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Synthesis of Novel Indole-Based Ring Systems by Acid-Catalysed Condensation from α-Amino Aldehydes and L-Trp-OMe

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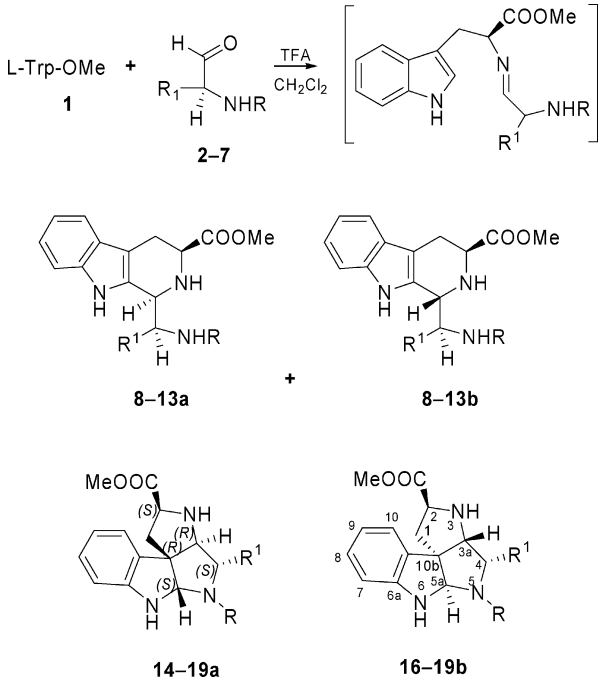
Acid-catalysed condensation of tryptophan with different α-amino aldehyde derivatives has been explored as a useful route to the synthesis of novel amino acid derived heterocycles and peptidomimetic scaffolds. By this approach, compounds containing a tetrahydro-β-carboline and a novel octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole system have been efficiently synthesized. Here we report the characterization of these new compounds and preliminary studies of the reactivity of the tetrahydro-β-carboline system.

Introduction

Amino acids and their derivatives are well known as versatile building blocks for pharmaceutical applications as well as essential starting points for the generation of molecular diversity.[1–3] In this context, and as part of a wide program to develop methodologies for generating peptidomimetics, we have focused our attention on the potential of α-amino aldehydes as a source of diverse biologically useful core compounds.

In this context we have recently reported an efficient condensation of α-amino aldehydes with cysteine or penicillamine to generate thiazolidine derivatives.[4] These structures offer considerable promise as combinatorial motifs and as β-turn mimetics. Also, we have reported that the condensation between an α-amino aldehyde and L-DOPA-OMe under acidic conditions furnishes the corresponding tetrahydroisoquinoline derivative which can subsequently be used as an intermediate template to form diazatricyclic lactam derivatives.[5] Herein we present the adaptation of this route, starting from α-amino aldehydes and L-Trp-OMe, to the synthesis of compounds containing the well-known tetrahydro-β-carboline system[6] and a novel indole-based tetracyclic ring system, that is, the octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole (Scheme 1).



Scheme 1. Condensation of L-Trp-OMe (**1**) with α-amino aldehydes **2**–**7**.

Fmoc-Gyl-H (**2**) and enantiopure protected α-amino aldehydes Fmoc-L-Ala-H (**3**), Fmoc-L-Phe-H (**4**), Boc-L-Phe-H (**5**), Fmoc-L-Asp(*t*Bu)-H (**6**) and Fmoc-L-Lys(Boc)-H (**7**) were prepared from the corresponding Fmoc-L-amino acids according to literature methods.[4a,7]

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Results and Discussion

As shown in Scheme 1, treatment for 12 h of a dichloromethane solution of L-Trp-OMe and α-amino aldehydes **2**–**7** at room temperature with 1 equiv. of TFA generated the *cis*- and *trans*-tetrahydro-β-carbolines **8**–**13a**,**b** (yields 20–33%). In addition, we obtained the unexpected compounds **14**–**19** (overall yields 35–63%) containing the novel octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole system.

Under these reaction conditions and as reported in Table 1, the *cis* isomers of the tetrahydro-β-carboline system (**8**–**11a**, entries 1–4) were predominant with respect to the *trans* isomers **8**–**11b** (ratio *cis*/*trans*, 3:1–2:1). The corresponding β-carbolines derived from Fmoc-L-Asp(*t*Bu)-H and Fmoc-L-Lys(Boc)-H (**12a**,**b** and **13a**,**b**, entries 5 and 6) were obtained with lower yields and diastereoselectivities (ratio *cis*/*trans*, 3:2). In the formation of the tetracyclic derivatives, unhindered amino aldehydes **2** and **3** exclusively gave isomers **14a** and **15a**, respectively, whereas α-amino aldehydes **4**–**7** bearing hindered groups in the side-chain also provided **16**–**19b** as minor isomers. These data indicate that the formation of the octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole system is particularly influenced by the character and size of the starting aldehydes. Moreover, Fmoc- or Boc-protecting groups used for the *N*-protection of the α-amino aldehydes had no effect on the condensation reaction (entries 3 and 4).

Assignments of each H and C atom were made by analysis of 2D NMR data, including COSY, HSQC, HMBC and ROESY. The configuration at C-1 for all the *cis*- and *trans*-tetrahydro-β-carbolines **8**–**13a**,**b** was determined by ^{1}H and ^{13}C NMR analysis and is supported by analogies in the literature.[6a,8] With respect to these derivatives, compounds **14**–**19** showed diagnostic spectroscopic signals for a quaternary C-10b and two methine groups C-3a and C-5a, the latter shifted remarkably downfield in the ^{1}H NMR spectrum.[9] Accordingly, the ^{13}C NMR spectra showed the disappearance of the indole C-2 and C-3 signals and the appearance of the corresponding fusion carbons C-5a and C-10b at δ = 82.7 and 63.2 ppm, respectively. The stereochemistry at these fusion positions in the major diastereoisomers was established on the basis of X-ray diffraction studies of compound **17a**[10] which indicated 3a*R*,5a*S*,10b*R* configurations at three new stereogenic centres, as depicted in the ORTEP diagram (Figure 1). Examination of the structure of **17a** reveals a *trans* disposition between the 2-methoxycarbonyl and the 4-phenylmethyl moieties (R_1). The orientation of the 5-*tert*-butoxycarbonyl group is directed by an intermolecular hydrogen bond in the crystal packing between the N(3) and the O(2) of the carbonyl group. Thus, the 2-methoxycarbonyl and the 4-*tert*-butoxycarbonyl groups were directed towards the less hindered *exo* face of the pyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole framework.

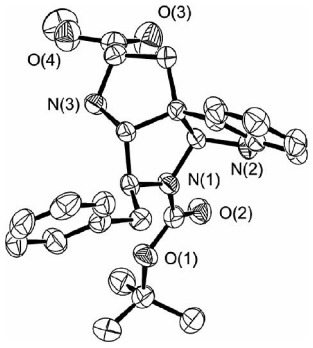


Figure 1. ORTEP representation of the structure of isomer **17a** at the 50% probability level. Hydrogen atoms have been omitted for clarity.

Unfortunately, we could not obtain good crystals for the analysis of **17b**. Therefore the assignments of the stereochemistry at the fusion positions in the minor diastereoisomer **17b** were attempted on the basis of the NOE correlations observed in the 2D ROESY spectra (Figure 2). Thus, NOE effects between 5a-H and 2-H and 1b-H and between 3a-H and 4-H and 4′a-H indicate a *cis* disposition between these protons. In contrast, exchange of magnetiza-

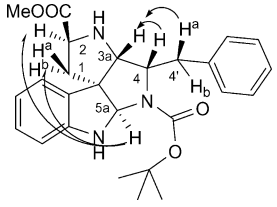
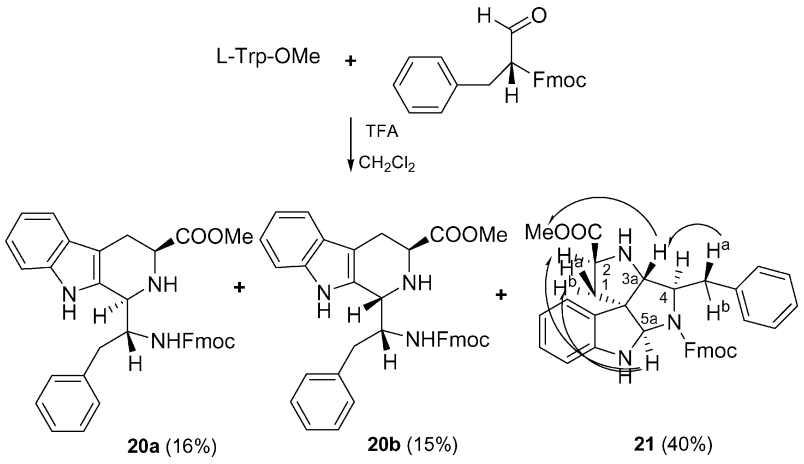


Figure 2. NOE effects observed in the ROESY 2D spectra for isomer **17b**.

Table 1. Yield and isomeric ratio of products **8**–**19a**,**b**.

Entry	Aldehyde	R	R^1	β-Carboline	% Yield	Tetracycle	% Yield
1	**2**	Fmoc	H	**8a**	20	**14a**	35
	2	Fmoc	H	**8b**	7	**14b**	–
2	**3**	Fmoc	CH_3	**9a**	22	**15a**	38
	3	Fmoc	CH_3	**9b**	11	**15b**	–
3	**4**	Fmoc	CH_2Ph	**10a**	20	**16a**	35
	4	Fmoc	CH_2Ph	**10b**	10	**16b**	7
4	**5**	Boc	CH_2Ph	**11a**	21	**17a**	36
	5	Boc	CH_2Ph	**11b**	10	**17b**	7
5	**6**	Fmoc	$CH_2COOtBu$	**12a**	14	**18a**	50
	6	Fmoc	$CH_2COOtBu$	**12b**	9	**18b**	12
6	**7**	Fmoc	$(CH_2)_4NHBoc$	**13a**	12	**19a**	48
	7	Fmoc	$(CH_2)_4NHBoc$	**13b**	8	**19b**	15



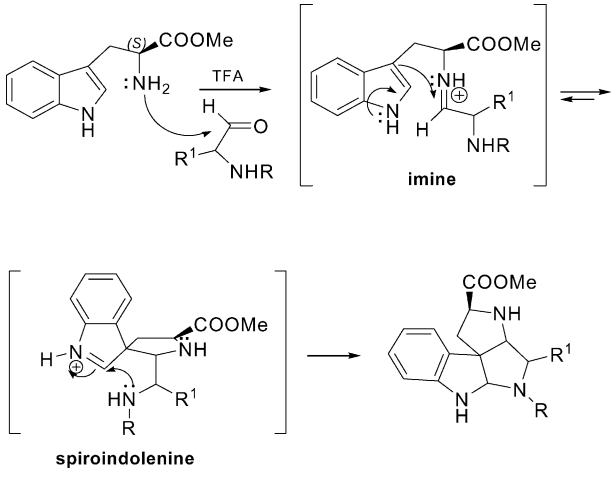
Scheme 2. Condensation the L-Trp-OMe with Fmoc-D-Phe-H.

tion between 4-H and/or 2-H and 5-H was not observed, in accord with a *trans* relationship between these protons.

