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Syntheses of chiral 1,3-disubstituted tetrahydro-β-carbolines via CIAT process: highly stereoselective Pictet–Spengler reaction of D-tryptophan ester hydrochlorides with various aldehydes

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Dedicated to Professor Li-Xin Dai in Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences on the occasion of his 85th birthday

ABSTRACT

A highly stereoselective Pictet–Spengler reaction of D-tryptophan methyl ester hydrochloride **1**-HCl with various aldehydes via a CIAT (crystallization-induced asymmetric transformation) process is described. It was revealed that the CIAT process should be performed in a mixed solvent of nitromethane and toluene, and a fine tuning of the ratio of nitromethane and toluene for each epimer mixture of **2**-HCl was necessary in order to get as high yields and stereoselectivities as possible. Enantiomerically pure *cis* (or *trans*) 1,3-disubstituted tetrahydro-β-carbolines **2a**–**2v** were obtained by recrystallization or flash chromatography after neutralization of the corresponding hydrochloride salts *cis*-**2**-HCl or *trans*-**2**-HCl.

1. Introduction

The asymmetric P–S (Pictet–Spengler) reaction of tryptamine[1–6] or tryptophan[7–12] with aldehydes provides an important and useful tool to construct chiral synthons containing tetrahydro-β-carbolines structural moieties which are present in many alkaloids[13–15] and in related biologically active molecules.[16–19]

Recently, the P–S reaction of D-tryptophan methyl ester with piperonal has attracted much attention from chemists and has been well studied by several groups[20–28] in order to obtain high *cis* stereoselectivity, as it is the key step in the synthesis of tadalafil, which is a cGMP-specific Type V phosphodiesterase (PDE5) inhibitor.[29–31] Orme et al.[22] have developed a practical method for obtaining high stereoselectivity (*cis*:*trans* = 97:3) for this reaction. Our group became interested in this particular reaction, and we have extensively studied the impact of solvents on the P–S reaction of D-tryptophan methyl ester hydrochloride with piperonal.[23] We have found that excellent *cis* stereoselectivity (*cis*:*trans* = 99:1) could be obtained when the reaction was performed in acetonitrile or nitromethane. A process of crystallization-induced asymmetric transformation (CIAT)[32–43,22,23] took place in the P–S reaction of D-tryptophan methyl ester hydrochloride with piperonal in an appropriate solvent, the large difference of solubility of both the diastereomer products, that is, hydrochloride salts of *cis* and *trans* 1,3-disubstituted tetrahydro-β-carbolines, played an important role and would shift the equilibrium between these two hydrochloride salts to the less soluble *cis* product, and thus caused high stereoselectivity.

Unfortunately, when we tried to extend this successful CIAT process to the P–S reaction of D-tryptophan methyl ester hydrochloride with other aldehydes, or even to the P–S reaction of piperonal with other D-tryptophan ester hydrochlorides, we failed to obtain high stereoselectivity.[23] This observation prompted us to investigate the scope and limitation of this particular CIAT process in detail. After an extensive study by our research group, finally we found that the selection of the solvent for this CIAT process is crucial, and the reaction can be successfully applied to other aldehydes and other D-tryptophan ester hydrochlorides. Herein, we report our recent work about this CIAT process.

2. Results and discussion

We have demonstrated that the P–S reaction of D-tryptophan methyl ester hydrochloride **1**-HCl with piperonal could give high selectivities and yields in isopropanol, butanol, pentanol, nitromethane, acetonitrile, 1,2-dichloroethane, and 1,2-dimethoxyethane;[23] as a result we first tried the direct P–S reaction of **1**-HCl with various other aldehydes in the above solvents. Unfortunately, the reaction did not give high stereoselectivities in most cases, because the CIAT process did not work well in the above solvents. However, we did observe that nitromethane seemed to be better than the other solvents, for example, the P–S reaction of **1**-HCl with 3,4,5-trimethoxybenzaldehyde in nitromethane gave the corresponding 1,3-*trans* disubstituted tetrahydro-β-carboline **2a**-HCl in high stereoselectivity and good yield (Table 1, entry 1). When we tried the same reaction in a mixed solvent of nitromethane and toluene (nitromethane/toluene = 1:1), it worked very well and produced **2a**-HCl in better stereoselectivity and a better yield (Table 1, entry 2). We found that the use of a mixed solvent of nitromethane

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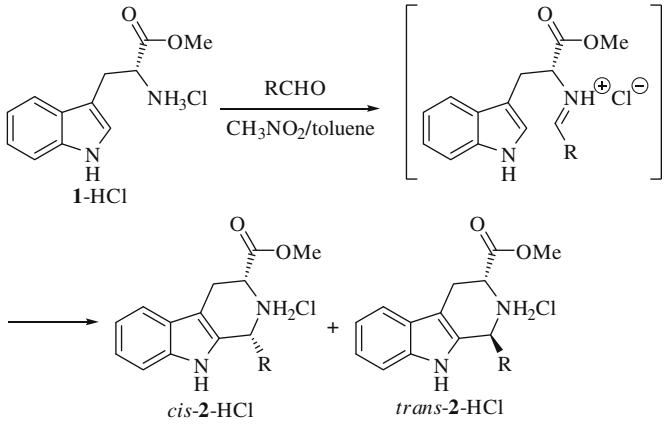
Table 1
Direct Pictet–Spengler reaction of D-tryptophan methyl ester hydrochloride **1**-HCl with aldehydes in a mixed solvent of CH_3NO_2 and toluene (see also Scheme 1)

Entry	Aldehyde	CH_3NO_2/toluene	Time (h)[a]	**2** (*cis*/*trans*)[b]	Yield[c] (%)
1	3,4,5-$(OMe)_3$–PhCHO	1:0	8	**2a** (2:98)	82
2	3,4,5-$(OMe)_3$–PhCHO	1:1	8	**2a** (1:99)	92
3	3,4-$(OMe)_2$–PhCHO	1:1	8	**2b** (1:99)	85
4	4-OMe–PhCHO	1:1	8	**2c** (1:99)	80
5	PhCHO	1:10	22	**2d** (98:2)	76
6	3-OMe-4-OH–PhCHO	1:1	8	**2e** (98:2)	83
7	4-OH–PhCHO	1:1	8	**2f** (99:1)	75
8	4-NO_2–PhCHO	1:1	18	**2g** (99:1)	81
9	2-NO_2–PhCHO	1:4	7	**2h** (99:1)	78
10	*i*-PrCHO	1:1	18	**2i** (1:99)	64
11	*n*-C_6H_{13}CHO	1:1	26	**2j** (98:2)	66

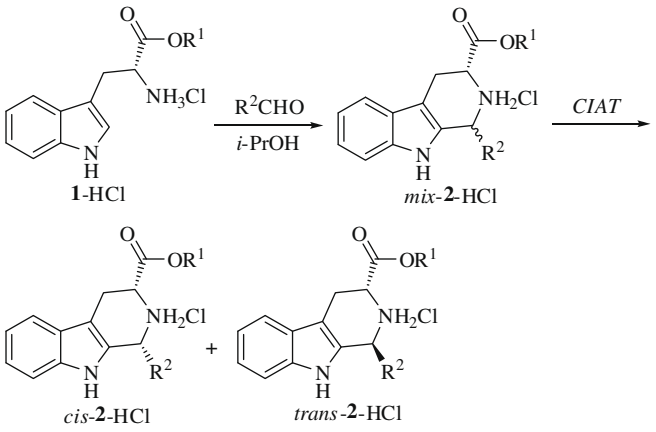
[a] Under reflux.
[b] Determined by HPLC or ^{1}H NMR.
[c] Isolated yield.

and toluene was crucial; high stereoselectivities for the P–S reaction of **1**-HCl with various aldehydes could be obtained by tuning the ratio of nitromethane and toluene for each aldehyde. Several aldehydes were tried, and the results are summarized in Table 1 (see also Scheme 1). As we can see from Table 1, in the case of aromatic aldehydes, the reaction gave high stereoselectivities and good yields, but for aliphatic aldehydes, the yields were moderate.



Scheme 1. Direct P–S reaction of **1**-HCl with aldehydes.

High stereoselectivities could be obtained for various aldehydes, but the yields were unsatisfactory, especially for the aliphatic aldehydes. Fortunately, this drawback could be overcome by performing the CIAT-based process according to a modified two-step procedure (Scheme 2); we first performed the P–S reaction in isopropanol to obtain an epimeric mixture of the hydrochloride salts of *cis* and *trans*-1,3-disubstituted tetrahydro-β-carbolines *mix*-**2**-HCl, and then carried out the CIAT process in a mixed solvent with different ratios of nitromethane and toluene. The modified two-step procedure was quite efficient, giving not only high yields, but also high stereoselectivities. Furthermore, it could be applicable to both aromatic aldehydes and aliphatic aldehydes. The P–S reaction of a variety of D-tryptophan ester hydrochlorides with various aldehydes in isopropanol was much faster than in the mixed solvent of nitromethane and toluene; it took around only 3–5 h to complete at reflux and produce *mix*-**2**-HCl in almost quantitative yields with low *cis*/*trans* selectivities at the range of 70:30 to 30:70. The results of the CIAT process of *mix*-**2**-HCl into *cis*-**2**-HCl or *trans*-**2**-HCl are listed in Table 2. Thirteen aromatic aldehydes (entries 1–8, 11–13, 16, and 17) and four aliphatic aldehydes (entries 9, 10, 14 and 15) have been examined, and three D-tryptophan ester hydrochlorides (entries 1–17, 18–21, and 22) have been tested.



