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Chiral ligands derived from *abrine*. Part 7: Effect of *O*, *S*, *N* in aromatic ring substituents at C-1 on enantioselectivity induced by tetrahydro-β-carboline ligands in diethylzinc addition to aldehydes†

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Abstract—The effect of *O*, *S* and *N* atoms in aromatic ring substituents at C-1 position of tetrahydro-β-carboline ligands on the enantioselectivity of diethylzinc additions to benzaldehyde was studied when esters or tertiary alcohol functions were present at C-3. A mechanism is proposed to explain why the ester ligands **2c** and **2d**, in which the pyridyl *N* atom is at C′-2 in **2c** and at C′-3 in **2d**, catalyzed the addition of diethylzinc to benzaldehyde to form the (*R*)- and (*S*)-enantiomers of 1-phenyl-1-propanol, respectively. An explanation was also proposed for the moderate enantioselectivity induced by *tert*-alcohol **3c** versus the very small enantioselectivity induced by **3d**, containing a 3-pyridyl function at C-1, during diethylzinc additions. A -CH_2-*t*-Bu substituent at C-1 leads to very high enantioselectivities.

1. Introduction

Asymmetric C–C single bond formation is fundamental to the construction of designed chiral target molecules. Various chiral molecules have been synthesized using chiral ligands. Many chiral catalysts and organometallic reagents have been employed in enantioselective additions and other reactions.[1] We recently reported that 1,2,3,4-tetrahydro-β-carboline amino acid esters, derived from a natural alkaloid, act as chiral ligands, exhibiting moderate enantioselectivities and yields during the addition of diethylzinc to benzaldehyde.[2b] Herein, we describe the total synthesis of these amino acid ester and corresponding tertiary alcohol ligands. Also, the effect of *O*, *S* and *N* heteroatoms in aromatic ring substituents located at C-1 on the enantioselectivity of diethylzinc addition reaction was examined. A mechanism is proposed to explain why the ligand **2c**, in which *N* atom is at C′-2 in the pyridyl ring, gives (*R*)-1-phenyl-propanol while ligand **2d**, where the pyridyl *N* atom is at C′-3, produced the (*S*)-enantiomer during addition of diethylzinc to benzaldehyde. The difference in enantioselectivity induced by 2-pyridyl-containing ligand **3c** (moderate *e.e.*) versus 3-pyridyl analog, **3d** (poor *e.e.*) is discussed and an explanation proposed.

2. Results and discussion

The non-racemic chiral amino acid ester ligands **2a**–**2f** were synthesized from the natural alkaloid *abrine*. *Abrine* is an unusual amino acid, which is easily available from the seed of *Abrus precatorius* collected in Yunnan Province, China. After esterification of *abrine* to methyl ester, **1**, the Pictet–Spengler condensation reaction[3] (Scheme 1) produced the corresponding chiral amino acid esters of the 1,2,3,4-tetrahydro-β-carboline series **2a**–**f**. These were used as the chiral ligands in the diethylzinc addition reaction. The enantioselectivities were determined at ambient temperature in toluene using 10 mol% of the ligand (Eq. (1) and Table 1).

The corresponding tertiary alcohol ligands **3a**–**f** were synthesized by the addition of ethylmagnesium chloride in THF to **2a**–**f**, respectively. Enantioselectivities induced by ligands **3a**–**f** in diethylzinc additions to benzaldehyde are summarized in Table 2.

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† This manuscript is dedicated to the memory of Ms. Bi-Tao Zhao who died on June 17, 2000 at the age of 27 after the course of this work. She will be missed.

