EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200235

Total Syntheses of Dichotomines A–D and the Stereochemical Revision of Dichotomines B–D

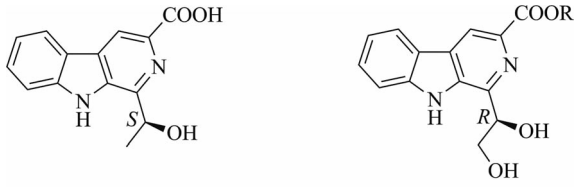
Qiang Zhang,[a] Jing Dong,[a] Xiao-Xin Shi,*[a] and Xia Lu[a]

Keywords: Total synthesis / Asymmetric synthesis / Nitrogen heterocycles / Alkaloids / Configuration determination

New asymmetric total syntheses of (–)-dichotomines A–D (**1**–**4**) starting from L-tryptophan methyl ester and 2,3-*O*-isopropylidene-D-glyceraldehyde are described. The absolute configuration of the stereogenic center of (–)-dichotomine A (**1**) was reconfirmed as (*S*), on the basis of the X-ray crystallographic analysis of the conjugate (i.e., **17**) of its methyl ester (i.e., **16**) with (*S*)-*N*-tosylproline, whereas the absolute configurations of the stereogenic centers of (–)-dichotomines B–D (**2**–**4**) were revised as (*R*).

Introduction

Dichotomines A, B, C, and D (Figure 1, **1**–**4**), four new β-carboline-type alkaloids, were first isolated by Yoshikawa and his colleagues in 2004[1] from the roots of *Stellaria dichotoma* L. var. *lanceolata* Bunge (Chinese name "Yin Chai Hu"), which are used in China as a folk medicine for the treating fevers.[2] Dichotomines A–D have shown antiallergic effects on the passive cutaneous anaphylaxis reaction in the ear and inhibitory activity on the release of β-hexosaminidase in RBL-2H3 cells. Dichotomine C has also shown inhibitory activity on the release of antigen-IgE-mediated TNF-α and IL-4 in RBL-2H3 cells.[1] To date, only dichotomine C has been synthesized, performed by Hibino and co-workers,[3] however, the other three alkaloids dichotomines A, B, and D have not been synthesized. Considering their various interesting physiological activities, we have been recently engaged in developing new synthetic approaches for dichotomines A–D and their derivatives. Herein, we disclose new asymmetric total syntheses for all of the four alkaloids dichotomines A–D, starting from L-tryptophan methyl ester and the readily available 2,3-*O*-isopropylidene-D-glyceraldehyde.



dichotomine A (**1**)

dichotomine B (**2**): R = H
dichotomine C (**3**): R = CH_3
dichotomine D (**4**): R = *n*Bu

Figure 1. Structure of dichotomines A–D.

Results and Discussion

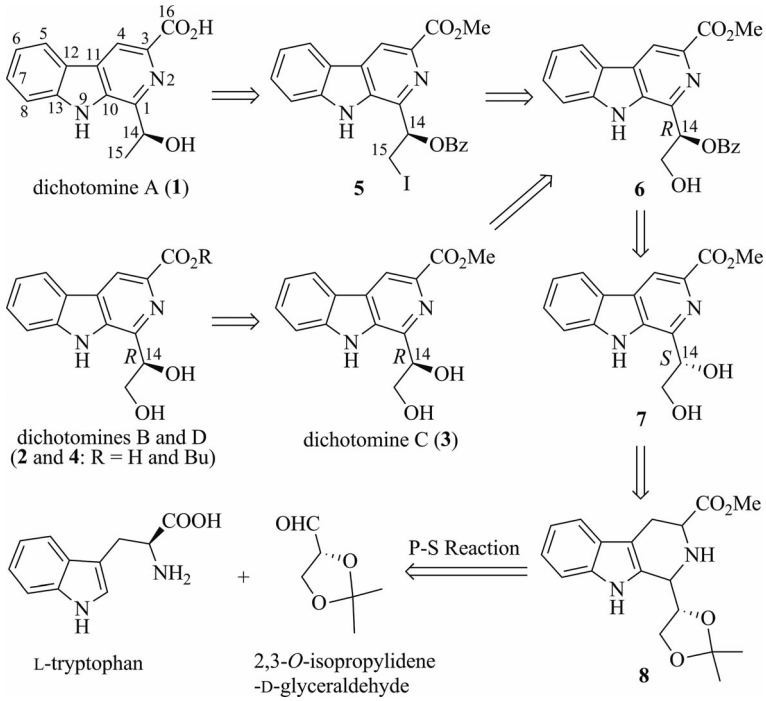
In the retrosynthetic analysis shown in Scheme 1, we speculate that dichotomine A (**1**) could be obtained from iodide **5** after dehalogenation at the terminal position (C-15) of the side chain and hydrolysis of the ester group. Dichotomines B–D (**2**–**4**) and compound **5** could be derived from compound **6**. We also speculate that compound **6** could be derived from intermediate **7** through a chiral inversion at the inner position (C-14) of the side chain, and **7** could be derived from tetrahydro-β-carboline intermediate **8** through an aromatization reaction. Intermediate **8** could be eventually obtained from a Pictet–Spengler reaction[4] of L-tryptophan methyl ester with readily available 2,3-*O*-isopropylidene-D-glyceraldehyde.[5]

As depicted in Scheme 2, our synthetic efforts began with the Pictet–Spengler reaction of L-tryptophan methyl ester[6] with 2,3-*O*-isopropylidene-D-glyceraldehyde (1.5 equiv.) in the presence of trifluoroacetic acid (TFA, 3 equiv.) in ethyl acetate. Tetrahydro-β-carboline **8** was obtained as a diastereomeric mixture of two epimers (*cis*/*trans*, 55:45) in a 94% combined yield. The mixture was used directly in the next step without the separation of the two epimers.

The reaction of compound **8** with *p*-toluenesulfonyl chloride (1.0 equiv.) and powdered potassium carbonate (3.0 equiv.) in the presence of a catalytic amount of pyridine (0.3 equiv.) in dichloromethane afforded *N*-tosyltetrahydro-β-carboline (**9**) also as a diastereomeric mixture of two epimers (*cis*/*trans*, 55:45) in a 97% combined yield. When compound **9** in anhydrous dimethyl sulfoxide was treated with

[a] Department of Pharmaceutical Engineering, School of Pharmacy, East China University of Science and Technology, 130 Mei-Long Road, Shanghai 200237, P. R. China
Fax: +86-216-4252052
E-mail: xxshi@ecust.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200235.



Scheme 1. Retrosynthetic analysis of dichotomines A–D (**1**–**4**).

an excess amount of powdered potassium carbonate (5.0 equiv.) and then stirred overnight at room temperature, a tandem β-elimination[7] and oxidative aromatization under air (O_2)[8] furnished β-carboline **10** in 88% yield. Exposing compound **10** to aqueous concentrated hydrochloric acid in tetrahydrofuran at room temperature resulted in the removal of the acetonide moiety to produce diol **7** in 91% yield.

The regioselective protection of the primary hydroxy of diol **7** by using triphenylmethyl chloride (TrCl, 1.3 equiv.) in the presence of triethylamine (2.0 equiv.) in dichloromethane afforded secondary alcohol **11** in 89% yield. A chiral inversion at the C-14 position was then achieved by treatment of secondary alcohol **11** successively with methanesulfonyl chloride (2.5 equiv.) and benzoic acid (BzOH, 5.0 equiv.) in presence of diisopropylethylamine (4.0 equiv.) in chloroform. Although intermediate **12** could not be isolated, because of its instability, benzoate **13** was obtained in 67% yield over the two steps with inversion to the (*R*) configuration (Walden inversion).[9]

