8:7 mixture of *cis* and *trans*-**11**, respectively (0.064 g, 0.312 mmol, 12%), also as a colorless oil. In the crude product, the *cis:trans* ratio of **11** is 3:4 (estimated by GC analysis).

Cis and *trans*-1,2,3,4-tetrahydro-1,2-dimethoxy-4-methylnaphthalene (**11**)

¹H NMR (500 MHz, CDCl₃): δ *cis* diastereoisomer: 1.35 (d, *J* = 6.9 Hz, 3H), 1.39-1.47 (m, 1H), 2.28 (ddd, *J* = 4.1, 5.2, 13.1, 1H), 2.88-3.03 (m, 2H), 3.44 (s, 1H), 3.53 (s, 1H), 3.75 (ddd, *J* = 3.0, 3.8, 6.5, 1H), 4.22 (d, *J* = 5.0 Hz, 1H), 7.17-7.24 (m, 6H), 7.34 (d, *J* = 7.2 Hz, 1H); *trans* diastereoisomer: 1.34 (d, *J* = 7.0 Hz, 3H), 1.84 (ddd, *J* = 3.1, 8.4, 13.7 Hz, 1H), 2.01-2.06 (m, 1H), 2.88-3.03 (m, 2H), 3.49 (s, 1H), 3.52 (s, 1H), 3.63 (ddd, *J* = 3.9, 6.9, 13.6, 1H), 4.37 (d, *J* = 7.0 Hz, 1H), 7.17-7.24 (m, 6H), 7.43 (d, *J* = 7.2 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 21.7, 21.9, 29.2, 31.5, 32.0, 34.9, 56.60, 56.63, 57.57, 57.61, 76.6, 80.02, 80.05, 82.0, 125.9, 126.1, 126.2, 127.0, 127.6, 127.8, 128.3, 129.5, 134.1, 135.5, 141.5, 141.8. IR (cm⁻¹): 756, 1095, 1460, 2823, 2927.

LRMS m/z: 206 (M^+ , 1), 174 (23), 159 (49), 148 (100). HRMS calc. For $[C_{13}H_{18}O_2 + Na]^+$: 229.1199.
Found: 229.1201.

Oxidation of 6,8-dimethyl-1,2-dihydronaphthalene (**12**) with HTIB in MeOH

The reaction was performed as indicated for **6**. A mixture of **12** (0.158 g, 1.00 mmol), HTIB (0.471 g, 1.20 mmol) and MeOH (4 mL) was stirred for 15 min at rt. The crude product was purified by flash column chromatography (hexanes/AcOEt 4:1) affording **13**² (0.063 g, 0.29 mmol, 29%), *trans*-**14**² (0.060 g, 0.27 mmol, 27%), and *cis*-**14**² (0.038, 0.17 mmol, 17%).

Oxidation of 4-methyl-1,2-dihydronaphthalene (**15**) with HTIB in MeOH

The reaction was performed as indicated for **6**. A mixture of **15** (0.150 g, 1.04 mmol), HTIB (0.410 g, 1.05 mmol) and MeOH (2 mL) was stirred for 20 min at rt. The crude product was purified by flash column chromatography (hexanes/AcOEt 10:1) affording *trans*-**16**^{2,6} (0.128 g, 0.622 mmol, 60%) and *cis*-**16**^{2,6} (0.0658 g, 0.319 mmol, 31%).

Reaction of 1,2-dihydronaphthalene (**6**) with HTIB in CH₃CN

A solution of **6** (0.0697 g, 0.535 mmol) and molecular sieves (3 Å, 0.035 g, 0.5 g/g substrate) in anhyd CH₃CN (4 mL) under N₂ was stirred for 5 min at 0 °C. HTIB (0.315 g, 0.855 mmol) was then added. The solution was stirred for 30 min at rt. After that, the solution was washed

with NaHCO₃ (10 mL) and the organic layer was extracted with AcOEt (50 mL), washed with brine (10 mL), dried over anhyd MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes) affording **21**⁷ (0.0206 g, 0.161 mmol, 30%).

