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An Efficient and General Method for the Stereodivergent Syntheses of Tadalafil-Like Tetracyclic Compounds

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A clean and general DBU-catalyzed epimerization at C-12a position of the tadalafil-like tetracyclic compounds has been fully studied. In addition, by using this clean epimerization as the key step, four stereomers of 6-d_1-tadalafil were stereodivergently synthesized from both L- and D-tryptophan methyl ester hydrochlorides and deuterated piperonal.

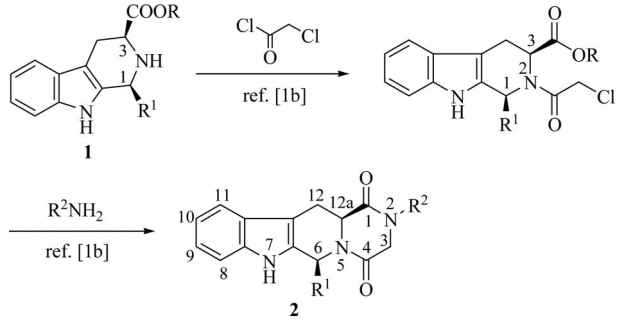
Introduction

In the recent years, the syntheses of tadalafil (Cialis®, IC351) and its analogues have aroused much interest from synthetic and medicinal chemists,[1] because it is a cGMP specific Type V phosphodiesterase (PDE5) inhibitor, and this kind of compounds could be used for the treatment of cardiovascular disease[2] and erectile dysfunction (ED).[1d,1e,3]

Although tadalafil and its analogues possess two stereogenic chiral centers at C-6 and C-12a positions in the tetracyclic scaffold, and have four stereomers with (6*R*,12a*R*), (6*R*,12a*S*), (6*S*,12a*S*) and (6*S*,12a*R*)-configurations, respectively, researches seemed to be focused on the (6*R*,12a*R*)-stereomer, while the three other stereomers were less investigated. However, many similar tetracyclic compounds, that possess different configurations of both chiral centers, exhibited various other biological activities,[4] or can be used as intermediates in the pharmaceutical syntheses.[5] Therefore, highly stereoselective syntheses of all four stereomers of tadalafil-like compounds are of considerable significance.

Results and Discussion

By using *cis* (1*S*,3*S*)- or (1*R*,3*R*)-1,3-disubstituted-tetrahydro-β-carboline **1** as starting material, which can be stereospecifically prepared from the Pictet–Spengler reaction of L-tryptophan methyl ester hydrochloride or D-tryptophan methyl ester hydrochloride with various aldehydes via a CIAT (crystallization-induced asymmetric transformation) process,[6] *cis* (6*S*,12a*S*)- or (6*R*,12a*R*)-2,6-disubstituted tadalafil-like tetracyclic compound **2** can be easily synthesized according to a known two-step procedure (Scheme 1).[1b] But synthesis of *trans* (6*S*,12a*R*)- or (6*R*,12a*S*)-tetracyclic compound **3** (Scheme 2) remains to be investigated. We have just observed an excellent transformation of tadalafil into 12a-*epi*-tadalafil (6*R*,12a*S*-stereomer) via DBU-catalyzed epimerization at C-12a position.[7] If this epimerization could be successfully applied to a variety of tetracyclic compound **2**, all four stereomers of tadalafil-like tetracyclic compounds could thus be stereodivergently synthesized from both L- and D-tryptophan (Scheme 2).



Scheme 1. Preparation of compound **2** from 1,3-disubstituted-tetrahydro-β-carboline **1**.

In order to gain a better insight into the base-catalyzed epimerization and to investigate the scope and limitation of the epimerization, all twenty tetracyclic compounds **2a**–**2t** were prepared from (1*S*,3*S*)-1,3-disubstituted-tetrahydro-β-carbolines **1** (Scheme 1), and were exposed to 0.5 equiv. of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in a mixed solvent of DMSO and ethanol (DMSO/EtOH = 1:5) at reflux. The results are summarized in Table 1. It can be seen that all the twenty *cis* tetracyclic compounds **2a**–**2t** were successfully epimerized under this condition to afford *trans* (6*S*,12a*R*)-2,6-disubstituted tetracyclic compounds **3a**–**3t** in excellent yields (Table 1, entries 1–20). Other bases such as NaOH, NaOEt and K_2CO_3 can also be used for the epimerization, but DBU gave the best yields.

