

A Convenient Synthesis of Indole-Substituted 2-Pyrrolidones and Their Cyclized Derivatives

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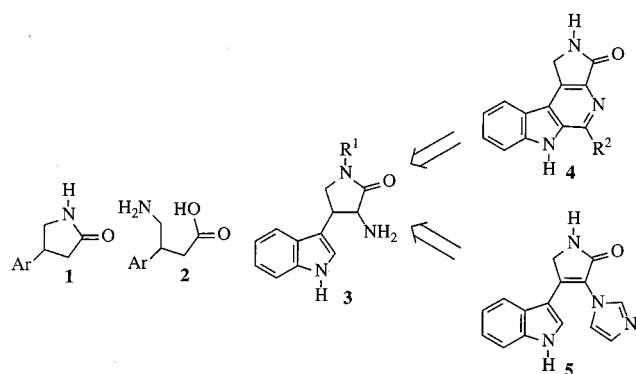
Keywords: Cyclizations / Drug research / Meldrum's acid derivatives / Nitrogen heterocycles / Pyrrolopyridindoles

Condensation between indole, Meldrum's acid, and benzyloxycarbonylacetaldehyde or aminoacetaldehyde derivatives yielded trimolecular adducts **7a–c**. The latter were cyclized to indole-substituted 2-pyrrolidones **15a–b** or

3-aminopyrrolid-2-ones **18a–b**, depending on the starting material. Derivative **18a** was transformed into pyrrolo-[3',4':5,6]pyrido[3,4-*b*]indol-3(2*H*)-ones **19a** and **20a** by a Pictet–Spengler condensation with benzaldehyde.

Introduction

4-Arylpyrrolidin-2-one derivatives **1** (Scheme 1) are cyclic analogs of 3-aryl- γ -aminobutyric acids (3-aryl-GABA) **2**, which are effective medicines (e.g. Baclofen[®]) for the treatment of neurological disorders. Surprisingly, their indolic derivatives (Ar = indole) are not common, and to the best of our knowledge, compounds like **3** (Scheme 1), bearing a primary amino group at position 3, were unknown until now. These latter compounds, furthermore, can serve as useful building blocks for the synthesis of pharmacologically active molecules. Among these, compounds of general structure **4** are potent tyrosine-kinase inhibitors,^[1] and compound **5** is very close to synthetic analogs of staurosporine.^[2,3]



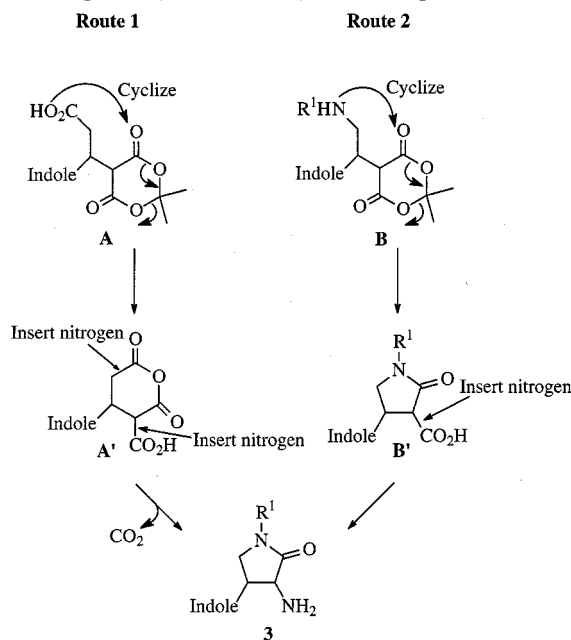
Scheme 1

In this paper, we report an efficient synthesis of indole-substituted 2-pyrrolidone derivatives **3**, as well as prelimin-

ary results concerning their conversion into pyrrolo[3',4':5,6]pyrido[3,4-*b*]indol-3-ones **4**.

Results and Discussion

Two routes, both based on the opening of the dioxane ring of a Meldrum's acid derivative (Scheme 2), were envisaged for the synthesis of **3**. In Route 1, intramolecular cyclization of **A** would lead to mixed anhydride **A'**, which, after submission to a double nitrogen insertion (by means of a Curtius reaction), would give the target compound **3**. In a less ambitious scheme (Route 2), the starting material is amine derivative **B**. In this case, intramolecular cyclization would give acid **B'**, further transformation of which by Curtius reaction would afford **3**. Decarboxylation of **A'** or **B'** would give **1** (Ar = Indole) as a side product.