Reaction of 1,2-dihydronaphthalene (**6**) with HTIB in CH₂Cl₂

HTIB (0.335 g, 0.855 mmol) was added to a stirred solution of **6** (0.111 g, 0.855 mmol) in CH₂Cl₂ (3 mL), at rt. After 20 min, the solution was washed with NaHCO₃ (10 mL) and the organic layer was extracted with AcOEt (50 mL), washed with brine (10 mL) and dried over anhyd MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes) affording **21**⁷ (0.0528 g, 0.412 mmol, 48%).

Oxidation of 4-methyl-1,2-dihydronaphthalenes (**15**) with HTIB in CH₃CN

The reaction was performed as indicated for **6**. A mixture of **15** (0.122 g, 0.845 mmol), molecular sieves (3 Å, 0.0607 g, 0.5 g/g substrate), HTIB (0.401 g, 1.02 mmol) in anhyd CH₃CN (4 mL) under N₂ was stirred for 10 min at 0 °C. The crude product was purified by flash column chromatography (gradient elution, hexanes and hexanes/AcOEt 10:1) affording **21**⁸ (0.0689 g, 0.430 mmol, 51%) and small amount of 1-methylnaphthalene⁹ (0.00300 g, 0.0211 mmol, 3%).

Oxidation of 1,4-dimethyl-1,2-dihydronaphthalene (**23**) with HTIB in CH₃CN

The reaction was performed as indicated for **6**. A mixture of **23** (0.124 g, 0.785 mmol), molecular sieves (3 Å, 0.0614 g, 0.5 g/g substrate), HTIB (0.374 g, 0.942 mmol) in anhyd CH₃CN (4 mL) under N₂ was stirred for 10 min at 0 °C. The crude product was purified by flash column chromatography (hexane/ethyl acetate 10:1) affording **24** (0.0815 g, 0.468 mmol, 60%), as colorless oil.

1-(3-Methyl-indan-1-yl)-ethanone (**24**)

Colorless oil; ¹H NMR (300 MHz, CDCl₃): δ *trans* diastereomer: 1.29 (d, *J* = 6.9 Hz, 3H), 1.80-1.87 (m, 1H), 2.17 (s, 3H), 2.55-2.63 (m, 1H), 3.40 (s, *J* = 7.3 Hz, 1H), 4.08 (dd, *J* = 3.3 and 8.7 Hz, 1H), 7.19-7.30 (m, 4H), selected signals for the *cis* diastereomer (other signals overlap with the *trans* form): 1.36 (d, *J* = 6.8 Hz, 3H), 2.22 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ *trans* diastereomer: 20.2, 27.6, 37.6, 38.3, 57.7, 123.8, 124.8, 126.6, 127.7, 140.4, 149.1, 208.5; *cis* diastereomer: 19.7, 30.0, 38.1, 38.4, 57.4, 123.5, 124.6, 126.6, 127.5, 140.6, 148.7, 209.0. IR (cm⁻¹): 757, 1709, 1355, 1476, 2959. LRMS *m/z*: 174 (M⁺, 7), 131 (100). HRMS calc. for [C₁₂H₁₄O + H]⁺: 175.1123, found 175.1126.

1-(3,4-dichlorophenyl)-1,2-dihydronaphthalene (**4**)

To a stirred solution of the tetralone **5** (4.67 g, 16.0 mmol) in anhyd MeOH (160 mL), was added dropwise NaBH₄ (0.609 g, 16.0 mmol) at 0 °C. The mixture was stirred at rt. After 2 h was observed complete consumption of the starting material. The reaction was quenched with H₂O (105 mL) and a 10% aqueous solution of HCl was added dropwise until pH around 5. The solvent was removed under reduced pressure and the residue was extracted with AcOEt, washed with brine, and dried over anhyd MgSO₄. The solvent was removed under reduced pressure, affording crude 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (4.70 g), as a yellow oil.