On the basis that the stereochemistry at C-2 and C-4 is fixed, we have assigned the configurations at C-3a, C-5a and C-10b in **17b** as 3a*S*,5a*R* and 10b*S*, respectively. Finally, the stereochemical assignments for compounds **14a**, **15a**, **16a**,**b**, **18a**,**b** and **19a**,**b** were made by correlation of their ^{1}H and ^{13}C NMR spectra with those of **17a** and **17b**. At this point, to determine the influence of the chirality of the amino aldehyde on the stereochemical outcome of the cyclization reaction, Fmoc-D-Phe-H was condensed with L-Trp-OMe under the above conditions (Scheme 2).

In this case we observed the formation of a mixture of *cis*- and *trans*-β-carbolines (**20a** and **20b**, 1:1 ratio) whereas the tetracyclic derivative **21** was obtained as a single isomer. The stereochemical assignments for the fusion positions C-3a, C-5a and C-10b of this compound are 3a*S*, 5a*R* and 10b*S*, respectively, and were established on the basis of NOE correlations observed in the 2D ROESY spectra. Thus, 5a-H showed NOE effects with 2-H and 1b-H, and the methyl ester demonstrated NOE effects with the 3a-H proton, which did not show a NOE with 2-H or 5-H. From these data it seems that the stereoselectivity of the condensation reactions is particularly influenced by the chirality of the starting aldehyde. Thus, the interactions between the phenyl moieties of the aldehyde group and the indole, which might contribute to the stabilization of both the intermediate and the final 3a*S*,5a*R*,10b*S* tetracyclic isomer, could explain the inversion in selectivity observed with the use of Fmoc-D-Phe-H when compared with the corresponding L derivative. The formation of the tetracyclic derivatives could be explained by a domino mechanism[11] involving an initial attack on the imine by the C-3 of indole with formation of a spiroindolenine,[12] followed by trapping of the iminium ion by the amide nitrogen (Scheme 3).

Regarding the synthesis of this class of ring system, Patek and co-workers have reported the formation of a pentacyclic analogue derived from 1-acyl-3-oxopiperazines by intramolecular *N*-acyliminium cyclization reactions.[13] More

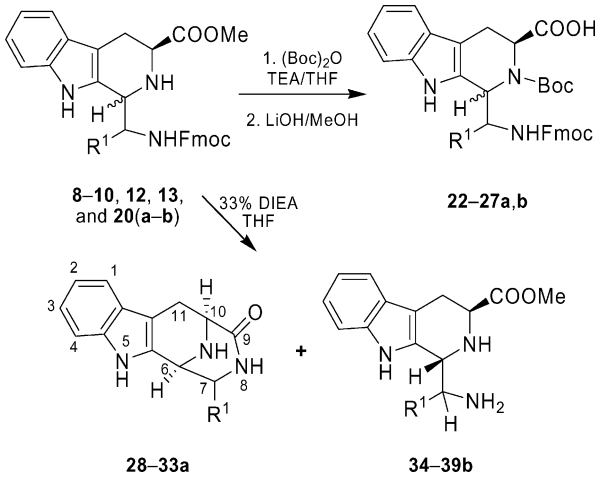


Scheme 3. Proposed mechanism for the synthesis of octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole derivatives.

recently, the synthesis and characterization of tetra- and pentacyclic derivatives obtained by the reaction of tryptamine with different aldehydes and amino aldehydes by the Pictet–Spengler reaction have been reported.[14]

Results of this preliminary study show the potential value of our synthetic approach to the generation of structural diversity which, in this case, was accomplished in one pot.

Scheme 4 illustrates the synthesis of a series of additional β-carbolines as building blocks with three points of diversity and different protecting groups. Protection of the free secondary amino group of compounds **8**–**10a**,**b**, **12a**,**b**, **13a**,**b** and **20a**,**b** with $(Boc)_2O$ in TEA and THF, and successive alkali hydrolysis (2 equiv. of LiOH in MeOH) afforded the derivatives **22**–**27a**,**b** in high yields (60% overall yields). As expected, the use in this step of LiOH produced a partial removal of the Fmoc-protecting group (about 20%, as detected by analytical HPLC), which can be reintroduced by treatment with Fmoc chloride in DMF using DIEA as base.



Scheme 4. Reaction of β-carboline derivatives.

Finally, the new 7-substituted *cis*-6,10-iminoazocino[4,5-*b*]indole derivatives **28**–**33a**[5,15,16] were easily obtained in quantitative yields by intramolecular lactamization of the corresponding *cis*-tetrahydro-β-carbolines **8**–**10a**, **12a**, **13a** and **20a** under conditions suitable for the cleavage of the Fmoc-protecting group using a 33% DIEA/THF solution at room temperature. Under these conditions, the *trans* diastereoisomers gave the corresponding Fmoc-deprotected tetrahydro-β-carbolines **34**–**39b**. The structures of these compounds were confirmed by analytical and spectroscopic data.

Conclusions

In summary, the preliminary results described herein show the real advantage of the acid-promoted condensation of L-Trp-OMe with amino aldehyde derivatives in the synthesis of both tetrahydro-β-carbolines and octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole derivatives. From a structural point of view, this latter class of compound represents an interesting example of conformationally rigid peptidomimetics with a cyclic structure.

In turn, structural manipulation of the tetrahydro-β-carboline derivatives allows access to new 7-substituted 6,10-iminoazocino[4,5-*b*]indole derivatives, as well as to orthogonally substituted tetrahydro-β-carbolines. Therefore, studies to explore the reactivity of the new octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indoles and the introduction of additional substituents into this ring system are in progress in our laboratory.

Experimental Section

General: Reagents, starting material and solvents were purchased from commercial suppliers and used as received. Analytical TLC was performed on plates coated with a 0.25 mm layer of silica gel 60 F_{254} Merck and preparative TLC on 20 × 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} Merck. Silica gel 60 (300–400 mesh, Merck) was used for flash chromatography. Melting points were measured with a Köfler apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 MC polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 500 spectrometer operating at 500 and 100 MHz, respectively. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si and J values are reported in Hz. Mass spectra were obtained using a FAB mass spectrometer.

General Procedure for the Synthesis of the Tetrahydro-β-carbolines 8–13 and 20 and Octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indoles Derivatives 14–19: L-Trp-OMe·HCl (2 g, 2 mmol) and TFA (2 mmol) were added to a solution of L-amino aldehydes **2**–**7** or Fmoc-D-Phe-H (2 mmol) in dichloromethane (40 mL) and the mixture was stirred at room temperature for 12 h. Then, the mixture was concentrated in vacuo and dichloromethane was added. The organic layer was washed with H_2O (2 × 25 mL), dried with Na_2SO_4, and the solvents evaporated. The title compounds were purified by flash chromatography (FC) using different eluents.

Methyl (1*S*,3*S*)-1-[(Fluorenylmethoxycarbonyl)aminomethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (8a): FC: EtOAc/*n*-hexane (3:2). White solid (193 mg, 20%), m.p. 157–158 °C. $[a]_D^{20}$ = +8.1 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97–3.01 (m, 1 H, 4′-H), 3.15–3.18 (m, 1 H, 4′′-H), 3.37–3.39 (m, 1 H, 1′-H), 3.68 (d, *J* = 1.0 Hz, 1 H, 1-H), 3.76 (s, 3 H, OCH_3), 4.20 (t, 1 H, CH Fmoc), 4.35–4.37 (m, 1 H, 1′-H), 4.41–4.44 (m, 2 H, CH_2 Fmoc), 5.63 (s, 1 H, NH), 7.12–7.16 (m, 2 H, 6-H, 7-H), 7.26 (t, *J* = 7.6 Hz, 2 H, CH Fmoc), 7.38 (t, 3 H, 8-H, aryl), 7.47 (d, *J* = 7.6 Hz, 1 H, 5-H), 7.52 (t, *J* = 7.6 Hz, 2 H, aryl), 7.74 (m, *J* = 7.6 Hz, 2 H, aryl), 8.71 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7 (C-4), 44.6 (C-3), 52.6 (C-1), 54.0 (C-1′), 118.3, 119.7, 122.3, 132.1, 136.4, 141.5, 144.1 (aryl), 157.2, 174.3 (C=O) ppm. FAB-MS: calcd. for $C_{29}H_{27}N_3O_4$ 481.2002; found 481.2021.

Methyl (1*R*,3*S*)-1-[(Fluorenylmethoxycarbonyl)aminomethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (8b): FC: EtOAc/*n*-hexane (3:2). White solid (70 mg, 7%), m.p. 159–160 °C. $[a]_D^{20}$ = +21.4 (*c* = 1.3, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.85 (dd, *J* = 8, 14.8 Hz, 1 H, 4′-H), 3.14 (dd, *J* = 4.4, 14.8 Hz, 1 H, 4′′-H), 3.65 (d, *J* = 1.2 Hz, 1 H, 1-H), 3.74–3.76 (m, 1 H, 3-H), 3.81 (s, 3 H, OCH_3), 4.07–4.11 (m, 1 H, 1′-H), 4.28–4.31 (m, 2 H, CH Fmoc, 1′-H), 4.37–4.40 (m, 2 H, CH_2 Fmoc), 5.89 (s, 1 H, NH), 7.06–7.13 (m, 2 H, 6-H, 7-H), 7.14–7.22 (m, 2 H, aryl), 7.24–7.36 (m, 2 H, aryl), 7.39 (t, *J* = 7.6 Hz, 1 H, 8-H), 7.46 (m, 3 H, 5-H, aryl), 7.68 (d, *J* = 7.6 Hz, 2 H, aryl), 8.71 (s, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (C-4), 44.7 (C-1), 51.1 (C-3), 52.5 (C-1), 118.1, 119.9, 122.3, 132.5, 136.6, 141.4, 144.0 (aryl), 157.1, 173.7 (C=O) ppm. FAB-MS: calcd. for $C_{29}H_{27}N_3O_4$ 481.2002; found 481.2081.