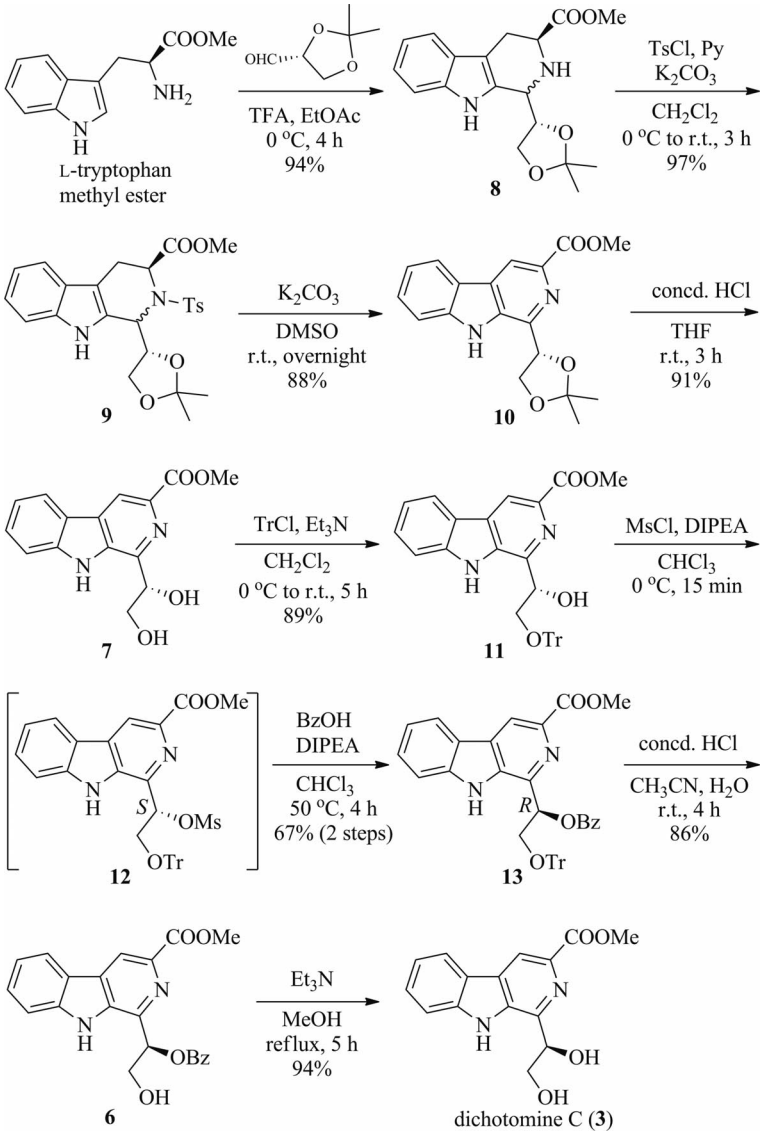
The removal of the triphenylmethyl group with concentrated hydrochloric acid in aqueous acetonitrile (CH_3CN/H_2O, 10:1) produced primary alcohol **6** in 86% yield. The methanolysis of compound **6** in refluxing methanol in the presence of triethylamine (3.0 equiv.) afforded dichotomine C (**3**) in 94% yield.

Next, dichotomines B (**2**) and D (**4**) were readily obtained from dichotomine C (**3**) after hydrolysis or transesterification reactions, respectively, as shown in Scheme 3. Dichotomine B (**2**) was obtained in 90% yield upon the treatment of dichotomine C (**3**) first with sodium hydroxide (3.0 equiv.) in aqueous methanol (CH_3OH/H_2O, 10:1) and then with acetic acid (6.0 equiv.). Dichotomine D (**4**) was obtained in 93% yield through the transesterification of dichotomine C (**3**) with butanol and potassium carbonate (0.2 equiv.) as the catalyst.

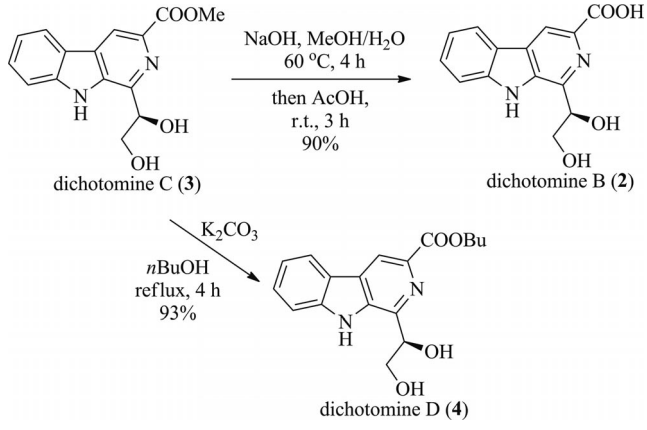
Finally, dichotomine A (**1**) was obtained through a five-step sequence of transformations as portrayed in Scheme 4. The key intermediate **6** was first exposed to methanesulfonyl chloride (2.0 equiv.) in dichloromethane in the presence of triethylamine (3.0 equiv.) to give mesylate **14** in 94% yield, which was then transformed into iodide **5** in 82% yield by means of a nucleophilic substitution of **14** with sodium iodide (5.0 equiv.) in refluxing acetone. The dehalogenation of iodide **5** at the terminal position (C-15) of the side chain was achieved by reductive hydrogenolysis with Pd/C (10%, w/w) as a catalyst, providing compound **15** in a nearly quantitative yield. The methanolysis of benzoate **15** by heating the reaction mixture to reflux in the presence of triethylamine (3.0 equiv.) afforded alcohol **16** in 92% yield. For the conclusion of the synthesis, the hydrolysis of **16** by treatment with sodium hydroxide (3.0 equiv.) in aqueous methanol furnished dichotomine A (**1**) in 93% yield.

Upon measuring the optical rotations, all of the four dichotomines A–D (**1**–**4**) obtained through the above total syntheses were found to be levorotatory. Although the absolute configurations of (–)-dichotomines A–D (**1**–**4**), isolated from the plant source, were determined by using Mosher's method in Yoshikawa's report[1] to have the (*S*) configuration, herein we reconfirm the absolute configurations of (–)-dichotomines A–D (**1**–**4**) by means of the X-ray crystallographic analysis of a conjugate (i.e., **17**) of dichotomine A methyl ester (**16**) with (*S*)-*N*-tosylproline.

As depicted in Scheme 5, the treatment of compound **16** with triethylamine (2.0 equiv.) and (*S*)-1-tosylpyrrolidine-2-carbonyl chloride (1.5 equiv.), which was readily prepared



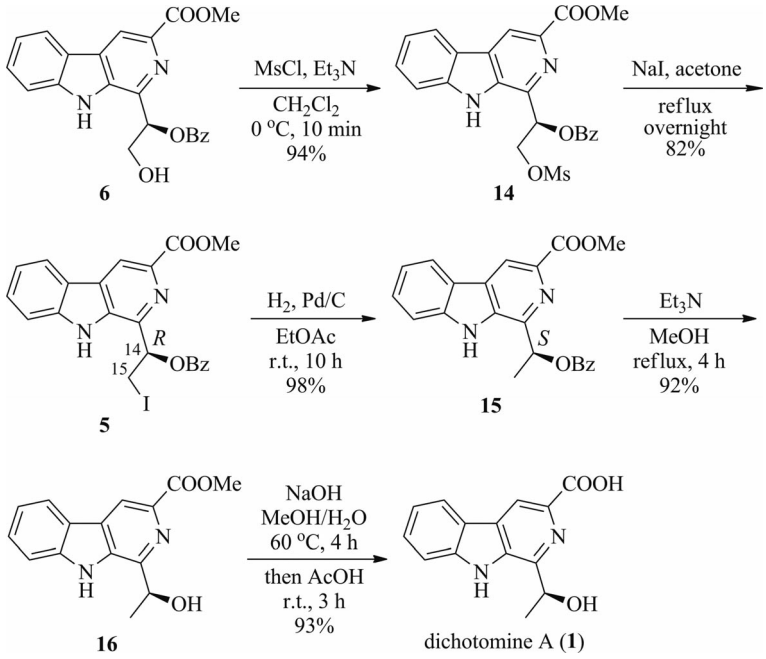
Scheme 2. Synthesis of dichotomine C (**3**).



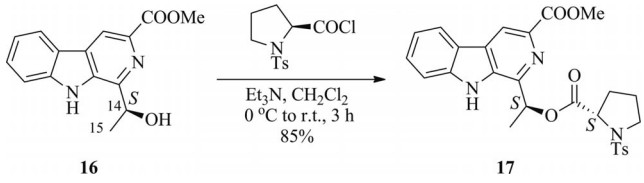
Scheme 3. Syntheses of dichotomines B (**2**) and D (**4**).

from the reaction of (*S*)-*N*-tosylproline[10] and thionyl chloride prior to use, provided **17** in 85% yield. Here, the (*S*)-*N*-tosylproline subunit was coupled with compound **16** and used as an internal reference for X-ray single crystal analysis of compound **17**. According to the ORTEP drawing of compound **17** as shown in Figure 2, the absolute configuration of the stereogenic center at the C-14 position of compound **17** was unequivocally determined as (*S*), and hence, the stereogenic centers of both dichotomine A (**1**) and its methyl ester **16** should also have the (*S*) absolute configuration.

Compounds **16** and **17** were derived from the same key intermediate **6**, and no change in the stereogenic center (C-14) was involved in these transformations as shown in Schemes 2 to 4. This means that compounds **16** and **17** as well as the four (–)-dichotomines A–D (**1**–**4**) should possess the same relative configuration at their C-14 positions. However, dichotomine A (**1**) possesses an (*S*) absolute configuration, whereas dichotomines B–D (**2**–**4**) possess the (*R*) absolute configuration because of the rearrangement in the sequence of the substituents to assign the configuration of



Scheme 4. Synthesis of dichotomine A (**1**).



Scheme 5. Preparation of compound **17** from compound **16**.