To a stirred solution of the 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol (4.70 g, 16.0 mmol) in anhyd toluene (130 mL) were added a few crystals of *p*-TsOH at rt. The mixture was

refluxed for 1 h. The organic phase was washed with sat solution of NaHCO₃ (twice), with brine, and dried over anhyd Na₂SO₄. The solvent was removed under reduced pressure giving a yellow oil. The residue was purified by flash column chromatography (gradient elution 0-30% AcOEt in hexanes), affording **4** (4.00 g, 14.5 mmol, 91%), as a white solid.

mp: 75.5-75.6 °C. ¹H NMR (200 MHz, CDCl₃): δ 2.44-2.77 (m, 2H), 4.08 (dd, *J* = 8.3, 7.9 Hz, 1H), 5.90-5.99 (m, 1H), 6.53 (d, *J* = 9.6 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 7.00-7.36 (m, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 31.6, 42.8, 126.4, 126.4, 127.2, 127.5, 127.7, 127.7, 128.1, 130.2, 130.3, 130.3, 132.3, 133.8, 136.4, 144.9. IR (cm⁻¹): 985, 1404, 1448, 1481, 1560, 2932, 3031. LRMS *m/z*: 274 (M⁺, 16), 129 [(M-C₆H₄Cl₂)⁺, 36], 100 (100). Anal. Calcd. for C₁₆H₁₂Cl₂: C, 69.84; H, 4.40. Found: C, 69.62; H, 4.70.

Reaction of **4** with HTIB

HTIB (0.518 g, 1.32 mmol) was added to a stirred solution of **4** (0.100 g, 0.363 mmol) in anhyd MeOH (1.5 mL). The mixture was stirred for 15 min. The organic layer was extracted with AcOEt, washed with H₂O, brine, and dried over anhyd MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (gradient elution 0–25% AcOEt in hexanes) affording **3** (0.0755 g, 0.224 mmol, 62%), and **25** (0.0427, 0.127 mmol, 35%). Analytical samples of pure *trans*-**25a** and *cis*-**25b** isomers were obtained by flash column chromatography (gradient elution 0–25% AcOEt in hexanes).

***trans*-1-(3,4-dichlorophenyl)-2,3-dihydro-3-(dimethoxymethyl)-1H-indene (3)**

Colorless oil. ^1H NMR (300 MHz, CDCl_3): δ 2.10-2.17 (m, 1H), 2.51-2.64 (m, 1H), 3.54-3.60 (m, 1H), 4.35 (d, $J = 6.9$ Hz, 1H), 4.41 (t, $J = 7.8$ Hz, 1H), 6.94-6.98 (m, 2H), 7.18-7.27 (m, 3H), 7.33 (d, $J = 7.8$ Hz, 1H), 7.44 (d, $J = 6.9$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 37.8, 46.8, 49.2, 53.4, 54.8, 107.1, 124.8, 125.8, 127.1, 127.4, 127.6, 129.8, 130.2, 130.4, 132.4, 143.0, 146.1, 146.2. IR (cm^{-1}): 758, 1061, 1121, 1470, 2830, 2934. LRMS m/z : 306 $[(\text{M}-\text{MeOH})^+, 2]$, 75 (100). Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{Cl}_2$: C, 64.11; H, 5.38. Found: C, 64.24; H, 5.56.

