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Asymmetric reduction of substituted indanones and tetralones catalyzed by chiral dendrimer and its application to the synthesis of (+)-sertraline

Guangyin Wang, Changwu Zheng and Gang Zhao*

Laboratory of Modern Organic Synthetic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, PR China

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Abstract—A recoverable dendrimeric supported prolinol was used as a catalyst in the asymmetric reduction of indanones and tetralones to give separable *cis* and *trans* isomers up to 97% ee. This method was also applied in the enantioselective synthesis of the antidepressant drug (+)-sertraline.

1. Introduction

An indane ring framework[1] or a tetrahydronaphthalene core[2] is often found in a large number of bioactive and pharmaceutically interesting substances. Molecules that contain a substructure of indanones or tetralones possessing stereogenic centers are even more useful as they can be used as starting materials for the synthesis of biologically active compounds or drugs, such as etoposide, SB209670, and sertraline (Fig. 1). These products are of current interest in the pharmaceutical industry and, therefore, their derivatives have been extensively evaluated for their biological activities.[3] There are only a few approaches to introduce chirality onto the indanone and tetralone ring systems. Tetralone ring systems are obtained through the preparation of chiral aryl carboxylic acids either by resolution or by asymmetric synthesis followed by Friedel–Crafts cyclization onto an aromatic ring.[4] The kinetic resolution of racemic substrates has also been employed.[5]

Recently, we have developed a new class of chiral dendrimers containing a prolinol core (Fig. 2) and applied them to the enantioselective reduction of ketones via $BH_3{\cdot}Me_2S$.[6]

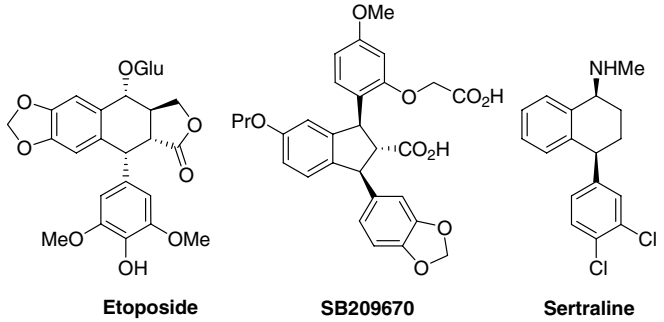

Figure 1. Molecules that contain the indanone or tetralone substructure.

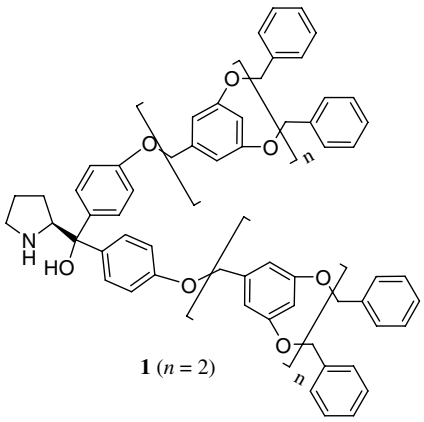

Figure 2. Chiral dendrimer containing a prolinol core.

* Corresponding author. E-mail: zhaog@mail.sioc.ac.cn

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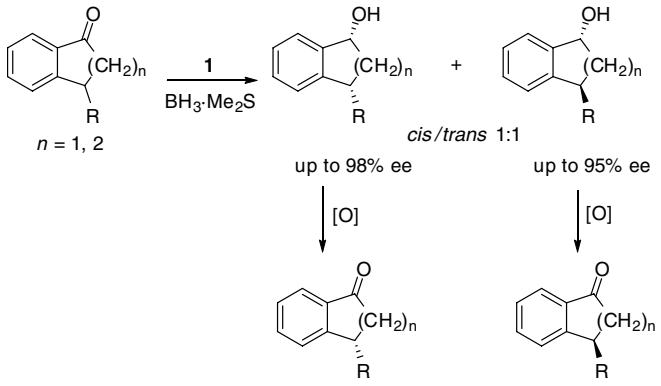
In our studies, we found that they are as efficient as the unsupported parent catalyst in the reactions and among these different generation dendrimers, the second generation ($n = 2$) **1** is an optimization of the availability and reusability. Herein, we report our work to obtain optically active substituted indane and tetrahydronaphthalene structures via asymmetric reduction catalyzed by a chiral dendrimer, including the enantioselective preparation of (+)-sertraline, an important antidepressant.