Scheme 2. Two-step synthesis of *cis*-**2**-HCl and *trans*-**2**-HCl from **1**-HCl via CIAT process.

Some observations on the above CIAT process should be discussed. Firstly, the yields of a two-step procedure (Table 2) are obviously better than the yields of a one-step procedure (Table 1) because in the one-step procedure, the P–S reaction probably competed against the Henry reaction[44–46] of the aldehydes with nitromethane, while in the two-step procedure, the P–S reaction was carried out in isopropanol, thus the Henry reaction could be avoided. Secondly, in the CIAT process, tuning the ratio of nitromethane and toluene for each epimer mixture of **2**-HCl was necessary in order to obtain as high yields and stereoselectivities as possible. While **2**-HCl was more soluble in nitromethane, more toluene was needed, or otherwise less toluene was needed. Thirdly, domination of the product *cis*-**2**-HCl or *trans*-**2**-HCl could not be predicted for all instances in Tables 1 and 2, the ratio of *cis*-**2**-HCl and *trans*-**2**-HCl probably depended only on the solubility difference between *cis*-**2**-HCl and *trans*-**2**-HCl in the mixed solvent. For example, the solubility of *cis*-**2c**-HCl, *trans*-**2c**-HCl, *cis*-**2d**-HCl, and *trans*-**2d**-HCl was measured in the mixed CH_3NO_2/toluene (see also Table 3), the ratio of solubility of *cis*- and *trans*-**2c**-HCl is 6.3:1 at room temperature and is 9.4:1 at refluxing temperature, while the ratio of solubility of *cis*- and *trans*-**2d**-HCl is 1:6.5 at room temperature and is 1:9.2 at refluxing temperature. The big difference of the solubility between *cis*- and *trans*-**2c**-HCl, as well as between *cis*- and *trans*-**2d**-HCl, favors high stereoselectivity; the CIAT process accordingly produces less soluble *trans*-**2c**-HCl and *cis*-**2d**-HCl as the major products. Fourthly, the stereochemistry of the major product *cis*-**2** or *trans*-**2** can be assigned by analyzing the corresponding ^{1}H–^{1}H NOESY spectra of each epimer shown in Tables 1 and 2. For example, as depicted in Figure 1, the proton at the C-3 position has an obvious

Table 2
Crystallization induced transformation (CIAT) of the *cis*/*trans* mixture (*mix*-**2**-HCl) into a single diastereomer of 1,3-disubstituted tetrahydro-β-carbolines (*cis*-**2**-HCl or *trans*-**2**-HCl)

Entry	*mix*-**2**		Solvents	Time[a] (h)	**2** (*cis*/*trans*)[b]	Yield[c] (%)
	R^1	R^2	CH_3NO_2/toluene			
1	Me	3,4,5-$(OMe)_3$–Ph	1:1	8	**2a** (1:99)	98
2	Me	3,4-$(OMe)_2$–Ph	1:1	8	**2b** (1:99)	97
3	Me	4-OMe–Ph	1:1	12	**2c** (1:99)	88
4	Me	Ph	1:10	20	**2d** (98:2)	85
5	Me	3-OMe-4-OH–Ph	1:1	8	**2e** (99:1)	94
6	Me	4-OH–Ph	1:1	8	**2f** (99:1)	96
7	Me	4-NO_2–Ph	1:1	18	**2g** (99:1)	95
8	Me	2-NO_2–Ph	1:4	7	**2h** (99:1)	96
9	Me	*i*-Pr	1:1	18	**2i** (1:99)	93
10	Me	*n*-Hexyl	1:1	26	**2j** (98:2)	92
11	Me	2-OMe–Ph	1:9	16	**2k** (95:5)	91
12	Me	2-OEt–Ph	1:9	16	**2l** (98:2)	89
13	Me	2-Cl–Ph	1:10	25	**2m** (95:5)	92
14	Me	Me	1:1	28	**2n** (97:3)	95
15	Me	Et	1:1	28	**2o** (98:2)	93
16	Me	3-OMe-4-OAc–Ph	1:1	16	**2p** (2:98)	88
17	Me	3-OMe-4-OBz–Ph	1:1	16	**2q** (99:1)	89
18	Et	3,4,5-$(OMe)_3$–Ph	1:6	18	**2r** (99:1)	95
19	Et	3,4-$(OMe)_2$–Ph	1:5	26	**2s** (2:98)	92
20	Et	4-OMe–Ph	1:5	20	**2t** (2:98)	85
21	Et	3,4-(OCH_2O)–Ph	1:5	18	**2u** (99:1)	87
22	*n*-Pr	3,4-(OCH_2O)–Ph	1:8	20	**2v** (98:2)	86

[a] Under reflux.
[b] Determined by HPLC or ^{1}H NMR.
[c] Isolated yield based on two steps (Scheme 2).

Table 3
Solubility of *cis*-**2c**-HCl, *trans*-**2c**-HCl, *cis*-**2d**-HCl, and *trans*-**2d**-HCl in the mixed CH_3NO_2/toluene

Entry	**2**-HCl	CH_3NO_2/toluene	*T* (°C)	Solubility (mg/100 mL)
1	*trans*-**2c**-HCl	1:1	20[a]	6
2	*cis*-**2c**-HCl	1:1	20[a]	38
3	*trans*-**2c**-HCl	1:1	97[b]	47
4	*cis*-**2c**-HCl	1:1	97[b]	441
5	*cis*-**2d**-HCl	1:10	20[a]	2
6	*trans*-**2d**-HCl	1:10	20[a]	13
7	*cis*-**2d**-HCl	1:10	101[b]	12
8	*trans*-**2d**-HCl	1:10	101[b]	110

[a] Room temperature.
[b] Refluxing.

correlation with the proton at C-1 position in the ^{1}H–^{1}H NOESY spectra of the compound *cis*-**2b** or *cis*-**2d**, while the proton at the C-3 position does not correlate with the proton at C-1 position in the ^{1}H–^{1}H NOESY spectra of the compound *trans*-**2b** or *trans*-**2d**, but correlates with the neighboring protons on the substituent at the C-1 position. Fifthly, when we attempted to purify hydrochloride salts *cis*-**2**-HCl or *trans*-**2**-HCl by recrystallization in order to remove the minor epimer impurity, we failed to obtain pure *cis*-**2**-HCl or *trans*-**2**-HCl, because solubilization of *cis*-**2**-HCl or *trans*-**2**-HCl during the course of the recrystallization shifted the equilibrium between *cis*-**2**-HCl and *trans*-**2**-HCl to the mid-point to give a mixture of epimers instead of pure compound. However, we were able to obtain pure compounds **2a**–**2v** by recrystallization or flash chromatography after neutralization of the corresponding hydrochloride salts (*cis*- or *trans*-**2**-HCl).

A plausible mechanism for the CIAT process is proposed in Scheme 3. There are three reasonable pathways[10,11,47–49] for the CIAT process. Path A involves double migration of the double bond catalyzed by acid. Path B involves a retro P–S reaction to form an imine intermediate. Path C involves the splitting of a carbon–nitrogen bond, rotation of a carbon–carbon bond, and reformation of a carbon–nitrogen bond.

In order to gain a better understanding of the proposed mechanism (Scheme 3), we designed and attempted the three following experiments. We first tried the P–S reaction of D-tryptophan methyl ester hydrochloride **1**-HCl with deuterated 3,4-dimethoxybenzaldehyde **3** which was prepared according to a modified procedure of the known method[50–52] (Scheme 4). After a CIAT process in CH_3NO_2/toluene (1:1), *trans*-d_1-**2b**-HCl was obtained in 97% yield (Scheme 5). This result means that path A could be excluded here, otherwise the above CIAT process (Scheme 5) should produce a mixture of non-deuterated *trans*-**2b**-HCl and deuterated *trans*-d_1-**2b**-HCl, because the feature of the acid-catalyzed path A is the proton-exchange between tetrahydro-β-carboline scaffold and the solvent media. We next attempted to trap the intermediates of path B and path C by adding 5 equiv of zinc powder into the solution of *trans*-**2b**-HCl in methanol,[53] after refluxing for 8 h, the *cis*-**2b**, *trans*-**2b,** and compound **4** (Scheme 6) were obtained in 43%, 45%, and 5% yield, respectively. The detection of the compound **4** implies that the mechanism of the CIAT process most likely follows path C, because compound **4** would be derived from the reduction of the intermediate of path C. However, we could not detect imine intermediate **5** (Scheme 6) of path B or its reduction product **6** after careful monitoring of the CIAT process by TLC and HPLC. Moreover, when adding 2 equiv of hydroxylamine hydrochloride into the suspension of *cis*-**2b**-HCl in the mixed solvent CH_3NO_2/toluene (1:1), *trans*-**2b**-HCl was obtained almost quantitatively after refluxing for 8 h; no oxime **7**, which would be derived from the imine intermediate **5**, was observed after careful analysis by TLC and HPLC. The failure to detect compounds **5**–**7** implies that the CIAT process probably does not follow the retro P–S reaction pathway (path B in Scheme 3).