***trans*-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1,2-dimethoxynaphthalene (*trans*-25)**

Yellow oil. ^1H NMR (300 MHz, CDCl_3): δ 1.83 (dt, $J = 13.2, 10.5$ Hz, 1H), 2.46 (ddd, $J = 13.2, 5.5, 3.7$ Hz, 1H), 3.42 (s, 3H), 3.59 (s, 3H), 3.71 (ddd, $J = 10.8, 7.2, 3.7$ Hz, 1H), 4.09 (dd, $J = 10.6, 5.6$ Hz, 1H), 4.47 (d, $J = 7.1$ Hz, 1H), 6.70 (d, $J = 7.8$ Hz, 1H), 6.99 (dd, $J = 8.3, 2.1$ Hz, 1H), 7.13 (dt, $J = 7.4, 1.0$ Hz, 1H), 7.22-7.27 (m, 2H), 7.37 (d, $J = 8.3$ Hz, 1H), 7.50 (d, $J = 7.7$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 35.4, 44.0, 56.6, 58.1, 79.9, 81.8, 126.7, 127.7, 128.2, 128.3, 128.4, 128.6, 130.5, 130.7, 132.5, 136.3, 138.5, 146.1. IR (cm^{-1}): 762, 1093, 1468, 2825, 2931. LRMS m/z : 304 $[(\text{M} - \text{CH}_3\text{OH})^+, 63]$, 246 (100).

***Cis*-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1,2-dimethoxynaphthalene (*cis*-25)**

Yellow oil. ^1H NMR (300 MHz, CDCl_3): δ 2.26-2.33 (m, 2H), 3.47 (s, 3H), 3.51 (s, 3H), 3.56-3.65 (m, 1H), 4.06 (t, J = 8.9 Hz, 1H), 4.42 (d, J = 2.6 Hz, 1H), 7.02 (dd, J = 8.3, 2.1 Hz), 7.19-7.22 (m, 2H), 7.28-7.37 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3): δ 31.8, 45.0, 56.4, 57.2, 77.5, 78.8, 126.2, 128.1, 128.9, 129.9, 130.5, 130.6, 130.6, 132.3, 134.6, 138.7, 146.9. IR (cm^{-1}): 753, 1078, 1107, 1467, 2823, 2880, 2933. LRMS m/z : 336 (M^+ , 0.6), 304 [$(\text{M} - \text{CH}_3\text{OH})^+$, 54], 246 (100).

Reaction of **4** with Thallium Trinitrate

To a stirred solution of **4** (1.37 g, 4.98 mmol) in TMOF (25 mL), was added $\text{TTN} \cdot 3\text{H}_2\text{O}$ (2.44 g, 5.50 mmol) at 0 °C, which promptly dissolved. The mixture was stirred for 5 min at 0 °C and an abundant precipitation was observed. The result suspension was filtered through a silica gel pad (200-400 mesh), using CH_2Cl_2 as eluent. The filtrate was washed with H_2O (twice), with brine, and dried over anhyd MgSO_4 . The solvent was concentrated under reduced pressure giving a yellow oil. The residue was purified by flash chromatography (gradient elution 0-30% AcOEt in hexanes) affording **3** (1.48 g, 4.39 mmol, 88%), as a colorless oil.

***trans*-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-indene-1-carboxylic acid (**26**)**

To a solution of **3** (0.585 g, 1.73 mmol) and anhyd acetone (9 mL) was added dropwise the Jones reagent ($\text{H}_2\text{SO}_4/\text{H}_2\text{O}/\text{CrO}_3$: ratio = 1:9:1) at 0 °C until the reaction mixture remained brown. After 24 h was observed complete consumption of the starting material and isopropanol was added to the solution until the mixture become green. The mixture was extracted with AcOEt, washed with H_2O , with brine, and dried over anhyd Na_2SO_4 . The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (gradient elution 20-50% AcOEt in hexanes), affording **26** (0.440 g, 1.43 mmol, 83%), as a white solid.

mp: 209.0-211.9 °C, ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 2.16-2.20 (m, 1H), 2.71-2.75 (m, 1H), 4.12 (dd, J = 8.1, 3.9 Hz, 1H), 4.52 (t, J = 8.1 Hz, 1H), 6.86 (d, J = 6.9 Hz, 1H), 7.09 – 7.24 (m, 3H), 7.33-7.39 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 40.3, 49.1, 49.3, 125.2, 125.5, 127.8, 128.4, 128.6, 129.6, 130.1, 131.1, 131.6, 141.7, 146.2, 146.5, 175.2. IR (cm^{-1}): 923, 1415, 1472, 1705, 2727, 2941. LRMS m/z : 261 $[(\text{M}-\text{CO}_2\text{H})^+]$, 32, 227 $[(\text{M}-\text{CO}_2\text{HCl})^+]$, 19] 306 (M^+ , 12), 94 (100). Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{O}_2\text{Cl}_2$: C, 62.56; H, 3.94. Found: C, 62.72; H, 4.18.