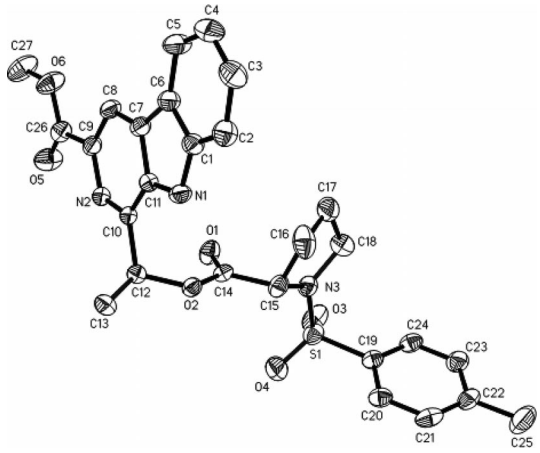


Figure 2. ORTEP drawing of compound **17**.

the stereogenic center (C-14). In Yoshikawa's report,[1] structures of dichotomines B–D (**2**–**4**) were correct, but their absolute configurations were incorrectly designated as (*S*). In Hinbino's report,[3] both the structures and absolute configurations of dichotomines B–D (**2**–**4**) were incorrect.

Conclusions

In conclusion, new asymmetric total syntheses of (–)-dichotomines A–D (**1**–**4**) starting from L-tryptophan methyl ester and 2,3-*O*-isopropylidene-D-glyceraldehyde were achieved. From these total syntheses, dichotomines A–D (**1**–**4**) were obtained in 9–13 steps and in 24%, 32%, 35%, and 33% overall yields, respectively. The absolute configuration of the stereogenic center of (–)-dichotomine A (**1**) was reconfirmed as (*S*), on the basis of the X-ray crystallographic analysis of a conjugate (i.e., **17**) of (–)-dichotomine A methyl ester (**16**) with (*S*)-*N*-tosylproline. However, the absolute configurations of the stereogenic center in (–)-dichotomines B–D (**2**–**4**) were revised as (*R*).

Experimental Section

General Methods: The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a Bruker AM-400 instrument at 400 MHz or 100 MHz. The chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. The IR spectroscopic data were recorded with a Nicolet Magna IR-550 spectrometer. The mass spectrometry data were recorded with HP5989A equipment. The optical rotations of chiral compounds were measured with a WZZ-1S polarimeter at room temperature, and the column chromatography was performed on silica gel (Qingdao Chemical Factory). All of the reagents and solvents were analytically pure and used as such without further purification. L-tryptophan methyl ester and 2,3-*O*-isopropylidene-D-glyceraldehyde were prepared according to known procedures.[7,5]

Methyl (3*S*)-1-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (8): L-Tryptophan methyl ester (15.02 g, 68.82 mmol) was dissolved in ethyl acetate

(150 mL), and the solution was cooled to 0 °C with an ice bath. After 2,3-*O*-isopropylidene-D-glyceraldehyde (13.43 g, 103.20 mmol) was added, trifluoroacetic acid (23.53 g, 206.36 mmol) was added dropwise within 30 min. The stirring was continued at 0 °C for 4 h, and then TLC showed that the reaction was complete. The reaction mixture was quenched by the addition of an aqueous solution of potassium carbonate until pH 9–10, and then the mixture was transferred to a separatory funnel. The organic layer was separated and washed with brine. The organic solution was dried with anhydrous $MgSO_4$. The solvent was evaporated under vacuum to give a crude oil which was purified by flash chromatography (EtOAc/hexane, 1:3) to produce compound **8** (21.35 g, 64.62 mmol) as an epimeric mixture (*cis*/*trans*, 55:45) in a combined yield of 94%. Data for *cis* epimer: m.p. 86.7–87.5 °C; $[\alpha]_D^{20}$ = –66.1 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, indole NH), 7.49 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.34 (d, *J* = 7.8 Hz, 1 H, 8-H), 7.16 (dd, ^1J = 7.7 Hz, ^2J = 7.3 Hz, 1 H, 6-H), 7.09 (dd, ^1J = 7.8 Hz, ^2J = 7.3 Hz, 1 H, 7-H), 4.09–4.19 (m, 3 H, 14-H and 15-H), 4.00–4.06 (m, 1 H, 1-H), 3.83 (dd, ^1J = 7.1 Hz, ^2J = 5.1 Hz, 1 H, 3-H), 3.72 (s, 3 H, $COOCH_3$), 3.09 (dd, ^1J = 15.3 Hz, ^2J = 5.0 Hz, 1 H, 4-H), 2.93 (dd, ^1J = 15.2 Hz, ^2J = 7.2 Hz, 1 H, 4-H′), 2.19 (br. s, 1 H, 2-H), 1.57 (s, 3 H, CCH_3), 1.37 (s, 3 H, CCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2 (*C*OOMe), 136.1 (Ar), 133.4 (Ar), 126.7 (Ar), 121.9 (Ar), 119.3 (Ar), 118.1 (Ar), 111.1 (Ar), 109.9 (Ar), 107.5 [$C(CH_3)_2$], 78.6 (C-14), 68.1 (C-15), 53.4 (C-1), 52.7 (C-3), 52.2 ($COOCH_3$), 27.1 (C-4), 25.4 (CCH_3), 25.3 (CCH_3) ppm. HRMS (ESI): calcd. for $C_{18}H_{23}N_2O_4$ [M + H]$^+$ 331.1658; found 331.1665. IR (KBr film): $\tilde{\nu}$ = 3376 (N–H), 2985, 2953, 1711 (C=O), 1445, 1373, 1212, 1154, 1053, 865, 744 cm^{-1}. Data for *trans* epimer: m.p. 86.7–87.5 °C; $[\alpha]_D^{20}$ = –12.3 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (s, 1 H, indole NH), 7.51 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.31 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.14–7.21 (m, 1 H, 6-H), 7.06–7.14 (m, 1 H, 7-H), 4.58–4.68 (m, 1 H, 14-H), 4.44–4.50 (m, 1 H, 15-H), 3.99–4.11 (m, 1 H, 15-H′), 3.82 (s, 3 H, $COOCH_3$), 3.71–3.79 (m, 1 H, 1-H), 3.53 (t, *J* = 8.1 Hz, 1 H, 3-H), 3.12–3.19 (m,1 H, 4-H), 2.75–2.87 (m, 1 H, 4-H′), 2.34 (br. s, 1 H, 2-H), 1.56 (s, 3 H, CCH_3), 1.41 (s, 3 H, CCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2 (*C*OOMe), 135.9 (Ar), 131.5 (Ar), 126.6 (Ar), 121.9 (Ar), 119.4 (Ar), 118.0 (Ar), 111.0 (Ar), 109.7 (Ar), 109.3 [$C(CH_3)_2$], 77.4 (C-14), 65.8 (C-15), 56.2 (C-1), 53.4 (C-3), 52.3 ($COOCH_3$), 26.4 (C-4), 25.4 (CCH_3), 24.6 (CCH_3) ppm. HRMS (ESI): calcd. for $C_{18}H_{23}N_2O_4$ [M + H]$^+$ 331.1658; found 331.1665. IR (KBr film): $\tilde{\nu}$ = 3379 (N–H), 2985, 2923, 1725 (C=O), 1688, 1460, 1434, 1360, 1246, 1218, 1159, 1087, 1007, 743 cm^{-1}.