3. Conclusion

In conclusion, we have developed a general method to synthesize enantiomerically pure *cis* (or *trans*) 1,3-disubstituted tetrahydro-β-carbolines **2a**–**2v** from D-tryptophan esters via a CIAT process. A direct Pictet–Spengler reaction of D-tryptophan

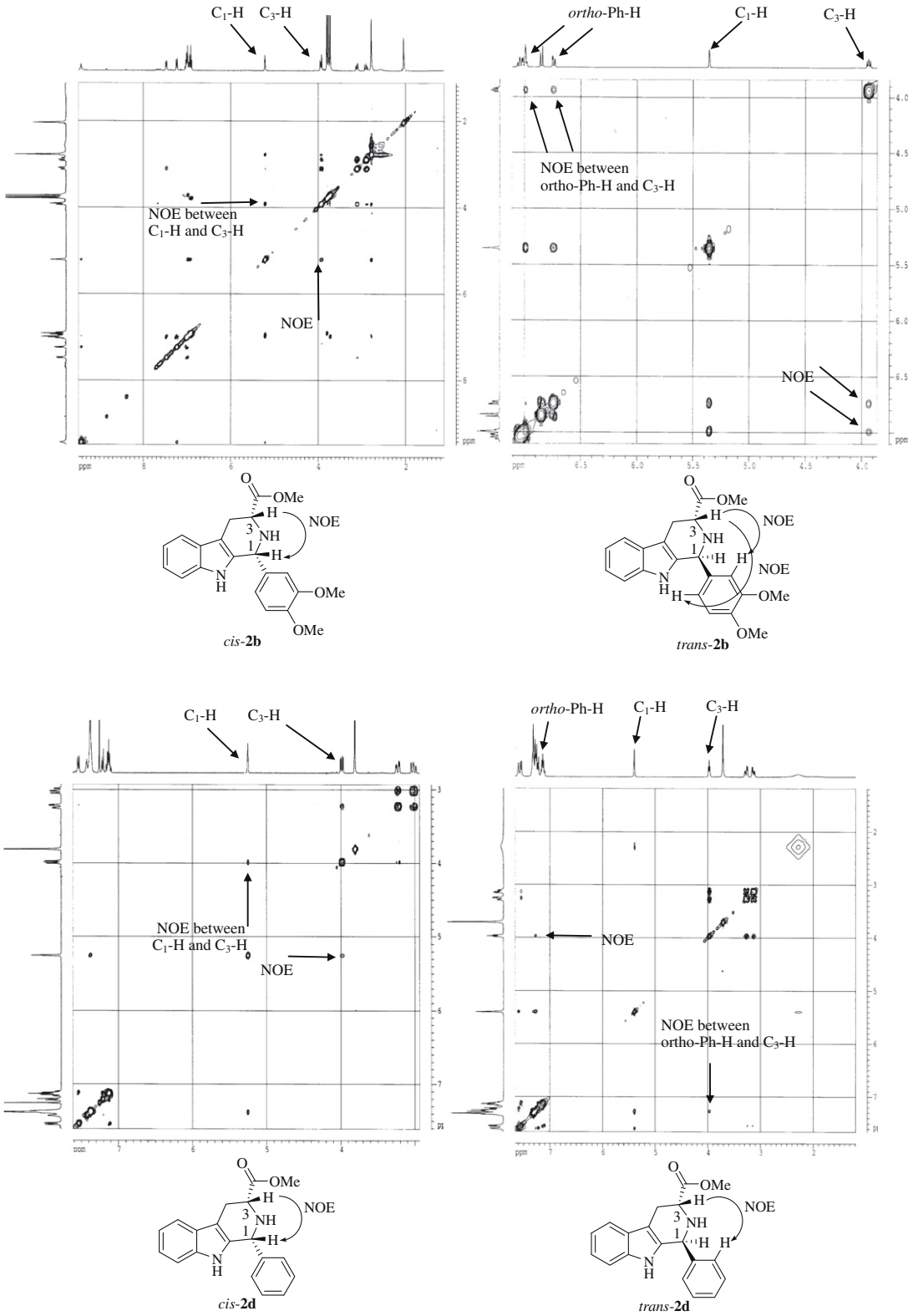
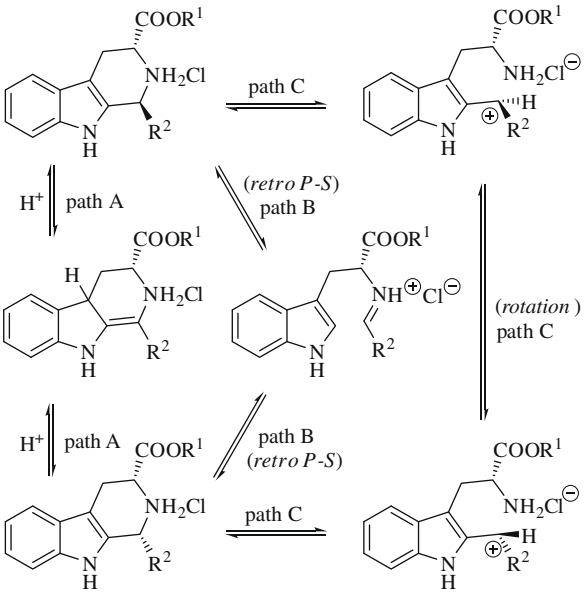
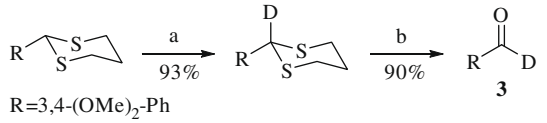


Figure 1. ^{1}H–^{1}H NOESY spectra and stereochemistry of *cis*-**2b** and *cis*-**2d** versus *trans*-**2b** and *trans*-**2d**.

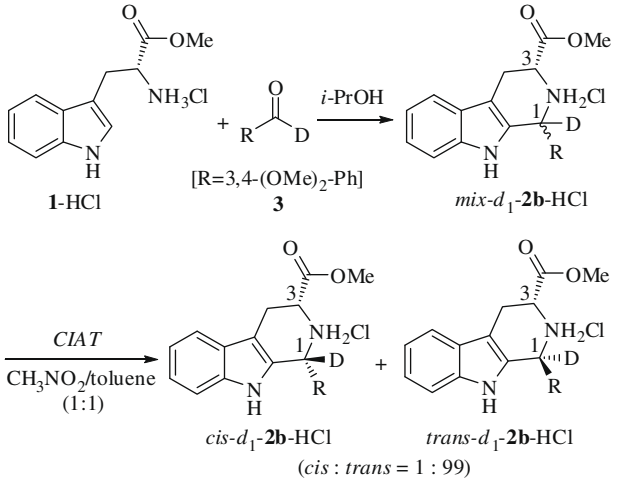
ester hydrochlorides with various aldehydes in a mixed solvent of nitromethane and toluene (see also Table 1) and a modified two-step procedure (see also Table 2) were studied extensively. It was found that a fine tuning of the ratio of nitromethane and toluene for each epimer mixture of **2**-HCl was necessary in order to get as high stereoselectivities and yields as possible. A plausible mechanism for the CIAT process has also been discussed, which most likely involves the splitting of a C–N bond, rotation of a C–C bond and reformation of a C–N bond (path C in Scheme 3).



Scheme 3. Plausible mechanism for the CIAT of **2**-HCl.



Scheme 4. Preparation of the deuterated 3,4-dimethoxy benzaldehyde **3**. Reagents and conditions: (a) 1.5 equiv of *n*-BuLi, −50 °C to −40 °C for 5 h in toluene, then large excess of D_2O; (b) 1.5 equiv of H_5IO_6, rt for 10 min in THF.

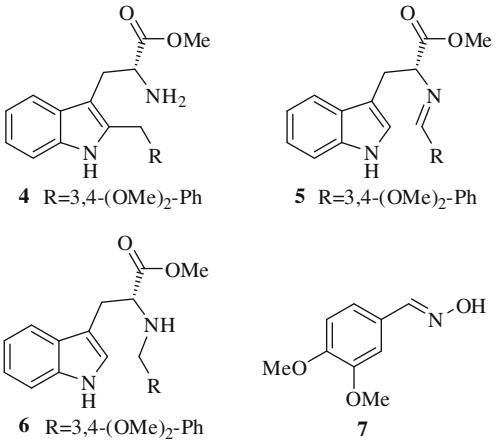


Scheme 5. The deuterium labeling test for the CIAT of **2b**-HCl.

4. Experimental

4.1. General method

Melting points are uncorrected. NMR spectra were acquired on Bruker AM-500, chemical shifts of ^1H NMR were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on Nicolet Magna IR-550. Mass spectra were recorded on HP5989A. Optical rotations were measured on WZZ-1S automatic polarimeter at room temperature. Column chromatography was performed on silica gel. All chemicals were analytically pure. The D-tryptophan ester hydrochloride **1**-HCl was prepared according to a known procedure.[22]



Scheme 6. Some proposed intermediates.