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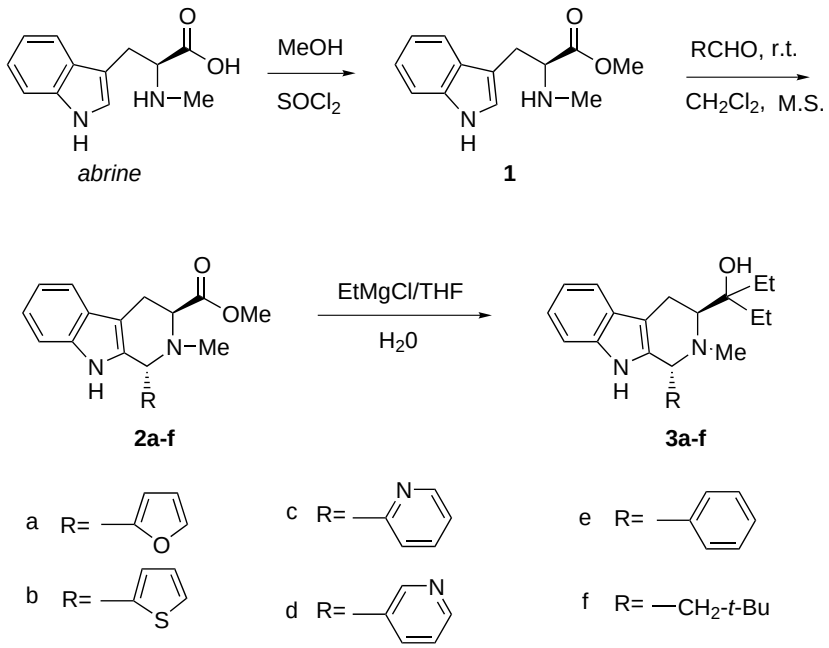
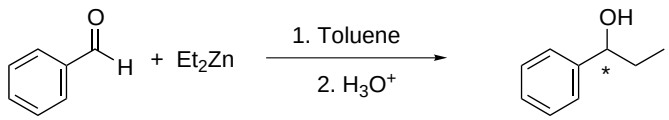


Scheme 1.

Table 1. Enantioselectivity induced by 1,2,3,4-tetrahydro-β-carboline ester ligands **2a**–**f** in diethylzinc addition to benzaldehyde



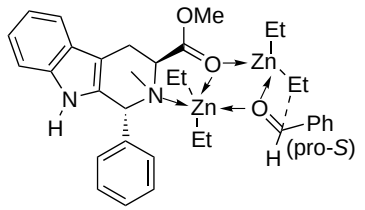
(1)

Entry	Catalyst[a]	Time (h)	Yield (%)[b]	*E.e.* (%)[c]	Configuration[d]
1	**2a**	96	83.0	15.8	*S*
2	**2b**	96	70.2	17.7	*S*
3	**2c**	96	74.2	38.9	*R*
4	**2d**	96	32.1	5.8	*S*
5	**2e**	96	81.5	13.2	*S*
6	**2f** (*trans*-)	96	31.0	10.0	*R*
7	**2f** (*cis*-)	96	31.2	15.3	*R*

[a] 10% mol catalyst used, the mole ratio of Et_2Zn/PhCHO is 2.0, the reactions were carried out in toluene at room temperature.
[b] Based on the isolated compound.
[c] Determined using a Chiracell OD column and eluting with isopropanol and *n*-hexane (5:95) at the flow rate 1 ml/min.
[d] The specific rotation value and rotation direction of 1-phenyl-1-propanol were used as the standard for the determination of the configuration of 1-phenyl-1-propanol, see Ref. 4 for the details.

The *O* and *S* atoms in the furan and thiophene rings of **2a** and **2b** have a much smaller effect on enhancing the enantioselectivity than the pyridyl nitrogen in **2c** and **2d**. Both **2c** and **2d** give the *R* configuration of 1-phenyl-1-propanol versus the *S* configuration which was favored using **2a** and **2b** (Table 1, entries 1, 2 and 3).

When the pyridyl nitrogen is *meta* to the bond connecting this ring to the β-carboline ring system **2d**, the opposite (*S*)-enantiomer is formed and the *e.e.* is very small (Table 1, entries 3 and 4). When the pyridyl ring at C-1 is replaced by a phenyl ring **2e**, the *e.e.* is still low and the (*S*)-enantiomer of 1-phenyl-1-propanol is formed. A mechanism which explains the configuration changes is proposed using transition state (TS) structures **6**–**8**. In general, the favored TS is described by **6** when there is no *N* atom at C′-2. However, when there is a *N* atom at C′-2, the ability of nitrogen to chelate with Zn changes the structure of the TS to **7**. We propose that TS **7** has the lower energy. Thus, using ligand **2c** leads to the *R* configuration of 1-phenyl-1-propanol as the major product.