2. Results and discussion

Various substituted indanones and tetralones were subjected to the chiral dendrimer catalyzed asymmetric reduction, which was previously developed by us. When racemic substrates were employed, the products were two *cis* and *trans* diastereoisomers that could be isolated by column chromatography. After the derived alcohols were oxidized to ketones, the optically active indanones or tetralones were acquired (Scheme 1).



Scheme 1.

Indanone could be substituted at the 2- and 3-positions and, therefore, we initially studied the effect of various substituents at these positions. The results are shown in Table 1. When the substituent at the 3-position was varied from a small methyl group to either a large *tert*-butyl or *cyclo*-hexyl group (entries 1, 3, 4, and 5), the reaction gave two *cis* and *trans* isomers in almost a 1:1 ratio. The *cis* isomers had an ee of about 80%, whereas the *trans* isomers had an ee of about 95%. The difference in ee between *cis* and *trans* isomers indicated that the preexistent stereogenic center had an influence on the reaction. The reduction that produced the *trans* isomer was a matched reaction while the reduction that produced the *cis* isomer was a mismatched reaction. When the substituent at the 3-position was an aromatic group, for example, phenyl (entry 2), the difference in ee between the *cis* and *trans* isomers was almost the same as for the alkyl substituent. The ratio of the *cis* and *trans* products increased to 1.5:1 when 2-substituted indanone was reduced (entry 6). However, the difference of ee was enlarged, with the *cis* isomers being 31% whereas *trans* isomers were 85%. The 2-substituent was closer to the carbonyl group, and as a result had a greater impact on the reduction than the 3-substituent. When the indanone had no substituent, the ee of the product was 94%, which was as high as the matched reaction (entry 7). Finally, a cyclopentanone substituted by an ester group was subjected to the reduction and the result was similar to that of above. An interesting phenomenon was that the γ-ester group was also reduced to an hydroxy group, which was same as the results for an α-keto ester and β-keto ester.

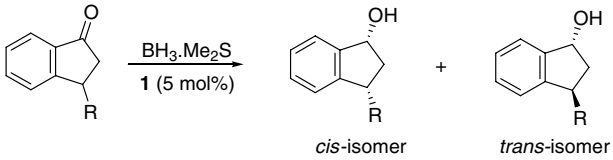
The relative configuration of the products was determined by 2D ^{1}H–^{1}H NOESY of **5a**–**7a** and **5b**–**7b** (Fig. 3). The absolute configuration at the 3-position in the *trans* isomer was confirmed by the comparison of the specific rotation of (*S*)-**2a** derived from **3a** with the literature value.[7] The results are consistent with a prediction via the mechanism of the CBS reaction. Although the configurations of the remaining compounds could not be assigned, in view of the same reaction mechanism, we assumed their configurations were as described in the Experimental.

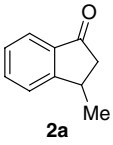
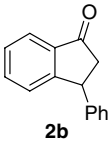
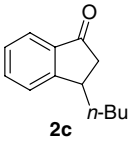
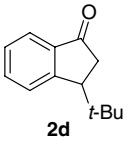
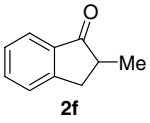
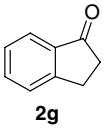
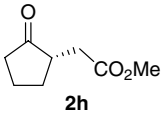
The results of the reductions of the tetralones are shown in Table 2. Similarly, except for the 2-substituted tetralone, 4-substituted tetralones were reduced to two *cis* and *trans* isomers in almost a 1:1 ratio (entries 1–7). Although the reduction that produced *trans* isomer was a mismatched reaction and the reduction that produced *cis* isomer was a matched reaction, which was different with indanone, the difference in ee between the *trans* isomer and *cis* isomer was small. The 4-substituent was too far from the carbonyl group to affect the stereoselectivity of the reduction. Similar to the 2-substituted indanone, 2-substituted tetralones had a more increased *cis*/*trans* ratio, 5.8:1, and difference in ee (entry 8). When the tetralone had no substituent, the ee of product was 98%, slightly higher than the substituted substrates (entry 7). While tetralone was replaced by substituted cyclohexanone, the reduction that produced the *cis* isomer was a matched reaction and the reduction that produced the *trans* isomer was a mismatched reaction. Compared with cyclopentanone, the difference between their ees was less obvious. The relative and absolute configurations of the products were determined by comparison of ^{1}H NMR and specific rotation of **17b** and (*S*)-**11f** with the literature.[4c,8] The configurations of the other compounds, in view of the same reaction mechanism, were assumed as described in the Experimental.

