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Synthesis of tadalafil (Cialis) from L-tryptophan

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ABSTRACT

The first synthesis of tadalafil **1** (Cialis) from L-tryptophan is described. The title compound **1** was synthesized via seven steps from L-tryptophan methyl ester hydrochloride in 42.3% overall yield. Two characteristic steps involved in this synthesis are the base-catalyzed epimerization of the C-3 position of (1*S*,3*S*)-1,2,3-trisubstituted-tetrahydro-β-carboline **3a** and the acid-catalyzed epimerization of the C-1 position of (1*S*,3*R*)-1,3-disubstituted-tetrahydro-β-carboline **5**. The (*S*)-configurations at C-1 and C-3 were inverted to (*R*)-configurations during the epimerization reactions. The base-catalyzed epimerization of C-3 of (1*S*,3*S*)-1,2,3-trisubstituted-tetrahydro-β-carbolines **3a**–**3e** was also studied in detail.

1. Introduction

The cyclic guanosine 3′,5′-monophosphate (cGMP) is an important secondary messenger that controls many physiological processes. The level of intracellular cGMP is determined by the activities of the cyclase that synthesizes it and the type-V phosphodiesterase (PDE5) that degrades it. Inhibition of PDE5 increases the level of cGMP, and therefore can be used as a therapeutic strategy, particularly for the treatment of cardiovascular diseases[1,2] and male erectile dysfunction (MED).[3–8]

PDE5 inhibitors, such as the three compounds as shown in Figure 1, have received considerable attention over the last decades. These three agents are well tolerated and have been approved by the FDA as first-line therapy for erectile dysfunction (ED). Recently the syntheses of tadalafil (Cialis) and related tetrahydro-β-carboline analogues have gathered much interest from synthetic and medicinal chemists,[5–20] because it is a cGMP specific PDE5 inhibitor with an improved PDE5/PDE6 selectivity compared with sildenafil (Vigra)[21–23] and vardenafil (Levitra).[24,25]

It should be noted that the title compound **1** (tadalafil) possesses an (*R*)-configuration at the C-12a position (see also Fig. 1), and has been synthesized from (*R*)-tryptophan (D-tryptophan) in all the reported methods.[5–20] Herein, we report the first synthesis of tadalafil **1** from (*S*)-tryptophan (L-tryptophan), which is more inexpensive than its antipode D-tryptophan.

2. Results and discussion

As depicted in Scheme 1, L-tryptophan methyl ester hydrochloride was first treated with 1.1 equiv of piperonal in nitromethane at reflux. Similar to D-tryptophan methyl ester hydrochloride, the highly stereoselective Pictet–Spengler reaction of L-tryptophan methyl ester hydrochloride with piperonal produced the hydrochloride salt of (1*S*,3*S*)-1,3-disubstituted-tetrahydro-β-carboline **2**-HCl via a CIAT process.[20,26] After neutralization of **2**-HCl, compound **2** was obtained in 95% yield and with 99% ee. Compound **2** was then treated with 1.2 equiv of benzyl chloroformate in ethyl acetate at around 5 °C in the presence of 3 equiv of potassium carbonate powder to afford (1*S*,3*S*)-1,2,3-trisubstituted-tetrahydro-β-carboline **3a** in 94% yield.

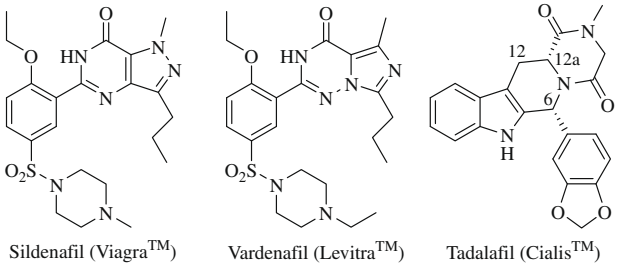

Figure 1. Structure of three PDE5 inhibitors.

The next step was the base-catalyzed epimerization of compound **3a** at the C-3 position to form (1*S*,3*R*)-1,2,3-trisubstituted-tetrahydro-β-carboline **4a**. We first tried the epimerization of compound **3a** in methanol at reflux in the presence of 0.5 equiv of sodium methoxide, monitoring by TLC showed that compound **4a** was gradually formed during the reaction, and the ratio of **4a** and **3a** increased meanwhile. Reflux was continued for more than 5 h, with the ratio of **4a** and **3a** becoming constant, meaning that the reaction was in equilibrium. Purification by flash chromatography gave pure compounds **4a** and **3a** in 89% combined yield and with a ratio of 74:26 (Table 1, entry 1). We also attempted the base-catalyzed epimerization of several (1*S*,3*S*)-1,2,3-trisubstituted-tetrahydro-β-carbolines **3b**–**3e** (Scheme 2) under various

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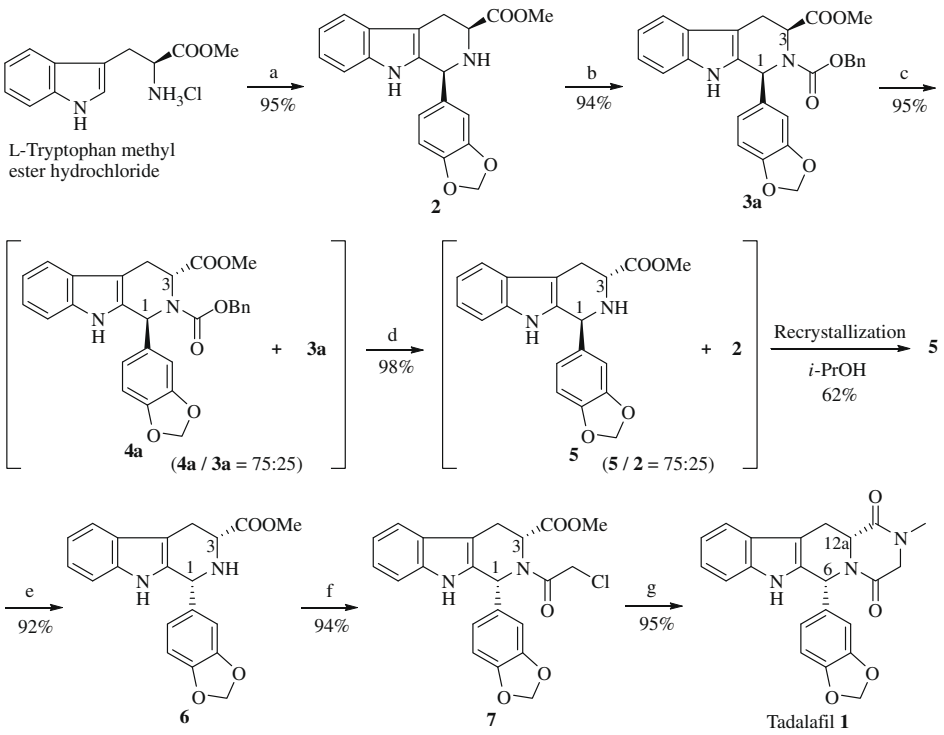