Methyl (3*S*)-1-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (9): Compound **8** (21.34 g, 64.59 mmol) and pyridine (1.53 g, 19.34 mmol) were dissolved in dichloromethane (150 mL), and the solution was cooled to 0 °C with an ice bath. Powdered potassium carbonate (26.97 g, 195.14 mmol) was added, and then *p*-toluenesulfonyl chloride (12.44 g, 65.25 mmol) was added in portions over 30 min. The ice bath was removed, and the mixture was stirred at room temperature for 3 h. Water (75 mL) was added, and the mixture was transferred to a separatory funnel. The organic phase was separated and washed successively with an aqueous solution of HCl (1 N, 60 mL), water (40 mL), and brine (40 mL). After the organic solution was dried with anhydrous $MgSO_4$, the solvent was removed under vacuum to give a crude solid which was purified by flash chromatography (EtOAc/hexane, 1:4) to afford compound **9** (30.33 g, 62.59 mmol) as an epimeric mixture (*cis*/*trans*, 55:45) in a combined yield of 97%. Data for *cis* epimer: m.p. 155.6–156.6 °C; $[\alpha]_D^{20}$ = –66.5 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H, indole NH), 7.74 (d, *J* = 8.2 Hz, 2 H, Ar in Ts), 7.39 (d, *J* = 7.8 Hz, 1 H, 5-H), 7.30 (d, *J* = 7.8 Hz, 1 H, 8-H), 7.10–7.18 (m, 3 H, Ar), 7.06 (dd, ^1J = 7.8 Hz, ^2J = 7.3 Hz, 1 H, 7-H), 4.76 (d, *J* = 9.1 Hz, 1 H, 14-H), 4.17–4.27 (m, 1 H, 1-H), 4.01–4.12 (m, 2 H, 15-H), 3.91 (s, 3 H, $COOCH_3$), 3.51–3.67 (m, 1 H, 3-H), 3.14 (dd, ^1J = 16.2 Hz, ^2J = 12.0 Hz, 1 H, 4-H), 2.94 (dd, ^1J = 16.2 Hz, ^2J = 4.0 Hz, 1 H, 4-H′), 2.28 (s, 3 H, $ArCH_3$), 1.52 (s, 3 H, CCH_3), 1.32 (s, 3 H CCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (*C*OOMe), 144.5 (Ar), 136.6 (Ar), 136.4 (Ar), 130.9 (Ar), 129.5 (Ar), 127.9 (Ar), 126.4 (Ar), 122.4 (Ar), 119.6 (Ar), 118.3 (Ar), 111.2 (Ar), 110.4 (Ar), 109.4 [$C(CH_3)_2$], 67.7 (C-14), 57.6 (C-15), 57.4 (C-3), 53.5 (C-1), 52.8 ($COOCH_3$), 27.0 (C-4), 25.4 [$C(CH_3)_2$], 22.8 [$C(CH_3)_2$], 21.6 ($ArCH_3$) ppm. HRMS (ESI): calcd. for $C_{25}H_{29}N_2O_6S$ [M + H]$^+$ 485.1746; found 485.1748. IR (KBr film): $\tilde{\nu}$ = 3410 (N–H), 2986, 2929, 1745 (C=O), 1598, 1492, 1334, 1271, 1222, 1159, 1068, 848, 744, 670, 581 cm^{-1}. Data for *trans* epimer: m.p. 155.6–156.6 °C; $[\alpha]_D^{20}$ = +147.7 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H, indole NH), 7.77 (d, *J* = 8.2 Hz, 2 H, Ar in Ts), 7.47 (d, *J* = 7.6 Hz, 1 H, 5-H), 7.32 (d, *J* = 7.7 Hz, 1 H, 8-H), 7.27 (d, *J* = 8.2 Hz, 2 H, Ar in Ts), 7.21 (dd, ^1J = 7.6 Hz, ^2J = 7.2 Hz, 1 H, 6-H), 7.12 (dd, ^1J = 7.7 Hz, ^2J = 7.2 Hz, 1 H, 7-H), 5.34–5.38 (m, 1 H, 14-H), 5.16 (d, *J* = 5.9 Hz, 1 H, 1-H), 4.96–5.03 (m, 1 H, 15-H), 4.01 (dd, ^1J = 8.7 Hz, ^2J = 7.1 Hz, 1 H, 15-H′), 3.70 (s, 3 H, $COOCH_3$), 3.42 (d, *J* = 15.5 Hz, 1 H, 3-H), 3.18 (dd, ^1J = 8.7 Hz, ^2J = 6.6 Hz, 1 H, 4-H), 2.58–2.70 (m, 1 H, 4-H′), 2.39 (s, 3 H, $ArCH_3$), 1.66 (s, 3 H, CCH_3), 1.45 (s, 3 H, CCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (*C*OOMe), 144.1 (Ar), 136.6 (Ar), 136.1 (Ar), 130.1 (Ar), 127.5 (Ar), 127.0 (Ar), 125.9 (Ar), 122.6 (Ar), 119.6 (Ar), 118.3 (Ar), 111.2 (Ar), 108.2 (Ar), 107.0 [$C(CH_3)_2$], 79.8 (C-14), 65.6 (C-15), 53.9 (C-1), 53.8 (C-3), 52.9 ($COOCH_3$), 26.7 (C-4), 23.6 [$C(CH_3)_2$], 21.6 [$C(CH_3)_2$], 21.5 ($ArCH_3$) ppm. HRMS (ESI): calcd. for $C_{25}H_{29}N_2O_6S$ [M + H]$^+$ 485.1746; found 485.1748. IR (KBr film): $\tilde{\nu}$ = 3457 (N–H), 2984, 2925, 1742 (C=O), 1598, 1454, 1340, 1210, 1163, 1038, 847, 745, 664, 571 cm^{-1}.

Methyl (*S*)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate (10): Powdered potassium carbonate (21.56 g, 156.00 mmol) was added to a solution of compound **9** (15.00 g, 30.96 mmol) in anhydrous DMSO (dimethyl sulfoxide, 75 mL). The suspension was then stirred at room temperature for 8 h (overnight), and the reaction was monitored by TLC. When the reaction was complete, the mixture was diluted with ethyl acetate (300 mL), and then water (350 mL) was added. The mixture was transferred to a separatory funnel, and the two layers were separated. The aqueous solution was extracted with ethyl acetate (2 × 90 mL), and the combined extracts were dried with anhydrous $MgSO_4$. Evaporation of the solvent gave a crude oil that was purified by flash chromatography (EtOAc/hexane, 1:6) to furnish compound **10** (8.90 g, 27.27 mmol, 88%) as a yellow oil. $[\alpha]_D^{20}$ = +13.9 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (br. s, 1 H, indole NH), 8.84 (s, 1 H, 4-H), 8.19 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.55–7.65 (m, 2 H, 7-H and 8-H), 7.32–7.40 (m, 1 H, 6-H), 5.74 (t, *J* = 6.6 Hz, 1 H, 14-H), 4.68 (dd, ^1J = 8.6 Hz, ^2J = 6.6 Hz, 1 H, 15-H), 4.39 (dd, ^1J = 8.6 Hz, ^2J = 6.6 Hz, 1 H, 15-H′), 4.04 (s, 3 H, $COOCH_3$), 1.62 [s, 3 H, $C(CH_3)_2$], 1.58 [s, 3 H, $C(CH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5 (*C*OOMe), 142.6 (C-1), 140.4 (C-3), 136.8 (Ar), 134.9 (Ar), 129.8 (Ar), 129.0 (Ar), 121.8 (Ar), 121.4 (Ar), 120.9 (Ar), 117.4 (Ar), 112.0 (Ar), 110.7 [$C(CH_3)_2$], 78.8 (C-14), 69.3 (C-15), 52.6 ($COOCH_3$), 26.3 [$C(CH_3)_2$], 25.0 [$C(CH_3)_2$] ppm. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O_4$ [M + H]$^+$ 327.1345; found 327.1344. IR (neat): $\tilde{\nu}$ = 3410 (N–H), 2991, 1698 (C=O), 1628, 1435, 1349, 1264, 1213, 1136, 1055, 862, 752 cm^{-1}.

Methyl (*S*)-1-(1,2-Dihydroxyethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (7): To a solution of compound **10** (8.90 g, 27.27 mmol) in tetrahydrofuran (80 mL) were added water (1 mL) and concentrated hydrochloric acid (2 mL). The resulting solution was stirred at room temperature, and the reaction was monitored by TLC. After the stirring was continued at room temperature for approximately 3 h, the reaction was complete. The solution was concentrated under vacuum to remove the THF, and the residue was partitioned between ethyl acetate (80 mL) and an aqueous solution of K_2CO_3 (10%, w/w, 40 mL). The aqueous phase was then extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined and dried with anhydrous Na_2SO_4. Evaporation of the solvent under vacuum gave the crude product as a yellow solid. Recrystallization of the yellow solid in methanol afforded compound **7** (7.10 g, 24.80 mmol, 91%) as yellow crystals; m.p. 198.2–199.4 °C. $[\alpha]_D^{20}$ = +17.4 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 13.17 (s, 1 H, indole NH), 9.07 (s, 1 H, 4-H), 8.48 (d, *J* = 8.0 Hz, 1 H, 5-H), 7.85 (d, *J* = 8.2 Hz, 1 H, 8-H), 7.74 (dd, ^1J = 8.2 Hz, ^2J = 7.4 Hz, 1 H, 7-H), 7.41 (dd, ^1J = 8.0 Hz, ^2J = 7.4 Hz, 1 H, 6-H), 5.79 (t, *J* = 4.9 Hz, 1 H, 14-H), 4.08 (s, 3 H, COOC*H*$_3$), 3.97–4.17 (m, 2 H, 15-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.6 (*C*OOMe), 144.8 (C-1), 143.1 (C-3), 133.3 (Ar), 131.1 (Ar), 130.9 (Ar), 127.7 (Ar), 123.0 (Ar), 121.8 (Ar), 119.8 (Ar), 117.8 (Ar), 113.2 (Ar), 70.5 (C-14), 64.6 (C-15), 53.4 (COO*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{15}H_{15}N_2O_4$ [M + H]$^+$ 287.1032; found 287.1030. IR (KBr film): $\tilde{\nu}$ = 3257 (N–H), 3169 (O–H), 2957, 1720 (C=O), 1626, 1520, 1434, 1360, 1272, 1078, 966, 768 cm^{-1}.