After the reduction was complete, the dendrimer-supported catalysts were precipitated by adding methanol and then recovered by filtration. The recovered dendrimers were reused after being dried and no loss of catalytic activity was observed. Tests on the reduction of **11f** (Table 3) show that the chiral dendrimer-supported catalyst can be recycled at least five times with little or no loss of performance.

Since the reduction of 4-substituted tetralones resulted in two separable diastereoisomers with high ee's, the method could be used for asymmetric synthesis of compounds, which contained the chiral tetralone structure. (+)-Sertraline **23**, an antidepressant sold by Pfizer under the trade name Zoloft, is a competitive inhibitor of synaptosomal serotonin uptake. It is produced commercially by the resolution of the racemate with D-mandelic acid.[2a] Even though

Table 1. Asymmetric reduction of substituted indanones[a]



Entry	Substrate	*cis* Isomer		*trans* Isomer	
		Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1	 **2a**	46 (**3a**)	82	46 (**3b**)	95
2	 **2b**	47 (**4a**)	78	48 (**4b**)	91
3	 **2c**	46 (**5a**)	80	46 (**5b**)	94
4	 **2d**	45 (**6a**)	80	46 (**6b**)	96
5	 **2e**	45 (**7a**)	78	46 (**7b**)	93
6	 **2f**	53 (**8a**)	31	36 (**8b**)	85
7	 **2g**	75 (**9**)	94	—	—
8	 **2h**	12 (**10a**)[d]	50[e]	50 (**10b**)[d]	87[e]

[a] Molar ratio: ketone/BMS/Cat. **1** = 1.0:1.1:0.05.
[b] After column chromatography.
[c] Determined by chiral HPLC.
[d] The product was 1,4-diol.
[e] Analytical sample was converted to its phenylcarbamate.

a few synthetic routes to the sertraline **23** have been reported,[4] a classical resolution method is still the feasible means of its production. In view of the structural resemblance of sertraline **23** to **17b**, we decided to synthesize sertraline using our developed method (Scheme 2). Pure *trans* isomer **17b** derived from asymmetric reduction of (±)-**11f**

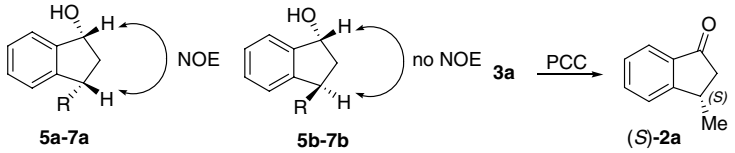
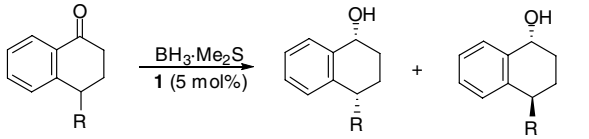


Figure 3. NOE of **5a**–**7a** and **5b**–**7b**.

Table 2. Asymmetric reduction of substituted tetralones[a]



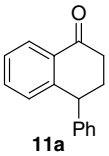
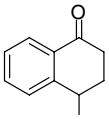
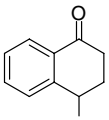
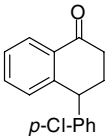
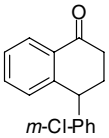
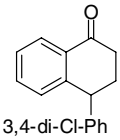
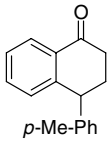
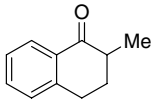
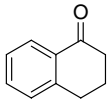
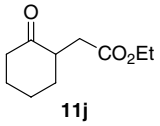
Entry	Substrate	*cis* Isomer		*trans* Isomer	
		Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1	 **11a**	46 (**12a**)	95	45 (**12b**)	88
2	 *p*-F-Ph **11b**	49 (**13a**)	97	48 (**13b**)	94
3	 *m*-F-Ph **11c**	— (**14**)[f]	97	— (**14**)[f]	95
4	 *p*-Cl-Ph **11d**	42 (**15a**)	95	42 (**15b**)	95
5	 *m*-Cl-Ph **11e**	41 (**16a**)	96	41 (**16b**)	94
6	 3,4-di-Cl-Ph **11f**	49 (**17a**)	97	49 (**17b**)	94