***trans*-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-indene-1-carboxamide (**27**)**

A solution of **26** (0.800 g, 2.60 mmol), of SOCl_2 (8 mL, 0.1 mol) and of 1 drop of DMF was refluxed for 2 h. The excess of SOCl_2 was removed by distillation under reduced pressure, affording a yellow oil. NH_3 was condensed at -75 °C and the mixture was stirred at 0 °C for 2 h. Then, the reaction mixture was allowed to warm to rt. The reaction was extracted with AcOEt, washed with water, with brine, and dried over anhyd MgSO_4 . The solvent was removed under reduced pressure

giving a yellow solid, which was purified by recrystallization with a mixture of hexanes and AcOEt affording **27** (0.639 g, 2.09 mmol, 80%), as a white solid.

mp: 169.0-169.1 °C. ^1H NMR (300 MHz, CDCl_3): δ 2.32 (dt, J = 13.2, 8.4 Hz, 1H), 2.86-2.95 (m, 1H), 4.05 (dd, J = 9.0, 3.3 Hz, 1H), 4.54 (t, J = 7.8 Hz, 1H), 5.65 (sl, 1H), 6.09 (sl, 1H), 6.99 (dd, J = 7.8, 1.8 Hz, 2H), 7.22-7.40 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3): δ 41.0, 49.5, 50.7, 124.7, 125.6, 127.5, 127.8, 128.5, 129.9, 130.5, 130.6, 132.6, 141.5, 144.8, 146.3, 176.0. IR (cm^{-1}): 1472, 1590, 1657, 1691, 3211, 3403. LRMS m/z : 305 (M^{++} , 39), 261 (100). Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{NOCl}_2$: C, 62.72; H, 4.28; N, 4.57. Found: C, 62.54; H, 4.42; N, 4.32.

***trans*-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-inden-1-amine hydrochloride (**28**)**

To a stirred solution of PIFA (0.904 g, 2.10 mmol) in CH_3CN (6 mL), and in distilled H_2O (6 mL) was added **27** (0.600 g, 1.96 mmol). The mixture was stirred at rt for 6 h. The reaction mixture was diluted with H_2O (45 mL), and conc HCl (4.5 mL) was added. The mixture was extracted with 45 mL of Et_2O (45 mL). The aqueous layer was concentrated at reduced pressure giving a solid, which was purified by recrystallization from Et_2O and EtOH, affording **28** (0.554 g, 1.76 mmol, 90%), as a white solid.

mp: 206.4-206.5 °C, ^1H NMR (300 MHz, CD_3OD): δ 2.51-2.58 (m, 1H), 2.65-2.71 (m, 1H), 4.74 (t, J = 7.7 Hz, 1H), 4.97 (dd, J = 7.0, 1.9 Hz, 1H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.38-7.44 (m, 1H), 7.44 (dd, J = 17.9, 8.3 Hz, 2H), 7.60-7.65 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 41.6, 49.3, 56.1, 126.4, 126.7, 128.9, 129.4, 131.0, 131.6, 131.8, 131.9, 133.6, 140.0, 146.0, 147.8. IR (cm^{-1}): 764, 804, 825, 1030, 1130, 1377, 1401, 1469, 1598, 2607, 2726, 2959, 3402. LRMS m/z : 278 [$(\text{M}-\text{Cl})^+$, 35], 276 [$(\text{M}-\text{H}_2\text{Cl})^+$, 49], 104 (100). HRMS calc. for $[\text{C}_{15}\text{H}_{14}\text{Cl}_3\text{N} - \text{NH}_3\text{Cl}]^+$: 261.0238. Found: 261.0226.