4.2. Typical procedure for the direct Pictet–Spengler reaction of D-tryptophan methyl ester hydrochloride with an aldehyde

To a solution of 3,4,5-trimethoxybenzaldehyde (2.36 g, 12.03 mmol) in a mixed solvent of nitromethane (12 mL) and toluene (12 mL) was added the powder of D-tryptophan methyl ester hydrochloride (2.57 g, 10.09 mmol). The suspension was heated at reflux and stirred for around 8 h, and the reaction was monitored by TLC after neutralization. When the reaction was complete, the mixture was cooled down to room temperature. A pale yellow solid was collected on a Buchner funnel by suction and rinsed with a small amount of freshly mixed solvent of nitromethane and toluene (1:1). The solid was then partitioned between ethyl acetate (40 mL) and an aqueous solution of potassium carbonate (1.80 g, 13.03 mmol) in water (20 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent under a vacuum gave a crude product, which was purified by recrystallization or flash chromatography to afford compound **2a** (3.67 g, 9.26 mmol) in 92% yield.

4.3. Typical two-step procedure of the reaction of D-tryptophan ester hydrochloride with an aldehyde

To a solution of 3,4,5-trimethoxybenzaldehyde (2.36 g, 12.03 mmol) in isoproponal (25 mL), was added the powder of D-tryptophan methyl ester hydrochloride (powder, 2.57 g, 10.09 mmol). The suspension was heated to reflux while stirring, the mixture gradually turned into a clear solution, and the reaction was monitored by TLC after neutralization. The reaction completed in around 4 h, and the reaction solution was then concentrated to dryness under a vacuum to give a crude solid product which was washed twice with toluene to remove excessive 3,4,5-trimethoxybenzaldehyde.

The above washed crude solid product was then suspended in a mixed solvent of nitromethane (12 mL) and toluene (12 mL), and the suspension was heated at reflux. After the stirring was continued at reflux for 8 h, the mixture was cooled down to room temperature. A pale yellow solid was collected on a Buchner funnel by suction and rinsed with a small amount of freshly mixed solvent of nitromethane and toluene (1:1). The solid was then partitioned between ethyl acetate (40 mL) and an aqueous solution of potassium carbonate (1.80 g, 13.03 mmol) in water (20 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent under a vacuum gave a crude product which was

purified by recrystallization or flash chromatography to afford compound **2a** (3.91 g, 9.86 mmol) in 98% yield.

4.4. Characterization data of 1,3-disubstituted tetrahydro-β-carbolines 2a–2v is as follows

4.4.1. (1*S*,3*R*)-Methyl 1-(3,4,5-trimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole-3-carboxylate *trans*-2a

White solid,[54] R_f on silica 0.45 (hexane–ethyl acetate, 1:1), mp 182–183 °C. $[\alpha]_D^{20} = +11.3$ (*c* 1.3, $CHCl_3$). ^1H NMR (acetone-d_6) δ 2.81 (br s, N–H, 1H), 3.04 (ddd, J_1 = 15.2 Hz, J_2 = 6.4 Hz, J_3 = 1.5 Hz, 1H), 3.17 (ddd, J_1 = 15.2 Hz, J_2 = 5.4 Hz, J_3 = 1.3 Hz, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 3.73 (s, 6H), 4.02 (t, *J* = 5.8 Hz, 1H), 5.38 (s, 1H), 6.68 (s, 2H), 7.00 (td, J_1 = 7.1 Hz, J_2 = 1.2 Hz, 1H), 7.04 (td, J_1 = 7.1 Hz, J_2 = 1.3 Hz, 1H), 7.26 (dd, J_1 = 6.9 Hz, J_2 = 1.2 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 9.63 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 397 (M^++1, 19), 396 (M^+, 100), 395 (21), 381 (19), 365 (6), 337 (23), 320 (13), 278 (20), 229 (7), 219 (4), 194 (4), 180 (4), 169 (14), 144 (4), 115 (2), 77 (1). IR (KBr) 3348, 3308, 2950, 1743, 1592, 1508, 1460, 1417, 1233, 1128 cm^{-1}. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.25; H, 6.13; N, 6.83.

4.4.2. (1*S*,3*R*)-Methyl 1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole-3-carboxylate *trans*-2b

White solid, R_f on silica 0.51 (hexane–ethyl acetate, 1:1), mp 191–192 °C (lit.[30] 194–196 °C). $[\alpha]_D^{20} = +25.4$ (*c* 1.7, $CHCl_3$). ^1H NMR (acetone-d_6) δ 3.00 (ddd, J_1 = 15.1 Hz, J_2 = 7.0 Hz, J_3 = 1.4 Hz, 1H), 3.15 (ddd, J_1 = 15.1 Hz, J_2 = 5.3 Hz, J_3 = 1.0 Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 3.93 (dd, J_1 = 6.9 Hz, J_2 = 5.4 Hz, 1H), 5.36 (s, 1H), 6.74 (dd, *J* = 8.2 Hz, J_2 = 2.0 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.97–7.07 (m, 3H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 9.63 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 367 (M^++1, 20), 366 (M^+, 100), 365 (24), 351 (19), 349 (28), 335 (4), 317 (4), 307 (29), 305 (17), 290 (17), 279 (8), 264 (6), 248 (27), 229 (7), 217 (5), 204 (9), 191 (4), 169 (13), 144 (5), 115 (2), 77 (1). IR (KBr) 3371, 2952, 1730, 1513, 1463, 1453, 1421, 1257, 1232, 1026, 818, 742 cm^{-1}. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.85; H, 5.89; N, 7.70.

4.4.3. (1*R*,3*R*)-Methyl 1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole-3-carboxylate *cis*-2b

White solid, R_f on silica 0.55 (hexane–ethyl acetate, 1:1), mp 174–175 °C (lit.[30] 174–176 °C). $[\alpha]_D^{20} = +21.9$ (*c* 1.6, $CHCl_3$). ^1H NMR (acetone-d_6) δ 2.90 (ddd, J_1 = 15.1 Hz, J_2 = 7.0 Hz, J_3 = 1.4 Hz, 1H), 3.11 (ddd, J_1 = 15.1 Hz, J_2 = 5.3 Hz, J_3 = 1.0 Hz, 1H), 3.72 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 3.92 (dd, J_1 = 10.9 Hz, J_2 = 4.1 Hz, 1H), 5.21 (s, 1H), 6.88–7.05 (m, 5H), 7.24 (dd, J_1 = 6.9 Hz, J_2 = 2.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 9.42 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 367 (M^++1, 21), 366 (M^+, 100), 365 (37), 351 (14), 335 (3), 307 (39), 289 (10), 279 (27), 248 (55), 229 (11), 217 (6), 169 (15), 144 (9). IR (KBr) 3353, 2935, 1737, 1517, 1454, 1263, 1165, 1139, 1027, 745 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{22}N_2O_4$: 366.1580; found: 366.1578.

4.4.4. (1*S*,3*R*)-Methyl 1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate *trans*-2c

White solid, R_f on silica 0.58 (hexane–ethyl acetate, 1:1), mp 219–220 °C (lit.[55] 193–194 °C). $[\alpha]_D^{20} = +44.0$ (*c* 2.0, $CHCl_3$). ^1H NMR (acetone-d_6) δ 2.72 (br s, N–H, 1H), 2.99 (ddd, J_1 = 15.1 Hz, J_2 = 7.3 Hz, J_3 = 1.2 Hz, 1H), 3.14 (ddd, J_1 = 15.1 Hz, J_2 = 5.2 Hz, J_3 = 1.0 Hz, 1H), 3.66 (s, 3H), 3.76 (s, 3H), 3.89 (dd, J_1 = 7.1 Hz, J_2 = 5.5 Hz, 1H), 5.36 (s, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.98–7.07 (m, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 9.64 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 337 (M^++1, 17), 336 (M^+, 100), 335 (22), 319 (18), 287 (4), 277 (35), 262 (16), 248 (21), 233 (8), 218 (25), 204 (12), 191 (4), 169 (11), 144 (7), 134 (5), 115 (3), 77 (1). IR (KBr) 3285, 2945, 1742, 1610, 1510, 1454, 1271, 1252, 1203, 1175, 1116, 1031, 840, 737 cm^{-1}.

4.4.5. (1*R*,3*R*)-Methyl 1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate *cis*-2d

White solid, R_f on silica 0.44 (hexane–ethyl acetate, 2:1), mp 226–227 °C (lit.[55] 184–185 °C). $[\alpha]_D^{20} = +14.2$ (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 3.02 (ddd, J_1 = 15.0 Hz, J_2 = 11.1 Hz, J_3 = 2.5 Hz, 1H), 3.23 (ddd, J_1 = 15.1 Hz, J_2 = 4.2 Hz, J_3 = 1.9 Hz, 1H), 3.81 (s, 3H), 3.99 (dd, J_1 = 11.1 Hz, J_2 = 4.2 Hz, 1H), 5.25 (t, *J* = 2.0 Hz, 1H), 7.11 (td, J_1 = 7.0 Hz, J_2 = 1.4 Hz, 1H), 7.15 (td, J_1 = 7.0 Hz, J_2 = 1.6 Hz, 1H), 7.21 (dd, J_1 = 6.5 Hz, J_2 = 2.0 Hz, 1H), 7.34–7.42 (m, 5H), 7.43 (br s, NH on the indole ring, 1H), 7.54 (dd, J_1 = 7.5 Hz, J_2 = 1.8 Hz, 1H). MS (EI) *m/z* (relative intensity) 307 (M^++1, 15), 306 (M^+, 82), 305 (21), 291 (6), 247 (38), 229 (12), 218 (100), 204 (9), 189 (3), 169 (13), 144 (10), 115 (5), 77 (2). IR (KBr) 3396, 3338, 2951, 2789, 1740, 1456, 1439, 1356, 1328, 1207, 747, 699 cm^{-1}.

