Stereocontrolled Synthesis of 3,6-Dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1,2-*b*]-*β*-carboline-1,4-diones

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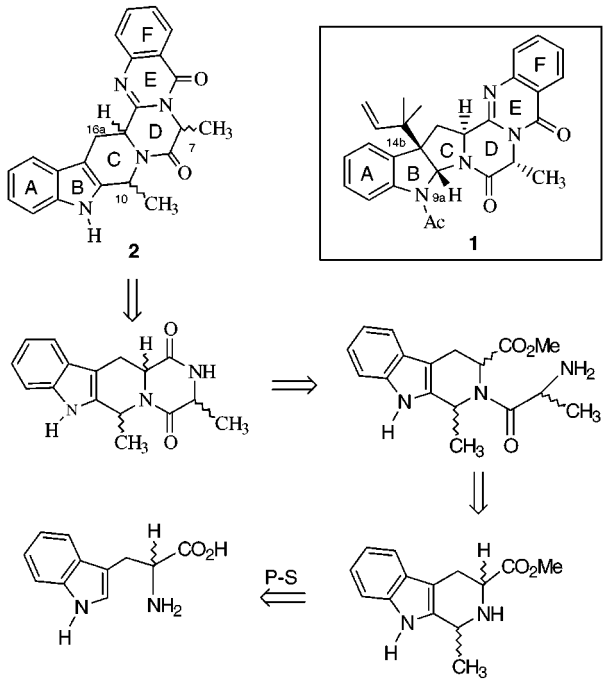
Introduction

Our current interest in MDR (multi drug resistance) reversal agents designed as analogues of the fungal metabolite *N*-acetylardeemin (**1**)[1,2] moved us to study the dehydro-C-homo analogues **2**, where rings A−C are formed by a 1,2,3,4-tetrahydro-*β*-carboline structure.

The synthesis of **2** was planned through the condensation of the corresponding tetracyclic piperazinediones with anthranilic acid (Scheme 1). The *N*-acylation of *cis*-tetrahydro-*β*-carbolines with L- or D-alanine, as well as the subsequent cyclization to the above-mentioned piperazinediones, are studied here, especially the chemical and stereochemical outcome of the cyclization step.

The diastereoselectivity of the classical Pictet−Spengler reaction to give tetrahydro-*β*-carbolines (THBCs) from L-tryptophan esters has been extensively studied.[3] According to these precedents, cis 1,3-disubstituted THBCs are the kinetically controlled products in acid conditions, while higher temperatures (thermodynamic control) lead to poor diastereoselectivity. In *cis*-THBCs, the C-1 and C-3 substituents may adopt an equatorial disposition, while in the trans isomers, a 1,3-diaxial interaction exists in either of the possible conformers. The thermodynamic stability of the trans isomers has been related to the fact that the interactions between the N_a-H group and the C-1 substituent, which would be equatorial, may be more significant than those between the axial C-1 substituent and the C-3 proton (or the C-1 proton and the C-3 substituent). This effect is obviously more significant in derivatives of N_a-substituted tryptophan esters. On the other hand, the trans isomers are exclusively formed in the reactions of N_b-benzyltryptophan esters with bulky aldehydes, such as cyclohexanecarbaldehyde or benzaldehyde,[4] probably because the *N*-benzyl substituent is locked at an equatorial configuration that makes an equatorial C-1 substituent in the cis isomers very unstable. Evidence that scission of the C(1)−N(2) bond occurs during epimerization of cis 1,3-disubstituted N_b-benzyl-1,2,3,4-tetrahydro-*β*-carbolines into their trans diastereomers under acidic conditions has been established.[5]

Scheme 1



Results and Discussion

Our first objetive was the synthesis of both enantiomers of *cis*-1-methyl-1,2,3,4-tetrahydro-*β*-carboline-3-carboxylic acid (**3**), which were prepared from L- or D-tryptophan and acetaldehyde following Brossi's procedure,[6] by using sulfuric acid as catalyst and kinetic conditions (24 h, rt). Their corresponding methyl ester hydrochlorides were obtained by treatment with thionyl chloride and dry methanol.[7] With these compounds at our disposal, the N-protected *N*-(aminoacyl)-THBCs (Table 1) were obtained by reaction of (1*S*,3*S*)-**4**·HCl (for **5** and **6**) and (1*R*,3*R*)-**4**·HCl (for **7** and **8**) with *N*-Cbz (compounds **a**) or *N*-Boc (compounds **b**) L- or D-alanine, using EDC [1-ethyl-3-[3′-(dimethylamino)propyl]carbodiimide]