Methyl (1*S*,3*S*,1′*S*)-1-[1′-(Fluorenylmethoxycarbonyl)aminoethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (9a): FC: EtOAc/*n*-hexane (3:2). White solid (218 mg, 22%), m.p. 178–179 °C. $[a]_D^{20}$ = –10.3 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.01 (d, *J* = 6.8 Hz, 3 H, 2′-H), 2.75–2.80 (m, 1 H, 4′-H), 3.07 (dd, *J* = 3.6, 15.2 Hz, 1 H, 4′′-H), 3.70 (dd, *J* = 3.6, 11.2 Hz, 1 H, 3-H), 3.85 (s, 3 H, OCH_3), 4.18 (t, 1 H, CH Fmoc), 4.30–4.33 (m, 2 H, 1-H, 1′-H), 4.31–4.34 (m, 2 H, CH_2 Fmoc), 7.14–7.21 (m, 2 H, 6-H, 7-H), 7.31 (m, 3 H, 8-H, aryl), 7.40–7.44 (m, 2 H, aryl), 7.49 (d, *J* = 7.6 Hz, 1 H, 5-H), 7.61 (d, *J* = 7.6 Hz, 2 H, aryl), 7.77 (d, *J* = 7.6 Hz, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 13.3 (C-2′), 25.4 (C-4), 49.3 (C-3), 56.4 (C-1), 56.5 (C-1′), 118.8, 119.8, 121.2, 132.7, 137.0, 141.5, 144.3 (aryl), 157.2, 173.9 (C=O) ppm. FAB-MS: calcd. for $C_{30}H_{29}N_3O_4$ 495.2158; found 495.2124.

Methyl (1*R*,3*S*,1′*S*)-1-[1′-(Fluorenylmethoxycarbonyl)aminoethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (9b): FC: EtOAc/*n*-hexane (3:2). White solid (110 mg, 11%), m.p. 180–181 °C. $[\alpha]_D^{20}$ = +7.2 (*c* = 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.35 (d, *J* = 6.6 Hz, 3 H, 2′-H), 2.73 (t, *J* = 12.8 Hz, 1 H, 4′-H), 3.05 (dd, *J* = 3.6, 15.2 Hz, 1 H, 4′′-H), 3.61 (s, 3 H, OCH_3), 4.10–4.13 (m, 1 H, CH Fmoc), 4.16–4.22 (m, 2 H, 3-H, 1′-H), 4.25 (d, *J* = 1.2 Hz, 1 H, 1-H), 4.37–4.40 (m, 2 H, CH_2 Fmoc), 6.98 (t, *J* = 7.6 Hz, 1 H, 6-H), 7.06 (t, *J* = 7.6 Hz, 1 H, 7-H), 7.29–7.34 (m, 3 H, 8-H, aryl), 7.38–7.44 (m, 3 H, 5-H, aryl), 7.66–7.70 (m, 2 H, aryl), 7.78 (t, *J* = 7.6 Hz, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 17.3 (C-2′), 24.2 (C-4), 49.5 (C-1), 52.8 (C-3), 55.2 (C-1′), 118.6, 119.6, 121.2, 132.1, 136.9, 141.3, 144.2 (aryl), 156.9, 174.3 (C=O) ppm. FAB-MS: calcd. for $C_{30}H_{29}N_3O_4$ 495.2158; found 495.2133.

Methyl (1*S*,3*S*,1′*S*)-1-[1′-(Fluorenylmethoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (10a): FC: EtOAc/*n*-hexane (2:3). White solid (229 mg, 20%), m.p. 191–192 °C. $[\alpha]_D^{20}$ = –21.3 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75–2.89 (m, 2 H, 4′-H, 2′-H), 3.03 (dd, *J* = 3.8, 13.6 Hz, 1 H, 2′′-H), 3.09–3.13 (m, 1 H, 4′′-H), 3.85 (dd, *J* = 3.2, 12.4 Hz, 1 H, 3-H), 3.82 (s, 3 H, OCH_3), 4.12 (t, 1 H, CH Fmoc), 4.27–4.30 (m, 2 H, CH_2 Fmoc), 4.51–4.56 (m, 2 H, 1-H, 1′-H), 5.65 (d, 1 H, NH), 7.12–7.20 (m, 3 H, 6-H, 7-H, 8-H), 7.25–7.29 (m, 3 H, 5-H, aryl), 7.32–7.58 (m, 7 H, aryl), 7.61 (d, *J* = 7.6 Hz, 2 H, aryl), 7.77 (d, *J* = 7.6 Hz, 2 H, aryl), 8.61 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (C-4), 38.5 (C-2′), 53.7 (C-3), 55.4 (C-1), 58.3 (C-1′), 118.6, 120.1, 121.4, 126.3, 128.5, 132.1, 137.2, 138.2, 141.8, 144.6 (aryl), 158.1, 174.3 (C=O) ppm. FAB-MS: calcd. for $C_{36}H_{33}N_3O_4$ 571.2471; found 571.2429.

Methyl (1*R*,3*S*,1′*S*)-1-[1′-(Fluorenylmethoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (10b): FC: EtOAc/*n*-hexane (2:3). White solid (115 mg, 10%), m.p. 195–196 °C. $[\alpha]_D^{20}$ = +7.4 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (dd, *J* = 3.6, 14.6 Hz, 1 H, 2′-H), 2.77–2.83 (m, 2 H, 2′′-H, 4′′-H), 3.03 (dd, *J* = 4.2, 13.6 Hz, 1 H, 4′′-H), 3.84 (s, 3 H, OCH_3), 4.01 (dd, *J* = 4.2, 12.8 Hz, 1 H, 3-H), 4.18 (t, 1 H, CH Fmoc), 4.27–4.31 (m, 1 H, 1′-H), 4.33–4.36 (m, 2 H, CH_2 Fmoc), 4.50 (d, *J* = 1.4 Hz, 1 H, 1-H), 7.09 (t, *J* = 8.0 Hz, 1 H, 6-H), 7.14–7.20 (m, 2 H, 7-H, 8-H), 7.23–7.29 (m, 4 H, aryl), 7.36–7.55 (m, 8 H, 5-H, aryl), 7.81 (d, *J* = 7.6 Hz, 2 H, aryl), 8.81 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1 (C-4), 39.0 (C-2′), 52.5 (C-1), 54.7 (C-3), 56.8 (C-1′), 118.5, 120.1, 121.1, 126.4, 128.5, 132.2, 137.4, 138.7, 141.7, 144.1 (aryl), 158.7, 174.3 (C=O) ppm. FAB-MS: calcd. for $C_{36}H_{33}N_3O_4$ 571.2471; found 571.2498.

Methyl (1*S*,3*S*,1′*S*)-1-[1′-(*tert*-Butoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (11a): FC: EtOAc/*n*-hexane (2:3). White solid (235 mg, 21%), m.p. 158–159 °C. $[\alpha]_D^{20}$ = +34.1 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, CH_3), 2.81–2.96 (m, 3 H, 2′-H, 2′′-H, 4′′-H), 3.15 (dd, *J* = 3.2, 14 Hz, 1 H, 4′′-H), 3.73 (dd, *J* = 3.2, 11.2 Hz, 1 H, 3-H), 3.84 (s, 3 H, OCH_3), 4.26 (d, *J* = 1.0 Hz, 1 H, 1-H), 4.47–4.50 (m, 1 H, 1′-H), 7.05–7.46 (m, 9 H, 5-H, 6-H, 7-H, 8-H, aryl), 8.73 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2 (C-4), 37.3 (C-2′), 52.1 (C-3), 54.2 (C-1), 56.1 (C-1′), 108.1, 110.7, 117.3, 117.6, 118.8, 121.2, 126.3, 127.9, 128.3, 129.1, 129.4, 131.5, 137.0, 138.6 (aryl), 157.0, 173.2 (C=O) ppm. FAB-MS: calcd. for $C_{26}H_{31}N_3O_4$ 449.2315; found 449.2323.

Methyl (1*R*,3*S*,1′*S*)-1-[1′-(*tert*-Butoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (11b): FC: EtOAc/*n*-hexane (2:3). White solid (118 mg, 10%), m.p. 162–163 °C. $[\alpha]_D^{20}$ = +41.0 (*c* = 1.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9 H, CH_3), 2.81–2.94 (m, 2 H, 2′-H), 3.15–3.27 (m, 2 H, 4-H), 3.62 (s, 3 H, OCH_3), 4.07–4.11 (m, 1 H, 3-H), 4.31–4.34 (m, 1 H, 1′-H), 4.44 (d, *J* = 1.4 Hz, 1 H, 1-H), 5.27 (s, 1 H, N*H*-Boc), 7.01–7.48 (m, 9 H, 5-H, 6-H, 7-H, 8-H, aryl), 8.68 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3 (C-4), 39.0 (C-2′), 51.9 (C-1), 55.0 (C-3), 55.5 (C-1′), 108.5, 111.3, 118.0, 118.1, 119.3, 121.8, 126.4, 127.3, 128.7, 129.2, 129.4, 132.1, 138.2, 138.6 (aryl), 156.3, 174.6 (C=O) ppm. FAB-MS: calcd. for $C_{26}H_{31}N_3O_4$ 449.2315; found 449.2343.

Methyl (1*S*,3*S*,1′*S*)-1-[2′-(*tert*-Butoxycarbonyl)-1′-(fluorenylmethoxycarbonyl)aminoethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (12a): FC: EtOAc/*n*-hexane (1:2). Oil (160 mg, 14%). $[\alpha]_D^{20}$ = –16.1 (*c* = 1.6, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, CH_3), 2.15–2.19 (m, 1 H, 2′-H), 2.39–2.43 (m, 1 H, 2′′-H), 2.79 (t, *J* = 13.2 Hz, 1 H, 4′-H), 3.13 (dd, *J* = 2.5, 14.0 Hz, 1 H, 4′′-H), 3.72 (dd, *J* = 2.5, 11.4 Hz, 1 H, 3-H), 3.82 (s, 3 H, OCH_3), 4.08 (br. s, 1 H, 1-H), 4.13 (t, 1 H, CH Fmoc), 4.40–4.45 (m, 2 H, CH_2 Fmoc), 4.50–4.52 (m, 1 H, 1′-H), 5.95 (d, 1 H, NH), 7.14–7.26 (m, 2 H, 6-H, 7-H), 7.31–7.50 (m, 6 H, 5-H, 8-H, aryl), 7.63 (d, *J* = 7.6 Hz, 2 H, aryl), 7.75 (d, *J* = 7.6 Hz, 2 H, aryl), 9.08 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4 (C-4), 38.0 (C-2′), 50.7 (C-3), 55.7 (C-1), 56.4 (C-1′), 111.5, 118.3, 120.1, 122.2, 125.3, 127.2, 128.0, 132.2, 136.8, 143.8, 144.1 (aryl), 156.5, 171.5, 173.5 (C=O) ppm. FAB-MS: calcd. for $C_{35}H_{37}N_3O_6$ 595.2682; found 595.2713.