4.4.6. (1*S*,3*R*)-Methyl 1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate *trans*-2d

White solid, R_f on silica 0.34 (hexane–ethyl acetate, 2:1). mp 220–221 °C (lit.[55] 161–162 °C). $[\alpha]_D^{20} = +44.5$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 3.14 (ddd, J_1 = 15.3 Hz, J_2 = 6.7 Hz, J_3 = 1.1 Hz, 1H), 3.23 (dd, J_1 = 14.5 Hz, J_2 = 4.4 Hz, 1H), 3.71 (s, 3H), 3.97 (dd, J_1 = 11.1 Hz, J_2 = 4.2 Hz, 1H), 5.40 (s, 1H), 7.13 (td, J_1 = 7.1 Hz, J_2 = 1.3 Hz, 1H), 7.16 (td, J_1 = 7.0 Hz, J_2 = 1.3 Hz, 1H), 7.18–7.36 (m, 6H), 7.55 (d, *J* = 7.0 Hz, 1H), 7.60 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 307 (M^++1, 20), 306 (M^+, 100), 305 (17), 289 (17), 274 (2), 257 (5), 247 (36), 232 (17), 218 (56), 204 (7), 169 (12), 144 (12), 115 (4). IR (KBr) 3401, 3052, 2951, 1730, 1456, 1353, 1329, 1206, 744, 701 cm^{-1}.

4.4.7. (1*R*,3*R*)-Methyl 1-(4-hydroxy-3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate *cis*-2e

White solid, R_f on silica 0.44 (hexane–ethyl acetate, 1:1), mp 179–180 °C. $[\alpha]_D^{20} = +39.8$ (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$) 3.01 (ddd, J_1 = 15.1 Hz, J_2 = 11.1 Hz, J_3 = 2.4 Hz, 1H), 3.22 (ddd, J_1 = 15.1 Hz, J_2 = 4.4 Hz, J_3 = 1.8 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 3.97 (dd, J_1 = 11.1 Hz, J_2 = 4.2 Hz, 1H), 5.18 (s, 1H), 6.85–6.93 (m, 3H), 7.12 (td, J_1 = 7.1 Hz, J_2 = 1.4 Hz, 1H), 7.15 (td, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H), 7.23 (dd, J_1 = 6.3 Hz, J_2 = 1.5 Hz, 1H), 7.46 (br s, NH on the indole ring, 1H), 7.54 (dd, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 173.18, 147.08, 146.01, 146.00, 136.13, 134.93, 127.20, 121.91, 121.54, 119.62, 118.18, 114.34, 110.97, 110.71, 108.67, 58.68, 56.99, 56.02, 52.26, 25.60. MS (EI) *m/z* (relative intensity) 353 (M^++1, 19), 352 (M^+, 100), 351 (34), 337 (14), 293 (31), 276 (11), 265 (26), 248 (12), 234 (15), 204 (9), 191 (3), 169 (10), 150 (3), 144 (5), 115 (2). IR (KBr) 3405, 3328, 2950, 1742, 1519, 1451, 1269, 1223, 746 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.53; H, 5.64; N, 8.04.

4.4.8. (1*R*,3*R*)-Methyl 1-(4-hydroxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate *cis*-2f

White solid, R_f on silica 0.44 (hexane–ethyl acetate, 1:1), mp 228–229 °C. $[\alpha]_D^{20} = +34.2$ (*c* 1.0, acetone). ^1H NMR (acetone-d_6) δ 2.45 (br s, N–H, 1H), 2.88 (ddd, J_1 = 14.7 Hz, J_2 = 11.1 Hz, J_3 = 2.5 Hz, 1H), 3.10 (ddd, J_1 = 14.9 Hz, J_2 = 4.1 Hz, J_3 = 1.8 Hz, 1H), 3.75 (s, 3H), 3.92 (dd, J_1 = 11.1 Hz, J_2 = 4.1 Hz, 1H), 5.19 (s, 1H), 6.79 (d, J_1 = 8.6 Hz, 2H), 6.98 (td, J_1 = 7.1 Hz, J_2 = 1.3 Hz, 1H), 7.02 (td, J_1 = 7.1 Hz, J_2 = 1.4 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 8.26 (s, ArOH, 1H), 9.42 (br

s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 323 (M^++1, 22), 322 (M^+, 100), 321 (32), 307 (14), 263 (44), 248 (9), 235 (57), 234 (59), 218 (21), 206 (14), 191 (4), 169 (14), 144 (12), 120 (5), 77 (1). IR (KBr) 3371, 3300, 3269, 2980, 1732, 1616, 1520, 1459, 1439, 1325, 1279, 1216, 1178, 830, 751, 741 cm^{-1}. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.80; H, 5.63; N, 8.69. Found: C, 70.51; H, 5.43; N, 8.65.

4.4.9. (1*R*,3*R*)-Methyl 1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate *cis*-2g

White solid, R_f on silica 0.45 (hexane–ethyl acetate, 2:1), mp 171–173 °C (lit.[55] 171–172 °C). $[\alpha]_D^{20} = +5.4$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 3.03 (ddd, J_1 = 15.0 Hz, J_2 = 11.1 Hz, J_3 = 2.5 Hz, 1H), 3.26 (ddd, J_1 = 15.2 Hz, J_2 = 4.1 Hz, J_3 = 1.8 Hz, 1H), 3.83 (s, 3H), 3.99 (dd, J_1 = 11.1 Hz, J_2 = 4.1 Hz, 1H), 5.39 (s, 1H), 7.14 (td, J_1 = 7.0 Hz, J_2 = 1.4 Hz, 1H), 7.17 (td, J_1 = 6.9 Hz, J_2 = 1.4 Hz, 1H), 7.22 (dd, J_1 = 7.2 Hz, J_2 = 1.3 Hz, 1H), 7.37 (br s, NH on the indole ring, 1H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 2H), 8.22 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 172.83, 148.32, 147.46, 136.30, 132.95, 129.45, 126.66, 123.65, 122.09, 119.61, 118.13, 110.98, 108.98, 57.75, 56.40, 52.19, 25.36. MS (EI) *m/z* (relative intensity) 352 (M^++1, 24), 351 (M^+, 100), 350 (18), 334 (46), 317 (7), 304 (29), 292 (65), 275 (6), 264 (49), 257 (13), 245 (34), 229 (18), 218 (72), 217 (74), 204 (9), 189 (6), 169 (22), 144 (13), 130 (5), 115 (6), 77 (2). IR (KBr) 3432, 2954, 1737, 1604, 1521, 1438, 1349, 1264, 1220, 860, 746 cm^{-1}.

4.4.10. (1*R*,3*R*)-Methyl 1-(2-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate *cis*-2h

White solid, R_f on silica 0.48 (hexane–ethyl acetate, 2:1), mp 173–174 °C (lit.[55] 177–178 °C). $[\alpha]_D^{20} = +22.6$ (*c* 6.6, $CHCl_3$). ^1H NMR (acetone-d_6) δ 2.96 (ddd, J_1 = 15.0 Hz, J_2 = 10.9 Hz, J_3 = 2.4 Hz, 1H), 3.12–3.23 (m, 2H), 3.76 (s, 3H), 3.96–4.04 (m, 1H), 5.81 (t, *J* = 1.7 Hz, 1H), 7.03 (td, J_1 = 7.0 Hz, J_2 = 1.4 Hz, 1H), 7.07 (td, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H), 7.24 (dd, J_1 = 7.7 Hz, J_2 = 1.6 Hz, 1H), 7.48–7.58 (m, 2H), 7.63 (d, *J* = 5.0 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 1H), 9.64 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 351 (M^+, 11), 334 (100), 333 (64), 317 (5), 304 (68), 292 (6), 274 (8), 257 (16), 245 (68), 229 (6), 217 (17), 204 (4), 189 (3), 169 (10), 149 (6), 130 (7), 115 (4), 77 (2), 41 (1). IR (KBr) 3402, 2952, 2850, 1736, 1627, 1527, 1453, 1354, 1265, 1220, 744 cm^{-1}.

4.4.11. (1*S*,3*R*)-Methyl 1-isopropyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate *trans*-2i

White solid, R_f on silica 0.47 (hexane–ethyl acetate, 2:1), mp 148–149 °C. $[\alpha]_D^{20} = -53.4$ (*c* 1.6, $CHCl_3$). ^1H NMR (acetone-d_6) δ 0.83 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 2.16–2.27 (m, 1H), 2.43 (br s, N–H, 1H), 2.99 (dd, J_1 = 5.5 Hz, J_2 = 1.3 Hz, 2H), 3.62 (s, 3H), 4.00 (t, *J* = 5.4 Hz, 1H), 4.20 (d, *J* = 4.3 Hz, 1H), 6.96 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.02 (td, J_1 = 7.1 Hz, J_2 = 1.2 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 9.76 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 272 (M^+, 7), 229 (100), 213 (9), 197 (4), 169 (32), 142 (1), 130 (1), 115 (2). IR (KBr) 3332, 2962, 2888, 1733, 1468, 1456, 1427, 1336, 1271, 1224, 1194, 1132, 1004, 835, 742, 629 cm^{-1}. Anal. Calcd for-$C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.17; H, 7.36; N, 10.05.