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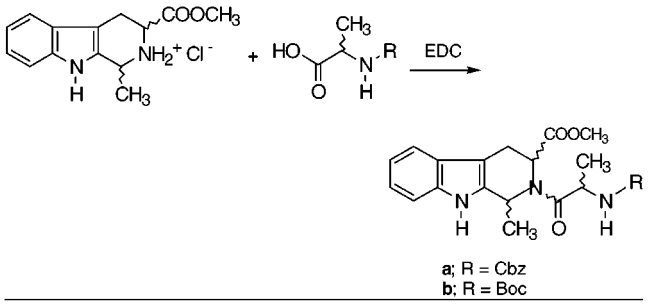
Table 1. Synthesis of *N*-Protected Compounds 5-8



starting compds	amino acid	R	product	yield (%)
(1*S*,3*S*)-**4**·HCl	Z-L-Ala	Cbz	(1*S*,3*S*,2′*S*)-**5a**	69
(1*S*,3*S*)-**4**·HCl	Z-D-Ala	Cbz	(1*S*,3*S*,2′*R*)-**6a**	41
(1*S*,3*S*)-**4**·HCl	Boc-L-Ala	Boc	(1*S*,3*S*,2′*S*)-**5b**	56
(1*S*,3*S*)-**4**·HCl	Boc-D-Ala	Boc	(1*S*,3*S*,2′*R*)-**6b**	61
(1*R*,3*R*)-**4**·HCl	Z-D-Ala	Cbz	(1*R*,3*R*,2′*R*)-**7a**	68
(1*R*,3*R*)-**4**·HCl	Z-L-Ala	Cbz	(1*R*,3*R*,2′*S*)-**8a**	57

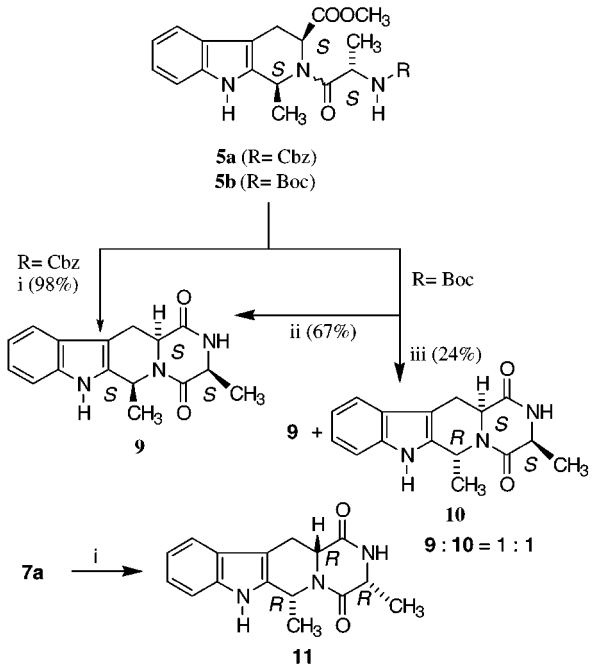
as coupling reagent.[8] Reactions with N-protected L-alanine gave compounds **5** and **8**, while reactions with N-protected D-alanine gave compounds **6** and **7**.

Although NMR spectra of compounds **5**−**8** were very complex, the relative proportion of the two N_a-H signals, which were clearly distinguished in their ^{1}H NMR spectra, showed mixtures of rotamers *s*-*E* and *s*-*Z* in a 2:1 ratio for compounds **5a** and **7a**, while in compounds **5b**, **6a**, **6b**, and **8a**, the rotamers *s*-*Z* were more important (*s*-*E*:*s*-*Z* = 1:1).[9] In open-chain dipeptides, the *s*-*Z* conformation is almost exclusive, but in *N*-(aminoacyl)-prolines, the ratio *s*-*E*:*s*-*Z* is 7:1, which is very favorable to their cyclization to pyrrolopiperazinedione derivatives.[10]