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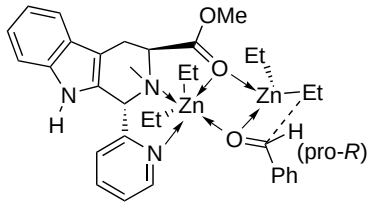

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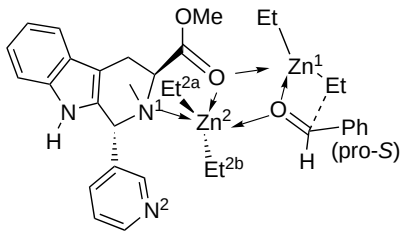
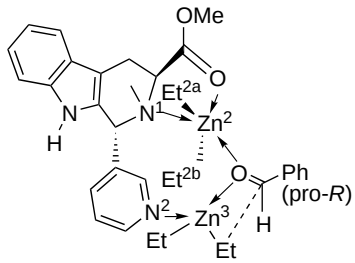


8a



8b

Table 2. The enantioselectivities induced by 1,2,3,4-tetrahydro-β-carboline alcohol ligands **3a**–**f** in the additions of diethylzinc to benzaldehyde[a]

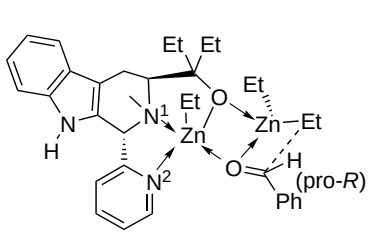
Entry	Catalyst[a]	Time (h)	Yield (%)[b]	*E.e.* (%)[c]	Configuration[d]
1	**3a**	48	57.3	5.3	*R*
2	**3b**	48	82.0	39.9	*R*
3	**3c**	48	64.3	32.3	*R*
4	**3d**	48	39.2	0.23	*R*
5[e]	**3e**	46	92.7	47.9	*R*
6[e]	**3f**	46	92.5	97.6	*R*

[a] 5% mol catalyst used in toluene at room temperature at a Et_2Zn/PhCHO mole ratio of 2.0.
[b] Based on the isolated compound.
[c] Determined using a Chiracell OD column eluting with isopropanol and *n*-hexane (5:95) at the flow rate of 1.0 ml/min (detected by UV at 254 nm).
[d] The specific rotation value and rotation direction of 1-phenyl-1-propanol were used as the standard for the determination of the configuration of 1-phenyl-1-propanol, see Ref. 4 for the details.
[e] See Ref. 2e for details.

When the pyridyl *N* atom is located at C′-3 position **2d**, this nitrogen (N^2) cannot chelate with Zn^2. Therefore, the TS structures **8a** and **8b** are postulated to be favored instead of structures like **6** or **7**. Two competitive pathways could operate using **2d** as represented by TS **8a** and TS **8b**. The presence of Et^{2b} forces the Ph group in benzaldehyde to be up and this geometry must be a pro-*S* center. The smaller ring system in TS **8a** (5/4/4) could be kinetically favorable versus the larger ring system in **8b**. A small contribution from the pathway through **8b** would lead to the predominance of the *S* configuration.

The amino alcohol ligands, **3a**–**f**, derived from esters **2a**–**f** can catalyze the diethylzinc addition to form (*R*)-1-phenyl-1-propanol. Ligand **3d** induced much lower enantioselectivity than **3c**. The nitrogen at C′-3 exerts a different effect than the C′-2 nitrogen. Possible TS structures **9** and **10** are proposed. The pyridyl nitrogen (N^2) in **9** can easily chelate with Zn (forming a 5-membered ring) and giving a trichelated TS structure. However, the pyridyl nitrogen of **3d** cannot chelate with Zn^1 in TS **10** because it would require significant ring strain. In this case, the pyridyl nitrogen (N^2) chelates the other $ZnEt_2$, instead, and at the same time, Zn^1 can accept a lone pair coordination from the PHCHO oxygen. When the Et^{2b} group is absent, benzaldehyde's phenyl ring in **10a** should be down. This forms a pro-*R* center. The small ring system (5/4/4) TS, **10a**, is more stable which would lead to a major product that has the *R* configuration. However, competition results in the low enantioselectivity. These experimental results are summarized in Table 2.

Table 3 lists the enantioselectivity of chiral ligand **3f** using different aldehydes as the substrates (Eq. (2)). Ligand **3f** contains the bulky 2,2-dimethylpropyl substituent at C-1 which exhibits the ability to produce high *e.e.* values in diethylzinc additions to aldehydes. Perhaps steric effects, which promote high *e.e.* values with seven aldehydes (Table 3), can also account for the unexpected observation that **3f** can't induce enantiose-



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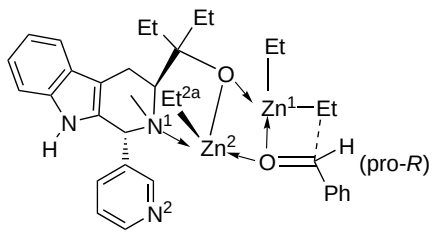
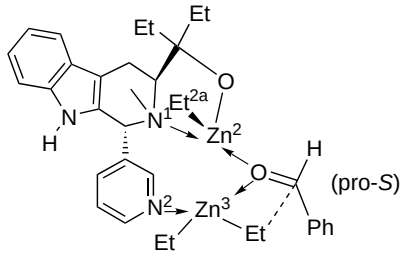


10a



10b

lectivity during the addition of diethylzinc to 2-naphthyl aldehyde and cinnamyl aldehyde. Many common chiral ligands give lower enantioselectivities in additions to aliphatic aldehydes than to aromatic aldehydes. However, **3f** produced excellent enantioselectivities with the aliphatic aldehydes tested.