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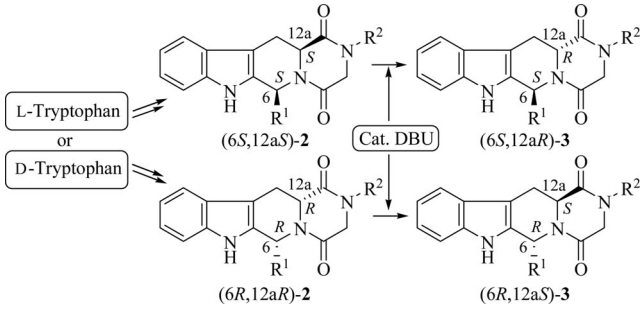


Scheme 2. Stereodivergent syntheses of all four stereomers of tadalafil and its analogues from both L- and D-tryptophan.

Table 1. The base-catalyzed epimerization at C-12a position of compound **2** to form compound **3**.[a]

Entry	2	R^1	R^2	3	% Yield[b]
1	**2a**	3,4-(OCH_2O)-C_6H_3	Et	**3a**	98
2	**2b**	3,4-(OCH_2O)-C_6H_3	Me	**3b**	98
3	**2c**	3,4-(OCH_2O)-C_6H_3	*n*Bu	**3c**	96
4	**2d**	3,4-(OCH_2O)-C_6H_3	Bn	**3d**	97
5	**2e**	3,4-(OCH_2O)-C_6H_3	2-HE[c]	**3e**	95
6	**2f**	3,4-(OCH_2O)-C_6H_3	*i*Pr	**3f**	95
7	**2g**	Me	Me	**3g**	97
8	**2h**	Me	Et	**3h**	96
9	**2i**	Me	*n*Bu	**3i**	96
10	**2j**	Me	Bn	**3j**	97
11	**2k**	3,4,5-$(OMe)_3$-C_6H_2	Me	**3k**	98
12	**2l**	3,4,5-$(OMe)_3$-C_6H_2	Et	**3l**	98
13	**2m**	*n*-Hex	Me	**3m**	97
14	**2n**	*n*-Hex	Bn	**3n**	95
15	**2o**	Ph	Et	**3o**	96
16	**2p**	Ph	Bn	**3p**	96
17	**2q**	2-OMe-C_6H_4	Me	**3q**	97
18	**2r**	2-OMe-C_6H_4	*i*Pr	**3r**	94
19	**2s**	2-OEt-C_6H_4	Bn	**3s**	95
20	**2t**	2-Cl-C_6H_4	*i*Pr	**3t**	96

[a] Condition: 0.5 equiv. of DBU, refluxing (80 °C) for 3 h in the mixed solvent of DMSO and EtOH (1:5). [b] Isolated yield. [c] 2-Hydroxyethyl.

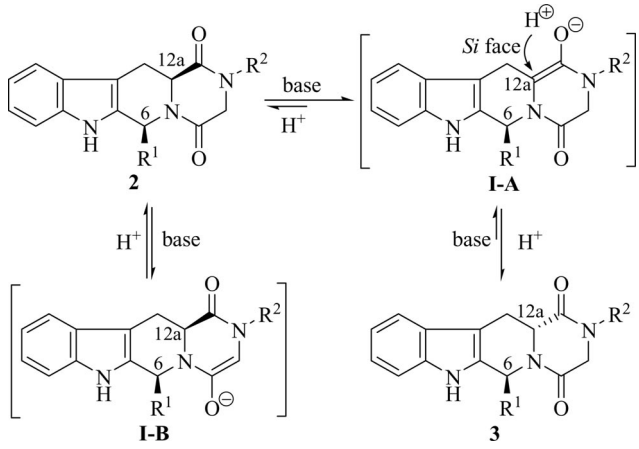
It is worthy to note that the base-catalyzed epimerization at C-3 position of 1,2,3-trisubstituted-tetrahydro-β-carbolines was reversible and gave a mixture of epimers in equilibrium,[8] but here the epimerization of compounds **2a**–**2t** was complete and gave compounds **3a**–**3t** in almost quantitative yields. Moreover, when compounds **3a**, **3b**, **3j**, **3m** and **3r** were treated with weak or strong bases in a mixture of solvents (DMSO and ethanol, 1:5) under different conditions (Table 2, Entries 1–8), no reversed epimerization was observed at all.

The base-catalyzed epimerization probably occurs via two steps (Scheme 3), the first step being the reaction of compound **2** with a base to form an enolate anion **I-A**, and the second step a protonation of the enolate **I-A** to form compound **3**. Protonation on the *Si* face of sp^2-hybrid C-12a of enolate **I-A** produces compound **3**, while protonation on the *Re* face of sp^2-hybrid C-12a of enolate **I-A** regenerates compound **2**. Another enolate **I-B** is likely formed under the same basic condition, but it does not change compound **2** after protonation.