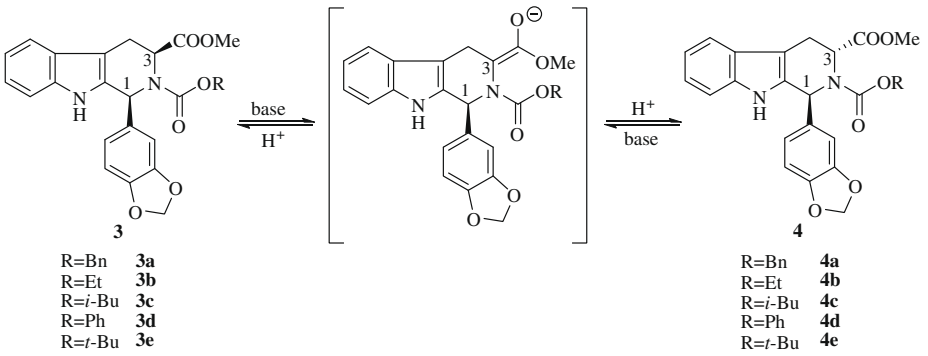
Scheme 1. Synthesis of tadalafil **1** from L-tryptophan methyl ester hydrochloride. Reagents and conditions: (a) 1.1 equiv of piperonal, refluxing in nitromethane for 5 h; then neutralized with a dilute aqueous solution of K_2CO_3; (b) 1.2 equiv of benzyl chloroformate and 3 equiv of the powder of K_2CO_3, in ethyl acetate, at around 5 °C for 2 h; (c) 0.25 equiv of DBU in acetonitrile, refluxing for 6 h; (d) catalytic amount of Pd/C, under an atmosphere of H_2, in ethanol, at room temperature for 12 h; (e) 1.2 equiv of HCl in ethyl acetate, at room temperature for 2 h; then the solvent was changed to nitromethane, refluxing for 5 h; then neutralized with a dilute aqueous solution of K_2CO_3; (f) 1.3 equiv of chloroacetyl chloride and 3 equiv of the powder of K_2CO_3, in ethyl acetate, at 5 °C to room temperature for 2 h; (g) 5 equiv of methylamine, in DMF, at room temperature for 10 h.

conditions, and the results are summarized in Table 1 (entries 5–16). As can be seen from Table 1, the best yields could be obtained by treating compounds **3a**–**3e** in acetonitrile at reflux in the presence of 0.25 equiv of DBU (entries 4, 7, 12, 14 and 16). A plausible mechanism for the base-catalyzed epimerization is proposed in Scheme 2, an enolate intermediate shown in square parentheses is involved in the epimerization. Moreover, the base-catalyzed epimerization is probably reversible, when compounds **4a** and **4b** were treated with 0.5 equiv of sodium methoxide in methanol at reflux (entries 17 and 19), or treated with 0.25 equiv

Table 1
Base-catalyzed epimerization at the C-3 position between compound **3** and compound **4**

Entry	Starting compound	Solvent	Base (equiv)	*T* (°C)	Time (h)	Product (ratio)[a]	Yield[b] (%)
1	**3a**	MeOH	CH_3ONa (0.5)	65[c]	5	**4a/3a** (74:26)	89
2	**3a**	DMSO	DBU[d] (0.5)	110	3	**4a/3a** (75:25)	90
3	**3a**	CH_3CN	DBU (0.5)	81[c]	5	**4a/3a** (75:25)	93
4	**3a**	CH_3CN	DBU (0.25)	81[c]	6	**4a/3a** (75:25)	95
5	**3b**	MeOH	CH_3ONa (0.5)	65[c]	5	**4b/3b** (71:29)	86
6	**3b**	DMSO	DBU (0.5)	110	3	**4b/3b** (76:24)	90
7	**3b**	CH_3CN	DBU (0.25)	81[c]	6	**4b/3b** (77:23)	92
8	**3b**	Toluene	DBU (1.0)	110[c]	22	**4b/3b** (69:31)	87
9	**3b**	1,4-dioxane	DBU (1.0)	101[c]	20	**4b/3b** (65:35)	85
10	**3c**	MeOH	CH_3ONa (0.5)	65[c]	5	**4c/3c** (75:25)	86
11	**3c**	DMSO	DBU (0.5)	110	3	**4c/3c** (71:29)	90
12	**3c**	CH_3CN	DBU (0.25)	81[c]	6	**4c/3c** (72:28)	91
13	**3d**	DMSO	DBU (0.5)	110	3	**4d/3d** (65:35)	88
14	**3d**	CH_3CN	DBU (0.25)	81[c]	6	**4d/3d** (70:30)	92
15	**3e**	DMSO	DBU (0.5)	110	3	**4e/3e** (76:24)	86
16	**3e**	CH_3CN	DBU (0.25)	81[c]	6	**4e/3e** (75:25)	91
17	**4a**	MeOH	CH_3ONa (0.5)	65[c]	8	**4a/3a** (74:26)	90
18	**4a**	CH_3CN	DBU (0.25)	81[c]	8	**4a/3a** (75:25)	95
19	**4b**	MeOH	CH_3ONa (0.5)	65[c]	8	**4b/3b** (71:29)	87
20	**4b**	CH_3CN	DBU (0.25)	81[c]	8	**4b/3b** (77:23)	92

[a] Determined by HPLC analysis.
[b] Combined yields isolated by flash chromatography.
[c] Under refluxing.
[d] 1,8-Diazabicyclo[5,4,0]undec-7-ene.



Scheme 2. Base-catalyzed epimerization at the C-3 position of compounds **3a**–**3e**.

of DBU in acetonitrile at reflux (entries 18 and 20), the epimerization also occurred, a mixture of **4a** and **3a**, or a mixture of **4b** and **3b**, could be obtained with almost the same ratios as that for the epimerization of **3a** (entries 1 and 4) or **3b** (entries 5 and 7).

Conformational analysis of compounds **3** and **4** explains the ratios of the product mixtures in Table 1, as shown in Figure 2; both compound **3** and compound **4** have a twist-chair conformer, but the COOMe group is axial in the conformer of compound **3**, while the COOMe group is equatorial in the conformer of compound **4**. Compound **4** is thermodynamically more stable than compound **3**, hence the base-catalyzed reversible epimerization would produce mixtures in which the more stable compounds **4a**–**4e** were major products. The less stability of compound **3** when compared with compound **4** is probably due to the repulsion between the indole ring and the axial COOMe group as depicted in Figure 2. Comparison between the ^{1}H NMR spectra of compounds **3** and **4** supports this assumption, the axial COOMe group of compound **3** exhibits a chemical shift (3.16 ppm for **3a**, 3.20 ppm for **3b**, 3.19 ppm for **3c**, 3.26 ppm for **3d** and 3.21 ppm for **3e**) at a relatively upper field due to the closeness of indole ring and COOMe, while equatorial COOMe group of compound **4** exhibits a normal chemical shift (3.48 ppm for **4a**, 3.55 ppm for **4b**, 3.53 ppm for **4c**, 3.58 ppm for **4d** and 3.54 ppm for **4e**).