Methyl (1*R*,3*S*,1′*S*)-1-[2′-(*tert*-Butoxycarbonyl)-1′-(fluorenylmethoxycarbonyl)aminoethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (12b): FC: EtOAc/*n*-hexane (1:2). Oil (107 mg, 9%). $[\alpha]_D^{20}$ = +5.9 (*c* = 1.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, CH_3), 2.56–2.62 (m, 2 H, 2′-H), 3.06–3.11 (m, 2 H, 4-H), 3.64 (s, 3 H, OCH_3), 4.02–4.11 (m, 1 H, 3-H), 4.22 (t, 1 H, CH Fmoc), 4.40–4.43 (m, 2 H, CH_2 Fmoc), 4.46 (br. s, 1 H, 1-H), 4.60–4.63 (m, 1 H, 1′-H), 5.69 (s, 1 H, NH), 7.09–7.19 (m, 2 H, 8-H, 6-H), 7.25–7.29 (m, 3 H, aryl, 5-H), 7.32–7.58 (m, 7 H, aryl, 7-H), 7.60 (d, *J* = 7.6 Hz, 2 H, aryl), 7.78 (d, *J* = 7.6 Hz, 2 H, aryl), 8.68 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5 (C-4), 38.3 (C-2′), 52.3 (C-1), 52.5 (C-3), 53.6 (C-1′), 111.3, 118.4, 120.1, 122.2, 125.2, 127.3, 127.9, 131.4, 136.5, 141.5, 144.2 (aryl), 156.3, 171.1, 174.5 (C=O) ppm. FAB-MS: calcd. for $C_{35}H_{37}N_3O_6$ 595.2682; found 595.2768.

Methyl (1*S*,3*S*,1′*S*)-1-[5′-(*tert*-Butoxycarbonylamino)-1′-(fluorenylmethoxycarbonylamino)pentyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (13a): FC: EtOAc/*n*-hexane (3:2). Oil (161 mg, 12%). $[\alpha]_D^{20}$ = –4.9 (*c* = 1.8, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.29 (m, 2 H, γ-H), 1.34–1.41 (m, 4 H, β-H, δ-H), 1.45 (s, 9 H, CH_3), 2.16–2.18 (m, 2 H, ε-H), 2.82 (d, *J* = 6.0, 13.2 Hz, 1 H, 4′-H), 3.79–3.83 (m, 1 H, 4′′-H), 3.72–3.77 (m, 1 H, 3-H), 3.80 (s, 3 H, OCH_3), 4.22 (t, 1 H, CH Fmoc), 4.42 (br. s, 1 H, 1-H), 4.45–4.47 (m, 2 H, CH_2 Fmoc), 4.60–4.62 (m, 1 H, 1′-H), 5.34 (d, 1 H, N*H*-Boc), 7.08–7.17 (m, 2 H, 8-H, 6-H), 7.28–7.58 (m, 6 H, aryl, 5-H, 7-H), 7.61 (d, *J* = 8.0 Hz, 2 H, aryl), 7.75 (d, *J* = 7.8 Hz, 2 H, aryl), 9.01 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 27.6, 29.2 (C-δ,γ,ε), 26.3 (C-4), 39.6 (C-β), 53.4 (C-3), 56.6 (C-1), 56.7 (C-1′), 111.6, 119.6, 120.2, 125.3, 127.3, 127.9, 132.8, 136.8, 141.6, 144.1 (aryl), 156.1, 156.8, 174.0 (C=O) ppm. FAB-MS: calcd. for $C_{38}H_{44}N_4O_6$ 652.3261; found 652.3273.

Methyl (1*R*,3*S*,1′*S*)-1-[5′-(*tert*-Butoxycarbonylamino)-1′-(fluorenylmethoxycarbonylamino)pentyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (13b): FC: EtOAc/*n*-hexane (3:2). Oil (102 mg, 8%). $[\alpha]_D^{20}$ = +15.8 (*c* = 1.3, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41

(s, 9 H, CH_3), 1.43–1.64 (m, 6 H, γ-H, β-H, δ-H), 2.61–2.64 (m, 2 H, ε-H), 3.10–3.14 (m, 1 H, 4′-H), 3.27 (dd, *J* = 4.0, 14.0 Hz, 1 H, 4′′-H), 3.61 (s, 3 H, OCH_3), 3.90–3.93 (m, 1 H, 3-H), 4.00–4.09 (m, 1 H, CH Fmoc), 4.16–4.22 (m, 2 H, CH_2 Fmoc), 4.35–4.39 (m, 1 H, 1′-H), 4.56 (br. s, 1 H, 1-H), 5.48 (d, 1 H, N*H*-Boc), 6.98 (t, *J* = 7.8 Hz, 1 H, 6-H), 7.06 (t, *J* = 7.8 Hz, 1 H, 7-H) 7.29–7.34 (m, 3 H, aryl, 8-H), 7.38–7.44 (m, 3 H, aryl, 5-H), 7.66–7.70 (m, 2 H, aryl), 7.78 (d, *J* = 7.6 Hz, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 29.6, 29.9 (C-δ,γ,ε), 23.3 (C-4), 40.4 (C-β), 49.5 (C-1), 53.3 (C-3), 54.2 (C-1′), 111.4, 119.6, 120.2, 125.0, 127.2. 127.6, 132.3, 136.6, 141.4, 144.2 (aryl), 157.0, 158.4, 174.9 (C=O) ppm. FAB-MS: calcd. for $C_{38}H_{44}N_4O_6$ 652.3261; found 652.3273.

Methyl (1*S*,3*S*,1′*R*)-1-[1′-(Fluorenylmethoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (20a): FC: EtOAc/*n*-hexane (2:3). White solid (183 mg, 16%), m.p. 187–189 °C. $[\alpha]_D^{20}$ = +29.7 (*c* = 1.0, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.79–2.89 (m, 3 H, 4′-H, 2′-H), 3.13 (dd, *J* = 3.8, 14.0 Hz, 1 H, 4′′-H), 3.80–3.83 (m, 1 H, 3-H), 3.86 (s, 3 H, OCH_3), 4.07 (t, 1 H, CH Fmoc), 4.13–4.21 (m, 2 H, CH_2 Fmoc), 4.35 (br. s, 1 H, 1-H), 4.52–4.58 (m, 1 H, 1′-H), 5.68 (d, 1 H, NH), 7.12–7.26 (m, 3 H, 6-H, 7-H, 8-H), 7.29–7.58 (m, 12 H, 5-H, aryl), 7.60–7.64 (d, 4 H, aryl), 8.56 (s, 1 H, NH indole) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6 (C-4), 38.6 (C-2′), 53.4 (C-3), 54.9 (C-1), 57.8 (C-1′), 109.2, 111.4, 118.4, 120.0, 121.4, 125.9, 127.4, 128.4, 132.5, 137.3, 138.1, 141.6, 144.6 (aryl), 158.1, 174.3 (C=O) ppm. FAB-MS: calcd. for $C_{36}H_{33}N_3O_4$ 571.2471; found 571.2571.

Methyl (1*R*,3*S*,1′*R*)-1-[1′-(Fluorenylmethoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (20b): FC: EtOAc/*n*-hexane (2:3). White solid (175 mg, 15%), m.p. 195–196 °C. $[\alpha]_D^{20}$ = +51.1 (*c* = 1.0, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.79–2.83 (m, 2 H, 2′-H), 3.17–3.23 (m, 2 H, 4-H), 3.66 (s, 3 H, OCH_3), 3.90–3.94 (m, 1 H, 3-H), 4.09 (t, 1 H, CH Fmoc), 4.32–4.37 (m, 1 H, 1′-H), 4.42–4.46 (m, 2 H, CH_2 Fmoc), 4.59 (br. s, 1 H, 1-H), 5.24 (d, 1 H, NH), 7.12–7.45 (m, 15 H, 5-H, 6-H, 7-H, 8-H, aryl), 7.50–7.58 (m, 2 H, aryl), 7.79 (d, *J* = 7.6 Hz, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7 (C-4), 39.1 (C-2′), 53.1 (C-1), 55.2 (C-3), 56.4 (C-1′), 108.6, 111.0, 118.3, 120.1, 121.4, 125.9, 127.3, 128.2, 132.4, 137.2, 138.1, 141.3, 144.5 (aryl), 158.1, 174.1 (C=O) ppm. FAB-MS: calcd. for $C_{36}H_{33}N_3O_4$ 571.2471; found 571.2565.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*R*,4*S*,5a*S*,10b*R*)-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (14a): FC: EtOAc/*n*-hexane (3:2). White solid (337 mg, 35%), m.p. 202–203 °C. $[\alpha]_D^{20}$ = –25.1 (*c* = 1.1, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.22–2.31 (m, 2 H, 1-H), 3.31–3.34 (m, 1 H, 3a-H), 3.60 (s, 3 H, CH_3 ester), 3.86 (d, *J* = 6.6 Hz, 1 H, 2-H), 4.38–4.42 (m, 1 H, CH Fmoc), 4.81–4.86 (m, 2 H, CH_2 Fmoc), 5.43 (s, 1 H, 5a-H), 6.30 (d, *J* = 8.4 Hz, 1 H, 7-H), 6.58 (d, *J* = 8.4 Hz, 1 H, 10-H), 6.69–6.72 (m, 2 H, 8-H, 9-H), 6.99–7.12 (m, 2 H, aryl), 7.36–7.62 (m, 4 H, aryl), 7.64–7.83 (m, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8 (C-1), 46.7 (C-4), 51.9 (OCH_3), 59.7 (C-2), 62.5 (C-10b), 75.9 (C-3a), 81.5 (C-5a), 108.6, 119.0, 123.2, 124.8, 125.2, 127.4, 127.6, 127.9, 128.6, 128.9, 130.4, 141.7, 144.4, 149.0 (aryl), 154.9, 174.2 (C=O) ppm. FAB-MS: calcd. for $C_{29}H_{27}N_3O_4$ 481.2002; found 481.2009.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*R*,4*S*,5a*S*,10b*R*)-4-Methyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (15a): FC: EtOAc/*n*-hexane (3:2). White solid (376 mg, 38%), m.p. 214–215 °C. $[\alpha]_D^{20}$ = –37.4 (*c* = 1.0, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.40–2.43 (m, 2 H, 1-H), 3.49–3.54 (m, 1 H, 4-H), 3.61 (s, 3 H, OCH_3), 3.79 (m, 1 H, 3a-H), 3.96 (dd, *J* = 4.2, 11.8 Hz, 1 H, 2-H), 4.36–4.39 (m, 1 H, CH Fmoc), 4.52–4.56 (m, 2 H, CH_2 Fmoc), 5.26 (s, 1 H, 5a-H), 6.47 (d, *J* = 8.4 Hz, 1 H, 7-H), 6.56 (d, *J* = 8.4 Hz, 1 H, 10-H), 6.69–6.72 (m, 2 H, 8-H, 9-H), 7.03–7.09 (m, 2 H, aryl), 7.30–7.44 (m, 3 H, aryl), 7.61–7.66 (m, 2 H, aryl), 7.77–7.79 (m, 1 H, aryl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.0 (C-1), 52.9 (C-4), 64.1 (C-10b), 67.4 (C-3a), 82.0 (C-5a), 113.1, 117.0, 125.9, 126.8, 133.1, 147.0 (aryl), 153.6, 173.2 (C=O) ppm. FAB-MS: calcd. for $C_{30}H_{29}N_3O_4$ 495.2158; found 495.2223.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*R*,4*S*,5a*S*,10b*R*)-4-Benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (16a): FC: EtOAc/*n*-hexane (2:3). White solid (399 mg, 35%), m.p. 247–248 °C. $[\alpha]_D^{20}$ = –27.9 (*c* = 1.0, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 2.03–2.07 (m, 1 H, 4′-H), 2.39–2.43 (m, 1 H, 1′-H), 2.51–2.55 (m, 1 H, 1′′-H), 2.87–2.90 (m, 1 H, 4′′-H), 3.66 (d, *J* = 3.8 Hz, 1 H, 3a-H), 3.74 (s, 3 H, OCH_3), 3.88 (dd, *J* = 4.2, 12.4 Hz, 1 H, 2-H), 4.19 (t, *J* = 4.0 Hz, 1 H, 4-H), 4.24–4.26 (m, 1 H, CH Fmoc), 4.43–4.49 (m, 2 H, CH_2 Fmoc), 5.00 (s, 1 H, 5a-H), 6.67–6.81 (m, 2 H, aryl), 6.94–7.02 (m, 2 H, aryl), 7.13–7.22 (m, 5 H, aryl), 7.38–7.55 (m, 8 H, aryl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.8 (C-4′), 39.9 (C-1), 57.4 (C-2), 63.8 (C-10b), 65.4 (C-4), 71.9 (C-3a), 82.6 (C-5a), 109.4, 118.7, 122.6, 126.2, 128.4, 128.9, 129.1, 130.0, 138.4, 149.6 (aryl), 155.7, 174.6 (C=O) ppm. FAB-MS: calcd. for $C_{36}H_{33}N_3O_4$ 571.2471; found 571.2547.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*S*,4*S*,5a*R*,10b*S*)-4-Benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (16b): FC: EtOAc/*n*-hexane (2:3). White solid (80 mg, 7%), m.p. 260–261 °C. $[\alpha]_D^{20}$ = +5.1 (*c* = 0.8, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 1.98–2.05 (m, 1 H, 4′-H), 2.31–2.36 (m, 1 H, 1′-H), 2.58–2.62 (m, 1 H, 1′′-H), 2.79–2.83 (m, 1 H, 4′′-H), 3.73 (s, 3 H, OCH_3), 3.78 (dd, *J* = 4.2, 12.4 Hz, 1 H, 3a-H), 3.95–4.00 (m, 1 H, 2-H), 4.12 (dd, *J* = 4.2, 12.0 Hz, 1 H, 4-H), 4.26–4.29 (m, 1 H, CH Fmoc), 4.41–4.48 (m, 2 H, CH_2 Fmoc), 5.40 (s, 1 H, 5a-H), 6.71–6.83 (m, 2 H, aryl), 7.02 (d, *J* = 7.8 Hz, 2 H, aryl), 7.18–7.26 (m, 5 H, aryl), 7.40–7.58 (m, 8 H, aryl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.7 (C-4′), 41.0 (C-1), 57. (C-2), 64.1 (C-10b), 65.9 (C-4), 70.8 (C-3a), 82.7 (C-5a), 109.3, 118.7, 123.1, 126.2, 128.4, 128.9, 129.2, 130.0, 138.6, 149.8 (aryl), 156.0, 174.5 (C=O) ppm. FAB-MS: calcd. for $C_{36}H_{33}N_3O_4$ 571.2471; found 571.2522.