Table 2. The reversed epimerization at C-12a position of compound **3** to form compound **2**.

Entry	3	Base (equiv.)	Conditions[a]	2	% Yield[b]
1	**3a**	DBU (2)	80 °C, 12 h	**2a**	0
2	**3a**	NaOH (0.5)	50 °C, 8 h	**2a**	0
3	**3a**	NaOEt (1)	70 °C, 8 h	**2a**	0
4	**3b**	DBU (2)	80 °C, 12 h	**2b**	0
5	**3b**	NaOEt (1)	70 °C, 8 h	**2b**	0
6	**3j**	DBU (2)	80 °C, 12 h	**2j**	0
7	**3m**	DBU (2)	80 °C, 12 h	**2m**	0
8	**3r**	DBU (2)	80 °C, 12 h	**2r**	0

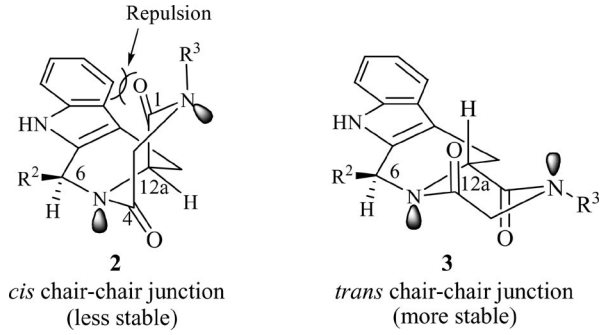
[a] In the mixed solvent of DMSO and EtOH (1:5). [b] 91–98% of compounds **3a**, **3b**, **3j**, **3m** and **3r** were recovered.



Scheme 3. A plausible mechanism for the base-catalyzed epimerization.

As can also be seen from Scheme 3, the epimerization seems to be reversible, because the enolate **I-A** can also be formed from the reaction of compound **3** with a base. But why did we not observe any evidence of the backward epimerization from compound **3** to compound **2** (Table 2)? This is probably due to the fact that there is a large energy barrier between compounds **3** and **2**, and compound **3** is much more stable than compound **2**. Comparison between the conformations of compounds **2** and **3** may support this assumption. As shown in Scheme 4, compound **2** has a more strained and less stable conformation in which the fused tetrahydro-β-carboline and piperazine have *cis* chair–chair junction, thermodynamic instability of compound **2** might be due to repulsion between a carbonyl group (C-1) and the indole ring; while compound **3** has a less strained and more stable conformation in which the fused tetrahydro-β-carboline and piperazine have *trans* chair–chair junction.

The *cis* structure of compounds **2a**–**2t** and *trans* structure of compounds **3a**–**3t** can be unequivocally determined by 2D NMR technique and NOE (nuclear Overhauser effect) analysis. For example, in the ^1H–^1H NOESY spectra of *cis* compound **2b** (Figure 1), the proton at C-6 and the proton at C-12a have an obvious correlation spot, meaning that H-6 and H-12a have *cis* relationship; while in ^1H-^1H NOESY spectra of *trans* compound **3b** (Figure 2), the proton at C-



Scheme 4. Conformations of compounds **2** and **3**.

12a does not correlate with the proton at C-6, but it correlates with the two neighboring protons on the aromatic ring at C-6 position, meaning that H-6 and H-12a have *trans* relationship.

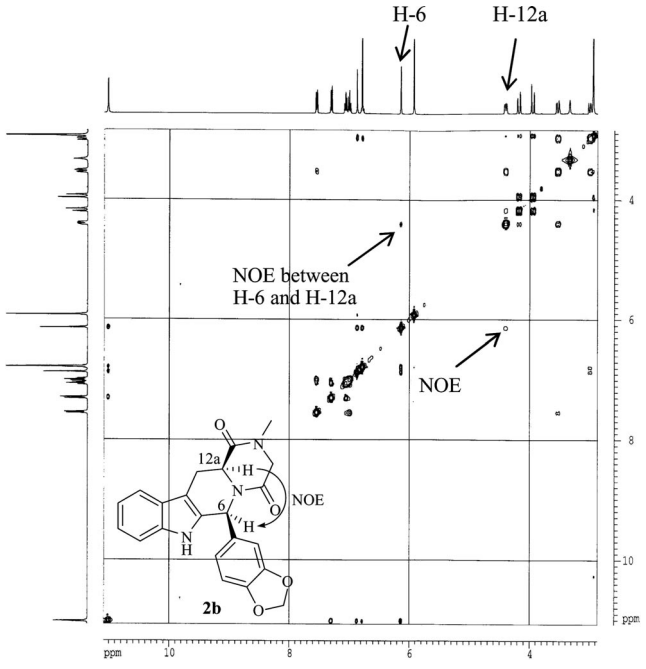


Figure 1. ^{1}H-^{1}H NOESY spectra and NOE of *cis* compound **2b**.