***tert*-Butyl *trans*-1-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-inden-3-ylcarbamate (**29**)**

To a stirred solution of **28** (0.277, 0.879 mmol) in CH₂Cl₂ (9 mL) and Et₃N (0.3 mL) was added Boc₂O (0.262 g, 1.20 mmol) at 0 °C. The mixture was stirred at rt. After 2 h was observed complete consumption of the starting material. The reaction was extracted with AcOEt, washed with water, with brine, and dried over anhyd MgSO₄. The product was purified by flash column chromatography (gradient elution 0-30% AcOEt in hexanes), affording the carbamate **29** (0.327 g, 0.864 mmol, 98%), as a colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 1.48 (s, 9H), 2.43 (t, *J* = 6.0 Hz, 2H), 4.45 (t, *J* = 6.9 Hz, 1H), 4.78 (d, *J* = 7.5 Hz, 1H), 5.30-5.33 (m, 1H), 6.92 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.00-7.03 (m, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 7.23-7.34 (m, 3H), 7.41-7.44 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 28.4, 43.9, 48.0, 54.8, 79.6, 124.7, 125.2, 127.1, 127.9, 128.8, 129.6, 130.4, 130.5, 132.5, 132.5, 143.4, 144.9, 155.5. IR (cm⁻¹): 760, 1027, 1053, 1169, 1247, 1366, 1474, 1503, 1695, 2931, 2975, 3330, 3430. LRMS *m/z*: 379 (M⁺, 2), 319 (100). HRMS calc. for [C₂₀H₂₁NC₂O₂ + Na]⁺: 400.0842. Found: 400.0841.

***trans*-3-(3,4-dichlorophenyl)-2,3-dihydro-*N*-methyl-1*H*-inden-1-amine
(indatraline) ((±)-**1**)**

hydrochloride

Under N₂, NaH (0.0080 g, 0.20 mmol, 60% in mineral oil) was washed with anhyd hexanes (twice). To this mixture was added dropwise a solution of **29** (0.0262 g, 0.0695 mmol) in a mixture of THF (1 mL) and of DMF (0.1 mL) at -45 °C. The mixture was stirred at -45 °C for 2.5 h. The reaction mixture was treated with MeI (0.0200 mL, 0.321 mmol) at -45 °C and stirred for 14 h. The

reaction was quenched at 0 °C with MeOH (50 µL), H₂O (140 µL) and extracted with AcOEt. The organic layer was washed with H₂O, with brine, and dried over anhyd Na₂SO₄. The solvent was removed under reduced pressure, affording a yellow oil which was dissolved in AcOEt (0.4 mL) and MeOH (0.4 mL). To this solution was added, AcCl (0.4 mL) dropwise at 0 °C. The mixture was stirred at rt for 1 h. The solvent was removed by distillation under reduced pressure, giving a crude yellow oil. The product was washed with hexanes, giving a yellow solid which was purified by recrystallization from a mixture of Et₂O and EtOH, affording (±)-indatraline (**1**) (0.0193 g, 0.0589 mmol, 85%), as a white solid.

mp: 178.0-180.0 °C, (Literature¹⁰: 184-186°C). ¹H NMR (300 MHz, CD₃OD): δ 2.46-2.56 (m, 1H), 2.78 (s, 3H), 2.80-2.85 (m, 1H), 4.74 (t, *J* = 7.8 Hz, 1H), 4.90-4.92 (m, 1H), 7.05-7.08 (m, 1H), 7.11 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.66-7.69 (m, 1H). ¹³C NMR (75 MHz, CD₃OD): δ 31.4, 39.8, 49.3, 64.1, 126.9, 127.1, 129.0, 129.3, 131.2, 131.9, 132.0, 132.0, 133.6, 138.2, 145.8, 148.6. IR (cm⁻¹): 764, 1129, 1467, 1596, 1636, 2440, 2924, 3434. LRMS *m/z*: 292 [(M-Cl)⁺, 45], 290 [(M-H₂Cl)⁺, 69], 260 [(M-CH₅NCl)⁺, 87], 42 (100). HRMS calc. For [C₁₆H₁₆Cl₃N - Cl]⁺: 292.0654. Found: 292.0663.