In the case of compounds **5**−**8**, when N-deprotection and cyclization were carried out, the nature of the protecting groups and the relative configuration of stereocenters showed their relevance. Thus, compound **5a** (Scheme 2), after hydrogenolysis with Pd/C in 1/1 methanol−acetic acid, spontaneously and quantitatively cyclized to the tetracyclic piperazinedione **9** (3*S*,6*S*,12a*S*) while **5b**, after deprotection with trifluoroacetic acid/dichloromethane, gave **9** in 67% yield. Deprotection by thermolysis of **5b** gave low yields of a 1:1 mixture of compounds **9** and **10** (3*S*,6*R*,12a*S*), which according to NOE experiments, are epimers at C-6. Both show a cis configuration in ring D, but ring C is cis in **9** and trans in **10**. We assume that the rearrangement of ring C from a cis to a trans stereochemistry involves some sort of retro-Pictet−Spengler reaction, which takes place before the cyclization reaction.

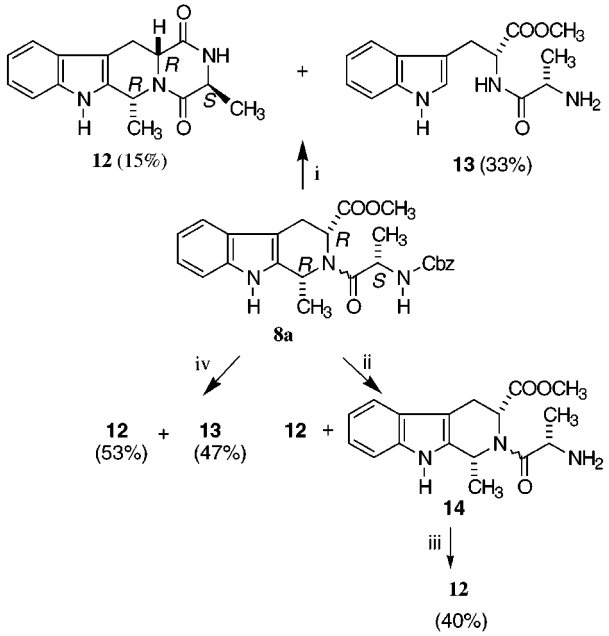
Compound **11** (3*R*,6*R*,12a*R*), enantiomer of compound **9**, was also quantitatively obtained by hydrogenolysis of **7a** under the same reaction conditions as for **5a**, but this treatment gave unsatisfactory results with **8a** (Scheme 3), affording the cyclic peptide anhydride **12** (3*S*,6*R*,12a*R*) in very low yield. Most of the starting material, perhaps because the *s*-*Z* conformation does not permit the cyclization, suffered hydrogenolysis of ring C to give L-alanyl-D-trypthophan methyl ester (**13**). Hydrogenation

Scheme 2[a]



[a] Key: (i) Pd/C, 1:1 MeOH/AcOH, 50 psi, 16 h; (ii) F_3CCO_2H/CH_2Cl_2, 4 h, rt; (iii) 200 °C, 30 min.

Scheme 3[a]



[a] Key: (i) Pd/C, 1:1 MeOH/AcOH, 50 psi, 16 h; (ii) Pd/C, AcOH (7×10^{-3} M), 50 psi; (iii) xylene, reflux; (iv) Pd/C, MeOH (7×10^{-3} M), 20 psi, 5 h.

in concentrated acetic acid using Suzuki's procedure[11] maintained the ring C unaltered but afforded a mixture of the N-deprotected intermediate **14** (which was not isolated) and small amounts of the tetracyclic piperazinedione **12**. Although this mixture could be cyclized by heating in refluxing xylene, the best yields of **12** (up to 53%) were obtained by hydrogenolysis of **8a** in methanol at lower pressures and shorter reaction times.