The clean epimerization described above provides a good and general method for stereodivergent syntheses of tadalafil-like tetracyclic compounds. For example, as depicted in Scheme 5, when we started with L-tryptophan methyl ester hydrochloride and the deuterated piperonal **4**, which was prepared as described in Scheme 6 via deprotection of a deuterated dithiane **5**, we could first obtain 1,3-disubstituted tetrahydro-β-carboline (1*S*,3*S*)-**6**. The *ent*-6-d_1-tadalafil (6*S*,12a*S*)-**7** was then obtained by following the two steps shown in Scheme 1, and 6-*epi*-6-d_1-tadalafil (6*S*,12a*S*)-**7** was finally obtained via the base-catalyzed epimerization. If we started with D-tryptophan methyl ester hydrochloride, d_1-tadalafil (6*R*,12a*R*)-**7** and 12a-*epi*-6-d_1-tadalafil (6*R*,12a*S*)-**7** could be obtained after following the

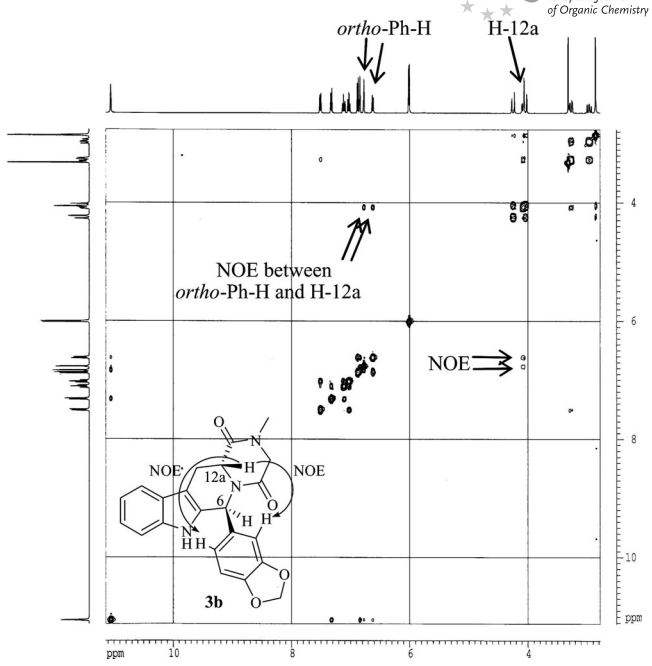
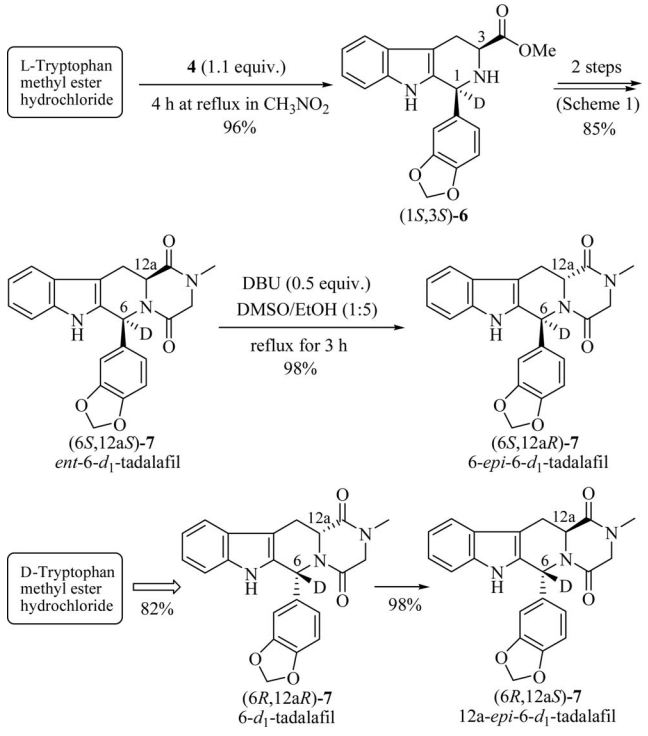


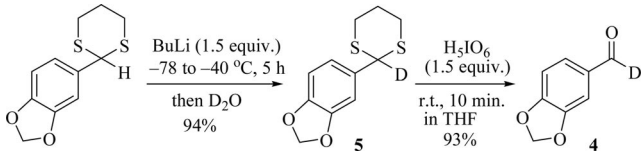
Figure 2. ^{1}H-^{1}H NOESY spectra and NOE of *trans* compound **3b**.

same sequence. Four stereomers of 6-d_1-tadalafil can thus be stereodivergently synthesized from both L- and D-tryptophan methyl ester hydrochlorides.