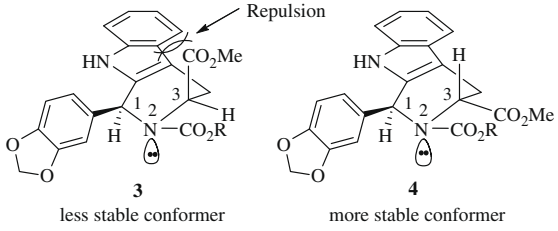


Figure 2. The twist-chair conformers of compounds **3** and **4**.

With the (1*S*,3*R*)-1,2,3-trisubstituted-tetrahydro-β-carbolines **4a**–**4e** in hand, we then attempted to remove the alkyoxycarbonyl groups at the N-2 position of compounds **4a**–**4e**. Unfortunately acidic reagents such as HCl, HBr, CF_3COOH and $SOCl_2$, which could cleave the C–N bond of alkylcarbamates,[27] did not work to give (1*S*,3*R*)-1,3-disubstituted-tetrahydro-β-carboline **5** in an acceptable yield. However, compound **4a** could be successfully converted to compound **5** in an excellent yield after reductive removal[28–30] of benzyloxycarbonyl group at the N-2 position. When pure compound **4a** was treated with a catalytic amount of Pd/C overnight at room temperature in ethanol under an atmosphere of hydrogen gas, compound **5** was obtained in nearly quantitative yield.

During the conversion of compound **3a** to compound **5**, chromatography was not necessary. When the mixture of **4a** and **3a** (75:25) was treated with catalytic amounts of Pd/C in ethanol at room temperature for 12 h under an atmosphere of hydrogen gas, the benzyloxycarbonyl group at the N-2 position in both compounds **4a** and **3a** was successfully removed, and a mixture of compounds **5** and **2** was formed in 98% yield. After recrystallization of the crude product (**5**/**2** = 75:25) in isopropanol, compound **5** could be obtained in 62% yield and with more than 99% purity.

The transformation of (1*S*,3*R*)-1,3-disubstituted-tetrahydro-β-carboline **5** to (1*R*,3*R*)-1,3-disubstituted-tetrahydro-β-carboline **6** could be carried out by first converting **5** into its hydrochloride salt **5**-HCl, and then performing a CIAT process[26,20] to afford the hydrochloride salt **6**-HCl. After neutralization of **6**-HCl, compound **6** was obtained in 92% yield. Herein, the (*S*)-configuration of C-1 of compound **5** was inversed to the (*R*)-configuration of C-1 of compound **6** during the CIAT process. This acid-catalyzed epimerization at C-1 position was very clean, and the (*R*)-configuration of C-3 of compound **5** remained intact. As shown in Figure 3, HPLC analysis

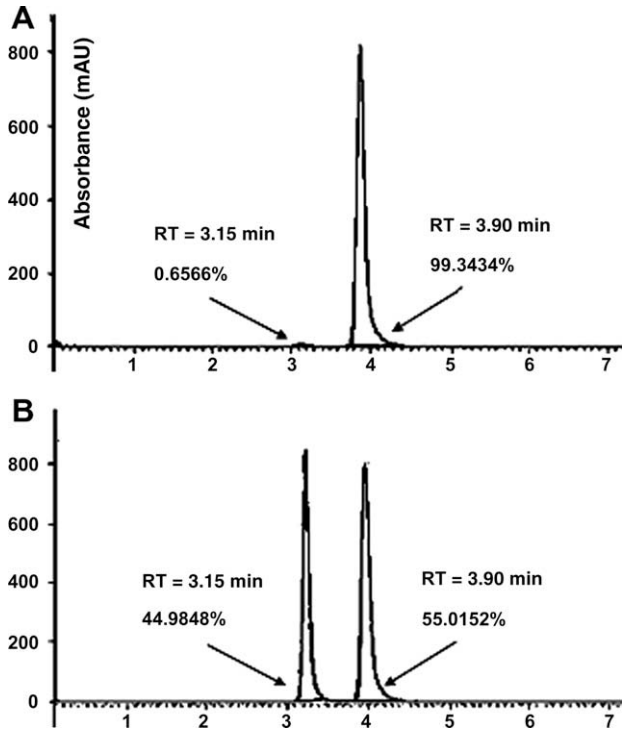


Figure 3. HPLC analysis of compound **6** by a chiral column (spectra A for compound **6**, and spectra B for a racemic mixture of compounds **6** and **2**). Conditions: Column: AS-H; Mobile phase: methanol (0.1% DEA); flow rate: 0.6 mL/min; wavelength: 214 nm.

showed that enantiomerical purity of compound **6** is 98.68% (er is 99.34:0.66).

Compound **6** was then treated with 1.3 equiv of chloroacetyl chloride in ethyl acetate in the presence of 3 equiv of the powder of K_2CO_3 to furnish compound **7** in 94% yield. Use of the powder of K_2CO_3 as the base gave a pale yellow crude solid **7**, while the use of Et_3N as the base gave a deep red crude solid **7**. Finally, compound **7** was converted into title compound **1** in 95% yield according to a known procedure,[20] and the analytical data showed that the compound **1** obtained from this synthesis is identical with the sample we obtained previously.[20]

3. Conclusion

The first synthesis of tadalafil **1** from the inexpensive L-tryptophan methyl ester hydrochloride has been discussed. The title compound **1** was obtained in 42.3% overall yield from a seven-step synthesis. A plausible mechanism for the base-catalyzed epimerization of compounds **3a**–**3e** to compounds **4a**–**4e** was proposed (Scheme 2), and it was revealed that the base-catalyzed epimerization at C-3 position is reversible, an equilibrium between compounds **3** and **4** is finally reached under reflux, and the reaction can produce a mixture of compounds **3** and **4** with the thermodynamically more stable compound **4** as the major product.