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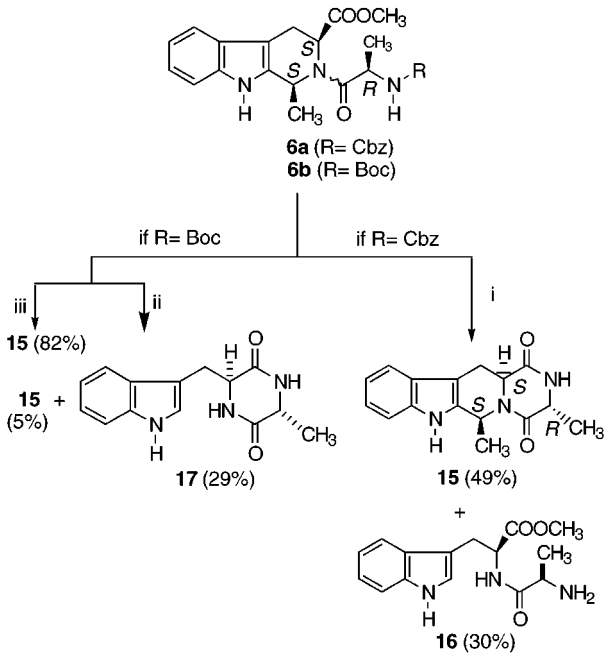
Scheme 4[a]



[a] Key: (i) Pd/C, MeOH (7×10^{-3} M), 20 psi, 5 h; (ii) 200 °C, 30 min; (iii) F_3CCO_2H, CH_2Cl_2, 4 h, rt.

Hydrogenolysis of **6a** in these reaction conditions (Scheme 4) produced, besides the desired piperazinedione **15** (3*R*,6*S*,12a*S*), the decomposition product D-alanyl-L-tryptophan methyl ester (**16**). To improve the yields of compound **15**, the cyclization of the Boc derivative **6b** was studied, but its pyrolysis was unsuccessful, giving only traces of compound **15** together with L-tryptophan-D-alanine anhydride (**17**), which is probably formed by cyclization of **16**. Finally, the treatment of **6b** with trifluoroacetic acid in dichloromethane gave a very good yield of **15** (82%).

It is clear that when the deprotection and cyclization sequence in *N*-(aminoacyl)-THBCs is prevented by geometric reasons, the retro-Pictet−Spengler reactions compete. The yields of this sequence go down from compounds **5** and **7**, which may be quantitatively cyclized, to compounds **6** and **8**. The synthesis of **12** and **15** may become difficult because of the greater proportion of the *s*-*Z* conformers in the starting *N*-(aminoacyl) compounds (**6** and **8**) in comparison to compounds **5** and **7** (see above). This assumption is supported by molecular mechanics calculations (MM2), which showed that interatomic distances between the amino and the carboxylate groups in the deprotected aminoacyl compounds derived from **6** and **8** are greater than 3 Å. Our experiments confirm previous reports about the effects produced by changes in the solvent on the population of rotamers and, consequently, on the success of the cyclization of dipeptides to piperazinediones.[12] According to results showed in Scheme 2 (i.e., the **9**:**10** ratio = 1:1), it can be concluded that diastereomers **9** and **10**, in which ring C adopts a cis and trans stereochemistry, respectively, have similar energies.

Selected NOE experiments have proved the stereochemistry described. The more significant spectroscopic data (see Experimental Section) can be summarized as follows: In the simplest piperazinedione **17**, only one carbonyl band at 1667 cm^{-1} appears in the IR spectrum. In tetracyclic compounds **9**, **10**, and **11**, with a cis stereochemistry for ring D, the absorption is shifted to higher frequencies: 1694 and 1658 cm^{-1} for compounds **9** and **11** and 1690 and 1676 cm^{-1} for compound **10**. On the contrary, enantiomers **12** and **15**, with a trans stereochemistry for ring D, show lower frequencies: 1620 and 1579 cm^{-1}. It is also significant in these compounds that the H-2 and H-3 protons are clearly coupled (^3J = 3.4 Hz). Finally, the diastereotopic H-12 methylene protons show more different chemical shifts in the tetracyclic piperazinediones **9**, **10**−**12**, and **15** than in the more flexible piperazinedione **17**.

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Experimental Section

General Methods. Melting points are uncorrected. IR spectra were recorded with all solid compounds compressed into KBr pellets and liquid compounds placed (neat or dissolved in the minimum amount of bromoform) between NaCl plates. NMR spectra were obtained at 250 or 300 MHz for ^1H and 75.4 or 62.9 MHz for ^{13}C with $CDCl_3$ and DMSO-d_6 as solvents in the Servicio de Resonancia, Universidad Complutense. Combustion elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense Madrid. Reactions were monitored by thin-layer chromatography, on aluminum plates coated with silica gel with fluorescent indicator. Solutions were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure (water aspirator) in a rotary evaporator. Separations by flash chromatography were performed on silica gel (230−400 mesh). All reagents were of commercial quality and were used as received.