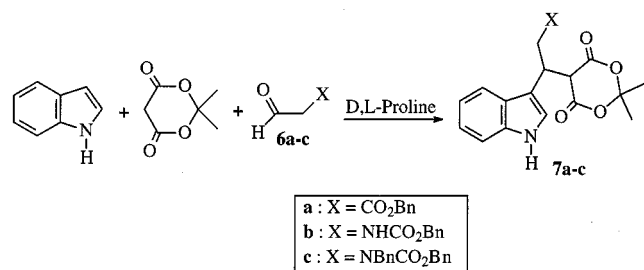
Scheme 2

Synthesis of type **A** or **B** derivatives could be achieved using a protocol that was developed in our laboratory,^[4]

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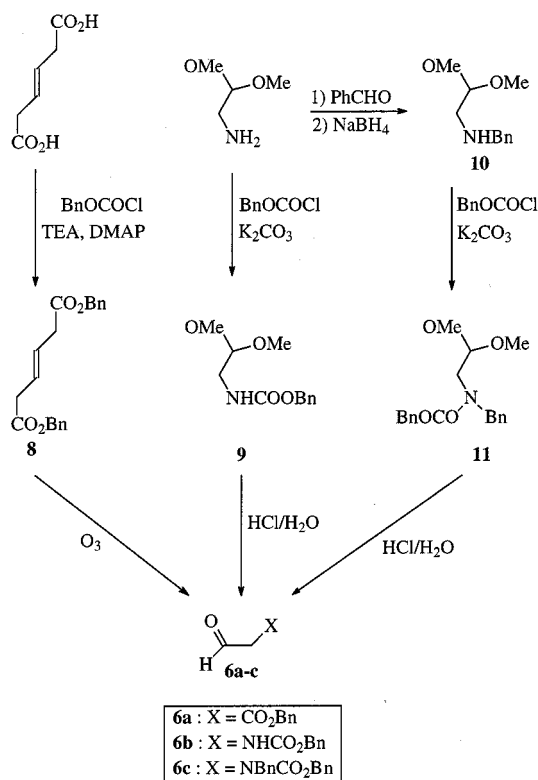
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based on results reported by Yonemitsu.^[5] It involved the trimolecular condensation between indole, Meldrum's acid, and aldehyde **6a–c**, in the presence of D,L-proline as catalyst (Scheme 3), giving compounds **7a–c** in good yields (64–76%).



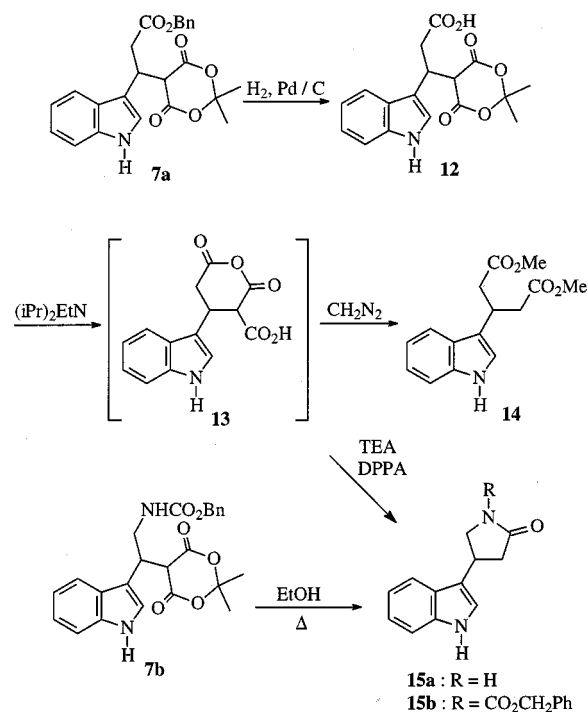
Scheme 3

For this purpose, we needed to synthesize aldehydes **6a–c**. Dibenzylation of *trans*-3-hexenedioic acid with benzyl chloroformate, triethylamine and a catalytic amount of 4-(dimethylamino)pyridine,^[6] giving **8** in 66% yield, and subsequent ozonolysis of the dibenzyl intermediate gave aldehyde **6a** (Scheme 4). This two-step procedure is a more convenient method than the one previously reported.^[7] Aldehydes **6b** and **6c** were obtained by hydrolysis of acetals **9** and **11**. The synthesis of **6b** has already been described,^[8,9] but **6c** is a new synthon, in which both *N*-protecting groups show different sensitivity to hydrogenolysis (see below). Because of their instability, aldehydes **6a–c** were used immediately in the crude state for the trimolecular condensation (see Experimental Section).