4. Experimental

4.1. General methods

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were acquired on Bruker AM-500, chemical shifts 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 (Qingdao Ocean Chemical Co. Ltd.). All reagents and solvents were analytically pure. The L-tryptophan methyl ester hydrochloride was prepared according to the same procedure as that for D-tryptophan methyl ester hydrochloride.[11]

4.2. (1*S*,3*S*)-Methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 2

To a solution of piperonal (3.33 g, 22.18 mmol) in nitromethane (50 mL), was added the powder of L-tryptophan methyl ester hydrochloride (5.14 g, 20.18 mmol). The suspension was heated to reflux and was stirred for around 5 h, and the reaction was monitored by TLC after neutralization. When the reaction was complete, the mixture was cooled down to 0 °C by an ice bath. A pale yellow solid was collected on a Buchner funnel by suction and rinsed with a small amount of nitromethane. The solid was then partitioned between ethyl acetate (100 mL) and an aqueous solution of potassium carbonate (3.60 g, 26.06 mmol) in water (40 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent under a vacuum gave a crude solid product which was purified by recrystallization in a mixed solvent of hexane and ethyl acetate (6:1) to afford compound **2** (6.71 g, 19.15 mmol) in 95% yield, mp 153–154 °C, $[\alpha]_D^{20} = -25$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (acetone- d_6) δ 2.84–2.92 (m, 1H), 3.07–3.13 (m, 1H), 3.76 (s, 3H), 3.90 (dd, J_1 = 11.2 Hz; J_2 = 4.1 Hz, 1H), 5.21 (s, 1H), 5.96 (d, J = 0.9 Hz, 1H), 5.97 (d, J = 0.8 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 1.6 Hz, 1H), 6.93 (dd, J_1 = 7.9 Hz; J_2 = 1.6 Hz, 1H), 6.96–7.05 (m, 2H), 7.24 (dd, J_1 = 7.1 Hz; J_2 = 0.9 Hz, 1H), 7.48 (dd, J_1 = 6.9 Hz; J_2 = 1.2 Hz, 1H), 8.01 (s, 1H). ^{13}C NMR (acetone-d_6) δ 174.15, 148.85, 148.48, 137.78, 136.98, 136.56, 128.27, 123.19, 122.24, 119.95, 118.87, 112.19, 109.86, 108.99, 108.66, 102.23, 59.30, 57.79, 52.59, 26.62. MS (*m*/*z*, relative intensity) 350 (M^+, 100), 333 (23), 291 (46), 274 (24), 263 (49), 233 (25), 204 (32), 169 (23), 144 (16), 115 (11), 77 (5), 44 (4). IR (KBr film) 3315, 2930, 1700, 1479, 1435, 1238, 1039, 740 cm^{-1}.

4.3. Typical procedure for preparations of (1*S*,3*S*)-1,2,3-trisubstituted-tetrahydro-β-carbolines 3a–3e

Compound **2** (3.21 g, 9.16 mmol) was dissolved in ethyl acetate (65 mL), after which powder of potassium carbonate (3.80 g, 27.49 mmol) was added. The mixture was stirred and cooled to around 5 °C by an ice bath. A solution of benzyl chloroformate (1.88 g, 11.02 mmol) in dichloromethane (10 mL) was then slowly added over 20 min. After the addition was completed, the reaction mixture was further stirred at 5 °C for 2 h. Water (50 mL) was then added, and the organic phase and the aqueous phase were separated. The organic phase was washed with brine (10 mL), and then was dried over anhydrous $MgSO_4$. Removal of the solvents by distillation under a vacuum produced a crude solid, which was purified by recrystallization in aqueous methanol (methanol/water = 9:1) to give compound **3a** (4.17 g, 8.61 mmol) in 94% yield.

Characterization data of (1*S*,3*S*)-1,2,3-trisubstituted-tetrahydro-β-carbolines **3a**–**3e** are as follows.

4.3.1. (1*S*,3*S*)-2-Benzyl 3-methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 3a

Off-white solid, mp 178–179 °C. $[\alpha]_D^{20} = +115$ (*c* 1.5, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 3.02 (dd, J_1 = 15.8 Hz, J_2 = 6.9 Hz, 1H), 3.16 (s, 3H), 3.38 (d, J = 15.7 Hz, 1H), 5.25 (s, 2H), 5.34 (d, J = 5.4 Hz, 1H), 5.96 (d, J = 1.9 Hz, 2H), 6.41 (s, 1H), 6.59 (d, J = 7.9 Hz, 1H), 6.69 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 7.02 (dd, J_1 = 7.5 Hz, J_2 = 7.2 Hz, 1H), 7.09 (dd, J_1 = 7.3 Hz, J_2 = 7.6 Hz, 1H), 7.28–7.41 (m, 6H), 7.51 (d, J = 7.7 Hz, 1H), 10.68 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.08, 155.17, 146.89, 146.52, 136.32, 133.89, 130.68, 128.17, 127.76, 127.72, 127.41, 126.26, 125.86, 121.82, 121.30, 118.54, 117.78, 111.10, 108.61, 107.33, 106.19, 100.78, 67.16, 53.47, 51.27, 51.26, 21.06. MS (EI) *m*/*z* (relative intensity) 485 (M^++1, 1), 484 (M^+, 2), 439 (1), 393 (6), 351 (3), 350 (19), 349 (100), 290 (5), 289 (20), 288 (2), 264 (5), 263 (2), 262 (4), 231 (2), 232 (2), 204 (4), 167 (1), 115 (1), 91 (8), 65 (1). IR (KBr film) 3312, 2952, 2908, 1739, 1675, 1489, 1442, 1421, 1292, 1238, 1208, 1039, 746 cm^{-1}. HRMS (EI) calcd for $C_{28}H_{24}N_2O_6$: 484.1634; found: 484.1632.

4.3.2. (1*S*,3*S*)-2-Ethyl 3-methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 3b

Obtained as a pale yellow solid in 93% yield, mp 93–94 °C. $[\alpha]_D^{20} = +132$ (*c* 0.3, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 1.28 (t, J = 7.0 Hz, 3H), 3.03 (dd, J_1 = 15.8 Hz, J_2 = 7.1 Hz, 1H), 3.20 (s, 3H), 3.38 (d, J = 15.8 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 5.29 (d, J = 5.4 Hz, 1H), 5.96 (s, 2H), 6.39 (s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.74 (s, 1H), 6.80 (d, J = 8.1 Hz, 1H), 7.02 (dd, J_1 = 7.5 Hz, J_2 = 7.3 Hz, 1H), 7.09 (dd, J_1 = 7.3 Hz, J_2 = 7.7 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 10.60 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.10, 155.17, 146.75, 146.37, 136.25, 133.94, 130.69, 125.76, 121.71, 121.14, 118.40, 117.62, 110.97, 108.47, 107.23, 106.11, 100.65, 61.52, 53.19, 51.12, 51.00, 20.92, 14.08. MS (EI) *m*/*z* (relative intensity) 423 (M^++1, 8), 422 (M^+, 30), 377 (2), 350 (18), 349 (100), 333 (5), 301 (4), 290 (6), 289 (24), 280 (5), 274 (8), 263 (4), 262 (8), 233 (2), 204 (10), 169 (6), 151 (5), 130 (2), 98 (4), 84 (4). IR (KBr film) 3394, 2981, 2951, 2904, 1741, 1694, 1489, 1440, 1413, 1302, 1237, 1039, 924, 744 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{22}N_2O_6$: 422.1478; found: 422.1491.