***N*-Acylation of Tetrahydro-*β*-carbolines. General Method. Synthesis of Compounds 5−8.** *N*-Carbobenzoxy- or *N*-Boc-L- or D-alanine (16.14 mmol) and EDC (12.28 mmol) were added to the corresponding tetrahydro-*β*-carboline hydrochloride (**4**·HCl). The reaction was kept in the dark under an anhydrous calcium chloride tube and was magnetically stirred for 24 h. After concentration to dryness at low pressure, the residue was extracted with a mixture of chloroform (15 mL) and 1 N hydrochloric acid (16 mL). The separated organic phase was washed with 1 N sodium bicarbonate (15 mL), dried, and concentrated. Purification of the residue by column chromatography with ethyl acetate for compounds **a** and 1:1 ethyl acetate/chloroform for compounds **b** as solvents gave compounds **5**−**8**. (NMR data for minor rotamers, when distinguishable, are given in parentheses.)

Methyl (1*S*,3*S*,2′*S*)-1,2,3,4-tetrahydro-1-methyl-*N*′-carbobenzoxy-L-alanyl-*β*-carboline-3-carboxylate (5a). Starting from (1*S*,3*S*)-**4** (2 g, 8.19 mmol) dissolved in 1,4-dioxane (3.6 mL), Cbz-L-alanine (4.2 g, 18.8 mL) and EDC (5.39 g, 14.0 mL), a yield of 2.2 g (69%) of **5a** was obtained. Mp: 241−242 °C. IR (KBr): 3361, 1743, 1694, 1628 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.81 (s, 1H) (8.04); 7.52 (d, 1H, J = 7.5 Hz); 7.30 (m, 6H); 7.16 (m, 2H); 5.98 (d, 1H, J = 6.7 Hz); 5.54 (q, 1H, J = 6.4 Hz); 5.13 (s, 2H); 5.02 (m, 2H); 3.64 (m, 4H); 3.04 (dd, 1H, J = 14.3, 5 Hz) (2.92); 1.52 (d, 3H, J = 6.6 Hz) (1.65); 1.42 (d, 3H, J = 6.4 Hz). ^{13}C NMR (DMSO-d_6, 63 MHz) δ: 173.5 (172.5); 172.0 (171.6); 155.5 (155.2); 136.4; 134.2; 128.0 (128.5); 126.3; 121.3; 118.8; 118.1; 111.2; 103.8; 65.6 (65.8); 53.0; 52.2; 49.2; 47.8; 22.0; 19.4 (19.2); 18.8 (18.3). Anal. Calcd for $C_{25}H_{27}N_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.46; H, 6.10; N, 9.13.

Methyl (1*R*,3*R*,2′*R*)-1,2,3,4-tetrahydro-1-methyl-*N*′-carbobenzoxy-D-alanyl-*β*-carboline-3-carboxylate (7a). Starting from (1*R*,3*R*)-**4**·HCl (0.64 g, 2.3 mmol) dissolved in 1,4-dioxane (1.2 mL), Cbz-D-alanine (0.70 g, 3.1 mmol), and EDC (0.75 g, 1.9 mmol), a yield of 0.7 g (68%) of **7a** was obtained. Mp, IR, ^1H NMR, and ^{13}C NMR were identical to the above-described enantiomer.

Methyl (1*R*,3*R*,2′*S*)-1,2,3,4-tetrahydro-1-methyl-*N*′-carbobenzoxy-L-alanyl-*β*-carboline-3-carboxylate (8a). Starting from (1*R*,3*R*)-**4** (1 g, 3.56 mmol) dissolved in 1,4-dioxane (1.8 mL), Cbz-L-alanine (1.09 g, 4.8 mmol), and EDC (1.17 g, 3.07

mmol), a yield of 0.9 g (57%) of **8a** was obtained. Mp 250−252 °C. IR (KBr): 3350, 1744, 1682, 1610 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 8.16 (s, 1H) (8.30); 7.52 (d, 1H, J = 6.8 Hz); 7.35 (m, 6H); 7.15 (m, 2H); 5.92 (d, 1H, J = 6.7 Hz); 5.62 (q, 1H, J = 6.5 Hz); 5.15 (m, 3H); 4.86 (m, 1H); 3.62 (m, 4H) (3.64); 2.96 (m, 1H) (2.40); 1.54 (d, 3H, J = 6.6 Hz) (1.67); 1.45 (d, 3H, J = 6.5 Hz) (1.34). ^{13}C NMR (DMSO-d_6, 63 MHz) δ; 176.2; 172.5 (172.7); 156.2 (156.0); 136.3; 136.2; 128.7 (128.4); 127.5; 123.3; 122.2; 119.6; 111.5; 109.4; 67.1; 52.8; 52.6; 50.7; 49.6; 27.5; 18.6; 18.5. Anal. Calcd for $C_{25}H_{27}N_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.49; H, 6.06; N, 9.36.