Scheme 4

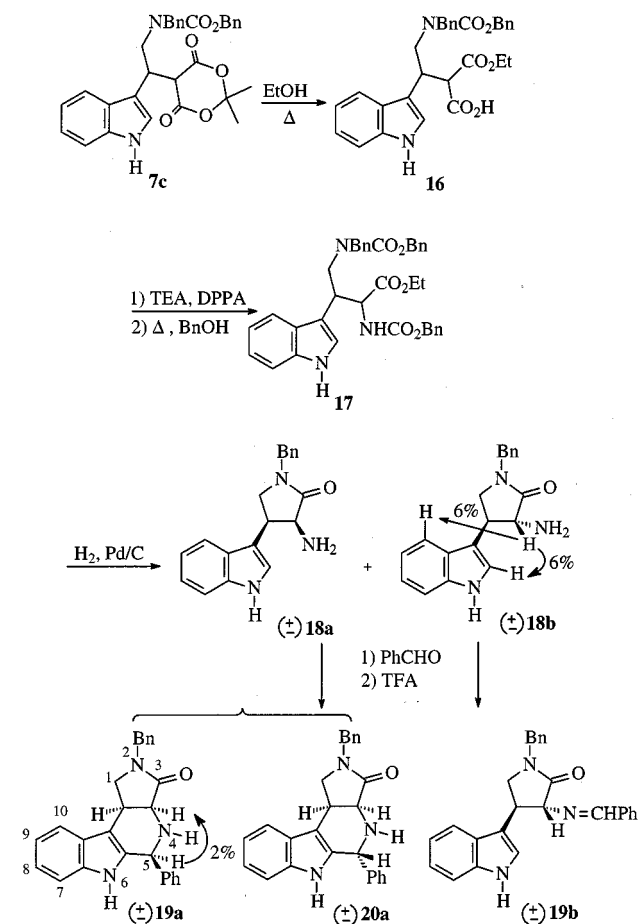
Route 1 (Scheme 5) starts with the debenzylation of **7a** by hydrogenolysis to give **12** in 79% yield. This, in the presence of Hünig's base, presumably gave the unstable anhydride **13** (IR absorption bands of the crude solution at 1881, 1763, and 1730 cm⁻¹). The crude mixture containing **13** was treated with diazomethane, affording diester **14** in 87% yield, presumably through ring opening followed by decarboxylation. This decarboxylation also occurred when the same mixture was allowed to react with diphenylphosphoryl azide (DPPA), giving lactam **15a** in moderate yield (22%). This route might indeed lead to 4-(1*H*-indol-3-yl)-pyrrolidin-2-one, but decarboxylation prevented access to its 3-amino derivative.



Scheme 5

As has been reported,^[10] an amide nitrogen atom can react with a Meldrum's acid derivative to give an imide. Therefore, we could envisage the intramolecular reaction of a carbamate nitrogen atom with a Meldrum's acid moiety. Indeed, an ethanolic solution of compound **7b** was refluxed to afford **15b** in fair yield (63%), but unfortunately again with the loss of the carboxylic group.

Route 2 potentially led to the same type of compound as did Route 1, but in a more convenient way; although decarboxylation still remained a problematic side reaction. Taking account of the fact that the rigid structure of the γ -lactam could enhance the rate of decarboxylation, we decided to perform the nitrogen insertion (through Curtius reaction) before the formation of the lactam ring. This required the opening of the Meldrum's acid moiety with an external nucleophile, such as ethanol.



Scheme 6

This was achieved by using compound **7c** (Scheme 6). Refluxing an ethanolic solution of **7c** yielded **16** as a 1:1 mixture of diastereomers in 90% yield. Yamada's modified Curtius reaction^[11] was applied to **16**, affording **17** as a mixture of diastereomers in the same ratio, in 63% yield. Cleavage of both carbamate functions, followed by cyclization, proceeded smoothly by hydrogenolysis in a one-pot reaction. Both diastereomers could be isolated by column chromatography, giving **18a** (less polar diastereomer) and **18b** (more polar diastereomer) in 38% and 37% yield, respectively.