Methyl (*S*)-1-[1-Hydroxy-2-(trityloxy)ethyl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (11): Compound **7** (7.05 g, 24.63 mmol) and triethylamine (4.98 g, 49.21 mmol) were dissolved in dichloromethane (70 mL), and the solution was cooled to 0 °C by an ice bath. Triphenylmethyl chloride (8.94 g, 32.07 mmol) was added in three portions over 20 min. The ice bath was removed, and the mixture was then stirred at room temperature, as the reaction was monitored by TLC. After the stirring was continued for approximately 5 h, the reaction was complete. Additional dichloromethane (100 mL) and an aqueous potassium carbonate solution (10%, w/w, 50 mL) were added, and the mixture was transferred to a separatory funnel. The two layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The extracts were combined and dried with anhydrous $MgSO_4$, and then the solvent was evaporated to give the crude product as off-white crystals, which were collected on a Büchner funnel and rinsed with a mixed solvent (ethyl acetate/hexane, 1:4) to furnish compound **11** (11.59 g, 21.93 mmol, 89%); m.p. 205.4–206.2 °C. $[\alpha]_D^{20}$ = +9.4 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1 H, indole NH), 8.76 (s, 1 H, 4-H), 8.14 (d, *J* = 7.8 Hz, 1 H, 5-H), 7.53 (dd, ^1J = 7.8 Hz, ^2J = 7.5 Hz, 1 H, 6-H), 7.32–7.40 (m, 6 H, Ar), 7.21–7.27 (m, 10 H, Ar), 7.19 (d, *J* = 8.2 Hz, 1 H, 8-H), 5.42 (t, *J* = 5.7 Hz, 1 H, 14-H), 4.70 (br. s, 1 H, O*H*), 4.00 (s, 3 H, COOC*H*$_3$), 3.82 (dd, ^1J = 9.6 Hz, ^2J = 5.7 Hz, 1 H, 15-H), 3.56 (dd, ^1J = 9.6 Hz, ^2J = 5.7 Hz, 1 H, 15-H′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6 (*C*OOMe), 143.9 (C-1), 143.3 (C-3), 140.5 (Ar), 135.7 (Ar), 135.3 (Ar), 129.3 (Ar), 128.9 (Ar), 128.6 (Ar), 128.0 (Ar), 127.3 (Ar), 121.7 (Ar), 121.4 (Ar), 120.7 (Ar), 117.2 (Ar), 112.0 (Ar), 87.8 (*C*Ph$_3$), 73.2 (C-14), 67.9 (C-15), 52.6 (COO*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{34}H_{28}N_2O_4$ [M]$^+$ 528.2049; found 528.2051. IR (KBr film): $\tilde{\nu}$ = 3422 (N–H, O–H), 3055, 2918, 1719 (C=O), 1626, 1492, 1430, 1343, 1255, 1086, 745, 707 cm^{-1}.

Methyl (*R*)-[1-(Benzoyloxy)-2-(trityloxy)ethyl]-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate (13): Compound **11** (8.59 g, 16.25 mmol) was dissolved in a chloroform (80 mL), and the solution was cooled to 0 °C with an ice bath. Methanesulfonyl chloride (4.66 g, 40.68 mmol) was added, and then DIPEA (*N*,*N*-diisopropylethylamine, 8.39 g, 64.92 mmol) was added dropwise at 0 °C over 15 min. After the addition of the reagents, TLC showed that the reaction was complete. Then, the reaction mixture was immediately quenched by the addition of an aqueous solution of potassium carbonate (15%, w/v, 40 mL). The organic phase was separated, dried with anhydrous $MgSO_4$, and filtered. To the organic solution was added benzoic acid (9.92 g, 81.23 mmol). The mixture was then heated and stirred at 50 °C for 4 h. The reaction solvent was concentrated under vacuum, and the residue was partitioned between ethyl acetate (100 mL) and an aqueous solution of potassium carbonate (15%, w/w, 75 mL). The organic layer was separated, washed with brine (10 mL), and dried with anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by chromatography (EtOAc/hexane, 1:5) to give compound **13** (6.89 g, 10.89 mmol, 67%) as a pale yellow solid; m.p. 120.3–121.9 °C. $[\alpha]_D^{20}$ = +6.1 (*c* = 1.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.51 (s, 1 H, indole NH), 8.86 (s, 1 H, 4-H), 8.18 (d, *J* = 7.9 Hz, 1 H, 5-H), 8.12 (d, *J* = 7.4 Hz, 2 H, Ar in Bz), 7.52–7.62 (m, 2 H, Ar), 7.48 (dd, ^1J = 7.8 Hz, ^2J = 7.4 Hz, 2 H, Ar in Bz), 7.31–7.40 (m, 3 H, Ar), 7.22–7.30 (m, 5 H, Ar), 7.09–7.18 (m, 9 H, Ar), 6.70 (t, *J* = 3.9 Hz, 1 H, 14-H), 4.09 (d, *J* = 3.9 Hz, 2 H, 15-H), 4.02 (s, 3 H, COOC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6 (*C*OOMe), 166.2 (Ph*C*OO), 143.3 (C-1), 140.6 (C-3), 140.5 (Ar), 137.2 (Ar), 136.2 (Ar), 133.6 (Ar), 130.0 (Ar), 129.9 (Ar), 129.8 (Ar), 129.0 (Ar), 128.7 (Ar), 128.0 (Ar), 127.2 (Ar), 121.9 (Ar), 121.6 (Ar), 121.0 (Ar), 118.1 (Ar), 112.1 (Ar), 87.5 [*C*(Ph)$_3$], 76.7 (C-14), 65.1 (C-15), 52.7 (COO*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{41}H_{32}N_2O_5$ [M]$^+$ 632.2311; found 632.2328. IR (KBr film): $\tilde{\nu}$ = 3335 (N–H), 3058, 2948, 1716 (C=O), 1626, 1598, 1493, 1449, 1350, 1262, 1108, 746, 707 cm^{-1}.

Methyl (*R*)-[1-(Benzoyloxy)-2-hydroxyethyl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (6): To a solution of compound **13** (5.80 g, 9.17 mmol) in acetonitrile (30 mL) and water (3 mL) was added concentrated hydrochloric acid (2 mL). The mixture was stirred at room temperature, and the reaction was monitored by TLC. After stirring for approximately 4 h, the reaction was complete. The reaction solution was diluted with ethyl acetate (70 mL), and an aqueous solution of potassium carbonate (15%, w/w, 30 mL) was added. The organic phase was separated and washed with brine (10 mL). The aqueous phase was then extracted with ethyl acetate (2 × 30 mL). The organic extracts were combined and dried with anhydrous Na_2SO_4. Evaporation of the solvents under vacuum gave the crude product which was purified by chromatography (EtOAc/hexane, 1:4) to give compound **6** (3.08 g, 7.89 mmol, 86%); m.p. 101.4–102.6 °C. $[\alpha]_D^{20}$ = –5.3 (*c* = 1.6, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.88 (s, 1 H, indole NH), 8.92 (s, 1 H, 4-H), 8.41 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.88 (d, *J* = 7.8 Hz, 2 H, Ar in Bz), 7.84 (d, *J* = 8.2 Hz, 1 H, 8-H), 7.56–7.67 (m, 2 H, Ar), 7.41 (dd, ^1J = 7.8 Hz, ^2J = 7.7 Hz, 2 H, Ar in Bz), 7.33 (dd, ^1J = 7.6 Hz, ^2J = 7.3 Hz, 1 H, Ar), 6.51 (d, *J* = 4.9 Hz, 1 H, O*H*), 5.57 (dd, ^1J = 10.6 Hz, ^2J = 4.7 Hz, 1 H, 14-H), 4.74–4.84 (m, 2 H, 15-H), 3.94 (s, 3 H, COOC*H*$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 166.0 (*C*OOMe), 165.7 (Ph*C*OO), 144.3 (C-1), 141.1 (C-3), 135.3 (Ar), 135.1 (Ar), 133.2 (Ar), 129.6 (Ar), 129.2 (Ar), 128.5 (Ar), 128.4 (Ar), 121.8 (Ar), 120.6 (Ar), 120.1 (Ar), 117.0 (Ar), 112.8 (Ar), 71.7 (C-14), 67.8 (C-15), 51.9 (COO*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{22}H_{18}N_2O_5$ [M]$^+$ 390.1216; found 390.1215. IR (KBr film): $\tilde{\nu}$ = 3372 (N–H, O–H), 2950, 1718 (C=O), 1626, 1498, 1434, 1350, 1263, 1111, 746, 712 cm^{-1}.