Table 2 (*continued*)

Entry	Substrate	*cis* Isomer		*trans* Isomer	
		Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
7	 *p*-Me-Ph	49 (**18a**)	94	48 (**18b**)	91
8	 **11h**	73 (**19a**)	18	12 (**19b**)	98
9	 **11i**	93 (**20a**)	98	—	—
10	 **11j**	51 (**21a**)[d]	94[e]	42 (**21b**)[d]	88[e]

[a] Molar ratio: ketone/BMS/Cat. **1** = 1.0:1.1:0.05.
[b] After column chromatography.
[c] Determined by chiral HPLC.
[d] The product was a 1,4-diol.
[e] Analytical sample was converted to its phenylcarbamate.
[f] Two isomers could not be separated.

Table 3. Recycling of chiral dendrimer **1** for the reduction of **11f**

Run (no.)	Yield (%)[a]	ee of *cis* isomer (%)[b]	ee of *trans* isomer (%)[b]
1	98	97.0	94.0
2	98	97.6	94.6
3	96	96.9	95.6
4	98	97.5	95.3
5	97	97.3	95.9

[a] After column chromatography.
[b] Determined by HPLC using a chiral stationary.

was oxidized to optically active tetralone (*S*)-**11f**. Imine **22** was obtained by the reaction of methylamine with (*S*)-**11f** in the presence of $TiCl_4$. Hydrogenation of **22** was catalyzed by Raney-Ni to produce sertraline **23** and its *trans* isomer in a 3:1 ratio. The physical and spectroscopic data of **23** are in agreement with the literature data.[5h]

3. Conclusions

In summary, the results reported here offer a practical and highly stereoselective methodology for the synthesis of optically active indanone and tetralone derivatives. Finally, we applied this method to the enantioselective synthesis of the antidepressant drug (+)-sertraline.

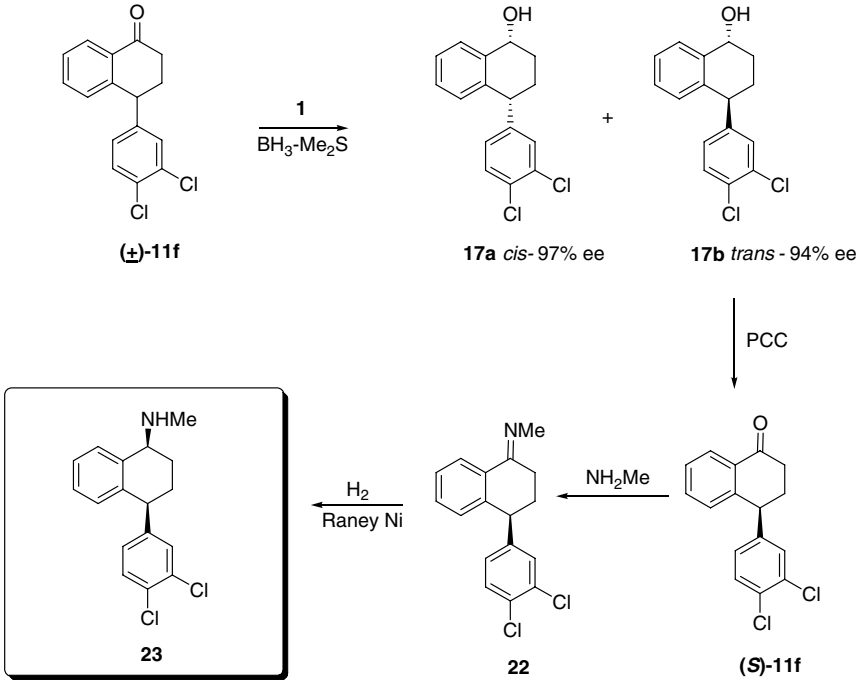
4. Experimental

4.1. General procedure for the asymmetric reduction of indanone and tetralone

Cat. **1** (0.05 mmol) was added to a 50 mL three-necked flask after which were added 8 mL THF and 0.5 mL $BH_3{\cdot}Me_2S$ (2.0 M in THF). The solution was heated at reflux and stirred for 0.5 h. Then a THF (8 mL) solution of indanone or tetralone (1.0 mmol) was added at a rate of 10 mL/h by a syringe pump. After the addition was completed, the mixture was treated with 10 mL methanol and filtered. The dendrimeric catalyst could be recovered by more than 95%. The resulting solution was evaporated and purified by Silica gel chromatography to give the corresponding *cis* (eluted first) and *trans* products.