Since $J_{3\text{-H}/4\text{-H}}$ coupling constant values in **18a** and **18b** are very close together (8.0 Hz and 9.0 Hz, respectively), *cis/trans* stereochemistry was assigned with the aid of nuclear Overhauser enhancements (nOe) (Scheme 6). From a precedent concerning the relative stereochemistry of 5-membered cycles,^[12] we studied interactions between a proton belonging to the 5-membered ring and protons belonging to the substituent located at the adjacent carbon atom of the ring. The distance between these protons is shorter in *trans* isomers than in *cis* isomers. For compound **18b** we indeed measured a strong (6%) nOe between the proton located next to the carbonyl group of the lactam ring and protons located at positions 2 and 4 of the indole moiety, which was not the case for compound **18a**. X-ray analysis confirmed the relative stereochemistry (Figure 1).

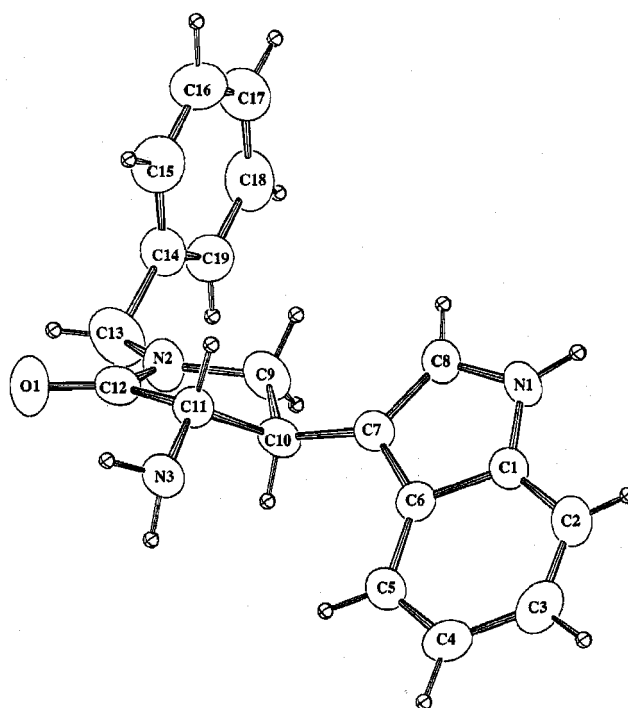


Figure 1. Molecular structure of compound **18b** as determined by X-ray diffraction; the numbering does not correspond to the systematic name

Further transformations could be carried out by a Pictet–Spengler reaction following Bailey's procedure,^[13] affording 2-benzylhexahydropyrrolo[3',4':5,6]pyrido[3,4-*b*]indol-3(2*H*)-one (**19a**) (less polar diastereomer) and **20a** (more polar diastereomer) in a 1:1 ratio (58% overall yield). As expected, this reaction did not take place when the *trans* diastereomer **18b** was used as starting material, presumably because of tension resulting from a *trans* ring junction. According to TLC, a new compound was formed (presumably the intermediate imine **19b**), but it decomposed during column chromatography and the starting amine was recovered completely.

The relative configuration at the new chiral center of compounds **19a** and **20a** could be assigned by measuring nOes between 5-H and 3a-H (Scheme 6). We also noticed that, in the case of compound **19a**, the ^{13}C NMR signals of C-5 and C-3a appear downfield compared to those of **20a** (see Experimental Section). This is in accordance with Coak's results^[14,15] concerning 1,3-disubstituted tetrahydro- β -carboline.

Conclusion

In conclusion, an efficient synthesis of new 3-amino-4-(1*H*-indol-3-yl)pyrrolidin-2-one derivatives was achieved. Compound **18a** was readily converted into new hexahydropyrrolo[3',4':5,6]pyrido[3,4-*b*]indol-3(2*H*)-one derivat-

ives. Extension of this approach to the synthesis of analogs of natural products is under way in our laboratory.

Experimental Section

General: Melting points were determined with a Reichert Thermo-var hot-stage apparatus and are uncorrected. – IR (film) spectra were measured with a Bomem FTIR instrument. – UV spectra were measured in MeOH, using a UNICAM 8700 UV/Vis spectrophotometer. – ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured with a Bruker AC 300 spectrometer. – Mass spectra were recorded with a VG Autospec apparatus. – All solvents were purified by following standard literature methods. – Chromatography was performed on silica gel 60 (Merck). Reactions were monitored using Merck TLC aluminium sheets (Kiesel-gel 60F₂₅₄).