Methyl (*R*)-1-(1,2-Dihydroxyethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (3): To a solution of compound **6** (1.08 g, 2.77 mmol) in

absolute methanol (10 mL) was added triethylamine (0.84 g, 8.30 mmol). The mixture was then heated to reflux and stirred at this temperature for 5 h, and then TLC showed that the reaction was complete. The removal of the solvent under vacuum gave the crude product as an off-white solid which was collected on a Büchner funnel and rinsed with small amount of ethyl acetate (2×) to furnish dichotomine C (0.745 g, 2.60 mmol, 94%); m.p. 196.7–199.1 °C, ref.[3] m.p. 196–198 °C. $[\alpha]_D^{20}$ = –17.2 (*c* = 0.6, MeOH), ref.[1] $[\alpha]_D^{27}$ = –16.6 (*c* = 0.50, MeOH). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 11.64 (s, 1 H, indole NH), 8.83 (s, 1 H, 4-H), 8.37 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.76 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.58 (dd, ^1J = 8.0 Hz, ^2J = 7.2 Hz, 1 H, 7-H), 7.29 (dd, ^1J = 7.9 Hz, ^2J = 7.2 Hz, 1 H, 6-H), 5.90–5.93 (m, 1 H, 14-H), 5.10 (br. s, 1 H, O*H*), 4.84 (br. s, 1 H, O*H*), 3.91 (s, 3 H, COOCH_3), 3.75–4.00 (m, 2 H, 15-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.6 (*C*OOMe), 144.8 (C-1), 143.1 (C-3), 133.3 (Ar), 131.1 (Ar), 130.9 (Ar), 127.7 (Ar), 123.0 (Ar), 121.8 (Ar), 119.8 (Ar), 117.8 (Ar), 113.2 (Ar), 70.5 (C-14), 64.6 (C-15), 53.4 (COO*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{15}H_{15}N_2O_4$ [M + H]$^+$ 287.1032; found 287.1030. IR (KBr film): $\tilde{\nu}$ = 3169 (N–H, O–H), 3059, 2957, 1720 (C=O), 1626, 1434, 1360, 1078, 966, 768 cm^{-1}.

Butyl (*R*)-1-(1,2-Dihydroxyethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4): To a solution of compound **3** (0.74 g, 2.58 mmol) in *n*-butanol (10 mL) was added a catalytic amount of potassium carbonate (72 mg, 0.52 mmol). The resulting mixture was heated to reflux and stirred for approximately 4 h. After TLC showed that the reaction was complete, the reaction solution was concentrated under vacuum to remove the *n*-butanol, and the residue was dissolved in ethyl acetate (10 mL). The resulting mixture was then filtered through a thin layer of Celite to remove the catalytic amount of potassium carbonate. The solvent was evaporated to dryness, and the residue was triturated with a mixed solvent (methanol/water, 2:1). After suction filtration and drying under vacuum, dichotomine D (0.79 g, 2.41 mmol, 93%) was obtained; m.p. 199.5–200.2 °C. $[\alpha]_D^{20}$ = –2.2 (*c* = 0.8, CHCl$_3$), ref.[1] $[\alpha]_D^{27}$ = –1.8 (*c* = 0.75, CHCl$_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.80 (s, 1 H, 4-H), 8.36 (d, *J* = 7.6 Hz, 1 H, 5-H), 7.75 (d, *J* = 7.8 Hz, 1 H, 8-H), 7.57 (dd, ^1J = 7.8 Hz, ^2J = 7.3 Hz, 1 H, 7-H), 7.28 (dd, ^1J = 7.6 Hz, ^2J = 7.3 Hz, 1 H, 6-H), 5.08 (t, *J* = 7.2 Hz, 1 H, 14-H), 4.30–4.38 [m, 2 H, COOCH_2(CH$_2$)$_2$CH$_3$], 3.79–3.94 (m, 2 H, 15-H), 1.68–1.81 (m, 2 H, CO$_2$CH$_2$CH_2CH$_2$CH$_3$), 1.39–1.54 [m, 2 H, CO$_2$(CH$_2$)$_2$-CH_2CH$_3$], 0.97 [t, *J* = 7.4 Hz, 3 H, CO$_2$(CH$_2$)$_3$CH_3] ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.5 (*C*OOBu), 146.1 (C-1), 141.3 (C-3), 135.3 (Ar), 135.1 (Ar), 128.2 (Ar), 128.1 (Ar), 121.7 (Ar), 120.7 (Ar), 119.8 (Ar), 116.5 (Ar), 112.9 (Ar), 74.7 (C-14), 65.3 (C-15), 64.2 [CO$_2$*C*H$_2$(CH$_2$)$_2$CH$_3$], 30.4 (CO$_2$CH$_2$*C*H$_2$-CH$_2$CH$_3$), 18.8 [CO$_2$(CH$_2$)$_2$*C*H$_2$CH$_3$], 13.6 [CO$_2$(CH$_2$)$_3$*C*H$_3$] ppm. HRMS (ESI): calcd. for $C_{18}H_{21}N_2O_4$ [M + H]$^+$ 329.1501; found 329.1502. IR (KBr film): $\tilde{\nu}$ = 3381 (N–H), 3241 (O–H), 2953, 1698 (C=O), 1625, 1568, 1465, 1374, 1346, 1247, 1043, 751 cm^{-1}.

(*R*)-1-(1,2-Dihydroxyethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid (2): To a solution of compound **3** (0.51 g, 1.78 mmol) in methanol (6 mL) was added a solution of sodium hydroxide (0.215 g, 5.38 mmol) in water (0.6 mL). The mixture was warmed to 60 °C, and the stirring was continued at 60 °C for 4 h. After the reaction solution was cooled to room temperature, acetic acid (0.64 g, 10.66 mmol) was added dropwise. After the stirring was continued at room temperature for 3 h, the solvent was evaporated to dryness under vacuum, and the residue was triturated with absolute methanol (15 mL). The mixture was passed through a thin layer of Celite (2 cm), and the pad of Celite was washed with absolute methanol (2×). The eluents were combined and concentrated under vacuum to give the crude solid product which was triturated with a mixed solvent (EtOAc/hexane, 1:1). Filtration and rinsing with a small amount of ethyl acetate afforded dichotomine B (0.436 g, 1.60 mmol, 90%); m.p. 287.1–288.9 °C. $[\alpha]_D^{20}$ = –18.6 (*c* = 1.0, MeOH), ref.[1] $[\alpha]_D^{27}$ = –19.0 (*c* = 1.00, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.83 (s, 1 H, indole NH), 8.86 (s, 1 H, 4-H), 8.39 (d, *J* = 7.6 Hz, 1 H, 5-H), 7.76 (d, *J* = 7.8 Hz, 1 H, 8-H), 7.60 (dd, ^1J = 7.8 Hz, ^2J = 7.4 Hz, 1 H, 7-H), 7.30 (dd, ^1J = 7.6 Hz, ^1J = 7.4 Hz, 1 H, 6-H), 5.19 (t, *J* = 5.6 Hz, 1 H, 14-H), 3.82–3.92 (m, 2 H, 15-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.6 (*C*OOH), 145.2 (C-1), 141.0 (C-3), 135.6 (Ar), 134.9 (Ar), 128.5 (Ar), 121.9 (Ar), 120.7 (Ar), 120.0 (Ar), 116.0 (Ar), 112.6 (Ar), 73.6 (C-14), 65.4 (C-15) ppm. HRMS (ESI): calcd. for $C_{14}H_{13}N_2O_4$ [M + H]$^+$ 273.9875; found 273.0872. IR (KBr film): $\tilde{\nu}$ = 3254 (N–H, O–H), 3069, 2962, 2906, 1651 (C=O), 1628, 1599, 1361, 1221, 1121, 1059, 899, 767 cm^{-1}.

Methyl (*R*)-[1-(Benzoyloxy)-2-(methylsulfonyloxy)ethyl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (14): Compound **6** (4.01 g, 10.27 mmol) was dissolved in dichloromethane (40 mL), and the solution was cooled to 0 °C by an ice bath. Methanesulfonyl chloride (2.35 g, 20.51 mmol) was added, and then triethylamine (3.12 g, 30.83 mmol) was added dropwise over 10 min. After the addition was finished, TLC showed that the reaction was complete. The reaction was then immediately quenched by the addition of water (20 mL), and the mixture was transferred to a separatory funnel. The organic phase was separated and washed with an aqueous potassium carbonate solution to pH 8. The organic solution was dried with anhydrous MgSO$_4$ and concentrated to dryness to give a crude product which was purified by flash chromatography (EtOAc/hexane, 1:3) to produce compound **14** (4.52 g, 9.65 mmol, 94%); m.p. 142.1–143.3 °C. $[\alpha]_D^{20}$ = +9.0 (*c* = 0.7, CHCl$_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.34 (s, 1 H, indole NH), 8.98 (s, 1 H, 4-H), 8.43 (d, *J* = 7.6 Hz, 1 H, 5-H), 8.10 (d, *J* = 8.1 Hz, 2 H, Ar in Bz), 7.77 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.62–7.71 (m, 2 H, Ar), 7.55 (dd, ^1J = 8.1 Hz, ^2J = 7.5 Hz, 2 H, Ar in Bz), 7.35 (dd, ^1J = 7.6 Hz, ^2J = 7.2 Hz, 1 H, 6-H), 6.82 (dd, ^1J = 8.2 Hz, ^2J = 3.8 Hz, 1 H, 14-H), 5.14 (dd, ^1J = 11.0 Hz, ^2J = 8.2 Hz, 1 H, 15-H), 4.92 (dd, ^1J = 11.0 Hz, ^2J = 3.8 Hz, 1 H, 15-H′), 3.91 (s, 3 H, COOCH_3), 3.32 (s, 3 H, SO$_2$CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.6 (Ph*C*OO), 165.2 (*C*OOCH$_3$), 141.2 (C-1), 137.8 (C-3), 136.2 (Ar), 135.2 (Ar), 133.8 (Ar), 129.6 (Ar), 129.2 (Ar), 129.1 (Ar), 128.9 (Ar), 128.8 (Ar), 122.2 (Ar), 120.9 (Ar), 120.6 (Ar), 118.2 (Ar), 112.5 (Ar), 71.8 (C-14), 69.0 (C-15), 52.1 (COO*C*H$_3$), 37.0 (SO$_2$*C*H$_3$) ppm. HRMS (ESI): calcd. for $C_{23}H_{21}N_2O_7S$ [M + H]$^+$ 469.1069; found 469.1071. IR (KBr film): $\tilde{\nu}$ = 3374 (N–H), 3031, 2936, 1726 (C=O), 1702 (C=O), 1625, 1599, 1436, 1356, 1268, 1174, 1113, 965, 715 cm^{-1}.