Scheme 5. Stereodivergent syntheses of four stereomers of 6-d_1-tadalafil from both L- and D-tryptophan methyl ester hydrochlorides.

Four deuterated compounds (6*R*,12a*R*)-**7**, (6*R*,12a*S*)-**7**, (6*S*,12a*S*)-**7** and (6*S*,12a*R*)-**7** may be quite useful for drug metabolism studies,[9] because they are optically pure, and



Scheme 6. Preparation of the deuterated piperonal **4**.

percentages of deuterium-labeling at C-6 position for each compound are higher than 99%.

Conclusions

In summary, a clean and general base-catalyzed epimerization at C-12a position of the *cis* tetracyclic compounds **2a**–**2t** was fully studied, and *trans* compounds **3a**–**3t** were obtained in excellent yields by performing the epimerization in a mixed solvent of DMSO and ethanol (1:5) at reflux in the presence of 0.5 equiv. of DBU. A plausible mechanism for the epimerization was discussed, it was revealed that the epimerization of *cis* compound **2** into *trans* compound **3** was clean and complete, and none of reverse epimerization from *trans* compound **3** to *cis* compounds **2** was detected. The wide scope of the epimerization of *cis* compound **2** into *trans* compound **3** provides an efficient and general method for stereodivergent syntheses of tadalafil-like tetracyclic compounds from both L- and D-tryptophan.

Experimental Section

General Methods: ^{1}H NMR and ^{13}C NMR spectra were acquired on Bruker AM-500, chemical shifts were given on the δ 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. Column chromatography was performed on silica gel (Qingdao Ocean Chemical Corp.). Optical rotations of chiral compounds were measured on WZZ-1S automatic polarimeter at room temperature.

General Procedure for the Base-Catalyzed Epimerization at C-12a of 2: To a solution of DBU (0.38 g, 2.50 mmol) in a mixed solvent of DMSO (3 mL) and ethanol (15 mL), was added compound **2a** (2.02 g, 5.00 mmol). The mixture was stirred and heated at reflux, and then the stirring was continued at reflux for about 3 h. After the reaction was complete, ethanol was removed by distillation under reduced pressure. The residue was cooled to room temperature, water (20 mL) was then slowly added while a vigorous stirring was continued, and off-white solid precipitated. The solid was collected on a Büchner funnel and rinsed with water. After drying in warm air, the crude product was purified by flash chromatography (eluent: $CHCl_3$/EtOAc = 4:1) to give compound **3a** (1.98 g, 4.91 mmol) in 98% yield, m.p. 267–268 °C. $[\alpha]_D^{20}$ = +278.9 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.07 (t, J = 7.2 Hz, 3 H), 2.96 (dd, J_1 = 14.3, J_2 = 12.0 Hz, 1 H), 3.22–3.32 (m, 2 H), 3.36–3.48 (m, 1 H), 4.04 (d, J = 17.7 Hz, 1 H), 4.08 (dd, J_1 = 12.7, J_2 = 4.0 Hz, 1 H), 4.28 (d, J = 17.7 Hz, 1 H), 6.01 (d, J = 4.0 Hz, 2 H), 6.62 (d, J = 8.0 Hz, 1 H), 6.77 (s, 1 H), 6.83 (s, 1 H), 6.88 (d, J = 8.0 Hz, 1 H), 7.02 (dd, J_1 = 7.3, J_2 = 7.7 Hz, 1 H), 7.11 (dd, J_1 = 7.3, J_2 = 8.0 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.52 (d, J = 7.7 Hz, 1 H), 11.05 (br. s, 1 H, NH on the indole ring) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 164.28, 162.57, 147.68, 147.30, 136.31, 132.91, 130.41, 125.97, 121.79, 121.68, 118.91, 118.13, 111.34, 108.43, 108.16, 107.58, 101.28, 52.16, 50.93, 48.38, 40.13, 26.65, 11.47 ppm. MS (EI): *m*/*z* (%) = 404 (21) [M$^+$ + 1], 403 (100) [M$^+$], 402 (7), 386 (2), 374 (2), 330 (1), 318 (4), 317 (5), 289 (7), 282 (10), 264 (6), 263 (33), 262 (30), 233 (10), 205 (4), 204 (7), 169 (4), 135 (1), 115 (1), 102 (1). IR (KBr): $\tilde{\nu}$ = 3316, 2980, 2960, 1663, 1490, 1461, 1328, 1242, 1159, 1039, 744 cm^{-1}. $C_{23}H_{21}N_3O_4$ (403.44): calcd. C 68.47, H 5.25, N 10.42; found C 68.19, H 5.14, N 10.48.