Benzyl 3-[2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl]-3-(1H-indol-3-yl)propanoate (7a): Ozonolysis of the alkene: A stirred solution of **8** (2.65 g, 8.18 mmol) in CH_2Cl_2 (150 mL) was cooled to -78°C . O_3 was bubbled through the solution for ca. 2 h, until it became blue. Excess Me_2S was added to the mixture, until the blue color disappeared. The solution was concentrated to a volume of 10 mL. – Condensation with indole and Meldrum's acid: The residue was dissolved in CH_3CN (100 mL) and to this solution were added indole (957 mg, 8.18 mmol), Meldrum's acid (1.18 g, 8.18 mmol), and D,L-proline (47 mg, 0.41 mmol) under nitrogen. The reaction mixture was stirred for 2 d at room temperature. The solvent was evaporated and column chromatography (eluent: acetone/hexane, 5:9) yielded 2.60 g of pale green solid (6.18 mmol, 76% yield). – M.p. 46°C . – UV: $\lambda_{\text{max}} = 205\text{ nm}$, 224, 270. – IR (film): $\nu = 3412\text{ cm}^{-1}$, 1778, 1741, 1298, 1205, 1165, 1101, 1013, 745. – ^1H NMR (CDCl_3): $\delta = 1.31$ (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3), 3.08 (dd, $J = 6.7, 17.0\text{ Hz}$, 1 H, CH_2CO), 3.51 (dd, $J = 9.5, 17.0\text{ Hz}$, 1 H, CH_2CO), 4.15 (d, $J = 3.0\text{ Hz}$, 1 H, Meldrum CH), 4.70 (m, 1 H, CH), 5.08 (d, $J = 4.0\text{ Hz}$, 2 H, CH_2Ph), 7.08–7.40 (m, 9 H, H_{arom}), 7.72 (d, $J = 8.0\text{ Hz}$, 1 H, indole 4-H), 8.28 (s, 1 H, indole NH). – ^{13}C NMR (CDCl_3): $\delta = 27.5$ (CH_3), 28.0 (CH_3), 31.8 (CH), 37.2 (CH_2CO), 49.5 (Meldrum CH), 66.4 (CH_2Ph), 105.1 (Meldrum acetonide carbon), 111.1 (indole C-7), 114.3 (indole C-3), 119.1, 119.9, 122.3, 123.6 (indole C-2), 126.3 (indole C-3a), 128.0 (Ph), 128.1 (Ph), 128.4 (Ph), 135.5, 135.6, 165.0 (Meldrum C=O), 165.6 (Meldrum C=O), 172.2 (ester C=O). – $\text{C}_{24}\text{H}_{23}\text{N}_1\text{O}_6$ (421.43). – MS (EI); m/z (%): 373 (15), 277 (92) [$\text{M}^+ - \text{Meldrum}$], 181 (25), 170 (58), 143 (100), 115 (60).

Benzyl {2-[2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl]-2-(1H-indol-3-yl)ethyl}carbamate (7b): Deprotection of the acetal: To a stirred solution of acetal **9** (3.50 g, 14.60 mmol) in THF (80 mL) was added 10% HCl solution (80 mL). The reaction mixture was stirred at room temperature for 12 h. The organic solvent was evaporated, and the aqueous residue was extracted with Et_2O ($3 \times 80\text{ mL}$). The combined extracts were washed with brine ($3 \times 80\text{ mL}$), dried (Na_2SO_4), and concentrated to a volume of 10 mL. – Condensation with indole and Meldrum's acid: The residue was dissolved in CH_3CN (100 mL) and to this solution were added indole (854 mg, 7.30 mmol), Meldrum's acid (1.05 g, 7.30 mmol), and D,L-proline (42 mg, 0.36 mmol), under nitrogen. The reaction mixture was stirred for 20 h at room temperature. The solvent was evaporated and column chromatography (eluent: acetone/hexane, 5:9) yielded 2.04 g of a light brown solid (4.68 mmol, 64% yield). – M.p. 62°C . – UV: $\lambda_{\text{max}} = 206\text{ nm}$, 272, 289. – IR (film): $\nu = 3343\text{ cm}^{-1}$, 3065, 2949, 1778, 1740, 1701, 1528, 1296, 1258, 743. – ^1H NMR