Methyl (1*S*,3*S*,2′*R*)-1,2,3,4-tetrahydro-1-methyl-*N*′-carbobenzoxy-D-alanyl-β-carboline-3-carboxylate (6a). Starting from (1*S*,3*S*)-**4** (1 g, 3.56 mmol) dissolved in 1,4-dioxane (1.8 mL), Cbz-L-alanine (1.09 g, 4.8 mmol), and EDC (1.17 g, 3.07 mmol), a yield of 0.64 g (41%) of **6a** was obtained. Mp, IR, ^1H NMR, and ^{13}C NMR were identical to the above-described enantiomer.

Methyl (1*S*,3*S*,2′*S*)-1,2,3,4-tetrahydro-1-methyl-*N*′-(*tert*-buthoxycarbonyl)-L-alanyl-β-carboline-3-carboxylate (5b). Starting from (1*S*,3*S*)-**4** (0.416 g, 1.48 mmol) dissolved in 1,4-dioxane (0.7 mL), Boc-L-alanine (0.259 g, 1.36 mmol), and EDC (0.45 g, 2.35 mmol), a yield of 0.230 g (56%) of **5b** was obtained. Mp: 185−186 °C. IR (KBr): 3290, 1727, 1687, 1636 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.94 (s, 1H) (7.90); 7.52 (d, 1H, J = 7.5 Hz); 7.32 (d, 1H, J = 6.8 Hz); 7.12 (m, 2H); 5.90 (s, 1H); 5.54 (q, 1H, J = 5.4 Hz); 4.80 (m, 2H); 3.67 (m, 4H); 3.06 (dd, 1H, J = 15.6 and 5.0 Hz); 1.46 (m, 12H); 1.38 (d, 3H, J = 5.4 Hz) (1.36). ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 174.4 (172.2); 170.7 (169.8); 155.6; 136.3; 133.4; 127.4; 123.1; 121.9; 119.4; 111.2; 109.4; 53.5; 52.5; 49.9; 48.4; 28.3; 27.5; 22.7; 19.7 (19.6). Anal. Calcd for $C_{22}H_{29}N_3O_5$: C, 63.60; H, 7.04; N, 10.11. Found: C, 63.74; H, 7.12; N, 10.22.

Methyl (1*S*,3*S*,2′*R*)-1,2,3,4-tetrahydro-1-methyl-*N*′-(*tert*-buthoxycarbonyl)-D-alanyl-β-carboline-3-carboxylate (6b). Starting from (1*S*,3*S*)-**4** (0.57 g, 2.04 mmol) dissolved in 1,4-dioxane (1 mL), Boc-D-alanine (0.311 g, 1.63 mmol), and EDC (0.75 g, 3.92 mmol), a yield of 0.694 g (61%) of **6b** was obtained. Mp: 204−206 °C. IR (KBr): 3320, 1750, 1690, 1647 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 9.10 (s, 1H) (9.24); 7.55 (m, 1H); 7.32 (m, 1H); 7.16 (m, 2H); 5.82 (d, 1H, J = 6 Hz) (5.88) 5.66 (q, 1H, J = 6.6 Hz); 5.37 (dd, 2H, J = 7, 5.6 Hz); 4.85 (m, 1H); 3.64 (s, 3H); 3.57 (dd, 1H, J = 15.6, 5.6 Hz); 2.97 (dd, 1H, J = 15.6, 7.0 Hz); 1.50 (m, 15H) ^{13}C NMR ($CDCl_3$, 63 MHz) δ 173.3 (173.6); 171.8 (171.4); 153.3; 136.3; 133.2; 126.3; 121.8; 119.3; 118.2; 110.9; 105.5; 54.1; 52.3; 49.9; 48.1; 28.3; 28.2 (28.0); 22.3; 19.3 (19.4). Anal. Calcd for $C_{22}H_{29}N_3O_5$: C, 63.60; H, 7.04; N, 10.11. Found: C, 63.81; H, 6.99; N, 10.29.