4.4.12. (1*R*,3*R*)-Methyl 1-hexyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3- carboxylate *cis*-2j

White solid, R_f on silica 0.66 (hexane–ethyl acetate, 2:1), mp 95–96 °C. $[\alpha]_D^{20} = +57.8$ (*c* 1.6, $CHCl_3$). ^1H NMR (acetone-d_6) δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.23–1.58 (m, 8H), 1.67–1.78 (m, 1H), 2.01–2.11(m, 1H), 2.15 (br s, N–H, 1H), 2.71 (ddd, J_1 = 14.7 Hz, J_2 = 11.1 Hz, J_3 = 2.5 Hz, 1H), 3.00 (ddd, J_1 = 14.8 Hz, J_2 = 4.1 Hz, J_3 = 1.8 Hz, 1H), 3.72 (dd, J_1 = 11.1 Hz, J_2 = 4.1 Hz, 1H), 3.76 (s, 3H), 4.20 (dd, J_1 = 6.2 Hz, J_2 = 1.8 Hz, 1H), 6.98 (td, J_1 = 7.1 Hz, J_2 = 1.0 Hz, 1H), 7.04 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 9.89 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 314 (M^+, 10), 296 (1), 267 (1), 255 (4), 229 (100), 197 (2), 169 (20), 156 (3), 144 (4), 115 (1), 85 (1), 73 (2), 60(3), 56 (4), 43(4). IR (KBr) 3397, 3056, 2927, 2852, 1734, 1452, 1327, 1270, 1216, 1170, 1046, 1009, 846, 741, 594 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{26}N_2O_2$: 314.1994; found: 314.1995.

4.4.13. (1*R*,3*R*)-Methyl 1-(2-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate *cis*-2k

White solid, R_f on silica 0.35 (hexane–ethyl acetate, 2:1), mp 184–185 °C (lit.[29] 195 °C). $[\alpha]_D^{20} = -14.1$ (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 3.00 (ddd, J_1 = 14.9 Hz, J_2 = 11.0 Hz, J_3 = 2.5 Hz, 1H), 3.21 (ddd, J_1 = 15.1 Hz, J_2 = 4.2 Hz, J_3 = 1.8 Hz, 1H), 3.80 (s, 3H), 3.90 (s, 3H), 3.99 (dd, J_1 = 11.0 Hz, J_2 = 4.2 Hz, 1H), 5.72 (s, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.98 (d, J_1 = 8.2 Hz,1H), 7.09 (td, J_1 = 7.0 Hz, J_2 = 1.4 Hz, 1H), 7.13 (td, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H), 7.22 (dd, J_1 = 6.2 Hz, J_2 = 1.6 Hz, 1H), 7.31 (td, J_1 = 8.2 Hz, J_2 = 1.7 Hz, 1H), 7.36 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.51 (dd, J_1 = 7.5 Hz, J_2 = 1.7 Hz, 1H), 7.71 (br s, NH on the indole ring, 1H). ^{13}C NMR ($CDCl_3$) δ 173.26, 157.13, 135.80, 134.73, 129.07, 129.00, 128.86, 126.94, 121.34, 121.01, 119.13, 117.74, 110.73, 110.72, 108.21, 56.65, 55.44, 51.93, 51.50, 25.54. MS (EI) *m/z* (relative intensity) 337 (M^++1, 20), 336 (M^+, 100), 335 (26), 321 (8), 305 (9), 277 (44), 260 (9), 249 (40), 234 (12), 218 (33), 204 (7), 191 (2), 169 (9), 144 (5), 130 (2), 115 (2), 77 (1). IR (KBr) 3423, 2949, 1736, 1600, 1493, 1463, 1438, 1243, 1028, 755, 741 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{20}N_2O_3$: 336.1474; found: 336.1475.

4.4.14. (1*R*,3*R*)-Methyl 1-(2-ethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate *cis*-2l

White solid, R_f on silica 0.48 (hexane–ethyl acetate, 2:1), mp 174–175 °C. $[\alpha]_D^{20} = +1.6$ (*c* 4.1, $CHCl_3$). ^1H NMR (acetone-d_6) δ 1.21 (t, *J* = 7.0 Hz, 3H), 2.65 (br s, N–H, 1H), 2.77 (ddd, J_1 = 14.7 Hz, J_2 = 10.9 Hz, J_3 = 2.5 Hz, 1H), 2.98 (ddd, J_1 = 14.8 Hz, J_2 = 4.1 Hz, J_3 = 1.8 Hz, 1H), 3.61 (s, 3H), 3.80 (dd, J_1 = 10.9 Hz, J_2 = 4.1 Hz, 1H), 3.86–3.95 (m, 1H), 3.99–4.08 (m, 1H), 5.56 (s, 1H), 6.75 (td, J_1 = 7.5 Hz, J_2 = 0.8 Hz, 1H), 6.82–6.91 (m, 3H), 7.07–7.15 (m, 2H), 7.20 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.33 (dd, J_1 = 6.6 Hz, J_2 = 1.8 Hz, 1H), 9.30 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 351 (M^++1, 22), 350 (M^+, 100), 349 (28), 335 (9), 321 (7), 305 (8), 291 (39), 276 (5), 263 (38), 248 (11), 234 (19), 218 (18), 204 (9), 191 (2), 182 (4), 169 (11), 157 (7), 144 (4), 130 (3), 115 (3), 77 (1). IR (KBr) 3396, 2977, 1736, 1597, 1494, 1455, 1328, 1242, 1117, 1044, 919, 744 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{22}N_2O_3$: 350.1630; found: 350.1632.

4.4.15. (1*R*,3*R*)-Methyl 1-(2-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate *cis*-2m

White solid, R_f on silica 0.71 (hexane–ethyl acetate, 2:1), mp 165–166 °C (lit.[55] 170–171 °C). $[\alpha]_D^{20} = -20.6$ (*c* 0.9, $CHCl_3$). ^1H NMR (acetone-d_6) δ 2.65 (br s, N–H, 1H), 2.92 (ddd, J_1 = 14.9 Hz, J_2 = 10.9 Hz, J_3 = 2.4 Hz, 1H), 3.15 (ddd, J_1 = 14.8 Hz, J_2 = 4.1 Hz, J_3 = 1.7 Hz, 1H), 3.75 (s, 3H), 4.00 (dd, J_1 = 10.5 Hz, J_2 = 3.1 Hz, 1H), 5.82 (s, 1H), 6.98–7.07 (m, 2H), 7.23–7.38 (m, 4H), 7.42–7.53 (m, 2H), 9.60 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 342 (M^++2, 34), 341 (M^++1, 26), 340 (M^+, 94), 325 (7), 305 (15), 281 (62), 279 (26), 253 (43), 245 (10), 229 (13), 218 (100), 217 (66), 204 (4), 189 (5), 169 (19), 144 (19), 115 (7), 77 (2). IR (KBr) 3413, 3058, 2952, 1736, 1468, 1439, 1322, 1268, 1219, 1051, 1035, 743 cm^{-1}.

4.4.16. (1*R*,3*R*)-Methyl 1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3- carboxylate *cis*-2n

White solid, R_f on silica 0.54 (dichloromethane–acetone, 3:1), mp 73–74 °C (lit.[56] 75–76 °C). $[\alpha]_D^{20} = +93.6$ (*c* 2.5, $CHCl_3$). ^1H NMR (acetone-d_6) δ 1.48 (d, J = 6.6 Hz, 1H), 2.72 (ddd, J_1 = 14.8 Hz, J_2 = 11.2 Hz, J_3 = 2.5 Hz, 1H), 3.00 (ddd, J_1 = 14.8 Hz, J_2 = 4.2 Hz, J_3 = 1.8 Hz, 1H), 3.75 (dd, J_1 = 11.1 Hz, J_2 = 4.1 Hz, 1H), 3.76 (s, 3H), 4.20–4.28 (m, 1H), 6.98 (td, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H), 7.04 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 9.92 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 245 (M^++1, 16), 244 (M^+, 100), 229 (92), 213 (2), 197 (4), 185 (41), 183 (25), 169 (59), 157 (72), 144 (9), 130 (10), 115 (8), 103 (2), 77 (2), 41 (1). IR (KBr) 3407, 2956, 2850, 1736, 1455, 1438, 1317, 1271, 1219, 1176, 1120, 745 cm^{-1}.

4.4.17. (1*R*,3*R*)-Methyl 1-ethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3- carboxylate *cis*-2o

White solid, R_f on silica 0.35 (hexane–ethyl acetate, 2:1), mp 83–84 °C. $[\alpha]_D^{20} = +9.8$ (*c* 1.6, $CHCl_3$). ^1H NMR (acetone-d_6) δ 0.98 (t, J = 7.4 Hz, 3H), 1.70–1.82 (m, 1H), 2.00–2.13 (m, 1H), 2.71 (ddd, J_1 = 14.8 Hz, J_2 = 10.9 Hz, J_3 = 2.5 Hz, 1H), 3.01 (ddd, J_1 = 14.8 Hz, J_2 = 4.1 Hz, J_3 = 1.8 Hz, 1H), 3.73 (dd, J_1 = 11.1 Hz, J_2 = 4.1 Hz, 1H), 3.76 (s, 3H), 4.16 (dd, J_1 = 5.1 Hz, J_2 = 2.5 Hz, 1H), 6.99 (td, J_1 = 7.0 Hz, J_2 = 1.2 Hz, 1H), 7.03 (td, J_1 = 7.1 Hz, J_2 = 1.2 Hz, 1H), 7.30 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 9.87 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 258 (M^+, 16), 234 (3), 229 (100), 197 (14), 182 (7), 169 (48), 156 (7), 144 (3), 130 (3), 115 (4), 102 (1), 77 (1). IR (KBr) 3399, 2960, 2849, 1736, 1452, 1437, 1331, 1271, 1218, 1174, 1046, 1008, 744 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{18}N_2O_2$: 258.1368; found: 258.1369.