3. Experimental

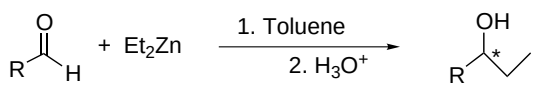
^{1}H and ^{13}C NMR spectra were recorded on AM-400 NMR and Bruker-300 NMR instruments. IR spectra were taken on a spectrometer. Melting points were recorded using a microscope melting point apparatus and were uncorrected. Optical rotations were recorded on a Perkin Elmer 241 polarimeter at 22°C. High resolution mass spectra (HRMS) were obtained using a VG-Autospec mass spectrometer and elemental analyses were performed on a Model-1106 instrument. All reactions were carried out under nitrogen protection and followed with TLC using UV active plates (F-254) or by spraying with 10% ethanol phosphomolybdic acid and heating. Et_2Zn (1.0 M in toluene) and other reagents were obtained commercially and used as received.

3.1. General procedures

3.1.1. Pictet–Spengler condensations. The aldehyde (1.05 equiv.) was injected into a solution of *abrine* methyl ester (1.0 equiv.) and TFA (0.25 equiv.) in dry dichloromethane in the presence of 4 Å molecule sieves and stirred overnight. After filtering and washing the flask with ethyl acetate, the combined organic solution was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel) using ethyl acetate and hexane (10:90 to 30:70) as eluant to give the 1,2,3,4-tetrahydro-β-carboline methyl esters.

3.1.2. Addition of ethyl Grignard to 1,2,3,4-tetrahydro-β-carbolines. The solution of 1,2,3,4-tetrahydro-β-carboline (1.0 mmol) in dry THF was cooled with an external ice-bath. Then the ethyl magnesium chloride Grignard reagent (4–5 equiv.) in THF was added by syringe under nitrogen protection. Then the solution was allowed to warm to room temperature. After the reaction was completed (checked with TLC), it was quenched with water while cooling with an ice-bath. The solution was extracted with ethyl acetate and the combined organic layer was dried over anhydrous

Table 3. The enantioselectivities induced by ligand **3f** in the addition of diethylzinc to different aldehydes



(2)

Entry[a]	R-CHO	Time (h)	Yield (%)[b]	*E.e.* (%)[c]	Configuration[d]
1	*c*-C_6H_{11}-	48	90.5	99.5[e]	*R*
2	4-MeOPh-	48	80.0	94.5	*R*
3	PhCH=CH-	48	64.4	0	–
4	2-naphthyl-	48	89.2	0	–
5	4-Me_2NPh-	48	89.7	87.7	*R*
6	$PhCH_2CH_2$-	48	93.5	92.4	*R*
7	3,5-diMeOPh-	48	93.0	95.9	*R*
8	4-BrPh-	48	95.3	96.0	*R*
9	Ph-	46	92.5	97.6	*R*

[a] 5% mol catalyst used in toluene at room temperature at a Et_2Zn/aldehyde mole ratio of 2.0.

[b] Based on the isolated compound.

[c] Determined using Chiracell OD column eluting with isopropanol and *n*-hexane (5:95) at the flow rate of 1.0 ml/min (detected by UV at 254 nm) except entry one.

[d] The specific rotation values and rotation directions of the known compounds were used as the standard for the determination of the configuration for all addition alcohols, see Ref. 5 for the details.

[e] The cyclohexanol was converted into benzyl ester and determined with double Chiralcell AD column eluting with isopropanol and *n*-hexane (3:97) at the flow rate of 1.0 ml/min (detected by UV at 254 nm).

$MgSO_4$. The organic solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel) using ethyl acetate and hexane (10:90 to 30:70) to give the 1,2,3,4-tetrahydro-β-carboline alcohol.