(CDCl_3): $\delta = 1.18$ (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 3.82 (m, 1 H, CH_2NH), 3.92 (d, $J = 3.0\text{ Hz}$, 1 H, Meldrum CH), 4.01 (m, 1 H, CH_2NH), 4.41 (br t, 1 H, CH), 5.10 (m, 2 H, CH_2Ph), 5.22 (br t, 1 H, carbamate NH), 7.05–7.40 (m, 9 H, H_{arom}), 7.68 (d, $J = 8.0\text{ Hz}$, 1 H, indole 4-H), 8.49 (s, 1 H, indole NH). – ^{13}C NMR (CDCl_3): $\delta = 27.7$ (CH_3), 27.9 (CH_3), 37.0 (CH), 44.0 (CH_2NH), 48.4 (Meldrum CH), 66.8 (CH_2Ph), 105.3 (Meldrum acetonide carbon), 111.1 (indole C-7), 111.9 (indole C-3), 119.2, 119.5, 122.3, 123.5 (indole C-2), 126.9 (indole C-3a), 128.0, 128.3, 128.4, 135.5, 136.2, 156.6 (carbamate C=O), 165.5 (Meldrum C=O), 165.6 (Meldrum C=O). – $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_6$ (436.45). – MS (EI); m/z (%): 334 (10) [$\text{M}^+ - \text{CH}_3\text{COCH}_3 - \text{CO}_2$], 203 (12), 143 (20), 117 (100).

Benzyl (Benzyl){2-[2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl]-2-(1H-indol-3-yl)ethyl}carbamate (7c): Deprotection of the acetal: To a stirred solution of **11** (27.65 g, 84.06 mmol) in CH_3CN (310 mL) was added 10% HCl solution (310 mL). The reaction mixture was stirred at room temperature for 12 h. The organic solvent was evaporated, and the aqueous residue was extracted with Et_2O ($3 \times 100\text{ mL}$). The combined organic extracts were washed with brine ($3 \times 100\text{ mL}$), dried (Na_2SO_4), and concentrated to a 10 mL volume. – Condensation of the aldehyde with indole and Meldrum's acid: The residue was dissolved in CH_3CN (200 mL) and to this solution were added indole (4.92 g, 42.00 mmol), Meldrum's acid (6.05 g, 42.00 mmol), and D,L-proline (242 mg, 2.10 mmol), under nitrogen. The reaction mixture was stirred for 20 h at room temperature. The solvent was evaporated and column chromatography (eluent: EtOAc /hexane, 3:7) afforded 15.46 g (29.40 mmol, 70% yield) of a light brown solid. – M.p. 116°C . – UV: $\lambda_{\text{max}} = 206\text{ nm}$, 272, 289. – IR (film): $\nu = 3424, 2949, 1778, 1742, 1690, 1296, 1234, 1013, 743$. – ^1H NMR (CDCl_3): $\delta = 1.25$ (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 3.78 (m, 2 H), 4.22 (m, 1 H), 4.45 (d, $J = 15.6\text{ Hz}$, 1 H, NCH_2Ph), 4.60 (t, $J = 3.0\text{ Hz}$, 1 H), 4.61 (d, $J = 15.6\text{ Hz}$, 1 H, NCH_2Ph), 5.17 (d, $J = 12.8\text{ Hz}$, 1 H, COOCH_2Ph), 5.23 (d, $J = 12.8\text{ Hz}$, 1 H, COOCH_2Ph), 7.00–7.40 (m, 14 H, H_{arom}), 7.55 (d, $J = 8.0\text{ Hz}$, 1 H, indole 4-H), 8.10 (s, 1 H, NH). – ^{13}C NMR (CDCl_3): $\delta = 27.7$ (CH_3), 28.1 (CH_3), 35.4 (CH), 48.6 (Meldrum CH), 50.5 (CH_2N), 51.4 (CH_2N), 67.7 (OCH_2Ph), 105.0 (Meldrum acetonide carbon), 111.0 (indole C-7), 112.9 (indole C-3), 119.2, 120.0, 122.4, 123.9 (indole C-2), 127.1 (indole C-3a), 127.4, 127.5, 128.1, 128.2, 128.4, 128.5, 135.5, 136.6, 137.7, 157.1 (carbamate C=O), 165.3 (Meldrum C=O), 165.5 (Meldrum C=O). – $\text{C}_{31}\text{H}_{30}\text{N}_2\text{O}_6$ (526.57). – MS (EI); m/z (%) = 442 (17), 382 (13) [$\text{M}^+ - \text{Meldrum}$], 325 (18), 300 (10), 290 (45) [$\text{M}^+ - \text{Meldrum} - \text{Bn}$], 247 (13), 156 (15), 143 (100), 115 (20).