Preparation of the Deuterated Dithiane 5: 2-(1,3-Benzodioxol-5-yl)-1,3-dithiane (2.40 g, 9.99 mmol) was dissolved in absolute tetrahydrofuran (40 mL), the solution was then cooled to –78 °C under N_2 with a dry-ice bath. A solution of *n*BuLi (1.6 M, 9.5 mL, 15.20 mmol) in cyclohexane was injected into the cooled solution via syringe. The reaction temperature was kept in the range of –78 to –40 °C, and the mixture was stirred at this temperature for about 5 h. Heavy water (1 mL) was quickly added into the flask, and the reaction mixture was warmed to room temperature. Solvents were removed by a rotavapor under vacuum, the residue was then partitioned between ethyl acetate (45 mL) and water (15 mL). The organic phase was separated and washed with brine (10 mL). After drying over anhydrous $MgSO_4$, ethyl acetate was removed by distillation under vacuum to give a crude oil which was purified by flash chromatography (eluent: EtOAc/hexane = 1:6) to produce 2-(1,3-benzodioxol-5-yl)-2-deuterio-1,3-dithiane (**5**) (2.27 g, 9.41 mmol) in 94% yield, m.p. 84–85 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84–1.97 (m, 1 H), 2.12–2.20 (m, 1 H), 2.89 (dt, J_1 = 13.8, J_2 = 3.7 Hz, 2 H), 3.04 (dt, J_1 = 14.4, J_2 = 2.0 Hz, 2 H), 5.95 (s, 2 H), 6.76 (d, J = 8.0 Hz, 1 H), 6.94 (dd, J_1 = 8.0, J_2 = 1.5 Hz, 1 H), 6.98 (d, J = 1.5 Hz, 1 H) ppm. MS: *m*/*z* (%) = 243 (7) [M$^+$ + 2], 242 (10) [M$^+$ + 1], 241 (77) [M$^+$], 208 (2), 197 (4), 176 (4), 169 (5), 168 (12), 167 (100), 166 (11), 165 (37), 162 (6), 149 (3), 136 (9), 135 (5), 132 (5), 123 (5), 107 (2), 77 (1). IR (KBr): $\tilde{\nu}$ = 2889, 1606, 1501, 1486, 1439, 1354, 1279, 1247, 1102, 1042, 940, 875, 816, 806, 738 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{11}DO_2S_2$: 241.0341; found 241.0343.

Preparation of the Deuterated Piperonal 4: To a solution of compound **5** (2.20 g, 9.12 mmol) in THF (25 mL), was added periodic acid (3.12 g, 13.69 mmol) in portions. After stirring was continued at room temperature for 10 min, the reaction mixture was cooled to 0 °C with a ice bath. Ethyl acetate (80 mL) and an aqueous solution of sodium sulfite (10%, w/v, 60 mL) were added. After a vigorous stirring was continued for 10 min, the organic phase was separated and washed with an aqueous solution of sodium sulfite (10%, w/v, 30 mL) once more. Concentration of the organic solution under vacuum gave a crude product which was purified by flash chromatography (eluent: EtOAc/hexane = 1:5) to afford the deuterated piperonal **4** (1.28 g, 8.47 mmol) in 93% yield, m.p. 36–37 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.09 (s, 2 H), 6.94 (d, J = 7.9 Hz, 1 H), 7.35 (d, J = 1.2 Hz, 1 H), 7.42 (dd, J_1 = 7.9, J_2 = 1.2 Hz, 1 H) ppm. MS: *m*/*z* (%) = 152 (10) [M$^+$ + 1], 151 (100) [M$^+$], 150 (46), 149 (98), 122 (6), 121 (23), 91 (6), 65 (6), 64 (5), 63 (6), 62 (3), 53 (2). IR (KBr): $\tilde{\nu}$ = 2999, 2920, 2110, 1663, 1621, 1601, 1494, 1449, 1262, 1102, 1036, 926, 806, 619 cm^{-1}. HRMS (EI): calcd. for $C_8H_5DO_3$: 151.0380; found 151.0381.