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2. NMR Spectra

Current Data Parameters
 NAME Eliane
 EXPNO 2
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20060622
 Time 14.14
 INSTRUM spect
 PROBHD 5 mm Dual 13C/
 PULPROG zgpg30
 TD 65536
 SOLVENT CDCl3
 NS 6144
 DS 4
 SWH 19607.844 Hz
 FIDRES 0.299192 Hz
 AQ 1.6712180 sec
 RG 32768
 DW 25.500 usec
 DE 6.00 usec
 TE 300.0 K
 D1 1.00000000 sec
 d11 0.03000000 sec
 d12 0.0002000 sec

===== CHANNEL f1 =====
 NUC1 13C
 P1 11.20 usec
 PL1 5.00 dB
 SFO1 75.4760505 MHz

===== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 100.00 usec
 PL2 0.00 dB
 PL12 20.92 dB
 PL13 120.00 dB
 SFO2 300.1312005 MHz

F2 - Processing parameters
 SI 32768
 SF 75.4677532 MHz
 MDW EM
 SSB 0
 LB 2.00 Hz
 GB 0
 PC 1.40

1D NMR plot parameters
 CX 23.00 cm
 CY 13.00 cm
 F1P 230.000 ppm
 F1 17357.58 Hz
 F2P -10.000 ppm
 F2 -754.68 Hz
 PPMCM 10.43478 ppm/cm
 HZCM 787.48956 Hz/cm

¹³C NMR (75 MHz, CDCl₃)

¹H NMR (CDCl₃, 200 MHz)

^{13}C NMR (CDCl_3 , 75 MHz)

¹H NMR (CDCl₃, 300 MHz)

¹³C NMR (CDCl₃, 75 MHz)

¹H NMR (CDCl₃, 300 MHz)

¹³C NMR (CDCl₃, 75 MHz)

¹H NMR (CDCl₃, 300 MHz)

¹³C NMR (CDCl₃, 75 MHz)

¹H NMR (DMSO-*d*₆, 300 MHz)

^{13}C NMR (DMSO- d_6 , 75 MHz)

¹H NMR (CDCl₃, 300 MHz)

13C OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl₃
Ambient temperature
INOVA-300 "inova1"

Relax. delay 0.235 sec
Pulse 45.0 degrees
Acq. time 1.785 sec
Width 18859.0 Hz
1024 repetitions
OBSERVE C13, 75.4216997 MHz
DECOUPLE H1, 299.9483516 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 34 min, 17 sec

¹³C NMR (CDCl₃, 75 MHz)

¹H NMR (CD₃OD, 300 MHz)

Pulse Sequence: s2pul

Solvent: CDCl₃

Ambient temperature

INOVA-300 "inova1"

Relax. delay 0.235 sec

Pulse 45.0 degrees

Acq. time 1.765 sec

Width 18859.0 Hz

2048 repetitions

OBSERVE C13, 75.4218924 MHz

DECOUPLE H1, 299.9483516 MHz

Power 35 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 131072

Total time 1 hr, 8 min, 34 sec

¹³C NMR (CD₃OD, 75 MHz)

¹H NMR (CDCl₃, 300 MHz)

^1H NMR (CD_3OD , 300 MHz)

Pulse Sequence: s2pu1

Solvent: cd3od

Ambient temperature

INOVA-300 "inova1"