4.2. (1*R*,3*S*)-3-Butyl-indan-1-ol 5a

White solid, mp = 64–65 °C, $[\alpha]_D^{28} = -56.8$ (*c* 0.75, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.36 (m, 1H), 7.27–7.23 (m, 3H), 5.14 (t, $J = 7.0$ Hz, 1H), 3.00–2.91 (m, 1H), 2.74–2.65 (m, 1H), 2.12 (s, 1H), 2.00–1.94 (m, 1H), 1.54–1.36 (m, 6H), 0.93 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 145.1, 128.1, 126.8, 123.8, 123.6, 75.2, 43.1, 41.8, 35.2, 29.8, 22.9, 14.1. IR (film) ν 3329, 3025, 2956, 2925, 2856, 1607, 1475, 1458, 1330, 1095, 1053 cm^{-1}. EIMS (*m*/*z*, abundance): 190 (M^+,



Scheme 2. Reagents and conditions: (a) $BH_3{\cdot}Me_2S$, **1** (5 mol %), THF, reflux; (b) PDC, CH_2Cl_2, rt; (c) $MeNH_2$, $TiCl_4$, Et_2O, −78 °C; (d) H_2, Raney-Ni, MeOH.

13.61), 133 (100), 115 (26.94), 105 (34.71), 91 (20.85), 77 (21.07). Anal. Calcd for $C_{13}H_{18}Ol$: C, 82.06; H, 9.53. Found: C, 81.89; H, 9.45. HPLC: 80% ee, Chiralcel OJ, 20 °C, 254 nm, 90:10 hexane/*i*-PrOH, 0.75 mL/min; $t_R = 7.47$ min (1*S*,3*R*), $t_R = 7.97$ min (1*R*,3*S*).

4.3. (1*R*,3*R*)-3-Butyl-indan-1-ol 5b

Colorless oil, $[\alpha]_D^{29} = -36.5$ (*c* 0.95, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.38 (m, 1H), 7.31–7.21 (m, 3H), 5.24 (dd, $J = 4.2$ and 5.5 Hz, 1H), 3.35–3.27 (m, 1H), 2.23–2.15 (m, 1H), 2.11–2.02 (m, 1H), 1.82–1.75 (m, 1H), 1.72 (s, 1H), 1.40–1.32 (m, 5H), 0.92 (t, $J = 6.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 144.7, 128.5, 126.9, 124.4, 124.2, 75.3, 42.7, 42.2, 35.2, 29.9, 22.8, 14.1. IR (film) ν 3324, 3024, 2956, 2925, 2856, 1606, 1477, 1458, 1332, 1054, 1022 cm^{-1}. EIMS (*m*/*z*, abundance): 190 (M^+, 9.78), 173 (17.04), 133 (100), 115 (40.91), 105 (34.59), 91 (19.11), 77 (18.46). Anal. Calcd for $C_{13}H_{18}Ol$: C, 82.06; H, 9.53. Found: C, 82.01; H, 9.42. HPLC: 94% ee, Chiralcel OJ, 20 °C, 254 nm, 90:10 hexane/*i*-PrOH, 0.75 mL/min; $t_R = 7.39$ min (1*S*,3*S*), $t_R = 8.73$ min (1*R*,3*R*).

4.4. (1*R*,3*R*)-3-*tert*-Butyl-indan-1-ol 6a

Colorless oil, $[\alpha]_D^{19} = -59.1$ (*c* 0.90, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.39 (m, 2H), 7.24–7.23 (m, 2H), 5.06 (t, $J = 6.6$ Hz, 1H), 2.94 (t, $J = 7.8$ Hz, 1H), 2.60–2.51 (m, 1H), 1.94 (br, 1H), 1.76–1.67 (m, 1H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 144.4, 127.7, 126.8, 126.0, 124.3, 74.3, 53.1, 38.8, 33.3, 28.3. IR (film) ν 3336, 3069, 3037, 2962, 2867, 1606, 1475, 1366, 1098, 1054 cm^{-1}. EIMS (*m*/*z*, abundance): 190 (M^+, 0.22), 173 (11.50), 133 (21.92), 116 (100), 105 (11.05), 91 (7.88), 77 (11.81), 57 (47.22). HRMS Calcd for $C_{13}H_{18}O$: 190.1358, Found: 190.1357. HPLC: 80% ee, Chiralcel AD, 20 °C, 254 nm, 90:10 hexane/*i*-PrOH, 0.75 mL/min; $t_R = 9.80$ min (1*R*,3*R*), $t_R = 10.63$ min (1*S*,3*S*).