3.1.3. Catalytic enantioselective additions of diethylzinc to aldehydes. A Et_2Zn solution (4.0 ml, 1 M in *n*-hexane) and the aldehyde (2.0 mmol) were added by syringe to a solution of chiral 1,2,3,4-tetrahydro-β-carboline (0.20 mmol) in dry toluene (8 ml) under N_2 protection at 0°C. The reaction solution then warmed to room temperature and stirred for 48 or 96 h. After quenching with 5% HCl aqueous solution, the mixture was extracted with ethyl acetate. The combined solution was dried over anhydrous $MgSO_4$ and condensed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in *n*-hexane) to give chiral 1-phenyl-1-propanol. The yields and enantioselectivities data were summarized in Tables 1–3.

3.1.4. Esterification of 1-cyclohexyl-1-propanol with benzyl chloride. Benzyl chloride (1.08 equiv.) and NEt_3 (1.5 equiv.) were added to a solution of 1-cyclohexyl-1-propanol (57 mg, 0.4 mmol), dichloromethane (10 ml) and catalytic quantity of DMAP in room temperature. After 48 h, the solution was filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel) using ethyl acetate and hexane (1:25) to give the corresponding ester (84 mg, 78.9 yield).

3.2. Spectral data

3.2.1. (1*S*,3*S*)-1-(2-Furyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline methyl ester 2a. Yield, 64.6%; mp 159–160.5°C, $[\alpha]_D$ −45.0 (*c* 0.506, $CHCl_3$); IR (KBr): 3339, 1708, 1453, 1010, 796, 746, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.54 (m, 1H), 7.43 (dd, $J=1.02$, 1.77 Hz, 1H), 7.30–7.26 (m, 1H), 7.20–7.10 (m, 2H), 6.39–6.36 (m, 2H), 5.40 (s, 1H), 4.05 (dd, $J=4.62$, 5.85 Hz, 1H), 3.70 (s, 3H), 3.27 (ddd, $J=1.68$, 5.91, 15.81 Hz, 2H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 153.3, 142.9, 136.3, 131.4, 126.9, 121.9, 119.4, 118.3, 110.9, 110.1, 109.2, 106.6, 60.4, 56.1, 51.6, 39.9, 23.5. Elemental analysis calcd for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03; O, 15.48. Found: C, 69.91; H, 6.03; N, 8.50.

3.2.2. (1*S*,3*S*)-1-(2-Thiophyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline methyl ester 2b. Yield, 78.1%; mp 178–180°C; $[\alpha]_D$ −54.2 (*c* 0.618, $CHCl_3$); IR (KBr): 3393, 2946, 1732, 1437, 1173, 744, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (m, 2H), 7.19–7.13 (m, 5H), 7.00 (dd, $J=3.45$, 5.04 Hz, 1H), 5.64 (s, 1H), 4.07 (dd, $J=3.15$, 6.21 Hz, 1H), 3.68 (s, 3H), 3.37 (ddd, $J=1.89$, 6.18, 15.63 Hz, 1H), 3.25 (ddd, $J=1.44$, 3.18, 15.63 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 146.8, 136.4, 134.0, 127.0, 126.2, 126.2, 121.8, 119.4, 118.3, 110.9, 105.4, 61.0, 57.6, 51.4, 40.3, 24.3. Elemental analysis calcd for $C_{18}H_{18}N_2O_2S$: C, 66.26; H, 5.52; N, 8.59; O, 9.82; S, 9.82. Found: C, 66.53; H, 5.83; N, 8.03.

3.2.3. (1*S*,3*S*)-1-(2-Pyridyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline methyl ester 2c. Yield, 80.1%; mp 178–179.5°C; $[\alpha]_D$ −200.5 (*c* 0.52, $CHCl_3$); IR (KBr): 2945, 1748, 1592, 1190, 1076, 800, 746, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.52 (m, 1H), 7.70–7.60 (m, 2H), 7.54 (m, 1H), 7.25–7.08 (m, 4H), 4.07 (dd, $J=3.87$, 5.25 Hz, 1H), 3.64 (s, 3H), 3.32 (m, 2H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 162.2, 148.8, 137.3, 136.6, 133.8, 126.8, 122.4, 121.4, 121.3, 119.1, 118.1, 111.0, 104.8, 63.6, 61.5, 51.4, 40.6, 24.2. Elemental analysis, calcd for $C_{19}H_{19}N_3O_2$: C, 71.03; H, 5.92; N, 13.08; O, 9.97. Found: C, 71.13; H, 6.25; N, 12.58.