Dibenzyl (E)-Hex-3-enedioate (8): A stirred solution of (E)-3-hexenedioic acid (1.80 g, 12.50 mmol) and triethylamine (3.83 mL, 27.50 mmol) in CH_2Cl_2 (100 mL) was cooled to 0°C with an ice bath. To this solution was added benzyl chloroformate (3.57 mL, 25.00 mmol), and 4-(dimethylamino)pyridine (153 mg, 1.25 mmol). After warming the mixture to room temperature, it was stirred for 12 h, then washed with 5% NaHCO_3 solution ($2 \times 50\text{ mL}$), 5% citric acid solution ($2 \times 50\text{ mL}$), and brine ($2 \times 50\text{ mL}$), dried (Na_2SO_4), and the solvent was then removed. The residue was purified by column chromatography (eluent: EtOAc /hexane, 2:8) to give 2.69 g (8.30 mmol, 66% yield) of white crystals. – M.p. 40°C . – UV: $\lambda_{\text{max}} = 207\text{ nm}$. – IR (film): $\nu = 3026\text{ cm}^{-1}$, 2944, 1726, 1383, 1302, 1184, 970, 741, 698. – ^1H NMR (CDCl_3): $\delta = 3.12$ (d, $J = 5.4\text{ Hz}$, 4 H, CH_2CO), 5.12 (s, 4 H, CH_2Ph), 5.72 (m, 2 H, CH), 7.34 (s, 10 H, Ph). – ^{13}C NMR (CDCl_3): $\delta = 37.4$ (CH_2CO), 66.1 (CH_2Ph), 125.6 (CH), 127.9 (Ph), 128.1 (Ph), 128.3 (Ph), 135.5 (Ph), 171.0 (C=O). – $\text{C}_{20}\text{H}_{20}\text{O}_4$. – MS (EI); m/z (%): 325 (53) [$\text{M}^+ + \text{H}$], 307 (10), 271 (30), 233 (55), 181 (100), 145 (40), 127 (95), 107 (77). – HRMS: calcd. 325.1439; found 325.1434.

Benzyl (2,2-Dimethoxyethyl)carbamate (9): To a stirred solution of (2,2-dimethoxyethyl)amine (1.63 mL, 14.96 mmol) in Et₂O (75 mL) were added H₂O (75 mL) and K₂CO₃ (6.20 g, 44.86 mmol). The reaction mixture was cooled to 0 °C and benzyl chloroformate (2.14 mL, 14.96 mmol) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 12 h. The phases were separated and the aqueous layer was extracted with Et₂O (2 × 50 mL). The combined organic extracts were washed with 5% citric acid solution (3 × 75 mL) and brine (2 × 75 mL), dried (Na₂SO₄), and the solvent was then removed to give 3.50 g (14.60 mmol, 97% yield) of colorless oil. – UV: λ_{max} = 207 nm. – IR (film): ν = 3337 cm⁻¹, 2944, 2835, 1722, 1535, 1254, 1130, 1065, 970, 698. – ¹H NMR (CDCl₃): δ = 3.32 (t, *J* = 6.0 Hz, 2 H, CH₂NH), 3.38 (s, 6 H, OCH₃), 4.39 (t, *J* = 6.0 Hz, 1 H, CH), 5.02 (br t, 1 H, NH), 5.11 (s, 2 H, CH₂Ph), 7.35 (m, 5 H, Ph). – ¹³C NMR (CDCl₃): δ = 42.5 (CH₂NH), 54.3 (CH₃), 66.8 (OCH₂), 102.8 (CH), 128.0, 128.1, 128.5, 136.4, 156.4 (C=O). – C₁₂H₁₇N₁O₄: Mr = 331.32. – MS (EI); *m/z* (%): 239 (5) [M⁺], 207 (30), 164 (100). – HRMS: calcd. 239.1157; found 239.1120.