4.5. (1*R*,3*S*)-3-*tert*-Butyl-indan-1-ol 6b

Colorless oil, $[\alpha]_D^{19} = -57.9$ (*c* 0.75, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.38 (m, 1H), 7.31–7.23 (m, 3H), 5.29 (t, $J = 6.6$ Hz, 1H), 3.08 (dd, $J = 1.5$ and 8.7 Hz, 1H), 2.56–2.48 (m, 1H), 1.97–1.87 (m, 1H), 1.76 (br, 1H), 0.92 (s, 9H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 146.4, 144.30, 127.47, 127.08, 126.78, 123.85, 75.73, 53.94, 40.12, 34.36, 27.94. IR (film) ν 3239, 2976, 2952, 2881, 1477, 1460, 1365, 1060 cm^{-1}. EIMS (*m*/*z*, abundance): 190 (M^+, 2.51), 173 (9.05), 133 (68.22), 116 (65.69), 105 (23.69), 91 (14.80), 77 (20.85), 57 (100). HRMS Calcd for $C_{13}H_{18}O$: 190.1358, Found: 190.1365. HPLC: 96% ee, Chiralcel AD, 20 °C, 254 nm, 90:10 hexane/*i*-PrOH, 0.75 mL/min; $t_R = 10.59$ min (1*S*,3*R*), $t_R = 11.93$ min (1*R*,3*S*).

4.6. (1*R*,3*R*)-3-Cyclohexyl-indan-1-ol 7a

Colorless oil, $[\alpha]_D^{23} = -31.9$ (*c* 0.80, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.38 (m, 1H), 7.30–7.22 (m, 3H), 5.13 (dd, $J = 6.3$ and 12.7 Hz, 1H), 3.01 (dd, $J = 7.8$ and 12.5 Hz, 1H), 2.55–2.45 (m, 1H), 1.94–1.66 (m, 6H), 1.45 (d, $J = 13.5$ Hz, 1H), 1.34–1.11 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 145.0, 127.9, 126.8, 124.3, 124.0, 75.2, 47.7, 40.5, 37.9, 32.1, 27.9, 26.9, 26.6, 26.5.

IR (film) ν 3322, 3024, 2924, 2850, 1601, 1476, 1448, 1329, 1095, 1056 cm^{-1}. EIMS (*m*/*z*, abundance): 216 (M^+, 1.38), 198 (7.38), 133 (34.34), 116 (100), 105 (9.01), 91 (7.57), 77 (7.88), 55 (17.32). HRMS Calcd for $C_{15}H_{20}O$: 216.1514, Found: 216.1519. HPLC: 78% ee, Chiralcel AD, 20 °C, 254 nm, 90:10 hexane/*i*-PrOH, 0.75 mL/min; t_R = 10.75 min (1*S*,3*S*), t_R = 11.70 min (1*R*,3*R*).

4.7. (1*R*,3*S*)-3-Cyclohexyl-indan-1-ol 7b

White solid, mp = 54–56 °C, $[\alpha]_D^{23} = -35.9$ (*c* 0.80, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.37 (m, 1H), 7.28–7.20 (m, 3H), 5.25 (t, *J* = 6.3 Hz, 1H), 3.27–3.21 (m, 1H), 2.40–2.32 (m, 1H), 1.99–1.60 (m, 1H), 1.77–1.57 (m, 6H), 1.42 (d, *J* = 14.4 Hz, 1H), 1.26–0.88 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 145.5, 128.1, 126.9, 125.0, 124.1, 75.8, 48.4, 41.9, 39.1, 31.6, 28.7, 26.7, 26.5, 26.5. IR (film) ν 3211, 2923, 2850, 1474, 1449, 1098, 1061 cm^{-1}. EIMS (*m*/*z*, abundance): 216 (M^+, 5.09), 198 (10.97), 133 (100), 116 (44.97), 105 (16.75), 91 (35.66), 77 (72.11), 55 (46.06). HRMS Calcd for $C_{15}H_{20}O$: 216.1514, Found: 216.1521. HPLC: 93% ee, Chiralcel AD, 14 °C, 254 nm, 90:10 hexane/*i*-PrOH, 0.75 mL/min; t_R = 11.03 min (1*S*, 3*R*), t_R = 112.34 min (1*R*,3*S*).