3.2.4. (1*S*,3*S*)-1-(3-Pyridyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline methyl ester 2d. Yield, 80.8%; mp 148–152°C, crystal phase changed, 232°C decomposed; $[\alpha]_D$ −88.3 (*c* 0.932, $CHCl_3$); IR (KBr): 3390, 2947, 1730, 1452, 1202, 742, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+C_5D_5N (a drop)): δ 10.4 (s, 1H), 8.43 (d, $J=1.6$ Hz, 1H), 8.23 (t, $J=3.6$ Hz, 1H), 7.42 (d, $J=8.8$ Hz, 1H), 7.39 (t, $J=4.0$ Hz, 1H), 7.00–6.89 (m, 4H), 5.21 (s, 1H), 3.84 (dd, $J=2.4$, 6.0 Hz, 1H), 3.45 (s, 3H), 3.25 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$+C_5D_5N (a drop)): δ 172.9, 150.0, 149.3, 137.7, 137.0, 136.2, 134.3, 126.4, 123.3, 121.1, 118.6, 117.7, 110.7, 105.3, 61.0, 59.6, 50.9, 39.9, 24.5. Elemental analysis, calcd for $C_{19}H_{19}N_3O_2$: C, 71.03; H, 5.92; N, 13.08; O, 9.97. Found: C, 71.23 H, 6.25; N, 12.66.

3.2.5. (1*R*,3*S*)-1-Phenyl-2-methyl-1,2,3,4-tetrahydro-β-carboline methyl ester 2e. Yield, 79.0%; mp 203–5°C; $[\alpha]_D$ +31.5 (*c* 1.11, $CHCl_3$); IR (KBr), 3400, 2950, 1725, 1450, 1310, 1170, 750, 700, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (m, 1H), 7.5–7.32 (m, 5H), 7.14–7.08 (m, 4H), 5.29 (s, 1H), 4.04 (dd, $J=2.24$, 6.33 Hz, 1H), 3.63 (s, 3H), 3.42 (ddd, $J=1.8$, 6.68, 15.96 Hz, 1H), 3.26 (ddd, $J=1.84$, 3.36, 17.44 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.9, 128.7, 128.1, 121.6, 119.4, 118.2, 110.9, 105.8, 62.2, 61.5, 51.2, 40.4, 29.7, 24.8. Elemental analysis, calcd for $C_{20}H_{20}N_2O_2$: C, 74.95; H, 6.25; N, 8.74; O, 10.00. Found: C, 74.86; H, 6.38; N, 8.64; HRMS (EI): calcd for $C_{20}H_{20}N_2O_2$ (M^+): 320.1525. Found: 320.1538.

3.2.6. (1*R*,3*S*)-1-(2,2-Dimethylpropyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline methyl ester *trans* 2f. Yield, 79.0%; $[\alpha]_D$ +27.5 (*c* 1.48, $CHCl_3$); IR (KBr), 3407, 2946, 1718, 1462, 1272, 1053, 738, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.53 (d, $J=7.23$ Hz, 1H), 7.33 (d, $J=7.44$ Hz, 1H), 7.21–7.11 (m, 2H), 3.97 (dd, $J=4.86$, 10.74 Hz, 1H), 3.81 (s, 3H), 3.11 (dd, $J=10.86$, 15.99 Hz, 1H), 2.91 (dd, $J=4.71$, 15.99 Hz, 1H), 2.42 (s, 3H), 1.83 (dd, $J=9.12$, 14.73 Hz, 1H), 1.56 (dd, $J=2.70$, 14.61 Hz, 1H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 136.0, 135.4, 127.1, 121.6, 119.5, 118.0, 110.7, 106.8, 58.0, 56.3, 51.9, 48.2, 37.3, 30.9, 30.0, 18.7; HRMS (FAB+): calcd for $C_{19}H_{26}N_2O_2$ (M+1): 315.2073. Found: 315.2093.

3.2.7. (1*R*,3*S*)-1-(2,2-Dimethylpropyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline methyl ester *cis*-2f. Yield, 12.5%; $[\alpha]_D$ −7.23 (*c* 1.91, $CHCl_3$); IR (KBr): 3407, 1718, 1426, 1050, 738 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.47 (d, $J=7.44$ Hz, 1H), 7.31 (d, $J=7.84$ Hz, 1H), 7.16–7.08 (m, 2H), 4.08 (s, 1H), 3.83 (d, $J=8.96$ Hz, 1H), 3.77 (s, 3H), 3.12 (ddd, $J=2.08$, 9.84, 15.76 Hz, 1H), 2.93 (dd, $J=3.93$, 15.76 Hz, 1H), 2.33 (s, 3H), 1.87 (dd, $J=6.44$, 14.96 Hz, 1H), 1.63 (dd, $J=4.32$, 14.96 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 135.7, 127.2, 121.6, 119.6, 118.0, 110.8, 106.9, 63.5, 57.6, 51.9, 44.0, 34.4, 30.9, 30.1, 20.6. Elemental analysis: calcd for $C_{19}H_{26}N_2O_2$: C, 72.61; H, 8.28; N, 8.92; O, 10.19. Found: C, 72.83; H, 8.55; N, 8.58.