5-*tert*-Butyl 2-Methyl (2*S*,3a*R*,4*S*,5a*S*,10b*R*)-4-Benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (17a): FC: EtOAc/*n*-hexane (2:3). White solid (324 mg, 36%), m.p. 250–251 °C. $[\alpha]_D^{20}$ = +6.3 (*c* = 1.0, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 1.39 (s, 9 H, Boc), 1.96–2.00 (m, 1 H, 4′-H), 2.44–2.47 (m, 2 H, 1-H), 2.82–2.85 (m, 1 H, 4′′-H), 3.60 (s, 1 H, 3a-H), 3.71 (s, 3 H, OCH_3), 3.97 (dd, *J* = 2.8, 11.4 Hz, 1 H, 2-H), 4.14 (m, 1 H, 4-H), 5.34 (s, 1 H, 5a-H), 6.67–6.81 (m, 2 H, aryl), 6.94–7.00 (m, 2 H, aryl), 7.13–7.22 (m, 5 H, aryl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.8 (C-4′), 42.6 (C-1), 60.1 (C-2), 63.2 (C-10b), 66.8 (C-4), 72.3 (C-3a), 82.7 (C-5a), 109.3, 118.7, 123.0, 126.2, 128.3, 128.8, 129.3, 130.8, 138.8, 149.9 (aryl), 156.3, 174.5 (C=O) ppm. FAB-MS: calcd. for $C_{26}H_{31}N_3O_4$ 449.2315; found 449.3311.

5-*tert*-Butyl 2-Methyl (2*S*,3a*S*,4*S*,5a*R*,10b*S*)-4-Benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (17b): FC: EtOAc/*n*-hexane (2:3). White solid (63 mg, 7%), m.p. 245–246 °C. $[\alpha]_D^{20}$ = +31.1 (*c* = 1.1, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 1.42 (s, 9 H, Boc), 1.95–2.04 (m, 1 H, 4′-H), 2.20–2.23 (m, 1 H, 1′-H), 2.61–2.66 (m, 1 H, 1′′-H), 2.83–2.86 (m, 1 H, 4′′-H), 3.71 (s, 3 H, OCH_3), 3.80 (br. s, 1 H, 3a-H), 3.97–

4.01 (m, 1 H, 2-H), 4.06 (dd, J = 4.2, 11.8 Hz, 1 H, 4-H), 5.45 (s, 1 H, 5a-H), 6.68–6.80 (m, 2 H, aryl), 6.94 (d, J = 7.8 Hz, 2 H, aryl), 7.13–7.23 (m, 5 H, aryl) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 39.5 (C-4′), 43.3 (C-1), 59.7 (C-2), 63.9 (C-10b), 67.0 (C-4), 71.2 (C-3a), 82.9 (C-5a), 109.3, 118.7, 123.0, 126.2, 128.3, 128.8, 129.3, 130.0, 138.5, 149.7 (aryl), 156.1, 174.5 (C=O) ppm. FAB-MS: calcd. for $C_{26}H_{31}N_3O_4$ 449.2315; found 449.2343.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*R*,4*S*,5a*S*,10b*R*)-4-(*tert*-Butoxycarbonylmethyl)-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (18a): FC: EtOAc/*n*-hexane (2:3). White solid (598 mg, 50%), m.p. 257–258 °C. $[\alpha]_D^{20}$ = –41.1 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.40 (s, 9 H, *t*Bu), 1.46 (dd, J = 9.6, 15.6 Hz, 1 H, 4′-H), 2.00 (dd, J = 4.0, 15.8 Hz, 1 H, 4′′-H), 2.35–2.41 (m, 1 H, 1-H), 2.45–2.49 (dd, J = 4.4, 13. 6 Hz, 1 H, 1-H), 3.63 (br. s, 1 H, 3a-H), 3.68 (s, 3 H, OCH_3), 4.02–4.08 (m, 2 H, 2-H, 4-H), 4.31 (t, 1 H, CH Fmoc), 4.49–4.51 (m, 2 H, CH_2 Fmoc), 5.28 (s, 1 H, 5a-H), 6.48 (d, J = 7.6 Hz, 1 H, 7-H), 6.56 (d, J = 7.6 Hz, 1 H, 10-H), 6.70 (t, J = 7.2 Hz, 1 H, 8-H), 7.05–7.08 (m, 2 H, 9-H, aryl), 7.30–7.39 (m, 3 H, aryl), 7.65–7.72 (m, 2 H, aryl), 7.83 (d, J = 7.6 Hz, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 38.2 (C-4′), 41.5 (C-1), 59.8 (C-2), 61.5 (C-10b), 63.3 (C-4), 73.9 (C-3a), 82.1 (C-5a), 109.3, 119.7, 122.8, 127.3, 128.8, 128.9, 129.7, 141.3, 144.1, 148.8 (aryl), 154.8, 170.6, 174.5 (C=O) ppm. FAB-MS: calcd. for $C_{35}H_{37}N_3O_6$ 595.2682; found 595.2735.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*S*,4*S*,5a*R*,10b*S*)-4-(*tert*-Butoxycarbonylmethyl)-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (18b): FC: EtOAc/*n*-hexane (2:3). White solid (143 mg, 12%), m.p. 265–266 °C. $[\alpha]_D^{20}$ = +12.3 (c = 0.9, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.40 (s, 9 H, *t*Bu), 1.55 (dd, J = 9.4, 16.0 Hz, 1 H, 4′-H), 2.29–2.31 (m, 1 H, 4′′-H), 2.39–2.45 (m, 2 H, 1-H), 3.60 (s, 3 H, OCH_3), 3.74 (br. s, 1 H, 3a-H), 4.04–4.07 (m, 1 H, 4-H), 4.17 (dd, J = 4.4, 9.3 Hz, 1 H, 2-H), 4.26 (t, 1 H, CH Fmoc), 4.67–4.69 (m, 2 H, CH_2 Fmoc), 5.01 (s, 1 H, 5a-H), 6.47 (d, J = 7.5 Hz, 1 H, 7-H), 6.57 (d, J = 7.5 Hz, 1 H, 10-H), 6.72 (t, J = 7.0 Hz, 1 H, 8-H), 7.06–7.08 (m, 2 H, 9-H, aryl), 7.35–7.41 (m, 3 H, aryl), 7.61–7.78 (m, 2 H, aryl), 7.82 (d, J = 7.6 Hz, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 38.3 (C-4′), 41.7 (C-1), 59.5 (C-2), 61.7 (C-10b), 63.5 (C-4), 73.1 (C-3a), 82.9 (C-5a), 109.0, 119.9, 122.8, 127.0, 127.8, 130.1, 141.4, 144.32, 149.3 (aryl), 155.3, 170.4, 174.5 (C=O) ppm. FAB-MS: calcd. for $C_{35}H_{37}N_3O_6$ 595.2682; found 595.2723.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*R*,4*S*,5a*S*,10b*R*)-4-[4′-(*tert*-Butoxycarbonylamino)butyl]-1,2,3,3a,4,5,5a,6-octahydropyrrolo-[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (19a): FC: EtOAc/*n*-hexane (2:3). White solid (627 mg, 48%), m.p. 272–274 °C. $[\alpha]_D^{20}$ = –23.9 (c = 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.78–0.82 (m, 2 H, γ-H), 1.07–1.10 (m, 2 H, δ-H), 1.20–1.24 (m, 2 H, β-H), 1.40 (s, 9 H, *t*Bu), 2.37–2.41 (m, 2 H, 1-H), 2.80–2.82 (m, 2 H, ε-H), 3.49 (br. s, 1 H, 3a-H), 3.68 (s, 3 H, OCH_3), 3.85 (dd, J = 4.8, 8.8 Hz, 1 H, 4-H), 3.99–4.03 (m, 1 H, 2-H), 4.23 (t, 1 H, CH Fmoc), 4.62–4.64 (m, 2 H, CH_2 Fmoc), 5.23 (s, 1 H, 5a-H), 6.46 (d, J = 7.6 Hz, 1 H, 7-H), 6.56 (d, J = 7.6 Hz, 1 H, 10-H), 6.70 (t, J = 7.2 Hz, 1 H, 8-H), 6.99–7.07 (m, 2 H, 9-H, aryl), 7.31–7.39 (m, 3 H, aryl), 7.64–7.68 (m, 2 H, aryl), 7.84 (d, J = 7.6 Hz, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 33.1 (C-β), 42.4 (C-1), 60.2 (C-2), 62.7 (C-10b), 66.4 (C-4), 73.5 (C-3a), 82.4 (C-5a), 108.8, 119.9, 124.9, 127.2, 128.7, 128.6, 130.6, 134.8, 141.6, 144.1, 148.8 (aryl), 155.1, 159.3, 171.3 (C=O) ppm. FAB-MS: calcd. for $C_{38}H_{44}N_4O_6$ 652.3261; found 652.3316.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*S*,4*S*,5a*R*,10b*S*)-4-[4′-(*tert*-Butoxycarbonylamino)butyl]-1,2,3,3a,4,5,5a,6-octahydropyrrolo-[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (19b): FC: EtOAc/*n*-hexane (2:3). White solid (195 mg, 15%), m.p. 277–278 °C. $[\alpha]_D^{20}$ = +18.5 (c = 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.80–0.83 (m, 2 H, γ-H), 1.08–1.11 (m, 2 H, δ-H), 1.22–1.27 (m, 2 H, β-H), 1.41 (s, 9 H, *t*Bu), 2.30–2.33 (m, 1 H, 1′-H), 2.40–2.44 (dd, J = 9.4, 15.0 Hz, 1 H, 1′′-H), 2.78–2.81 (m, 2 H, ε-H), 3.42–3.44 (m, 1 H, 4-H), 3.55 (br. s, 1 H, 3a-H), 3.59 (s, 3 H, OCH_3), 4.31 (t, 1 H, CH Fmoc), 4.47–4.51 (dd, J = 5.6, 10.1 Hz, 1 H, 2-H), 4.69–4.73 (m, 2 H, CH_2 Fmoc), 5.02 (s, 1 H, 5a-H), 6.47 (d, J = 7.6 Hz, 1 H, 7-H), 6.53 (d, J = 7.6 Hz, 1 H, 10-H), 6.68 (t, J = 7.2 Hz, 1 H, 8-H), 6.97–7.03 (m, 2 H, 9-H, aryl), 7.30–7.39 (m, 3 H, aryl), 7.58–7.76 (m, 2 H, aryl), 7.84 (d, J = 7.6 Hz, 2 H, aryl) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 32.7 (C-β), 42.6 (C-1), 60.1 (C-2), 63.3 (C-10b), 66.7 (C-4), 73.1 (C-3a), 82.9 (C-5a), 109.1, 118.8, 124.6, 127.2, 127.6, 128.2, 130.3, 134.6, 141.3, 144.3, 149.2 (aryl), 155.6, 159.5, 171.9 (C=O) ppm. FAB-MS: calcd. for $C_{38}H_{44}N_4O_6$ 652.3261; found 652.3432.