Preparation of (1*S*,3*S*)-6: To a solution of the deuterated piperonal **4** (1.28 g, 8.47 mmol) in nitromethane (20 mL), was added L-tryptophan methyl ester hydrochloride (2.00 g, 7.85 mmol). The suspension was heated and stirred at reflux for about 4 h. Then the mixture was cooled to room temperature. A pale yellow solid was collected on a Büchner funnel by suction and rinsed with a small

amount of nitromethane. The solid was then partitioned between ethyl acetate (50 mL) and an aqueous solution of potassium carbonate (1.60 g, 11.58 mmol) in water (20 mL). The organic layer was separated and dried with anhydrous $MgSO_4$. Evaporation of the solvent under a vacuum gave a crude oil which was purified by chromatography (eluent: EtOAc/hexane = 1:4) to afford (1*S*,3*S*)-**6** (2.65 g, 7.54 mmol) as white crystals in 96% yield, m.p. 90–92 °C. $[\alpha]_D^{20}$ = –21.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.99 (dd, J_1 = 15.0, J_2 = 11.2 Hz, 1 H), 3.21 (dd, J_1 = 15.0, J_2 = 4.1 Hz, 1 H), 3.82 (s, 3 H), 3.96 (dd, J_1 = 11.1, J_2 = 4.1 Hz, 1 H), 5.95 (s, 2 H), 6.80 (d, *J* = 7.9 Hz, 1 H), 6.82 (d, *J* = 1.3 Hz, 1 H), 6.88 (dd, J_1 = 7.9, J_2 = 1.3 Hz, 1 H), 7.10–7.17 (m, 2 H), 7.23 (d, *J* = 7.7 Hz, 1 H), 7.47 (br. s, 1 H, NH on the indole ring), 7.53 (d, J_1 = 7.5 Hz, 1 H) ppm. MS (EI): *m*/*z* (%) = 352 (19) [M^+ + 1], 351 (100) [M^+], 350 (13), 349 (13), 336 (12), 334 (6), 333 (14), 293 (9), 292 (46), 291 (6), 290 (10), 289 (13), 277 (6), 274 (9), 265 (15), 264 (56), 263 (48), 249 (4), 235 (7), 234 (16), 233 (9), 230 (12), 207 (7), 206 (14), 205 (24), 170 (16), 148 (6), 145 (11), 117 (3), 103 (3), 77 (1). IR (KBr): $\tilde{\nu}$ = 3370, 2950, 1732, 1487, 1437, 1278, 1245, 1038, 742 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{17}DN_2O_4$: 351.1329; found 351.1330.

(6*S*,12a*S*)-6-(1,3-Benzodioxol-5-yl)-6-deuterio-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (6*S*,12a*S*)-7: To a solution of compound (1*S*,3*S*)-**6** (2.20 g, 6.26 mmol) in ethyl acetate (60 mL), was added powder of potassium carbonate (3.03 g, 21.92 mmol). The suspension was stirred and cooled to 0 oC with an ice-bath, and then a solution of chloroacetyl chloride (1.06 g, 9.39 mmol) in dichloromethane (5 mL) was added dropwise over 30 min. After the addition was finished, stirring was continued for about 2 h. The reaction was then quenched by adding water (30 mL). The organic layer was separated and washed with brine (10 mL), and then the organic solution was dried with anhydrous $MgSO_4$. Removal of the solvent under a vacuum gave pale yellow solid which was dissolved in DMF (25 mL), and an aqueous solution of methylamine (3.24 g, 30% w/w, 31.30 mmol). The mixture was then stirred overnight at room temperature. Water (125 mL) was added dropwise over 30 min, and white solid precipitated during the addition. The white solid was collected on a Büchner funnel and rinsed with water. The crude solid was purified by flash chromatography (eluent: $CHCl_3$/EtOAc = 4:1) to give compound (6*S*,12a*S*)-**7** (2.08 g, 5.33 mmol) as an off-white solid in 85% yield, m.p. 298–299 °C. $[\alpha]_D^{20}$ = –66.8 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 2.92 (s, 3 H), 2.96 (dd, J_1 = 15.8, J_2 = 11.7 Hz, 1 H), 3.51 (dd, J_1 = 15.8, J_2 = 4.5 Hz, 1 H), 3.94 (d, *J* = 17.0 Hz, 1 H), 4.17 (d, *J* = 17.0 Hz, 1 H), 4.39 (dd, J_1 = 11.7, J_2 = 4.5 Hz, 1 H), 5.91 (s, 2 H), 6.77 (s, 2 H), 6.86 (s, 1 H), 6.99 (dd, J_1 = 7.7, J_2 = 7.3 Hz, 1 H), 7.05 (dd, J_1 = 7.8, J_2 = 7.3 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 1 H), 7.54 (d, *J* = 7.7 Hz, 1 H), 11.03 (br. s, 1 H, NH on the indole ring) ppm. MS (EI): *m*/*z* (%) = 391 (20) [M^+ + 1], 390 (100) [M^+], 389 (7), 319 (3), 318 (5), 290 (5), 275 (3), 269 (11), 268 (6), 265 (6), 264 (32), 263 (36), 262 (7), 235 (3), 234 (11), 233 (5), 206 (6), 205 (11), 204 (3), 170 (8), 116 (1), 102 (1). IR (KBr): $\tilde{\nu}$ = 3412, 3330, 2904, 1676, 1650, 1489, 1435, 1402, 1317, 1246, 1041, 748 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{18}DN_3O_4$: 390.1438; found 390.1440.