(3*S*,6*S*,12a*S*)-3,6-Dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1,2-*b*]-β-carboline-1,4-dione (9), (3*S*,6*R*,12a*S*)-3,6-Dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1,2-*b*]-β-carboline-1,4-dione (10), and (3*SR*,6*R*,12a*R*)-3,6-Dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1,2-*b*]-β-carboline-1,4-dione (11). Method A. To a solution of 0.45 g (1.59 mmol) of **5a** or **7a** in a 1/1 mixture of acetic acid/methanol (100 mL) was added 0.22 g of 10% C−Pd. After reduction with hydrogen (50 psi, 16 h), filtration, and concentration, the residue was purified by column chromatography on silica gel (1/2 ethyl acetate/chloroform) to give 0.277 g (98% yield) of **9** or **11**.

Method B. A solution of 0.100 g (0.3 mmol) of **5b** in a 1/2 mixture of trifluoroacetic acid/dichloromethane (2 mL) was magnetically stirred for 4 h at room temperature. After neutralization with 10% ammonium hydroxide, the dichloromethane extracts were dried under anhydrous sodium sulfate, filtered, and evaporated to give a residue that, by column chromatography on silica gel (1/2 ethyl acetate/chloroform), gave 0.06 g (67% yield) of **9**.

Method C. Heating of **5b** (0.300 g, 0.9 mmol) at 200 °C for 30 min under a stream of argon, followed by purification by column chromatography on silica gel (1/2 ethyl acetate/chloroform), afforded 0.030 g (12% yield) of **9** and 0.030 g (12% yield) of **10**.

Data for Compound **9**. Mp: 238−240 °C. IR (KBr): 3293, 3121, 1694, and 1658 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.93 (s, 1H); 7.57 (d, 1H, J = 7.0 Hz); 7.38 (d, 1H, J = 7.0 Hz); 7.20 (m, 2H); 5.90 (s, 1H); 5.44 (q, 1H, J = 6.5 Hz); 4.20 (m, 2H); 3.62 (dd, 1H, J = 15.7, 4.6 Hz); 3.10 (dd, 1H, J = 15.7, 15.1 Hz); 1.57 (d, 3H, J = 6.7 Hz); 1.50 (d, 3H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 169.8; 165.7; 136.0; 135.1; 126.1; 121.9; 119.8; 118.1; 111.3; 105.4; 56.6; 56.0; 48.7; 23.3; 22.1; 16.8. Anal. Calcd for $C_{16}H_{17}N_3O_2 \cdot H_2O$: C, 63.77; H, 6.10; N, 13.94. Found: C, 63.66; H, 6.31; N, 13.75.

Data for Compound **10**. Mp: 291−292 °C. IR (KBr): 3320, 3090, 1690, 1676 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ: 11.03 (s, 1H); 8.41 (s, 1H); 7.33 (d, 1H; J = 7.5 Hz); 7.32 (d, 1H; J = 7.5 Hz); 7.03 (m, 2H); 5.26 (q, 1H, J = 6.2 Hz); 4.20 (dd, 1H, J = 11.7, 4.7 Hz); 4.10 (q, 1H, 11.7 Hz); 3.50 (dd, 1H, J = 15.4, 4.7 Hz); 2.78 (dd, 1H, J = 11.7, 15.4 Hz); 1.37 (d, 3H, J = 6.2 Hz); 1.34 (d, 3H, J = 6.6 Hz). ^{13}C NMR (DMSO-d_6, 63 MHz) δ: 170.3; 170.1; 135.8; 135.7; 125.8; 120.8; 118.7; 117.8; 111.2; 104.4; 55.3; 49.1; 47.6; 23.2; 21.8; 19.2. Anal. Calcd for $C_{16}H_{17}N_3O_2 \cdot H_2O$: C, 63.77; H, 6.10; N, 13.94. Found: C, 64.39; H, 6.19; N, 13.78.

Data for compound **11**. They were identical to those of compound **9**.