4.4.18. (1*S*,3*R*)-Methyl-1-(4-acetoxy-3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate *trans*-2p

White solid, R_f on silica 0.35 (hexane–ethyl acetate, 2:1), mp 121–122 °C. $[\alpha]_D^{20} = +30.4$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$) 2.31 (s, 3H), 3.16 (dd, J_1 = 15.4 Hz, J_2 = 6.0 Hz, 1H), 3.27 (dd, J_1 = 15.4 Hz, J_2 = 5.7 Hz, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 4.00 (t, J = 5.8 Hz, 1H), 5.38 (s, 1H), 6.82 (dd, J_1 = 8.1 Hz, J_2 = 1.6 Hz, 1H), 6.95 (d, J = 1.2 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.16 (t, J = 6.7 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.71 (br s, NH on the indole ring, 1H). ^{13}C NMR ($CDCl_3$) δ 173.96, 169.12, 151.20, 140.87, 139.30, 136.16, 132.87, 126.70, 122.45, 121.74, 120.40, 119.22, 117.98, 112.32, 111.05, 107.97, 55.75, 54.51, 52.32, 51.97, 24.63, 20.49. MS (EI) *m/z* (relative intensity) 395 (M^++1, 24), 394 (M^+, 100), 393 (11), 379 (9), 351 (22), 335 (76), 321 (8), 293 (31), 278 (19), 264 (18), 248 (27), 229 (17), 204 (14), 169 (25), 144 (19), 115 (4). IR (KBr) 3401, 2960, 1764, 1736, 1508, 1455, 1274, 1218, 1198, 1162, 1122 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{22}N_2O_5$: 394.1529; found: 394.1532.

4.4.19. (1*R*,3*R*)-Methyl-1-(4-benzoyloxy-3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate *cis*-2q

White solid, R_f on silica 0.45 (hexane–ethyl acetate, 2:1), mp 125–126 °C. $[\alpha]_D^{20} = +8.1$ (*c* 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$) 3.02 (ddd, J_1 = 14.7 Hz, J_2 = 11.1 Hz, J_3 = 2.3 Hz, 1H), 3.24 (ddd, J_1 = 15.1 Hz, J_2 = 4.1 Hz, J_3 = 1.5 Hz, 1H), 3.73 (s, 3H), 3.82 (s, 3H), 3.98 (dd, J_1 = 11.2 Hz, J_2 = 4.2 Hz, 1H), 5.25 (s, 1H), 7.00 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H), 7.04 (d, J = 1.5 Hz, 1H), 7.10–7.17 (m, 3H), 7.24 (d, J = 6.0 Hz, 1H), 7.48–7.55 (m, 3H), 7.62 (d, J = 7.5 Hz, 1H), 7.64 (br s, NH on the indole ring, 1H), 8.21 (d, J = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 173.08, 164.76, 151.66, 139.99, 139.71, 136.18, 134.38, 133.49, 130.22, 129.15, 128.46, 126.97, 123.01, 121.83, 120.78, 119.46, 118.04, 112.70, 111.07, 108.61, 58.58, 56.86, 55.87, 52.15, 25.58. MS (EI) *m/z* (relative intensity) 457 (M^++1, 16), 456 (M^+, 61), 455 (17), 441 (8), 397 (27), 369 (11), 351 (4), 335 (7), 291 (5), 264 (10), 248 (34), 229 (11), 204 (9), 169 (10), 144 (9), 105 (100), 77 (18). IR (KBr) 3994, 2965, 2848, 1738, 1605, 1453, 1268, 1202, 1122, 1062, 709 cm^{-1}. HRMS (EI) calcd for $C_{27}H_{24}N_2O_5$: 456.1685; found: 456.1687.

4.4.20. (1*R*,3*R*)-Ethyl 1-(3,4,5-trimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole-3-carboxylate *cis*-2r

White solid, R_f on silica 0.55 (hexane–ethyl acetate, 1:1), mp 107–108 °C. $[\alpha]_D^{20} = +20.5$ (*c* 0.4, $CHCl_3$). ^1H NMR (acetone-d_6) δ 1.30 (t, J = 7.1 Hz, 3H), 2.60 (br s, N–H, 1H), 2.90 (ddd, J_1 = 14.8 Hz, J_2 = 11.1 Hz, J_3 = 2.4 Hz, 1H), 3.12 (ddd, J_1 = 14.9 Hz, J_2 = 4.1 Hz, J_3 = 1.7 Hz, 1H), 3.72 (s, 3H), 3.76 (s, 6H), 3.93 (dd, J_1 = 11.1 Hz, J_2 = 4.2 Hz, 1H), 4.17–4.30 (m, 2H), 5.23 (s, 1H), 6.75 (s, 2H), 6.99 (td, J_1 = 7.0 Hz, J_2 = 1.3 Hz, 1H), 7.03 (td, J_1 = 7.0 Hz, J_2 = 1.4 Hz, 1H), 7.23 (dd, J_1 = 6.3 Hz, J_2 = 1.5 Hz, 1H), 7.48 (dd, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 1H), 9.47 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 411 (M^++1, 22), 410 (M^+, 100), 409 (28), 393 (4), 381 (21), 337 (59), 322 (5), 309 (26), 294 (6), 278 (45), 262 (6), 247 (7), 234 (5), 219 (3), 194 (6), 180 (3), 169 (15), 144 (7), 117 (1). IR (KBr) 3347, 2939, 2841, 1735, 1595, 1507, 1462, 1422, 1330, 1267, 1233, 1181, 1127, 744 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{26}N_2O_5$: 410.1842; found: 410.1843.

4.4.21. (1*S*,3*R*)-Ethyl-1-(3,4-dimethoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole-3-carboxylate *trans*-2s

White solid, R_f on silica 0.40 (hexane–ethyl acetate, 1:1), mp 167–168 °C. $[\alpha]_D^{20} = +26.0$ (*c* 1.9, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 3.16 (dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H), 3.29 (dd, J_1 = 14.3 Hz, J_2 = 5.5 Hz, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 4.00 (t, J = 5.7 Hz, 1H), 4.10–4.25 (m, 2H), 5.39 (s, 1H), 6.76–6.84 (m, 1H), 6.80 (s, 1H), 6.89 (br s, NH on the indole ring, 1H), 7.09–7.14 (m, 2H), 7.25 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 6.3 Hz, 2H). MS (EI) *m/z* (relative intensity) 381 (M^++1, 21), 380 (M^+, 100), 363 (19), 351 (32), 335 (3), 317 (3), 307 (42), 305 (17), 290 (16), 279 (11), 264 (7), 248 (30), 233 (6), 217 (5), 204 (8), 191 (3), 169 (11), 144 (7), 115 (2). IR (KBr) 3362, 2980, 1731, 1600, 1514, 1465, 1454, 1256, 1186, 1138, 1026, 858, 743 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{24}N_2O_4$: 380.1736; found: 380.1737.

4.4.22. (1*S*,3*R*)-Ethyl-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate *trans*-2t

White solid, R_f on silica 0.40 (hexane–ethyl acetate, 2:1), mp 166–167 °C. $[\alpha]_D^{20} = +49.7$ (*c* 0.3, $CHCl_3$). ^1H NMR ($CHCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 3.11 (ddd, J_1 = 15.3 Hz, J_2 = 6.8 Hz, J_3 = 1.3 Hz, 1H), 3.25 (ddd, J_1 = 15.3 Hz, J_2 = 5.3 Hz, J_3 = 1.3 Hz, 1H), 3.79 (s, 3H), 3.94 (t, J = 6.5 Hz, 1H), 4.10–4.25 (m, 2H), 5.38 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.10–7.27 (m, 5H), 7.55 (d, J = 6.4 Hz, 2H). MS (EI) *m/z* (relative intensity) 351 (M^++1, 21), 350 (M^+, 100), 349 (16), 333 (20), 321 (28), 304 (4), 287 (3), 277 (43), 262 (17), 248 (17), 234 (7), 218 (17), 204 (7), 191 (2), 169 (8), 144 (10), 134 (5), 115 (2). IR (KBr) 3425, 3279, 3213, 2950, 1737, 1609, 1510, 1453, 1368, 1272, 1252, 1193, 1181, 1110, 1030, 847, 740 cm^{-1}. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.79; H, 6.12; N, 7.80.