Methyl (*R*)-[1-(Benzoyloxy)-2-iodoethyl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (5): To a solution of compound **14** (4.02 g, 8.58 mmol) in acetone (30 mL) was added sodium iodide (6.44 g, 42.96 mmol). The suspension was then heated at reflux and stirred under argon overnight. After the reaction was cooled to room temperature, the solvent was removed by distillation under vacuum, and the residue was partitioned between ethyl acetate (80 mL) and an aqueous solution of sodium sulfite (10%, w/w, 30 mL). The organic phase was separated and dried with anhydrous MgSO$_4$. After removal of the solvent, the crude product was purified by flash chromatography (EtOAc/hexane, 1:3) to give compound **5** (3.52 g, 7.04 mmol, 82%) as a white solid; m.p. 187.3–188.1 °C. $[\alpha]_D^{20}$ = +10.1 (*c* = 0.5, CHCl$_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.33 (s, 1 H, indole NH), 8.93–8.98 (m, 1 H, Ar), 8.40–8.44 (m, 1 H, 5-H and 4-H), 8.06–8.10 (m, 2 H, Ar), 7.46–7.80 (m, 5 H, Ar), 7.32–7.36 (m, 1 H, Ar), 6.64–6.70 (m, 1 H, 14-H), 3.93–3.97 (m, 2 H, 15-H), 3.90 (s, 3 H, COOCH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ =

165.6 (PhCOO), 165.0 ($COOCH_3$), 141.2 (C-1), 139.9 (C-3), 136.1 (Ar), 134.9 (Ar), 133.7 (Ar), 129.5 (Ar), 129.1 (Ar), 129.0 (Ar), 128.8 (Ar), 122.2 (Ar), 120.8 (Ar), 120.5 (Ar), 117.9 (Ar), 112.5 (Ar), 74.1 (C-14), 52.1 ($COOCH_3$), 5.0 (C-15) ppm. HRMS (ESI): calcd. for $C_{22}H_{18}IN_2O_4$ $[M + H]^+$ 501.0311; found 501.0313. IR (KBr film): $\tilde{\nu}$ = 3393 (N–H), 2922, 2852, 1730 (C=O), 1705 (C=O), 1625, 1597, 1432, 1349, 1263, 1111, 747, 712 cm^{-1}.

Methyl (*S*)-1-[1-(Benzoyloxy)ethyl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (15): A solution of compound **5** (3.02 g, 6.04 mmol) in ethyl acetate (35 mL) was placed in a three-necked round-bottomed flask, which was equipped with a magnetic stir bar, a gas inlet, and an outlet. The Pd/C catalyst (10%, 300 mg) was added, and the flask was then purged several times with hydrogen gas. The reaction mixture was vigorously stirred under an atmosphere of hydrogen gas at room temperature for 10 h. After the reaction was complete, the mixture was passed through a thin layer of Celite to remove the catalyst. Evaporation of solvent under vacuum gave a pale yellow solid which was washed several times with a mixed solvent (ethyl acetate/hexane, 1:2) to afford compound **15** (2.19 g, 5.85 mmol, 97%) as an off-white solid; m.p. 201.2–203.7 °C. $[\alpha]_D^{20}$ = –20.2 (*c* = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1 H, indole NH), 8.86 (s, 1 H, 4-H), 8.17 (d, *J* = 7.9 Hz, 1 H, 5-H), 8.08 (d, *J* = 7.7 Hz, 2 H, Ar in Bz), 7.52–7.63 (m, 3 H, Ar), 7.43 (dd, ^1J = 7.8 Hz, ^2J = 7.7 Hz, 2 H, Ar in Bz), 7.31–7.38 (m, 1 H, 6-H), 6.81 (q, *J* = 6.6 Hz, 1 H, 14-H), 4.06 (s, 3 H, $COOCH_3$), 2.02 (d, *J* = 6.6 Hz, 3 H, 15-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9 (PhCOO), 166.6 ($COOCH_3$), 142.0 (C-1), 140.6 (C-3), 137.1 (Ar), 135.4 (Ar), 133.5 (Ar), 130.2 (Ar), 129.8 (Ar), 129.7 (Ar), 129.1 (Ar), 128.6 (Ar), 121.8 (Ar), 121.7 (Ar), 121.1 (Ar), 118.0 (Ar), 112.2 (Ar), 72.3 (C-14), 52.7 ($COOCH_3$), 18.6 (C-15) ppm. HRMS (ESI): calcd. for $C_{22}H_{19}N_2O_4$ $[M + H]^+$ 375.1345; found 375.1342. IR (KBr film): $\tilde{\nu}$ = 3389 (N–H), 3063, 2927, 1704 (C=O), 1626, 1597, 1435, 1354, 1260, 1115, 1061, 744, 714 cm^{-1}.

Methyl (*S*)-1-(1-Hydroxyethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (16): To a solution of compound **15** (2.01 g, 5.37 mmol) in absolute methanol (20 mL) was added triethylamine (1.63 g, 16.11 mmol). The mixture was heated to reflux and stirred at this temperature for 4 h, and then TLC showed that the reaction was complete. The removal of the solvent under vacuum gave the crude product as an off-white solid which was triturated with a mixed solvent (EtOAc/hexane, 1:1). Filtration of the mixture and drying the solid furnished compound **16** (1.33 g, 4.92 mmol, 92%); m.p. 137.3–138.7 °C. $[\alpha]_D^{20}$ = –67.7 (*c* = 0.7, MeOH). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.71 (s, 1 H, indole NH), 8.87 (s, 1 H, 4-H), 8.35 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.83 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.56 (dd, ^1J = 8.0 Hz, ^2J = 7.5 Hz, 1 H, 7-H), 7.28 (dd, ^1J = 7.7 Hz, ^2J = 7.5 Hz, 1 H, 6-H), 5.95 (d, *J* = 3.7 Hz, 1 H, O*H*), 5.34 (q, *J* = 6.6 Hz, 1 H, 14-H), 3.94 (s, 3 H, $COOCH_3$), 1.65 (d, *J* = 6.6 Hz, 3 H, 15-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.1 ($COOCH_3$), 148.7 (C-1), 141.0 (C-3), 135.1 (Ar), 134.0 (Ar), 128.4 (Ar), 128.3 (Ar), 121.6 (Ar), 120.7 (Ar), 119.9 (Ar), 116.6 (Ar), 112.8 (Ar), 69.8 (C-14), 51.8 ($COOCH_3$), 22.6 (C-15) ppm. HRMS (ESI): calcd. for $C_{15}H_{15}N_2O_3$ $[M + H]^+$ 271.1083; found 271.1077. IR (KBr film): $\tilde{\nu}$ = 3344 (N–H), 3263 (O–H), 2968, 2926, 1715 (C=O), 1625, 1566, 1497, 1434, 1310, 1261, 1014, 758, 742 cm^{-1}.

(*S*)-1-(1-Hydroxyethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid (1): To a solution of compound **16** (1.03 g, 3.81 mmol) in methanol (10 mL) was added a solution of sodium hydroxide (0.46 g, 11.50 mmol) in water (0.6 mL). The mixture was warmed to 60 °C, and the stirring was continued at this temperature for 4 h. After the reaction solution was cooled to room temperature, acetic acid (1.37 g, 22.81 mmol) was added dropwise. After the stirring was continued at room temperature for 3 h, the solvent was evaporated to dryness under vacuum, and the residue was triturated with absolute methanol (15 mL). The mixture was passed through a thin layer of Celite (2 cm), and the pad of Celite was washed with absolute methanol (2×). The eluents were combined and concentrated under vacuum to give the crude solid product which was triturated with a mixed solvent (EtOAc/hexane = 1:1). Filtration and rinsing with a small amount of ethyl acetate afforded dichotomine A (0.91 g, 3.55 mmol, 93%) as off-white crystals; m.p. 267.3–267.7 °C. $[\alpha]_D^{20}$ = –10.1 (*c* = 1.2, MeOH), ref.[1] $[\alpha]_D^{27}$ = –9.7 (*c* = 0.85, MeOH). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 11.86 (s, 1 H, indole NH), 8.89 (s, 1 H, 4-H), 8.40 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.80 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.61 (dd, ^1J = 7.5 Hz, ^2J = 8.0 Hz, 1 H, 7-H), 7.27–7.38 (dd, ^1J = 7.9 Hz, ^2J = 7.5 Hz, 1 H, 6-H), 5.36 (q, *J* = 6.5 Hz, 1 H, 14-H), 1.63 (d, *J* = 6.5 Hz, 3 H, 15-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 172.0 (*C*OOH), 153.2 (C-1), 146.3 (C-3), 141.0 (Ar), 139.0 (Ar), 133.8 (Ar), 133.6 (Ar), 127.0 (Ar), 126.1 (Ar), 125.2 (Ar), 121.3 (Ar), 118.0 (Ar), 73.9 (C-14), 28.3 (C-15) ppm. HRMS (ESI): calcd. for $C_{14}H_{13}N_2O_3$ $[M + H]^+$ 257.0926; found 257.0920. IR (KBr film): $\tilde{\nu}$ = 3242 (N–H, O–H), 2921, 2851, 1706 (C=O), 1645, 1595, 1448, 1358, 1122, 1056, 896, 758 cm^{-1}.