3.2.8. (1*S*,3*S*)-1-(2-Furyl)-3-(1-ethyl-1-hydroxypropyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline 3a. Yield, 71.6%; $[\alpha]_D$ +8.58 (*c* 1.37, $CHCl_3$); IR (KBr): 3541, 3255, 2924, 1460, 1135, 1012, 744, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.55 (d, $J=7.68$ Hz, 1H), 7.40 (d, $J=1.44$ Hz, 1H), 7.31 (d, $J=7.92$ Hz, 1H), 7.20–7.10 (m, 2H), 6.26 (dd, $J=2.2$, 3.16 Hz, 1H), 5.96 (d, $J=1.72$ Hz, 1H), 4.91 (s, 1H), 3.15 (dd, $J=3.48$, 11.6 Hz, 1H), 3.01 (dd, $J=11.84$, 15.72 Hz, 1H), 2.64 (dd, $J=3.64$, 15.8 Hz, 1H), 2.63 (s, 3H), 1.77 (m, 1H), 1.67 (m, 1H), 1.55 (m, 1H), 1.43 (m, 1H), 1.30 (s, 6H), 0.87 (t, $J=7.40$ Hz, 3H), 0.53 (t, $J=7.48$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 136.6, 129.8, 127.2, 122.0, 119.5, 118.3, 111.1, 110.8, 109.3, 60.9, 57.4, 37.4, 31.9, 29.7, 29.5, 28.4, 22.7, 15.4, 7.6, 7.5. HRMS (FAB+): calcd for $C_{21}H_{26}N_2O_2$ (M+1): 339.2073. Found: 339.2123.

3.2.9. (1*S*,3*S*)-1-(2-Thiophyl)-3-(1-ethyl-1-hydroxypropyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline 3b. Yield, 70.3%; $[\alpha]_D$ +87.7 (*c* 1.55, $CHCl_3$); IR (KBr): 3255, 2926, 1623, 1454, 851, 745, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.60 (d, $J=7.59$ Hz, 1H), 7.38 (d, $J=7.50$ Hz, 1H), 7.30–7.14 (m, 3H), 6.87 (dd, $J=3.51$, 5.13 Hz, 1H), 6.69 (m, 1H), 5.00 (s, 1H), 3.18 (dd, $J=3.75$, 11.46 Hz, 1H), 3.02 (ddd, $J=0.99$, 11.69, 15.57 Hz, 1H), 2.63 (s, 3H), 2.66–2.60 (m, 1H), 2.31 (s, 1H), 1.76–1.43 (m, 5H), 0.83 (t, $J=7.44$ Hz, 3H), 0.60 (t, $J=6.53$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6, 136.3, 131.7, 127.2, 126.2, 125.9, 125.6, 121.9, 119.5, 118.3, 111.0, 110.5, 75.5, 62.4, 56.1, 37.5, 29.7, 28.3, 15.5, 7.9, 7.5; HRMS (FAB+): calcd for $C_{21}H_{26}N_2OS$ (M+1): 335.1844. Found: 355.1800.

3.2.10. (1*S*,3*S*)-1-(2-Pyridyl)-3-(1-ethyl-1-hydroxypropyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline 3c. Yield, 66.3%; $[\alpha]_D$ −189.8 (*c* 1.03, $CHCl_3$); IR (KBr): 3575, 2928, 2592, 1455, 1322, 1005, 750, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.36 (d, $J=4.44$ Hz, 1H), 7.67–7.60 (m, 2H), 7.48 (d, $J=7.04$ Hz, 1H), 7.21 (d, $J=7.16$ Hz, 1H), 7.14 (t, $J=6.4$ Hz, 1H), 7.13–7.02 (m, 2H), 5.49 (s, 1H), 4.02 (m, 2H), 3.30 (m, 2H), 2.60 (s, 3H), 1.25 (m, 1H), 1.05 (t, $J=7.16$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 162.3, 148.4, 137.5, 136.7, 133.7, 126.8, 122.5, 121.6, 121.4, 119.0, 118.1, 109.9, 104.9, 63.6, 61.7, 60.3, 40.6, 29.7, 24.7, 14.1. Elemental analysis: calcd for $C_{22}H_{27}N_3O$: C, 75.64; H, 7.74; N, 12.03; O, 4.58. Found: C, 75.84; H, 7.99; N, 11.71.