(3*S*,6*R*,12a*R*)-3,6-Dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1,2-*b*]-β-carboline-1,4-dione (12). To a solution of 0.34 g (0.7 mmol) of **8a** in methanol (100 mL) was added 0.7 g of 10% C−Pd. After reduction with hydrogen (20 psi, 5h), filtration, and concentration, the residue was purified by column chromatography on silica gel (1/2 ethyl acetate/chloroform) to give 0.053 g (53% yield) of **12**. Mp: 243−244 °C. IR (KBr): 3432, 3286, 1620, 1579 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ: 11.05 (s, 1H); 8.46 (d, 1H, J = 3.4 Hz); 7.52 (d, 1H; J = 7.3 Hz); 7.32 (d, 1H; J = 7.2 Hz); 7.02 (m, 2H); 5.20 (q, 1H, J = 6.2 Hz); 4.24 (dd, 1H, J = 11.4, 4.1 Hz); 3.94 (dq, 1H, J = 7.1, 3.4 Hz); 3.44 (dd, 1H, J = 15.4, 1 Hz); 2.72 (dd, 1H, J = 15.4, 11.4 Hz); 1,42 (d, 3H, J = 6.2 Hz); 1.32 (d, 3H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6, 63 MHz) δ: 169.5; 167.5; 136.0; 135.7; 125.9; 120.8; 118.7; 117.7; 111.2; 104.7; 54.5; 50.9; 48.0; 23.2; 22.5; 19.5. Anal. Calcd for $C_{16}H_{17}N_3O_2 \cdot H_2O$: C, 63.77; H, 6.10; N, 13.94. Found: C, 64.04; H, 6.32; N, 13.69.

(3*R*,6*S*,12a*S*)-3,6-Dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1,2-*b*]-β-carboline-1,4-dione (15). A solution of 0.138 g (0.41 mmol) of **6b** in a 1/2 mixture of trifluoroacetic acid/dichloromethane (2 mL) was magnetically stirred for 4 h at room temperature. After neutralization with 10% ammonium hydroxide, the dichloromethane extracts were dried under anhydrous sodium sulfate, filtered, and evaporated to give a residue that after purification afforded 0.094 g (82% yield) of **15**. Mp, IR, ^1H NMR, and ^{13}C NMR were identical to the above-described enantiomer **12**.

Data for **13** and **16**. Mp: 247−248 °C. IR (KBr): 3410, 1733, 1652 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 8.57 (s, 1H); 7.55 (d, 1H, J = 7.5 Hz); 7.34 (d, 1H; J = 7.5 Hz); 7.10 (m, 2H); 6.91 (s, 1H); 4.15 (q, 1H, J = 6.7 Hz); 3.77 (m, 6H); 2.02 (s, 2H); 1.40 (m, 4H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 176.1; 170.5; 135.9; 127.7; 123.2; 122.0; 119.3; 118.5; 112.2; 111.3; 56.9; 53.3; 26.2; 25.3; 16.5. Anal. Calcd for $C_{15}H_{20}N_3O_3$: C, 62.05; H, 6.94; N, 14.47. Found: C, 62.24; H, 6.92; N, 14.40.

(3*S*,6*R*)-3-(3′-Indolylmethyl)-6-methylpiperazine-2,5-dione (17). Heating of **6b** (0.46 g, 1.4 mmol) at 200 °C for 30 min under a stream of argon, followed by purification by column chromatography (ethyl acetate), gave 0.100 g (29%) of **17**. Mp: 280−282 °C. IR (KBr): 3325, 3197, 1667 cm^{-1}. ^1H NMR (DMSO-d_6, 250 MHz) δ: 10.91 (s, 1H); 8.04 (s, 1H); 7.91 (s, 1H); 7.53 (d, 1H; J = 7.7 Hz); 7.32 (d, 1H; J = 7.7 Hz); 7.05 (s, 1H); 6.97 (m, 2H); 4.02 (q, 1H, J = 7 Hz); 3.24 (dd, 1H, J = 14.5, 4.5 Hz); 2.96 (m, 2H); 1.32 (d, 3H, J = 7 Hz). ^{13}C NMR (DMSO-d_6, 63 MHz) δ: 170.3; 169.9; 137.7; 129.3; 126.3; 122.7; 120.5; 120.2; 113.0; 110.2; 57.7; 50.5; 30.9; 20.1. Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.62; H, 5.46; N, 16.44. Found: C, 65.68; H, 5.52; N, 16.22.

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