5-Fluorenylmethyl 2-Methyl (2*S*,3a*S*,4*R*,5a*R*,10b*S*)-4-Benzyl-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3′,2′:3,4]pyrrolo[2,3-*b*]indole-2,5-dicarboxylate (21): FC: EtOAc/*n*-hexane (2:3). White solid (457 mg, 40%), m.p. 250–251 °C. $[\alpha]_D^{20}$ = +12.6 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.65 (t, J = 13.2 Hz, 1 H, 4′-H), 2.10–2.13 (m, 2 H, 1-H, 4′′-H), 2.51 (dd, J = 7.6, 13.8 Hz, 1 H, 1-H), 3.57 (s, 1 H, 3a-H), 3.68 (s, 3 H, OCH_3), 3.81 (t, J = 7.4 Hz, 1 H, 2-H), 3.96 (dd, J = 4.0, 11.2 Hz, 1 H, 4-H), 4.15 (t, 1 H, CH Fmoc), 4.64–4.69 (m, 2 H, CH_2 Fmoc), 5.33 (s, 1 H, 5a-H), 6.50 (d, J = 7.2 Hz, 1 H, 7-H), 6.61 (d, J = 8.0 Hz, 1 H, 10-H), 6.76–6.83 (m, 2 H, 8-H, 9-H), 7.06–7.17 (m, 5 H, aryl), 7.30–7.42 (m, 4 H, aryl), 7.63–7.64 (m, 4 H, aryl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.7 (C-4′), 42.8 (C-1), 63.5 (C-10b), 65.9 (C-2), 66.7 (C-4), 70.5 (C-3a), 82.9 (C-5a), 109.3, 118.7, 119.9, 123.0, 124.6, 126.1, 127.1, 127.6, 128.2, 128.8, 129.1, 138.1, 141.5, 144.2, 149.9 (aryl), 155.6, 174.5 (C=O) ppm. FAB-MS: calcd. for $C_{36}H_{33}N_3O_4$ 571.2471; found 571.2535.

Synthesis of the Tetrahydro-β-carboline-3-carboxylic Acid Derivatives 22–27a,b: $(Boc_2)O$ (1 mmol) and KOH (pH = 8) were added to a solution of the tetrahydro-β-carbolines, the *cis* (**8**–**10a**, **12a**, **13a** and **20a**) or *trans* (**8**–**10b**, **12b**, **13b** and **20b**) isomer, (0.2 mmol) in H_2O/dioxane (20:20 mL) and the mixture was stirred at room temperature for 16 h. Then the reaction mixture was concentrated and purified by flash chromatography using EtOAc/*n*-hexane (1:2) as eluent. LiOH 1 N (2 equiv.) was then added to a solution of the corresponding 2-*N*-Boc-protected derivatives (0.3 mmol) in MeOH (20 mL) and the mixture was stirred at room temperature for 2 h. Afterwards, the reaction mixture was neutralized sequentially with 1 N HCl, concentrated and diluted with EtOAc. The organic phase was successively washed with H_2O (2 × 25 mL) and brine (2 × 25 mL), dried with Na_2SO_4 and the solvents evaporated to dryness. The resulting orthogonally protected tetrahydro-β-carboline-carboxylic acids **22**–**27a**,**b** were collected as solids.

(1*S*,3*S*)-2-(*tert*-Butoxycarbonyl)-1-[(fluorenylmethoxycarbonyl)-aminomethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (22a): White solid (74 mg, 65%), m.p. 239–240 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.31 (s, 9 H, Boc), 2.49 (dd, J = 3.4, 15.6 Hz, 1 H, 4′-H), 2.77–2.81 (m, 1 H, 4′′-H), 2.89 (dd, J = 1.6, 15.6 Hz, 1 H, 1′-H), 3.32 (dd, J = 5.2, 15.6 Hz, 1 H, 1′′-H), 3.82 (dd, J = 3.2, 11.2 Hz, 1 H, 3-H), 4.18–4.22 (m, 1 H, 1-H) ppm. FAB-MS: calcd. for $C_{33}H_{33}N_3O_6$ 567.2369; found 567.2486.

(1*R*,3*S*)-2-(*tert*-Butoxycarbonyl)-1-[(fluorenylmethoxycarbonyl)-aminomethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (22b): White solid (78 mg, 69%), m.p. 251–253 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.28 (s, 9 H, Boc), 2.59–2.65 (m, 1 H, 4′-

H), 2.73 (dd, *J* = 4.0, 15.1 Hz, 1 H, 4′′-H), 2.83 (dd, *J* = 4.0, 14.6 Hz, 1 H, 1′-H), 3.49 (dd, *J* = 4.2, 8.8 Hz, 1 H, 1′′-H), 4.01 (dd, *J* = 4.0, 11.6 Hz, 1 H, 3-H), 4.22–4.25 (m, 1 H, 1-H) ppm. FAB-MS: calcd. for $C_{33}H_{33}N_3O_6$ 567.2369; found 567.2425.

(1*S*,3*S*,1′*S*)-2-(*tert*-Butoxycarbonyl)-1-[1′-(fluorenylmethoxycarbonyl)aminoethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (23a): White solid (78 mg, 67%), m.p. 268–269 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.18 (d, *J* = 6.2 Hz, 3 H, 2′-H), 1.28 (s, 9 H, Boc), 2.75–2.80 (m, 1 H, 4′-H), 3.07 (dd, *J* = 3.6, 15.2 Hz, 1 H, 4′′-H), 3.85 (dd, *J* = 3.5, 11.2 Hz, 1 H, 3-H), 4.30–4.33 (m, 2 H, 1-H, 1′-H) ppm. FAB-MS: calcd. for $C_{34}H_{35}N_3O_6$ 581.2526; found 581.2572.

(1*R*,3*S*,1′*S*)-2-(*tert*-Butoxycarbonyl)-1-[1′-(fluorenylmethoxycarbonyl)aminoethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (23b): White solid (70 mg, 60%), m.p. 280–281 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.29 (d, *J* = 6.6 Hz, 3 H, 2′-H), 2.73 (t, *J* = 12.8 Hz, 1 H, 4′-H), 3.05 (dd, *J* = 3.6, 15.2 Hz, 1 H, 4′′-H), 4.06–4.08 (m, 1 H, 3-H), 4.22–26 (m, 1 H, 1′-H), 4.28 (d, *J* = 1.2 Hz, 1 H, 1-H) ppm. FAB-MS: calcd. for $C_{34}H_{35}N_3O_6$ 581.2526; found 581.2570.

(1*S*,3*S*,1′*S*)-2-(*tert*-Butoxycarbonyl)-1-[1′-(fluorenylmethoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (24a): White solid (213 mg, 65%), m.p. 278–279 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.30 (s, 9 H, Boc), 2.53 (dd, *J* = 3.6, 14.8 Hz, 1 H, 4′-H), 2.75–2.81 (m, 2 H, 4′′-H, 2′-H), 2.97 (dd, *J* = 3.2, 15.6 Hz, 1 H, 2′′-H), 3.93 (dd, *J* = 3.6, 13.6 Hz, 1 H, 3-H), 4.12 (d, *J* = 1.2 Hz, 1 H, 1-H), 4.40–4.43 (m, 1 H, 1′-H) ppm. FAB-MS: calcd. for $C_{40}H_{39}N_3O_6$ 657.2839; found 657.2926.