3.2.11. (1*S*,3*S*)-1-(3-Pyridyl)-3-(1-ethyl-1-hydroxypropyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline 3d. Yield, 77.4%; $[\alpha]_D$ +26.5 (*c* 0.72, $CHCl_3$); IR (KBr), 3398, 2968, 1453, 1143, 743, 712, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 3H), 7.57 (d, $J=7.56$ Hz, 1H), 7.41 (7.80 Hz, 1H), 7.31 (d, $J=7.84$ Hz, 1H), 7.19–7.11 (m, 3H), 4.75 (s, 1H), 3.01 (dd, $J=10.80$, 15.40 Hz, 1H), 2.74 (dd, $J=3.80$, 11.60 Hz, 1H), 2.65 (s, 3H), 2.63 (dd, $J=3.88$, 19.88 Hz, 1H), 1.57 (m, 2H), 1.45 (m, 1H), 1.34 (m, 1H), 0.71 (t, $J=7.44$ Hz, 3H), 0.34 (t, $J=7.44$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 148.4, 137.5, 136.6, 136.3, 130.3, 127.3, 122.8, 122.0, 119.5, 118.3, 111.5, 111.0, 76.1, 64.2, 55.6, 38.2, 29.5, 27.9, 15.3, 7.7, 7.5; HRMS (FAB+): calcd for $C_{22}H_{27}N_3O_2$ (M+1): 350.2232. Found: 350.2164.

3.2.12. (1*R*,3*S*)-1-Phenyl-3-(1-ethyl-1-hydroxypropyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline 3e. Yield, 70.7%; $[\alpha]_D$ +14.0 (*c* 2.87, $CHCl_3$); IR (KBr): 3380, 2940, 1450, 1330, 1000, 750, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.61 (d, $J=7.56$ Hz, 1H), 7.36–7.18 (m, 8H), 4.82 (s, 1H), 3.00 (m, 2H), 2.68 (s, 3H), 2.65 (m, 1H), 1.63 (m, 2H), 1.43 (m, 2H), 0.80 (t, $J=7.4$ Hz, 3H), 0.37 (t, $J=7.44$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 136.4, 131.9, 129.0, 128.0, 127.4, 127.3, 121.7, 119.4, 118.2, 111.0, 111.0, 75.5, 66.4, 55.5, 38.3, 29.5, 28.2, 15.5, 7.7, 7.3; Elemental analysis: calcd for $C_{23}H_{28}N_2O$: C, 79.26; H, 8.04; N, 8.04; O, 4.60, found: C, 79.31; H, 8.11; N, 7.91; HRMS (FAB+): calcd for $C_{23}H_{28}N_2O$ (M+1): 349.2280. Found: 349.2274.

3.2.13. (1*R*,3*S*)-1-(2,2-Dimethylpropyl)-3-(1-ethyl-1-hydroxypropyl)-2-methyl-1,2,3,4-tetrahydro-β-carboline 3f. Yield, 76.8%; $[\alpha]_D$ −15.9 (*c* 1.31, $CHCl_3$); IR (KBr): 3375, 2946, 1460, 1338, 974, 742, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.52 (d, $J=6.78$ Hz, 1H), 7.33 (dd, $J=1.26$, 6.66 Hz, 1H), 7.15 (m, 2H), 3.63 (d, $J=8.16$ Hz, 1H), 3.20 (dd, $J=3.66$, 11.7 Hz, 1H), 2.89 (ddd, $J=1.17$, 11.76, 15.54 Hz, 1H), 2.58 (dd, $J=3.69$, 15.51 Hz, 1H), 2.47 (s, 3H), 1.80 (m, 3H), 1.10 (s, 9H), 0.99 (t, $J=7.44$ Hz, 3H), 0.94 (t, $J=7.47$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3, 136.0, 127.2, 121.5, 119.4, 117.9, 110.7, 109.1, 74.4, 60.6, 57.5, 49.0, 37.6, 31.1, 29.9, 29.3, 15.7, 8.1. Elemental analysis: calcd for $C_{22}H_{34}N_2O$: C, 77.13; H, 9.93; N, 8.18; O, 4.67. Found: 77.09; H, 10.04; N, 8.10; HRMS (FAB+): calcd for $C_{22}H_{34}N_2O$ (M+1): 343.2749. Found: 343.2669.

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