4.3.3. (1*S*,3*S*)-2-Isobutyl 3-methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 3c

Obtained as a pale yellow solid in 94% yield, mp 91–93 °C. $[\alpha]_D^{20} = +131$ (*c* 0.2, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 0.93 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 1.91–1.99 (m, 1H), 3.03 (dd, J_1 = 15.8 Hz, J_2 = 7.1 Hz, 1H), 3.19 (s, 3H), 3.36 (dd, J_1 = 15.8 Hz, J_2 = 2.6 Hz, 1H), 3.91–4.00 (m, 2H), 5.26 (dd, J_1 = 7.1 Hz, J_2 = 2.5 Hz, 1H), 5.95 (s, 2H), 6.38 (s, 1H), 6.64 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H), 6.74 (d, J = 1.5 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 7.02 (dd, J_1 = 7.2 Hz, J_2 = 7.1 Hz, 1H), 7.09 (dd, J_1 = 7.9 Hz, J_2 = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 10.64 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.28, 155.46, 147.02, 146.59, 136.48, 134.26, 130.99, 125.99, 121.80, 121.27, 118.56, 117.75, 111.17, 108.69, 107.33, 106.16, 100.82, 71.74, 53.48, 51.38, 51.21, 27.51, 21.18, 18.59, 18.58. MS (EI) *m/z* (relative intensity) 451 (M^++1, 6), 450 (M^+, 21), 391 (3), 377 (1), 351 (3), 350 (18), 349 (100), 333 (5), 290 (6), 289 (22), 274 (5), 263 (4), 262 (6), 233 (2), 205 (3), 204 (7), 169 (4), 115 (1), 57 (1). IR (KBr film) 3396, 2962, 1743, 1685, 1489, 1414, 1238, 1039, 744 cm^{-1}. HRMS (EI) calcd for $C_{25}H_{26}N_2O_6$: 450.1791; found: 450.1813.

4.3.4. (1*S*,3*S*)-3-Methyl 2-phenyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 3d

Obtained as an off-white solid in 96% yield, mp 111–112 °C. $[\alpha]_D^{20} = +116$ (*c* 0.3, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 3.17 (dd, J_1 = 15.8 Hz, J_2 = 7.0 Hz, 1H), 3.26 (s, 3H), 3.46 (dd, J_1 = 15.9 Hz, J_2 = 2.3 Hz, 1H), 5.48 (d, J = 5.6 Hz, 1H), 5.98 (s, 2H), 6.50 (s, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 1.3 Hz, 1H), 6.84 (d, J = 7.1 Hz, 1H), 7.04 (dd, J_1 = 7.3 Hz, J_2 = 7.1 Hz, 1H), 7.11 (dd, J_1 = 7.1 Hz, J_2 = 7.2 Hz, 1H), 7.18 (d, J = 7.7 Hz, 2H), 7.25 (dd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.42 (dd, J_1 = 7.9 Hz, J_2 = 7.9 Hz, 2H), 7.55 (d, J = 7.8 Hz, 1H), 10.68 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 170.88, 153.76, 151.00, 146.91, 146.61, 136.36, 133.56, 130.46, 129.07, 125.76, 125.18, 121.96, 121.38, 121.32, 118.54, 117.77, 111.10, 108.57, 107.44, 106.12, 100.79, 53.95, 51.71, 51.42, 20.98. MS (EI) *m/z* (relative intensity) 471 (M^++1, 11), 470 (M^+, 40), 410 (2), 378 (4), 377 (19), 350 (17), 349 (100), 334 (8), 333 (5), 317 (4), 302 (2), 291 (4), 290 (4), 289 (18), 274 (10), 263 (16), 262 (23), 233 (8), 232 (6), 205 (7), 204 (16), 169 (3), 135 (3), 102 (2), 77 (4). IR (KBr film) 3397, 2894, 1713, 1628, 1489, 1403, 1303, 1238, 1200, 1039, 746 cm^{-1}. HRMS (EI) calcd for $C_{27}H_{22}N_2O_6$: 470.1478; found: 470.1479.

4.3.5. (1*S*,3*S*)-2-*t*-Butyl 3-methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 3e

Obtained as an off-white solid in 92% yield, mp 93–95 °C. $[\alpha]_D^{20} = +122$ (*c* 1.2, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 1.48 (s, 9H), 3.01 (dd, J_1 = 15.4 Hz, J_2 = 6.2 Hz, 1H), 3.21 (s, 3H), 3.31 (d, J = 15.7 Hz, 1H), 5.19 (d, J = 6.2 Hz, 1H), 5.96 (s, 2H), 6.33 (s, 1H), 6.67 (d, J = 7.7 Hz, 1H), 6.78 (s, 1H), 6.80 (d, J = 8.1 Hz, 1H), 7.01 (dd, J_1 = 7.2 Hz, J_2 = 6.9 Hz, 1H), 7.08 (dd, J_1 = 7.8 Hz, J_2 = 7.5 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 10.67 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.45, 154.27, 146.79, 146.28, 136.20, 134.42, 131.23, 125.79, 121.43, 121.11, 118.42, 117.65, 111.01, 108.29, 107.25, 105.94, 100.66, 80.34, 53.06, 51.13, 51.12, 27.81, 21.11. MS (EI) *m/z* (relative intensity) 450 (M^+, 2), 395 (4), 394 (17), 393 (7), 377 (3), 351 (17), 350 (86), 349 (100), 335 (10), 333 (16), 301 (3), 292 (6), 291 (28), 290 (11), 289 (36), 276 (8), 274 (10), 264 (12), 263 (30), 262 (30), 233 (10), 232 (7), 204 (18), 169 (12), 144 (9), 115 (4), 102 (3), 57 (2), 41 (2). IR (KBr film) 3403, 2978, 1741, 1692, 1488, 1398, 1303, 1238, 1165, 1039, 1007, 744 cm^{-1}. HRMS (EI) calcd for $C_{25}H_{26}N_2O_6$: 450.1791; found: 450.1796.