4.8. (1*R*,4*S*)-4-(2-Chlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol 16a

Colorless oil, $[\alpha]_D^{24} = -43.4$ (*c* 0.92, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.47 (d, *J* = 7.5 Hz, 1H), 7.40–7.37 (m, 1H), 7.26–7.12 (m, 3H), 6.94–6.91 (m, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 4.86 (t, *J* = 5.1 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 1H), 2.17–1.96 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 139.3, 138.9, 134.0, 130.8, 129.7, 129.5, 128.8, 128.1, 127.5, 126.9, 126.8, 68.2, 41.9, 30.0, 26.1. IR (film) ν 3347, 3061, 3021, 2936, 2863, 1569, 1472, 1437, 1079, 1035 cm^{-1}. EI-MS (*m*/*z*, abundance): 258 (11.25, M^+), 240 (100), 205 (76.13), 178 (29.10), 165 (23.18), 120 (95.65), 101 (53.99), 89 (34.64). HRMS Calcd for $C_{16}H_{14}OCl$ ($M-H^+$): 257.0733, Found: 257.0734. HPLC: 96% ee, Daicel Chiralcel OJ column, 20 °C, λ = 254 nm, hexane/*i*-PrOH = 90:10, flow = 0.75 mL/min; t_R = 10.34 min (1*R*,4*S*), t_R = 11.01 min (1*S*,4*R*).

4.9. (1*R*,4*R*)-4-(2-Chlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol 16b

Colorless oil, $[\alpha]_D^{24} = -24.7$ (*c* 0.92, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.54 (d, *J* = 8.1 Hz, 1H), 7.40–7.05 (m, 5H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.68–6.65 (m, 1H), 4.89 (m, 1H), 4.69 (t, *J* = 6.3 Hz, 1H), 2.40–2.28 (m, 1H), 2.15–2.01 (m, 1H), 1.92–1.75 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 140.0, 138.5, 133.9, 130.6, 129.9, 129.6, 128.2, 127.9, 127.5, 126.9, 126.7, 68.3, 41.6, 29.9, 26.3. IR (film) ν 3413, 3061, 3021, 2931, 2862, 1604, 1569, 1473, 1265, 1080 cm^{-1}. EI-MS (*m*/*z*, abundance): 258 (6.59, M^+), 240 (100), 205 (57.06), 178 (23.80), 165 (18.54), 120 (79.17), 101 (41.80), 89 (23.92). HRMS Calcd for $C_{16}H_{14}OCl$ ($M-H^+$): 257.0733, Found: 257.0731. HPLC: 94% ee, Daicel Chiralcel OJ column, 20 °C, λ = 254 nm, hexane/*i*-PrOH = 90:10, flow = 0.75 mL/min; t_R = 11.47 min (1*S*,4*S*), t_R = 12.06 min (1*R*,4*R*).

4.10. (1*R*,4*R*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol 17a

Colorless oil, $[\alpha]_D^{24} = -52.5$ (*c* 1.14, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 5.4 Hz, 1H), 7.26–7.15 (m, 3H), 6.99–6.96 (m, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 4.83 (t, *J* = 4.2 Hz, 1H), 3.98 (t, *J* = 7.8 Hz, 1H), 2.29 (br, 1H), 2.10–1.96 (m, 4H). IR (film) ν 3356, 2939, 2867, 1557, 1488, 1467, 1396, 1264, 1030, 739 cm^{-1}. HPLC: 97% ee, Daicel Chiralcel AD column, 20 °C, λ = 254 nm, hexane/*i*-PrOH = 90:10, flow = 0.75 mL/min; t_R = 10.04 min (1*S*,4*S*), t_R = 10.09 min (1*R*,4*R*).