Relax. delay 0.235 sec

Pulse 45.0 degrees

Acq. time 1.765 sec

Width 18859.0 Hz

6416 repetitions

OBSERVE C13, 75.4218897 MHz

DECOUPLE H1, 299.9495333 MHz

Power 35 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 131072

Total time 5 hr, 42 min, 50 sec

^{13}C NMR (CDCl_3 , 75 MHz)

S40

DEPT 135 (CDCl₃, 75 MHz)

Cosy (CD₃OD, 300 MHz)

HSQC (CD₃OD, 500 MHz)

3. X-Ray Analysis

After the chemical experiment, synthesis and crystallization, suitable sized clear crystals of **26** and **28** were selected for the X-ray diffraction experiment. Intensity data were measured at room temperature (298 K) and with MoK α radiation ($\lambda = 0.71073$ Å) from a graphite monochromator, using the Enraf-Nonius Cad4Mach3 diffractometer. The C, Cl, N and O atoms were clearly solved using direct methods and full-matrix least-squares refinement of these atoms with anisotropic thermal parameters were carried on. All hydrogen atoms were positioned stereochemically and were refined with mixed procedures. The main crystal, collection and structure refinement data for **26** and **28** are summarized in Table S-1. In Figures S-1 to S-6 are shown further details about the X-ray diffraction experiments.

Table S-1. Crystal data and structure refinement for compounds **26** and **28**.

	26	28
Empirical formula	C ₁₆ H ₁₂ Cl ₂ O ₂	C ₃₀ H ₃₀ Cl ₆ N ₂ O ₁
Molecular weight	307.16	647.26
Crystal system	Monoclinic	
Space group	P2 ₁ /c	
a (Å)	9.223(5)	11.026(6)
b (Å)	19.117(8)	8.925(5)
c (Å)	7.979(5)	33.270(16)
α (degree)	90	90
β (degree)	91.50(4)	108.60(4)
γ (degree)	90	90
Cell Volume (Å ³)	1406.3(13)	3103(3)
Z	4	4
Density (calculated) g/cm ³	1.451	1.385
Absorp. Coefficient (mm ⁻¹)	0.459	0.581
F(000)	632	1336
Crystal size (mm ³)	0.200 x 0.225 x 0.300	0.200 x 0.280 x 0.280
$\theta_{\max}$ (degree)	25.47	25.00
Reflections collected	2805	5841
Independent reflections	2608	5453
R(int)	0.0400	0.0452
Completeness to $\theta_{\max}$ (%)	99.9	99.9
Data / restraint / parameters	2608 / 0 / 181	5453 / 0 / 361
Goodness-of-fit on F ²	0.995	1.078
R1, wR2 [$ I > 2\sigma(I)$]	0.0503, 0.1257	0.0445, 0.1135
R1, wR2 [all data]	0.1096, 0.1500	0.1019, 0.1353
$\Delta\rho_{\max}$ and $\Delta\rho_{\min}$ (e.Å ⁻³)	0.497 and -0.334	0.329 and -0.290

Figure S-1: ORTEP-3 view of **26** showing the atom labelling and 50% probability ellipsoids. H atoms are shown as spheres of arbitrary radii.

Figure S-2: ORTEP-3 view of **26** showing the dimer linked by intermolecular H bonds (O1-H1...O2ⁱ). Symmetry code: ⁱ -x+1, -y, -z

Figure S-3: View of the network of hydrogen bonds onto the bc plane which stabilizes the packing of **26**. The dimers are stacked along [100]. Hydrogen's are omitted for clarity.

Figure S-4: ORTEP-3 view of **28** showing the atom labelling and 50% probability ellipsoids. Two molecules are present in the asymmetric unit. Two chlorides and a water molecule are also present in the asymmetric unit. H atoms are shown as spheres of arbitrary radii.

Figure S-5: Packing view of **28** onto the ac plane.

Figure S-6: View of **28** showing the superposition of the two molecules present in the asymmetric unit. The chloride atoms CL1 and CL2 do not match each other showing that crystal present two different atropisomer in the solid state.