4.4. Typical procedure for the base-catalyzed epimerization of (1*S*,3*S*)-1,2,3-trisubstituted-tetrahydro-β-carbolines 3a–3e to prepare (1*S*,3*R*)-1,2,3-tri-substituted-tetrahydro-β-carbolines 4a–4e

To a solution of compound **3a** (3.50 g, 7.22 mmol) in acetonitrile (20 mL), was added 1,8-diazabicyclo[5,4,0]undec-7-ene (275 mg, 1.81 mmol). The solution was heated to reflux, and stirring was then continued for 6 h. Removal of acetonitrile by distillation under a vacuum gave a residue, which was dissolved in toluene (60 mL). The organic phase was washed successively with 1 M aqueous HCl solution (10 mL), water (10 mL) and brine (10 mL). After the organic phase was dried over anhydrous $MgSO_4$, the solution was concentrated in vacuo to give a crude product, which was purified by chromatography to afford compound **4a** (2.50 g, 5.16 mmol) in 71.4% yield and compound **3a** (0.83 g, 1.71 mmol) in 23.7% yield.

Characterization data of (1*S*,3*R*)-1,2,3-trisubstituted-tetrahydro-β-carbolines **4a**–**4e** are as follows.

4.4.1. (1*S*,3*R*)-2-Benzyl 3-methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 4a

Off-white solid, mp 100–101 °C. $[\alpha]_D^{20} = +41$ (*c* 0.4, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 3.30 (dd, J_1 = 15.8 Hz, J_2 = 5.5 Hz, 1H), 3.35 (dd, J_1 = 15.8 Hz, J_2 = 3.7 Hz, 1H), 3.48 (s, 3H), 5.02 (d, J = 12.7 Hz, 1H), 5.08 (d, J = 4.8 Hz, 1H), 5.11 (d, J = 12.8 Hz, 1H), 5.93 (d, J = 8.2 Hz, 2H), 6.02 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 6.97 (dd, J_1 = 7.5 Hz, J_2 = 7.3 Hz, 1H), 7.03 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 7.10–7.35 (m, 6H), 7.43 (d, J = 7.8 Hz, 1H), 10.70 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.62, 155.95, 147.10, 146.14, 137.00, 136.34, 136.12, 134.11, 127.98, 127.57, 127.20, 125.79, 121.04, 119.61, 118.64, 117.62, 111.08, 107.75, 106.95, 103.62, 100.71, 66.71, 56.30, 55.26, 51.79, 22.68. MS (EI) *m/z* (relative intensity) 485 (M^++1, 3), 484 (M^+, 10), 439 (1), 393 (3), 351 (4), 350 (22), 349 (100), 290 (5), 289 (20), 264 (2), 263 (2), 262 (5), 232 (2), 205 (3), 204 (5), 169 (3), 115 (1), 91 (13), 65 (1). IR (KBr fim) 3400, 2955, 2905, 1741, 1700, 1489, 1444, 1399, 1238, 1092, 1038, 928, 744 cm^{-1}. HRMS (EI) calcd for $C_{28}H_{24}N_2O_6$: 484.1634; found: 484.1635.

4.4.2. (1*S*,3*R*)-2-Ethyl 3-methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 4b

Off-white solid, mp 89–90 °C. $[\alpha]_D^{20} = +49$ (*c* 0.4, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 1.09 (t, J = 7.0 Hz, 3H), 3.27 (dd, J_1 = 15.0 Hz, J_2 = 5.5 Hz, 1H), 3.35 (dd, J_1 = 15.0 Hz, J_2 = 4.1 Hz, 1H), 3.55 (s, 3H), 4.00–4.08 (m, 2H), 5.00 (dd, J_1 = 4.8 Hz, J_2 = 4.9 Hz, 1H), 5.93 (d, J = 5.3 Hz, 2H), 6.02 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.90 (s, 1H), 6.97 (dd, J_1 = 7.5 Hz, J_2 = 7.3 Hz, 1H), 7.04 (dd, J_1 = 7.4 Hz, J_2 = 7.6 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 10.63 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.59, 156.03, 147.01, 146.06, 136.92, 136.32, 134.08, 125.78, 120.99, 119.72, 118.59, 117.56, 111.03, 107.67, 106.97, 103.83, 100.66, 61.10, 56.14, 54.97, 51.74, 22.61, 13.86. MS (EI) *m/z* (relative intensity) 423 (M^++1, 7), 422 (M^+, 28), 377 (2), 350 (18), 349 (100), 333 (5), 313 (5), 301 (4), 290 (5), 289 (21), 274 (8), 264 (5), 263 (5), 262 (9), 239 (4), 205 (4), 204 (10), 169 (7), 144 (2), 109 (3), 95 (4), 84 (4). IR (KBr film) 3402, 2955, 1742, 1699, 1489, 1402, 1238, 1037, 744 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{22}N_2O_6$: 422.1478; found: 422.1491.

4.4.3. (1*S*,3*R*)-2-Isobutyl 3-methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 4c

White solid, mp 110–111 °C. $[\alpha]_D^{20} = +55$ (*c* 0.2, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 0.79 (d, J = 6.6 Hz, 6H), 1.73–1.81 (m, 1H), 3.29

(dd, J_1 = 15.6 Hz, J_2 = 5.4 Hz, 1H), 3.34 (dd, J_1 = 15.8 Hz, J_2 = 4.0 Hz, 1H), 3.53 (s, 3H), 3.75 (dd, J_1 = 10.4 Hz, J_2 = 6.1 Hz, 1H), 3.83 (dd, J_1 = 10.4 Hz, J_2 = 6.5 Hz, 1H), 5.04 (dd, J_1 = 5.1 Hz, J_2 = 4.5 Hz, 1H), 5.92 (d, J = 6.8 Hz, 2H), 6.00 (s, 1H), 6.79 (d, J = 8.0 Hz, 6H), 6.88 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 6.91 (d, J = 1.5 Hz, 1H), 6.96 (dd, J_1 = 7.7 Hz, J_2 = 7.1 Hz, 1H), 7.03 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 10.68 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.54, 156.05, 146.99, 145.98, 137.00, 136.22, 134.11, 125.69, 120.86, 119.39, 118.48, 117.45, 110.94, 107.61, 106.74, 103.51, 100.55, 71.21, 56.12, 55.02, 51.62, 27.12, 22.57, 18.27, 18.22. MS (EI) *m/z* (relative intensity) 451 (M^++1, 5), 450 (M^+, 19), 377 (2), 351 (3), 350 (17), 349 (100), 333 (4), 301 (1), 290 (5), 289 (17), 274 (4), 263 (4), 262 (6), 233 (2), 205 (3), 204 (7), 169 (4), 144 (1), 57 (1). IR (KBr film) 3400, 2953, 1748, 1698, 1489, 1405, 1238, 1038, 744 cm^{-1}. HRMS (EI) calcd for $C_{25}H_{26}N_2O_6$: 450.1791; found: 450.1799.