Methyl {(*S*)-1-[(*S*)-1-Tosylpyrrolidine-2-carbonyloxy]ethyl}-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (17): To a solution of compound **16** (0.50 g, 1.85 mmol) in dichloromethane (8 mL) was added (*S*)-1-tosylpyrrolidine-2-carbonyl chloride (0.80 g, 2.78 mmol). After the solution was cooled to 0 °C with an ice bath, a solution of triethylamine (0.37 g, 3.66 mmol) in dichloromethane (5 mL) was added dropwise over 10 min. After the addition was finished, the ice bath was removed, and the solution was stirred at room temperature for 3 h. An aqueous solution of potassium carbonate (10%, w/w, 10 mL) was added, and the mixture was transferred to a separatory funnel. The organic phase was separated and washed successively with water (5 mL) and brine (5 mL). After the organic solution was dried with anhydrous $MgSO_4$, the solvent was removed under vacuum to give the crude solid product which was purified by flash chromatography (EtOAc/hexane, 1:6) to afford compound **17** (0.82 g, 1.57 mmol, 85%) as an off-white solid; m.p. 267.3–267.7 °C. $[\alpha]_D^{20}$ = –101 (*c* = 0.42, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 10.44 (s, 1 H, indole NH), 8.80 (s, 1 H, 4-H), 8.11 (d, *J* = 7.8 Hz, 1 H, 5-H), 7.66–7.776 (m, 3 H, Ar), 7.50 (dd, ^1J = 7.6 Hz, ^2J = 7.5 Hz, 1 H, 8-H), 7.20–7.30 (m, 3 H, 7-H, 6-H, and Ar), 6.44 (q, *J* = 6.1 Hz, 1 H, 14-H), 4.26 (d, *J* = 7.7 Hz, 1 H, OCOC*H*N), 3.98 (s, 3 H, $COOCH_3$), 3.48–3.60 (m, 1 H, NC*H*HCH$_2$CH$_2$), 3.20 (dd, ^1J = 15.5 Hz, ^2J = 8.7 Hz, 1 H, NCH*H*CH$_2$CH$_2$), 2.37 (s, 3 H, ArCH_3), 2.06–2.15 (m, 1 H, NCH$_2$C*H*HCH$_2$), 1.90–2.02 (m, 1 H, NCH$_2$CH*H*CH$_2$), 1.80 (d, *J* = 6.1 Hz, 3 H, 15-H), 1.51–1.67 (m, 2 H, NCH$_2$CH$_2$C*H*$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (*C*OOCH), 166.7 ($COOCH_3$), 144.5 (C-1), 142.9 (C-3), 141.4 (Ar), 136.3 (Ar), 134.3 (Ar), 133.4 (C-10), 130.1 (Ar), 129.0 (Ar), 127.6 (Ar), 121.4 (Ar), 121.3 (Ar), 120.7 (Ar), 117.7 (Ar), 112.9 (Ar), 76.2 (C-14), 61.0 (OCO*C*H), 52.7 (N*C*H$_2$), 49.3 ($COOCH_3$), 29.6 (NCH*C*H$_2$CH$_2$), 24.8 (NCH$_2$*C*H$_2$CH$_2$), 21.6 (ArCH_3), 19.8 (C-15) ppm. HRMS (ESI): calcd. for $C_{27}H_{28}N_3O_6S$ $[M + H]^+$ 522.1699; found 522.1698. IR (KBr film): $\tilde{\nu}$ = 3373 (N–H), 2923, 1733 (C=O), 1625, 1596, 1497, 1453, 1346, 1245, 1156, 1098, 816, 745, 665, 592 cm^{-1}.

CCDC-855428 (for **17**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Crystal data and structure refinement for compound **17**; ^{1}H and ^{13}C NMR spectra for compounds **1**–**11** and **13**–**17**.

Acknowledgments

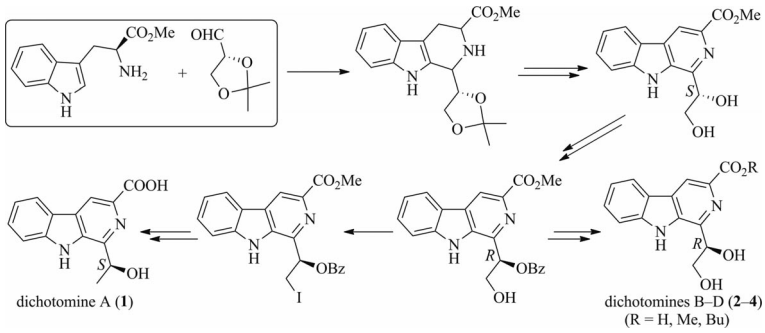
We are grateful to the National Natural Science Foundation of China (NSFC) (grant number 20972048) and the Shanghai Educational Development Foundation (grant number 03SG27) for the financial support of this work.

[1] B. Sun, T. Morikawa, H. Matsuda, S. Tewtrakul, L. J. Wu, S. Harima, M. Yoshikawa, *J. Nat. Prod.* **2004**, *67*, 1464–1469.
[2] K. Yasukawa, S. Yamanouchi, M. Takido, *Yakugaku Zasshi* **1981**, *101*, 64–66.
[3] K. Omura, T. Choshi, S. Watanabe, Y. Satoh, J. Nobuhiro, S. Hibino, *Chem. Pharm. Bull.* **2008**, *56*, 237–238.
[4] a) A. Pictet, T. Spengler, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036; b) E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797–1842; c) J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem.* **2011**, *123*, 8692–8719; *Angew. Chem. Int. Ed.* **2011**, *50*, 8538–8564; d) X.-X. Shi, S.-L. Liu, W. Xu, Y.-L. Xu, *Tetrahedron: Asymmetry* **2008**, *19*, 435–442.
[5] C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Schantz, N. L. Sear, C. S. Vianco, *J. Org. Chem.* **1991**, *56*, 4056–4058.
[6] M. W. Orme, M. J. Martinelli, C. W. Doecke, J. M. Pawlak, E. C. Chelius, World Patent WO 04/011463, **2004**; *Chem. Abstr.* **2004** ,*140*, 146170.
[7] a) D. T. Amos, A. R. Renslo, R. L. Danheiser, *J. Am. Chem. Soc.* **2003**, *125*, 4970–4971; b) T. Ishikawa, I. Manabe, T. Aikawa, T. Kudo, S. Saito, *Org. Lett.* **2004**, *6*, 2361–2364; c) K. Kitahara, T. Toma, J. Shimokawa, T. Fukuyama, *Org. Lett.* **2008**, *10*, 2259–2261.
[8] J. Dong, X.-X. Shi, J.-J. Yan, J. Xing, Q. Zhang, S. Xiao, *Eur. J. Org. Chem.* **2010**, 6987–6992.
[9] X.-X. Shi, C.-L. Shen, J.-Z. Yao, L.-D. Nie, N. Quan, *Tetrahedron: Asymmetry* **2010**, *21*, 277–284.
[10] a) M. P. Doyle, D. Shahashov, L. Zhou, P. Y. Zavalij, C. Welch, Z. Pirzada, *Organometallics* **2011**, *30*, 3619–3627; b) Z.-j. Han, R. Wang, Y.-f. Zhou, L. Liu, *Eur. J. Org. Chem.* **2005**, 934–938.

Received: February 28, 2012
Published Online: ■

Total Synthesis

Keywords: Total synthesis / Asymmetric synthesis / Nitrogen heterocycles / Alkaloids / Configuration determination



New asymmetric total syntheses of (–)-dichotomines A–D (**1**–**4**) starting from L-tryptophan methyl ester and 2,3-*O*-isopropylidene-D-glyceraldehyde are described. The absolute configuration of the stereogenic center of (–)-dichotomine A (**1**) was reconfirmed as (*S*), whereas the absolute configurations of the stereogenic centers of (–)-dichotomines B–D (**2**–**4**) were revised as (*R*).