(6*S*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-6-deuterio-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (6*S*,12a*R*)-7: To a solution of DBU (215 mg, 1.41 mmol) in a mixed solvent of DMSO (2 mL) and ethanol (10 mL), was added compound (6*S*,12a*S*)-**7** (1.10 g, 2.82 mmol). The mixture was stirred and heated to reflux. Stirring was then continued at reflux temperature for about 3 h. Ethanol was removed by distillation under a vacuum, the residue was then cooled to room temperature. Water (20 mL) was slowly added while stirring, an off-white solid precipitated. The off-white solid was collected on a Büchner funnel and rinsed with water. The crude solid was purified by flash chromatography (eluent: $CHCl_3$/EtOAc = 4:1) to afford compound (6*S*,12a*R*)-**7** (1.08 g, 2.77 mmol) in 98% yield. Off-white solid, m.p. 295–297 °C. $[\alpha]_D^{20}$ = +300.0 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, [D_6]-DMSO): δ = 2.84 (s, 3 H), 2.95 (dd, J_1 = 15.3, J_2 = 11.8 Hz, 1 H), 3.25 (dd, J_1 = 15.3, J_2 = 4.2 Hz, 1 H), 4.03 (d, *J* = 17.6 Hz, 1 H), 4.07 (dd, J_1 = 11.8, J_2 = 4.2 Hz, 1 H), 4.24 (d, *J* = 17.6 Hz, 1 H), 6.00 (d, *J* = 6.8 Hz, 2 H), 6.60 (dd, J_1 = 8.0, J_2 = 1.2 Hz, 1 H), 6.76 (d, *J* = 1.2 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.01 (dd, J_1 = 7.7, J_2 = 7.4 Hz, 1 H), 7.10 (dd, J_1 = 7.4, J_2 = 7.9 Hz, 1 H), 7.31 (d, *J* = 7.9 Hz, 1 H), 7.50 (d, *J* = 7.7 Hz, 1 H), 11.07 (br. s, 1 H, NH on the indole ring) ppm. MS (EI): *m*/*z* (%) = 391 (26) [M^+ + 1], 390 (100) [M^+], 389 (12), 361 (3), 319 (5), 318 (7), 290 (10), 269 (8), 268 (10), 265 (8), 264 (39), 263 (41), 262 (9), 234 (15), 233 (7), 206 (8), 205 (13), 170 (6), 115 (2), 102 (1). IR (KBr): $\tilde{\nu}$ = 3421, 2945, 1658, 1489, 1437, 1402, 1317, 1246, 1039, 741 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{18}DN_3O_4$: 390.1438; found 390.1432.

(6*R*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-6-deuterio-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (6*R*,12a*R*)-7: Compound (6*R*,12a*R*)-**7** was prepared in 82% yield from D-tryptophan through the same sequential procedures as that for (6*S*,12a*S*)-**7**. Off-white solid, m.p. 295–296 °C. $[\alpha]_D^{20}$ = +69.9 (*c* = 0.4, $CHCl_3$). Characterization data of (6*R*,12a*R*)-**7** is identical with that of (6*S*,12a*S*)-**7**.

(6*R*,12a*S*)-6-(1,3-Benzodioxol-5-yl)-6-deuterio-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (6*R*,12a*S*)-7: Compound (6*R*,12a*S*)-**7** was prepared from (6*R*,12a*R*)-**7** in 98% yield according to the same procedure as that for (6*S*,12a*R*)-**7**. Off-white solid, m.p. 293–294 °C. $[\alpha]_D^{20}$ = –295.1 (*c* = 0.3, $CHCl_3$). Characterization data is identical with that of (6*S*,12a*R*)-**7**.

Supporting Information (see footnote on the first page of this article): Characterization data of compounds **3b**–**3t**; ^{1}H NMR spectra of compounds **3a**–**3t**, **4**, **5**, (1*S*,3*S*)-**6**, (1*R*,3*R*)-**6**, (6*S*,12a*S*)-**7** and (6*S*,12a*R*)-**7**; ^{13}C NMR spectra of compounds **3a**, **3f**, **3h**, **3i**, **3o**, and **3q**–**3t**.

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