4.4.4. (1*S*,3*R*)-3-Methyl 2-phenyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 4d

White solid, mp 120–121 °C. $[\alpha]_D^{20} = +89$ (c 0.7, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 3.39 (dd, J_1 = 15.4 Hz, J_2 = 5.4 Hz, 1H), 3.45 (dd, J_1 = 15.8 Hz, J_2 = 3.5 Hz, 1H), 3.58 (s, 3H), 5.25 (d, J = 5.1 Hz, 1H), 5.94 (d, J = 9.4 Hz, 2H), 6.12 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.91–7.01 (m, 5H), 7.05 (dd, J_1 = 7.9 Hz, J_2 = 8.0 Hz, 1H), 7.19 (dd, J_1 = 7.4 Hz, J_2 = 7.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.35 (dd, J_1 = 7.8 Hz, J_2 = 8.0 Hz, 2H), 7.48 (d, J = 7.8 Hz, 1H), 10.74 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.41, 154.36, 150.62, 147.04, 146.12, 136.57, 136.29, 133.72, 128.98, 125.64, 125.09, 121.03, 121.00, 119.62, 118.60, 117.60, 111.05, 107.73, 106.87, 103.54, 100.65, 56.51, 55.62, 51.99, 22.55. MS (EI) *m/z* (relative intensity) 471 (M^++1, 11), 470 (M^+, 42), 439 (1), 411 (2), 378 (5), 377 (20), 350 (18), 349 (100), 347 (8), 334 (7), 333 (5), 317 (4), 316 (4), 315 (6), 291 (4), 290 (4), 289 (16), 274 (9), 263 (17), 262 (25), 233 (8), 232 (6), 205 (8), 204 (16), 169 (3), 135 (2), 94 (1), 77 (3). IR (KBr film) 3396, 2955, 2894, 1712, 1490, 1439, 1240, 1201, 1039, 923, 741 cm^{-1}. HRMS (EI) calcd for $C_{27}H_{22}N_2O_6$: 470.1478; found: 470.1484.

4.4.5. (1*S*,3*R*)-2-*t*-Butyl 3-methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2,3-dicarboxylate 4e

White solid, mp 108–110 °C. $[\alpha]_D^{20} = +42$ (c 0.6, $CHCl_3$). ^{1}H NMR 70 °C (DMSO-d_6) δ 1.29 (s, 9H), 3.24 (dd, J_1 = 15.4 Hz, J_2 = 5.1 Hz, 1H), 3.30 (d, J_1 = 15.3 Hz, J_2 = 2.6 Hz, 1H), 3.54 (s, 3H), 4.95 (d, J = 5.1 Hz, 1H), 5.93 (d, J = 7.5 Hz, 2H), 5.94 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 6.95 (dd, J_1 = 7.4 Hz, J_2 = 7.3 Hz, 1H), 7.02 (dd, J_1 = 7.2 Hz, J_2 = 7.7 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 10.65 (br s, NH on the indole ring, 1H). ^{13}C NMR 70 °C (DMSO-d_6) δ 171.67, 155.04, 146.94, 145.90, 137.20, 136.26, 134.23, 125.75, 120.85, 119.46, 118.47, 117.49, 110.96, 107.58, 106.83, 103.74, 100.57, 79.98, 55.98, 54.75, 51.57, 27.55, 22.55. MS (EI) *m/z* (relative intensity) 451 (M^++1, 2), 450 (M^+, 5), 394 (16), 377 (4), 351 (18), 350 (92), 349 (100), 335 (13), 334 (10), 333 (24), 301 (4), 291 (30), 290 (12), 289 (35), 276 (12), 274 (16), 264 (11), 263 (26), 262 (29), 248 (4), 233 (10), 232 (8), 229 (9), 205 (10), 204 (20), 169 (14), 148 (5), 144 (11), 115 (4), 102 (3), 57 (4). IR (KBr film) 3396, 2978, 1742, 1698, 1489, 1444, 1369, 1239, 1166, 1039, 930, 744 cm^{-1}. HRMS (EI) calcd for $C_{25}H_{26}N_2O_6$: 450.1791; found: 450.1790.

4.5. (1*S*,3*R*)-Methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 5

A solution of the mixture of compounds **4a** and **3a** (2.42 g, 4.99 mmol, **4a**/**3a** = 75:25) in ethanol (25 mL) was transferred into a three-necked round-bottomed flask, which was equipped with a gas inlet, a gas outlet and a stirrer bar, after which palladium on charcoal (10%, 250 mg) was added. The flask was purged with hydrogen gas several times, and then the mixture was stirred at room temperature under an atmosphere of hydrogen gas for 12 h. After the reaction was complete (TLC), the mixture was filtered to remove palladium on charcoal, and the filtrate was concentrated under a vacuum to give a mixture of compounds **5** and **2** (1.71 g, 4.88 mmol, **5**/**2** = 75:25) in 98% yield. The mixture of compounds **5** and **2** was recrystallized in isopropanol to afford pure compound **5** (1.09 g, 3.11 mmol) as white amorphous solid in 62% yield, mp 187–188 °C, $[\alpha]_D^{20} = +33$ (c 1.0, $CHCl_3$). ^{1}H NMR (acetone-d_6) δ 2.96–3.03 (m, 1H), 3.10–3.17 (m, 1H), 3.65 (s, 3H), 3.91 (dd, J_1 = 6.9 Hz; J_2 = 5.3 Hz, 1H), 5.34 (s, 1H), 5.94 (d, J = 0.9 Hz, 1H), 5.95 (d, J = 0.9 Hz, 1H), 6.72–6.78 (m, 2H), 6.81 (d, J = 0.8 Hz, 1H), 6.97–7.07 (m, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 9.72 (s, 1H). ^{13}C NMR (acetone-d_6) δ 174.39, 148.22, 147.51, 137.59, 137.02, 134.63, 127.53, 122.15, 121.65, 119.20, 118.22, 111.45, 109.13, 108.11, 107.67, 101.56, 54.83, 52.71, 51.72, 52.05. MS *m/z* (relative intensity) 350 (M^+, 86), 333 (34), 289 (52), 274 (39), 262 (45), 233 (44), 204 (100), 169 (58), 144 (33), 115 (34), 102 (19), 77 (10), 63 (14). IR (KBr film) 3316, 2950, 2893, 1705, 1479, 1438, 1238, 1040, 744 cm^{-1}.