(1*R*,3*S*,1′*S*)-2-(*tert*-Butoxycarbonyl)-1-[1′-(fluorenylmethoxycarbonylamino)-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (24b): White solid (85 mg, 67%), m.p. 281–282 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.27 (s, 9 H, Boc), 2.49–2.60 (m, 3 H, 4′-H, 4′′-H, 2′-H), 2.79 (dd, *J* = 3.8, 15.6 Hz, 1 H, 2′′-H), 4.12–4.15 (m, 2 H, 3-H, 1-H), 4.31 (dd, *J* = 3.8, 14.2 Hz, 1 H, 1′-H) ppm. FAB-MS: calcd. for $C_{40}H_{39}N_3O_6$ 657.2839; found 657.2921.

(1*S*,3*S*,1′*S*)-2-(*tert*-Butoxycarbonyl)-1-[2′-(*tert*-butoxycarbonyl)-1′-(fluorenylmethoxycarbonylamino)ethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (25a): White solid (80 mg, 60%), m.p. 285–287 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.36 (s, 9 H, CH_3), 2.15–2.19 (m, 1 H, 2′-H), 2.39–2.43 (m, 1 H, 2′′-H), 2.75–2.80 (m, 1 H, 4′-H), 3.13 (dd, *J* = 3.5, 14.0 Hz, 1 H, 4′′-H), 3.90 (dd, *J* = 3.5, 11.4 Hz, 1 H, 3-H), 4.12 (br. s, 1 H, 1-H), 4.40–4.42 (m, 1 H, 1′-H) ppm. FAB-MS: calcd. for $C_{39}H_{43}N_3O_8$ 681.3050; found 681.3132.

(1*R*,3*S*,1′*S*)-2-(*tert*-Butoxycarbonyl)-1-[2′-(*tert*-butoxycarbonyl)-1′-(fluorenylmethoxycarbonyl)aminoethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (25b): White solid (88 mg, 65%), m.p. 279–280 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.56–2.62 (m, 2 H, 2′-H), 3.06–3.11 (m, 2 H, 4-H), 4.02–4.11 (m, 1 H, 3-H), 4.31 (br. s, 1 H, 1-H), 4.39–4.42 (m, 1 H, 1′-H) ppm. FAB-MS: calcd. for $C_{39}H_{43}N_3O_8$ 681.3050; found 681.3132.

(1*S*,3*S*,1′*S*)-2-(*tert*-Butoxycarbonyl)-1-[5′-(*tert*-butyoxycarbonyl)-amino-1′-(fluorenylmethoxycarbonyl)aminopentyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (26a): White solid (95 mg, 63%), m.p. 290–292 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.20–1.24 (m, 2 H, γ-H), 1.29–1.38 (m, 4 H, β-H, δ-H), 2.15–2.17 (m, 2 H, ε-H), 2.82 (d, *J* = 5.6, 14.1 Hz, 1 H, 4′-H), 3.62–3.65 (m, 1 H, 4′′-H), 3.91–3.93 (m, 1 H, 3-H), 4.32 (br. s, 1 H, 1-H), 4.43–4.45 (m, 1 H, 1′-H) ppm. FAB-MS: calcd. for $C_{42}H_{50}N_4O_8$ 738.3629; found 738.3734.

(1*R*,3*S*,1′*S*)-2-(*tert*-Butoxycarbonyl)-1-[5′-(*tert*-butyoxycarbonyl)-amino-1′-(fluorenylmethoxycarbonyl)aminopentyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (26b): White solid (91 mg, 62%), m.p. 287–289 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.32–1.38 (m, 2 H, δ-H), 1.43–1.64 (m, 4 H, β-H, γ-H), 2.53–2.60 (m, 2 H, ε-H), 3.14–3.25 (m, 2 H, 4′-H), 4.16–4.18 (m, 1 H, 3-H), 4.31–4.36 (m, 1 H, 1′-H), 4.52 (br. s, 1 H, 1-H) ppm. FAB-MS: calcd. for $C_{42}H_{50}N_4O_8$ 738.3629; found 738.3694.

(1*S*,3*S*,1′*R*)-2-(*tert*-Butoxycarbonyl)-1-[1′-(fluorenylmethoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (27a): White solid (87 mg, 65%), m.p. 271–273 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.77–2.89 (m, 3 H, 4′-H, 2′-H), 3.13 (dd, *J* = 3.8, 14.0 Hz, 1 H, 4′′-H), 4.00–4.03 (m, 1 H, 3-H), 4.24 (br. s, 1 H, 1-H), 4.42–4.48 (m, 1 H, 1′-H) ppm. FAB-MS: calcd. for $C_{40}H_{39}N_3O_6$ 657.2839; found 657.2924.

(1*R*,3*S*,1′*R*)-2-(*tert*-Butoxycarbonyl)-1-[1′-(fluorenylmethoxycarbonyl)amino-2′-phenylethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (27b): White solid (90 mg, 68%), m.p. 272–274 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.79–2.83 (m, 2 H, 2′-H), 3.17–3.23 (m, 2 H, 4-H), 4.13–4.16 (m, 1 H, 3-H), 4.29–4.32 (m, 1 H, 1′-H), 4.49 (br. s, 1 H, 1-H) ppm. FAB-MS: calcd. for $C_{40}H_{39}N_3O_6$ 657.2839; found 657.2924.

Synthesis of Hexahydroazocino[4,5-*b*]indole Derivatives 28–33 and Tetrahydro-β-carboline Derivatives 34–39: Diisopropylethylamine (3 mL) was added to a solution of corresponding *cis*-tetrahydro-β-carboline derivatives **8**–**10a**, **12a**, **13a** or **20a** (0.5 mmol) in dry tetrahydrofuran (7 mL) and the mixture was stirred at room temperature for 2 h. Then the solution was evaporated under reduced pressure and the corresponding hexahydroazocino[4,5-*b*]indole derivatives **28**–**33** were precipitated by treatment of the crude residue with EtOAc/*n*-hexane. Under these conditions the *trans* isomers **8**–**10b**, **12b**, **13b** or **20b** gave the corresponding Fmoc-deprotected tetrahydro-β-carbolines **34**–**39** which were purified by flash chromatography using $CHCl_3$/CH_3OH (9:1) as eluent.

(6*S*,10*S*)-6,10-Imino-6,7,8,9,10,11-hexahydro-5*H*-azocino[4,5-*b*]indol-9-one (28): White solid (96 mg, 85%), m.p. 146–147 °C. $[\alpha]_D^{20}$ = +7.3 (*c* = 0.8, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 3.07–3.11 (m, 1 H, 11′-H), 3.40 (dd, *J* = 6.0, 15.6 Hz, 1 H, 11′′-H), 3.62 (d, *J* = 13.6 Hz, 1 H, 7′-H), 4.02 (dd, *J* = 4.0, 13.6 Hz, 1 H, 7′′-H), 4.51 (d, *J* = 5.2 Hz, 1 H, 10-H), 5.19 (d, *J* = 3.6 Hz, 1 H, 6-H), 7.08 (t, *J* = 7.6 Hz, 1 H, 3-H), 7.19 (t, *J* = 7.6 Hz, 1 H, 2-H), 7.38 (d, *J* = 7.6 Hz, 1 H, 1-H), 7.48 (d, *J* = 7.6 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 23.8 (C-11), 45.6 (C-7), 46.0 (C-6), 53.7 (C-10), 106.1 (C-11a), 111.8 (C-1), 117.9 (C-4), 119.9 (C-3), 123.7 (C-2), 125.9 (C-11b), 126.1 (C-5a), 137.0 (C-4a), 167.7 (C=O) ppm. FAB-MS: calcd. for $C_{13}H_{13}N_3O$ 227.1059; found 227.1121.

(6*S*,7*S*,10*S*)-6,10-Imino-7-methyl-6,7,8,9,10,11-hexahydro-5*H*-azocino[4,5-*b*]indol-9-one (29): White solid (102 mg, 87%), m.p. 163–165 °C. $[\alpha]_D^{20}$ = +19.3 (*c* = 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.33 (d, *J* = 6.4 Hz, 3 H, CH_3), 2.94 (dd, *J* = 1.2, 16 Hz, 1 H, 11′-H), 3.12 (dd, *J* = 10.0, 16.4 Hz, 1 H, 11′′-H), 3.64 (dd, *J* = 1.0, 6.4 Hz, 1 H, 7-H), 3.86–3.90 (m, 1 H, 10-H), 4.04 (d, *J* = 1.0 Hz, 1 H, 6-H), 6.98 (t, *J* = 7.6 Hz, 1 H, 3-H), 7.07 (t, *J* = 7.6 Hz, 1 H, 2-H), 7.28 (d, *J* = 7.6 Hz, 1 H, 1-H), 7.39 (d, *J* = 7.6 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 16.9 (CH_3), 22.5 (C-11), 45.0 (C-6), 48.2 (C-10), 49.8 (C-7), 106.8 (C-11a), 112.4 (C-1), 118.0 (C-4), 119.6 (C-3), 124.1 (C-2), 125.4 (C-11b), 126.1 (C-5a), 136.9 (C-4a), 166.9 (C=O) ppm. FAB-MS: calcd. for $C_{14}H_{15}N_3O$ 241.1215; found 241.1263.

(6*S*,7*S*,10*S*)-7-Benzyl-6,10-imino-6,7,8,9,10,11-hexahydro-5*H*-azocino[4,5-*b*]indol-9-one (30): White solid (126 mg, 80%), m.p. 181–

183 °C. $[\alpha]_D^{20}$ = –23.5 (*c* = 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 3.28–3.34 (m, 3 H, 11′-H, 7′-H, 7′′-H), 3.44 (dd, *J* = 5.6, 16.4 Hz, 1 H, 11′′-H), 3.99 (t, *J* = 7.2 Hz, 1 H, 7-H), 4.47 (d, *J* = 5.6 Hz, 1 H, 10-H), 4.88 (d, *J* = 1.2 Hz, 1 H, 6-H), 7.05 (t, *J* = 7.2 Hz, 1 H, 3-H), 7.14 (t, *J* = 7.2 Hz, 1 H, 2-H), 7.31–7.47 (m, 7 H, 1-H, 4-H, aryl) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 24.3 (C-11), 40.5 (C-7′), 47.3 (C-6), 52.1 (C-10), 58.2 (C-7), 105.8 (C-11a), 111.5 (C-1), 118.0 (C-4), 119.7 (C-3), 123.0 (C-2), 125.8 (C-11b), 127.3 (C-5a), 129.0, 129.4, 136.4 (aryl), 137.0 (C-4a), 168.0 (C=O) ppm. FAB-MS: calcd. for $C_{20}H_{19}N_3O$ 317.1528; found 317.1608.