4.4.23. (1*R*,3*R*)-Ethyl-1-(benzo[d][1,3]dioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole-3-carboxylate *cis*-2u

White solid, R_f on silica 0.61 (hexane–ethyl acetate, 2:1). $[\alpha]_D^{20} = +32.2$ (*c* 1.0, ethyl acetate). ^1H NMR (C_6D_6) δ 0.95 (t, J = 7.2 Hz, 3H), 3.07 (ddd, J_1 = 14.8 Hz, J_2 = 11.0 Hz, J_3 = 2.5 Hz, 1H), 3.20 (ddd, J_1 = 15.0 Hz, J_2 = 4.2 Hz, J_3 = 1.7 Hz, 1H), 3.70 (dd, J_1 = 11.0 Hz, J_2 = 4.2 Hz, 1H), 3.95–4.04 (m, 2H), 4.73 (s, 1H), 5.31 (s, 2H), 6.56–6.64 (m, 2H), 6.79 (br s, NH on the indole ring, 1H), 6.85 (s, 1H), 6.87–6.92 (m, 1H), 7.15–7.22 (m, 2H), 7.52–7.55 (m, 1H). MS (EI) *m/z* (relative intensity) 365 (M^++1, 19), 364 (M^+, 100), 363 (19), 347 (31), 335 (48), 318 (6), 301 (10), 291 (72),

274 (44), 262 (50), 233 (35), 204 (95), 191 (10), 169 (60), 144 (47), 115 (22), 102 (19), 77 (16), 51 (6). IR (KBr) 3399, 2925, 1731, 1487, 1442, 1243, 1037, 811, 743 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{20}N_2O_4$: 364.1423; found: 364.1429.

4.4.24. (1*R*,3*R*)-Propyl 1-(benzo[d][1,3]dioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido [3,4-*b*]indole-3-carboxylate *cis*-2v

White solid, R_f on silica 0.63 (hexane–ethyl acetate, 2:1). $[\alpha]_D^{20} = +36.2$ (*c* 1.0, ethyl acetate). ^1H NMR (C_6D_6) δ 0.72 (t, J = 7.4 Hz, 3H), 1.40–1.48 (m, 2H), 3.09 (ddd, J_1 = 14.8 Hz, J_2 = 12.1 Hz, J_3 = 1.5 Hz, 1H), 3.22 (ddd, J_1 = 14.9 Hz, J_2 = 4.1 Hz, J_3 = 1.5 Hz, 1H), 3.72 (dd, J_1 = 11.0 Hz, J_2 = 4.2 Hz, 1H), 3.90–4.01 (m, 2H), 4.73 (s, 1H), 5.31 (s, 2H), 6.56–6.67 (m, 2H), 6.75 (br s, NH on the indole ring, 1H), 6.86 (s, 1H), 6.87–6.91 (m, 1H), 7.15–7.21 (m, 2H), 7.51–7.57 (m, 1H). MS (EI) *m/z* (relative intensity) 379 (M^++1, 20), 378 (M^+, 100), 377 (11), 361 (24), 335 (55), 318 (8), 301 (6), 291 (73), 274 (49), 262 (50), 233 (32), 204 (94), 191 (17), 169 (50), 144 (41), 115 (21), 102 (16), 77 (11), 43 (24). IR (KBr) 3391, 2966, 1732, 1487, 1442, 1243, 1207, 1038, 928, 810, 741 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{22}N_2O_4$: 378.1580; found: 378.1579.

4.5. Preparation of deuterated 3,4-dimethoxybenzaldehyde 3

A solution of 2-(3,4-dimethoxyphenyl)-1,3-dithiane (1.51 g, 5.89 mmol) in dry toluene (15 mL) was cooled to −78 °C under N_2 by a dry-ice bath. A solution of *n*-BuLi (1.6 M, 5.5 mL, 8.80 mmol) in cyclohexane was then injected into the above cooled solution via syringe. The reaction temperature was kept in the range of −50 °C to −40 °C, and the mixture was stirred at this temperature for around 5 h. Heavy water (0.5 mL) was added dropwise, and the mixture was warmed to room temperature. Toluene (20 mL) and water (10 mL) were added, and the organic phase was separated and dried over anhydrous $MgSO_4$. After evaporation of solvents and purification by chromatography, 2-deutero-2-(3,4-dimethoxyphenyl)-1,3-dithiane (1.41 g, 5.48 mmol) was obtained in 93% yield.

To a solution of 2-deutero-2-(3,4-dimethoxyphenyl)-1,3-dithiane (1.20 g, 4.66 mmol) in THF (20 mL), was added periodic acid (1.59 g, 6.98 mmol).[52] After stirring was continued at room temperature for 10 min, the mixture was diluted with ethyl acetate (50 mL). The organic solution was transferred into a separatory funnel and washed twice with an aqueous solution of sodium sulfite (10%, 2 × 50 mL). Concentration of the organic solution under vacuum gave a crude product, which was purified by flash chromatography to produce the aldehyde **3** (702 mg, 4.20 mmol) in 90% yield, mp 45–46 °C. ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 3.98 (s, 3H), 6.99 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.48 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H). MS (EI) *m/z* (relative intensity) 168 (M^++1, 9), 167 (M^+, 100), 165 (39), 152 (16), 137 (5), 122 (3), 96 (14), 78 (7), 51 (3). IR (KBr) 3018, 2998, 2983, 2947, 2121, 1677, 1587, 1468, 1420, 1273, 1249, 1160, 1139, 1019, 890, 795, 717, 640, 569 cm^{-1}.

4.6. Deuterium labeling test for the CIAT of 2b-HCl

To a solution of the deuterated 3,4-dimethoxybenzaldehyde **3** (680 mg 4.07 mmol) in isoproponal (10 mL) was added D-tryptophan methyl ester hydrochloride (powder, 943 mg, 3.70 mmol). The mixture was heated at reflux, and stirring was continued for 4 h. The reaction solution was then concentrated to dryness under a vacuum to give a crude solid product.

Nitromethane (6 mL) and toluene (6 mL) were added, and the resulting suspension was heated at reflux. After the stirring was continued at reflux for 8 h, the mixture was cooled down to room temperature. A pale yellow solid was collected on a Buchner funnel by suction and rinsed with a small amount of freshly mixed solvent of nitromethane and toluene (1:1). The solid was then partitioned between ethyl acetate (20 mL) and an aqueous solution of potassium carbonate (665 mg, 4.81 mmol) in water (5 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent under a vacuum gave a crude product, which was purified by flash chromatography to afford compound *trans*-d_1-**2b** (1.33 g, 3.62 mmol) as a white solid in 98% yield, mp 179–180 °C, R_f on silica 0.51 (hexane–ethyl acetate, 1:1), $[\alpha]_D^{20} = +24.5$ (*c* 1.0, $CHCl_3$). ^1H NMR (acetone-d_6) δ 3.00 (dd, J_1 = 15.1 Hz, J_2 = 7.0 Hz, 1H), 3.14 (dd, J_1 = 15.1 Hz, J_2 = 5.3 Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 3.94 (dd, J_1 = 6.9 Hz, J_2 = 5.4 Hz, 1H), 6.73 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.97–7.07 (m, 3H), 7.27 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 9.67 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 368 (M^++1, 22), 367 (M^+, 100), 365 (14), 352 (16), 349 (24), 317 (6), 308 (34), 290 (18), 280 (11), 249 (32), 230 (10), 218 (5), 205 (8), 170 (20), 145 (11). IR (KBr) 3374, 2970, 1730, 1514, 1464, 1443, 1409, 1261, 1238, 1172, 1138, 1025, 740 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{21}DN_2O_4$: 367.1642; found: 367.1643.

4.7. CIAT process of *trans*-2b-HCl in methanol in the presence of zinc powder

To a solution of *trans*-**2b**-HCl (1.10 g, 2.73 mmol) in methanol (15 mL) were added zinc powder (893 mg, 13.65 mmol) and concentrated hydrochloric acid (0.25 mL). The mixture was heated at reflux, and then stirring was continued under reflux for 8 h. The reaction mixture was filtered by suction to remove the excessive zinc powder, and the filtrate was concentrated under vacuum to give a residue which was partitioned between ethyl acetate (50 mL) and an aqueous solution of potassium carbonate (15%, 20 mL). The organic phase was separated and dried over anhydrous $MgSO_4$, and then removal of solvent gave a crude oil, which was chromatographed to afford *cis*-**2b** (431 mg, 1.18 mmol) in 43% yield, *trans*-**2b** (451 mg, 1.23 mmol) in 45% yield, and (*R*)-methyl 2-amino-3-(2-(3,4-dimethoxybenzyl)-1*H*-indol-3-yl) propanoate **4** (52 mg, 0.14 mmol) in 5% yield, respectively. Characterization data of compound **4**: $[\alpha]_D^{20} = +17.3$ (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 3.06 (dd, J_1 = 14.4 Hz, J_2 = 8.1 Hz, 1H), 3.31 (dd, J_1 = 14.4 Hz, J_2 = 5.2 Hz, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 3.82–3.87 (m, 1H), 3.85 (s, 3H), 4.08 (s, 2H), 6.73 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 7.06–7.15 (m, 2H), 7.21 (d, J = 7.1 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.82 (br s, NH on the indole ring, 1H). MS (EI) *m/z* (relative intensity) 368 (M^+, 2), 351 (1), 309 (1), 281 (15), 280 (100), 264 (4), 248 (8), 234 (4), 204 (4), 191 (2), 151 (6), 144 (23), 115 (2), 77 (1). IR (KBr) 3363, 2937, 2837, 1728, 1591, 1514, 1462, 1261, 1234, 1140, 1028, 744 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{24}N_2O_4$: 368.1736; found: 368.1738.

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