4.6. (1*R*,3*R*)-Methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 6

To a solution of compound **5** (1.02 g, 2.91 mmol) in ethyl acetate (15 mL), was added concentrated hydrochloric acid (0.30 mL, 12 M, 3.60 mmol). The mixture was stirred at room temperature for 2 h, after which the solvent was removed by a rotavapor. Nitromethane (7 mL) was added, the suspension was heated to reflux, and stirring was continued for around 5 h. After the mixture was cooled to room temperature, a pale yellow solid was collected on a Buchner funnel by suction and rinsed with small amount of nitromethane. The pale yellow solid was then partitioned between ethyl acetate (30 mL) and aqueous solution of K_2CO_3 (0.51 g, 3.69 mmol) in water (10 mL), the organic phase was separated and washed with brine (10 mL) and then dried over anhydrous $MgSO_4$. Removal of solvent in vacuo gave a crude solid product which was collected on a Buchner funnel and rinsed with a mixed solvent of ethyl acetate (5 mL) and hexane (20 mL) to furnish compound **6** (0.94 g, 2.68 mmol) in 92% yield, mp 154–156 °C, $[\alpha]_D^{20} = +25$ (c 0.9, $CHCl_3$). ^{1}H NMR (acetone-d_6) δ 2.85–2.92 (m, 1H), 3.07–3.13 (m, 1H), 3.76 (s, 3H), 3.90 (dd, J_1 = 11.1 Hz; J_2 = 4.1 Hz, 1H), 5.21 (s, 1H), 5.96 (d, J = 0.9 Hz, 1H), 5.97 (d, J = 0.8 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 1.6 Hz, 1H), 6.93 (dd, J_1 = 7.9 Hz; J_2 = 1.6 Hz, 1H), 6.96–7.05 (m, 2H), 7.24 (dd, J_1 = 7.1 Hz; J_2 = 0.9 Hz, 1H), 7.48 (dd, J_1 = 6.9 Hz; J_2 = 1.2 Hz, 1H), 8.01 (s, 1H). ^{13}C NMR (acetone-d_6) δ 174.15, 148.85, 148.48, 137.78, 136.98, 136.56, 128.27, 123.19, 122.24, 119.95, 118.87, 112.19, 109.86, 108.99, 108.66, 102.23, 59.30, 57.79, 52.59, 26.62. MS *m/z* (relative intensity) 350 (M^+, 100), 333 (23), 291 (46), 274 (24), 263 (49), 233 (25), 204 (32), 169 (23), 144 (16), 115 (11), 77 (5), 44 (4). IR (KBr film) 3315, 2930, 1700, 1479, 1435, 1238, 1039, 740 cm^{-1}.

4.7. (1*R*,3*R*)-Methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-chloroacetyl)-2,3,4,9-tetra-hydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate 7

Compound **6** (0.91 g, 2.60 mmol) was dissolved in ethyl acetate (25 mL), and the powder of K_2CO_3 (1.08 g, 7.81 mmol) was added. The mixture was stirred and cooled by an ice bath to around 5 °C, a solution of chloroacetyl chloride (0.39 g, 3.45 mmol) in dichloromethane (5 mL) was slowly added over 20 min, and then the mixture was further stirred for 2 h. Water (10 mL) was added, after which the organic phase was separated and washed with brine

(10 mL). After the organic solution was dried over anhydrous $MgSO_4$, the solvents were removed by distillation in vacuo to give a crude solid which was purified by recrystallization in methanol to furnish compound **7** (1.04 g, 2.44 mmol) in 94% yield, mp 230–231 °C, $[\alpha]_D^{20} = -126$ (*c* 1.2, $CHCl_3$). ^1H NMR (DMSO-d_6) δ 3.02 (s, 3H), 3.07 (dd, J_1 = 15.8 Hz; J_2 = 6.9 Hz, 1H), 3.46 (d, J = 15.8 Hz, 1H), 4.43 (d, J = 13.9 Hz, 1H), 4.84 (d, J = 13.9 Hz, 1H), 5.20 (d, J = 6.7 Hz, 1H), 5.97 (d, J = 10.1 Hz, 2H), 6.45 (d, J = 8.1 Hz, 1H), 6.63 (s, 1H), 6.75 (s, 1H), 6.80 (d, J = 8.1 Hz, 1H), 7.02 (dd, J_1 = 7.5 Hz; J_2 = 7.4 Hz, 1H), 7.09 (dd, J_1 = 7.2 Hz; J_2 = 7.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 10.87 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 170.47, 166.87, 147.05, 146.79, 136.50, 133.65, 129.99, 125.95, 122.54, 121.66, 118.78, 118.17, 111.32, 109.28, 107.63, 106.36, 101.11, 52.44, 51.84, 51.44, 43.26, 21.14. MS *m/z* (relative intensity) 428 (M^++2, 5), 426 (M^+, 15), 391 (20), 349 (100), 331 (5), 289 (32), 274 (13), 262 (6), 231 (4), 204 (13), 169 (6), 144 (2), 115 (3), 102 (2), 77 (3). IR (KBr film) 3245, 2945, 1734, 1657, 1501, 1486, 1435, 1414, 1309, 1285, 1236, 1211, 1157, 1037, 934, 870, 806, 745, 692 cm^{-1}.

4.8. (6*R*,12a*R*)-6-(Benzo[*d*][1,3]dioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione 1

Compound **7** (1.02 g, 2.39 mmol) was converted into title compound **1** (884 mg, 2.27 mmol) as an off-white solid in 95% yield according to a known procedure,[20] mp 301–302 °C (lit.[10] 302–303 °C), $[\alpha]_D^{20} = +71$ (*c* 1.2, $CHCl_3$) {lit.[10] $[\alpha]_D^{20} = +71$ (*c* 1.0, $CHCl_3$)}. ^1H NMR (lit.[20]) (DMSO-d_6) δ 2.92 (s, 3H), 2.96 (dd, J_1 = 11.8 Hz; J_2 = 15.8 Hz, 1H), 3.51 (dd, J_1 = 4.5 Hz; J_2 = 15.8 Hz, 1H), 3.94 (d, J = 17.1 Hz, 1H), 4.17 (d, J = 17.2 Hz, 1H), 4.39 (dd, J_1 = 4.2 Hz; J_2 = 11.6 Hz, 1H), 5.91 (s, 2H), 6.12 (s, 1H), 6.77 (s, 2H), 6.86 (s, 1H), 6.99 (dd, J_1 = 7.8 Hz; J_2 = 7.1 Hz, 1H), 7.05 (dd, J_1 = 7.8 Hz; J_2 = 7.2 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.54 (d, 7.9 Hz, 1H), 11.02 (s, NH on the indole ring). ^{13}C NMR (lit.[20]) (DMSO-d_6) δ 166.88, 166.56, 147.06, 146.08, 137.00, 136.23, 133.96, 125.78, 121.25, 119.34, 118.89, 118.10, 111.32, 107.98, 107.00, 104.78, 100.91, 55.52, 55.34, 51.47, 32.86, 23.16. MS *m/z* (relative intensity) 390 (M^++1, 21), 389 (M^+, 100), 317 (5), 289 (7), 268 (10), 262 (37), 233 (9), 204 (9), 169 (4), 115 (1), 102 (1). IR (KBr film) 3326, 2902, 1676, 1649, 1489, 1437, 1400, 1323, 1269, 1241, 1150, 939, 922, 746 cm^{-1}. Anal. Calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79. Found: C, 68.02; H, 4.68; N, 10.76.

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