4.11. (1*R*,4*S*)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol 17b[8]

Colorless oil, $[\alpha]_D^{24} = +1.6$ (*c* 1.00, $CHCl_3$) {lit.[8] $[\alpha]_D^{25} = 5.0$ (*c* 0.5, $CHCl_3$)}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55 (d, *J* = 7.5 Hz, 1H), 7.34–7.44 (m, 4H), 6.87–6.82 (m, 2H), 4.86 (t, *J* = 5.1 Hz, 1H), 4.13 (t, *J* = 6.3 Hz, 1H), 2.38–2.30 (m, 1H), 2.14–2.06 (m, 1H), 1.97 (br, 1H), 1.82–1.73 (m, 2H). IR (film) ν 3361, 3059, 2939, 2862, 1557, 1468, 1265, 1131, 1030, 738 cm^{-1}. HPLC: 94% ee, Daicel Chiralcel OJ column, 20 °C, λ = 254 nm, hexane/*i*-PrOH = 90:10, flow = 1.0 mL/min; t_R = 10.68 min (1*R*,4*S*), t_R = 11.88 min (1*S*,4*R*).

4.12. (*S*)-4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-one 11f[4c]

Compound **17b** (600 mg, 2.06 mmol) was dissolved in 5.0 mL dichloromethane and cooled to 0 °C in an ice-water bath. PCC (1.2 g) was added to the solution and stirred overnight at room temperature. Celite and ether were added with complete stirring. The mixture was filtrated and the filtrate concentrated. The residue was purified by silica gel chromatography to give a white solid (*S*)-**11f** in 98% yield. $[\alpha]_D^{24} = +65.8$ (*c* 1.20, benzene) {lit.[4c] $[\alpha]_D^{23} = +71.3$ (*c* 1.1, benzene)}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12 (d, *J* = 7.8 Hz, 1H), 7.49–7.36 (m, 3H), 7.26–7.22 (m, 1H), 6.96–6.94 (m, 2H), 4.28 (dd, *J* = 4.5 and 7.8 Hz, 1H), 2.76–2.57 (m, 2H), 2.51–2.48 (m, 1H), 2.31–2.21 (m, 1H). IR (film) ν 2941, 2859, 1686, 1596, 1468, 1284, 1030 cm^{-1}. HPLC: 97% ee, Daicel Chiralcel OD column, 20 °C, λ = 254 nm, hexane/*i*-PrOH = 90:10, flow = 1.0 mL/min; t_R = 10.68 min (*S*), t_R = 11.92 min (4*R*).

4.13. (*S*)-*N*-(4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2*H*)-ylidene)methanamine 22[5h]

Compound (*S*)-**11f** (0.54 g, 1.85 mmol) was placed in a dry Schlenk flask under argon. Anhydrous ether (5 mL) was added, and the reaction flask cooled to −78 °C. Condensed methylamine (1.0 mL, 34 mmol) was introduced via cannula, followed by the addition of $TiCl_4$ (0.30 mL). The reaction mixture was allowed to warm to room temperature slowly and stirred overnight. The reaction mixture was filtered through a pad of Celite and washed with ether. The combined filtrates were concentrated to give a white solid that could be used without purification in 93% yield: $[\alpha]_D^{24} = +91.9$ (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.22–8.18 (m, 1H), 7.36–7.19 (m, 4H), 6.91–

6.88 (m, 2H), 4.16 (dd, $J = 4.2$ and 6.7 Hz, 1H), 3.32 (s, 3H), 2.60–2.46 (m, 2H), 2.34–2.23 (m, 1H), 2.18–2.07 (m, 1H). IR (film) ν 3059, 2926, 2852, 1688, 1633, 1595, 1470, 1284 cm^{-1}.

4.14. (+)-Sertraline 23[5h]

Imine **22** (109 mg, 0.35 mmol) was dissolved in methanol and hydrogenated over Raney-Ni. When the imine disappeared (detected by TLC), the catalyst was filtered, and the methanol was evaporated. The residue was purified by silica gel chromatography to give (+)-sertraline **23** as a yellow oil in 98% yield: $[\alpha]_D^{26} = +36.5$ (c 1.00, MeOH) {lit.[8] $[\alpha]_D^{25} = 39.7$ (c 0.3, MeOH)}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45 (d, $J = 7.7$ Hz, 1H), 7.33–7.10 (m, 4H), 6.86–6.81 (m, 2H), 4.13 (t, $J = 5.4$ Hz, 1H), 3.78 (t, $J = 5.0$ Hz, 1H), 2.52 (s, 3H), 2.40–2.31 (m, 1H), 2.00–1.91 (m, 1H), 1.80–1.69 (m, 2H), 1.49 (br, 1H). IR (film) ν 3024, 3060, 2935, 2857, 2790, 1469, 1394, 1130, 1029 cm^{-1}.

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