(6*S*,7*S*,10*S*)-7-(*tert*-Butoxycarbonylmethyl)-6,10-imino-6,7,8,9,10,11-hexahydro-5*H*-azocino[4,5-*b*]indol-9-one (31): White solid (151 mg, 89%), m.p. 187–189 °C. $[\alpha]_D^{20}$ = –9.2 (*c* = 0.7, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.48 (s, 9 H, *t*Bu), 2.18 (dd, *J* = 9.2, 16.0 Hz, 1 H, 7′-H), 2.73 (dd, *J* = 4.8, 16.1 Hz, 1 H, 7′′-H), 2.97 (d, *J* = 14.8 Hz, 1 H, 11′-H), 3.15 (dd, *J* = 6.8, 14.6 Hz, 1 H, 11′′-H), 3.93 (d, *J* = 6.8 Hz, 1 H, 10-H), 4.25 (d, *J* = 4.6 Hz, 1 H, 6-H), 4.31 (dd, *J* = 4.4, 9.2 Hz, 1 H, 7-H), 7.00 (t, *J* = 8.0 Hz, 1 H, 3-H), 7.10 (t, *J* = 6.8 Hz, 1 H, 2-H), 7.33 (d, *J* = 8.0 Hz, 1 H, 4-H), 7.41 (d, *J* = 7.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 27.2 (C-11), 39.7 (C′), 48.7 (C-7), 53.7 (C-6), 55.6 (C-10), 109.4 (C-11a), 111.3 (C-1), 118.5 (C-4), 119.8 (C-3), 122.5 (C-2), 127.0 (C-11b), 129.7 (C-5a), 135.9 (C-4a), 170.8, 172.7 (C=O) ppm. FAB-MS: calcd. for $C_{19}H_{23}N_3O_3$ 341.1739; found 341.1829

(6*S*,7*S*,10*S*)-7-[4′-(*tert*-Butoxycarbonylamino)butyl]-6,10-imino-6,7,8,9,10,11-hexahydro-5*H*-azocino[4,5-*b*]indol-9-one (32): White solid (179 mg, 90%), m.p. 221–223 °C. $[\alpha]_D^{20}$ = +15.3 (*c* = 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 1.27–1.31 (m, 4 H, δ-H, γ-H), 1.41 (s, 9 H, *t*Bu), 1.52–1.57 (m, 2 H, β-H), 2.98–3.08 (m, 5 H, ε-H, 7′-H, 7′′-H, 11′-H), 3.15 (dd, *J* = 6.4, 16.0 Hz, 1 H, 11′′-H), 3.93 (m, 1 H, 7-H), 3.98 (d, *J* = 5.2 Hz, 1 H, 10-H), 4.34 (d, *J* = 4.0 Hz, 1 H, 6-H), 6.99 (t, *J* = 6.8 Hz, 1 H, 3-H), 7.09 (t, *J* = 7.6 Hz, 1 H, 2-H), 7.35 (d, *J* = 8.0 Hz, 1 H, 4-H), 7.40 (d, *J* = 7.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 22.7 (C-γ), 26.8 (C-11), 29.8 (C-δ), 31.8 (C-β), 39.7 (C-ε), 49.0 (C-7), 52.7 (C-6), 58.0 (C-10), 107.5 (C-11a), 111.1 (C-1), 117.5 (C-4), 118.9 (C-3), 121.7 (C-2), 126.7 (C-11b), 129.3 (C-5a), 136.8 (C-4a), 166.3, 173.7 (C=O) ppm. FAB-MS: calcd. for $C_{22}H_{30}N_4O_3$ 398.2318; found 398.2413.

(6*S*,7*R*,10*S*)-7-Benzyl-6,10-imino-6,7,8,9,10,11-hexahydro-5*H*-azocino[4,5-*b*]indol-9-one (33): White solid (138 mg, 87%), m.p. 195–196 °C. $[\alpha]_D^{20}$ = +18.9 (*c* = 1.3, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 2.46 (dd, *J* = 10.0, 14.0 Hz, 1 H, 7′-H), 3.30–3.36 (m, 2 H, 11′-H, 7′′-H), 3.42 (dd, *J* = 6.0, 15.9 Hz, 1 H, 11′′-H), 4.48–4.53 (m, 2 H, 7-H, 10-H), 5.20 (d, *J* = 3.2 Hz, 1 H, 6-H), 7.11 (t, *J* = 7.6 Hz, 1 H, 3-H), 7.23 (t, *J* = 8.0 Hz, 1 H, 2-H), 7.30–7.37 (m, 5 H, aryl), 7.40 (d, *J* = 8.0 Hz, 1 H, 4-H), 7.53 (d, *J* = 8.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 24.3 (C-11), 37.3 (C-7′), 49.8 (C-6), 52.0 (C-10), 56.2 (C-7), 107.1 (C-11a), 112.0 (C-1), 118.0 (C-4), 120.0 (C-3), 124.2 (C-2), 125.9 (C-11b), 127.3 (C-5a), 129.0, 129.5, 136.0 (aryl), 137.5 (C-4a), 168.2 (C=O) ppm. FAB-MS: calcd. for $C_{20}H_{19}N_3O$ 317.1528; found 317.1608.

Methyl (1*R*,3*S*)-1-Aminomethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (34): White solid (120 mg, 93%), m.p. 101–102 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.64 (dd, *J* = 8.0, 14.8 Hz, 1 H, 4′-H), 3.10 (dd, *J* = 4.4, 14.8 Hz, 1 H, 4′′-H), 3.21–3.30 (m, 2 H, 1′-H), 3.65–3.69 (m, 1 H, 3-H), 3.77 (s, 3 H, OCH_3), 4.02 (br. s, 1 H, 1-H), 7.15–7.19 (m, 2 H, 6-H, 8-H), 7.28 (d, *J* = 7.6 Hz, 1 H, 7-H), 7.46–7.49 (m, 1 H, 5-H) ppm. FAB-MS: calcd. for $C_{14}H_{17}N_3O_2$ 259.1321; found 259.1475.

Methyl (1*R*,3*S*,1′*S*)-1-(1′-Aminoethyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (35): White solid (130 mg, 95%), m.p. 115–116 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.19 (d, *J* = 6.6 Hz, 3 H, 2′-H), 2.55 (t, *J* = 12.8 Hz, 1 H, 4′-H), 2.98 (dd, *J* = 3.6, 15.2 Hz, 1 H, 4′′-H), 3.42–3.45 (m, 1 H, 1′-H), 3.59 (s, 3 H, OCH_3), 4.02–4.05 (m, 1 H, 3-H), 4.18 (d, *J* = 1.2 Hz, 1 H, 1-H), 6.93 (t, *J* = 7.6 Hz, 1 H, 6-H), 7.11 (t, *J* = 7.6 Hz, 1 H, 7-H), 7.31 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.38 (d, *J* = 8.0 Hz, 1 H, 5-H) ppm. FAB-MS: calcd. for $C_{15}H_{19}N_3O_2$ 273.1477; found 273.1512.

Methyl (1*R*,3*S*,1′*S*)-1-(1′-Amino-2′-phenylethyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (36): White solid (158 mg, 91%), m.p. 142–143 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.65 (dd, *J* = 3.6, 14.6 Hz, 1 H, 2′-H), 2.81–2.88 (m, 2 H, 2′′-H, 4′-H), 3.09 (dd, *J* = 4.2, 13.6 Hz, 1 H, 4′′-H), 3.62 (s, 3 H, OCH_3), 3.82–3.85 (m, 1 H, 1′-H), 4.09 (dd, *J* = 4.2, 12.8 Hz, 1 H, 3-H), 4.21 (d, *J* = 1.4 Hz, 1 H, 1-H), 7.04 (t, *J* = 8.0 Hz, 1 H, 6-H), 7.18–7.23 (m, 2 H, 7-H, 8-H), 7.39 (d, *J* = 7.8 Hz, 1 H, 5-H) ppm. FAB-MS: calcd. for $C_{21}H_{23}N_3O_2$ 349.1790; found 349.1837.

Methyl (1*R*,1′*S*,3*S*)-1-[1′-Amino-2′-(*tert*-butoxycarbonyl)ethyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (37): Colourless oil (178 mg, 96%). ^{1}H NMR (400 MHz, CD_3OD): δ = 2.20 (dd, *J* = 3.6, 14.4 Hz, 1 H, 2′-H), 2.54–2.57 (m, 2 H, 2′′-H, 4′-H), 3.15 (dd, *J* = 4.0, 15.6 Hz, 1 H, 4′′-H), 3.72 (s, 3 H, OCH_3), 3.91–3.93 (m, 1 H, 1′-H), 4.06 (dd, *J* = 4.2, 12.8 Hz, 1 H, 3-H), 4.24 (d, *J* = 1.4 Hz, 1 H, 1-H), 7.04 (t, *J* = 8.0 Hz, 1 H, 6-H), 7.15 (t, *J* = 8.0 Hz, 1 H, 7-H), 7.39 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.39 (d, *J* = 7.8 Hz, 1 H, 5-H) ppm. FAB-MS: calcd. for $C_{20}H_{27}N_3O_4$ 373.2002; found 373.2051.

Methyl (1*R*,3*S*,1′*S*)-1-[5′-(*tert*-Butoxycarbonylamino)-1′-aminopentyl]-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (38): White solid (203 mg, 95%), m.p. 162–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.33 (m, 2 H, γ-H, δ-H), 1.41 (s, 9 H, CH_3), 1.62–1.67 (m, 2 H, β-H), 2.53–2.57 (m, 2 H, ε-H), 3.10–3.14 (m, 2 H, 4′-H), 3.46–3.49 (m, 1 H, 1′-H), 3.62 (s, 3 H, OCH_3), 3.71–3.73 (m, 1 H, 3-H), 4.00 (br. s, 1 H, 1-H), 7.00 (t, *J* = 7.6 Hz, 1 H, 6-H), 7.10 (t, *J* = 8.0 Hz, 1 H, 7-H), 7.36–7.40 (m, 2 H, 8-H, 5-H) ppm. FAB-MS: calcd. for $C_{23}H_{34}N_4O_4$ 430.2580; found 430.2623.

Methyl (1*R*,1′*R*,3*S*)-1-(1′-Amino-2′-phenylethyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (39): White solid (166 mg, 95%), m.p. 142–143 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.63 (dd, *J* = 8.8, 14.6 Hz, 1 H, 2-H), 2.91 (dd, *J* = 4.2, 13.6 Hz, 1 H, 4′′-H), 3.07–3.10 (m, 2 H, 2′′-H, 4′′-H), 3.53 (s, 3 H, OCH_3), 3.92–3.95 (m, 1 H, 1-H, 3-H), 4.39 (br. s, 1 H, 1-H), 6.99 (t, *J* = 8.0 Hz, 1 H, 6-H), 7.13–7.18 (m, 2 H, 7-H, 8-H), 7.37 (d, *J* = 8.0 Hz, 1 H, 5-H) ppm. FAB-MS: calcd. for $C_{21}H_{23}N_3O_2$ 349.1790; found 349.1837.

Supporting Information (see also the footnote on the first page of this article): As example, the experimental 1D and 2D NMR spectroscopic data for compounds **17a**, **17b** and **21** are reported.

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