Benzyl(2,2-dimethoxyethyl)amine (10): To a solution of (2,2-dimethoxyethyl)amine (10.67 mL, 98.11 mmol) in dry toluene (150 mL) was added benzaldehyde (10.00 mL, 98.11 mmol). The mixture was heated to 80 °C and stirred at this temperature for 12 h. The solvent was then removed in vacuo, and the residue was dissolved in methanol (120 mL). The mixture was stirred, cooled in an ice bath and sodium tetrahydroborate (3.78 g, 100.00 mmol) was added portionwise. After completion of the addition, the mixture was stirred at room temperature for 24 h. The methanol was removed in vacuo, and the white residue was dissolved in EtOAc (150 mL), washed with water (3 × 120 mL), dried (Na₂SO₄), and the solvent was then removed to give 17.79 g of **10** as a colorless oil (91.23 mmol, 93% yield). – UV: λ_{max} = 203 nm. – IR (film): ν = 2934 cm⁻¹, 2905, 2832, 1495, 1452, 1194, 1130, 1067, 739, 698. – ¹H NMR (CDCl₃): δ = 1.59 (s, 1 H, NH), 2.76 (d, *J* = 5.4 Hz, 2 H, CH₂CH), 3.38 (s, 6 H, OCH₃), 3.81 (s, 2 H, CH₂NH), 4.49 (t, *J* = 5.4 Hz, 1 H, CH), 7.31 (m, 5 H, H_{arom}). – ¹³C NMR (CDCl₃): δ = 50.5, 53.8, 53.9 (CH₃), 103.9 (CH), 126.9, 128.1, 128.4, 140.1. – C₁₁H₁₇N₁O₂: Mr = 203.25. – MS (EI); *m/z* (%): 195 (3) [M⁺], 164 (25), 120 (100), 106 (13). – HRMS: calcd. 195.1259; found 195.1258.

Benzyl (Benzyl)(2,2-dimethoxyethyl)carbamate (11): To a solution of **10** (16.91 g, 86.74 mmol) in Et₂O (150 mL) was added K₂CO₃ (35.96 g, 260.20 mmol) and water (150 mL). After cooling the reaction mixture with an ice bath, benzyl chloroformate (12.38 mL, 86.74 mmol) was added dropwise. After 2 h, the layers were separated, and the aqueous layer was extracted with Et₂O (2 × 100 mL). The combined organic extracts were washed with water (3 × 100 mL) and dried (Na₂SO₄). The solvent was then removed to give 27.82 g of **11** as a yellowish oil (84.56 mmol, 97% yield). – UV: λ_{max} = 208 nm. – IR (film): ν = 2947 cm⁻¹, 1703, 1418, 1242, 1122. – ¹H NMR ([D₅]pyridine): δ = 3.28 (s, 1.5 H, OCH₃), 3.32 (s, 1.5 H, OCH₃), 3.51 (d, *J* = 4.0 Hz, 1 H, CHCH₂), 3.63 (d, *J* = 4.0 Hz, 1 H, CHCH₂), 4.64 (t, *J* = 4.0 Hz, 0.5 H, CH), 4.74 (s, 1 H, NCH₂), 4.79 (t, *J* = 4.0 Hz, 0.5 H, CH), 4.84 (s, 1 H, NCH₂), 5.34 (s, 1 H, OCH₂), 5.38 (s, 1 H, OCH₂), 7.20–7.55 (m, 10 H, H_{arom}). – ¹³C NMR (CDCl₃): δ = 47.7, 48.7, 51.4, 54.5 (OCH₃), 67.3 (OCH₂), 103.4 (CH), 103.9 (CH), 127.2, 127.8, 127.9, 128.4, 136.6, 137.7, 156.4 (C=O). – C₁₉H₂₃N₁O₄: Mr = 329.38. – MS (EI); *m/z* (%): 298 (100) [M⁺ – OCH₃], 254 (54), 222 (49), 181 (39), 162 (29), 118 (31). – HRMS: calcd. 298.1443; found 298.1437.

3-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-(1H-indol-3-yl)propionic Acid (12): To a solution of **7a** (850 mg, 2.02 mmol) in absolute ethanol (50 mL) was added 10% Pd/C (127 mg). The mixture

was stirred under H₂ at atmospheric pressure at room temperature for 20 h. The suspension was filtered through Celite®, and the solvent was evaporated to give 525 mg (1.59 mmol, 79% yield) of a clear orange solid. – M.p. 44 °C. – UV: λ_{max} = 205 nm, 272, 289. – IR (film): ν = 3410 cm⁻¹, 2980, 1175, 1740, 1304, 1206, 1101, 1017, 746. – ¹H NMR ([D₆]DMSO): δ = 1.32 (s, 3 H, CH₃), 1.72 (s, 3 H, CH₃), 3.10 (m, 2 H, CH₂), 4.51 (br t, *J* = 9.0 Hz, 1 H, CH), 4.68 (d, *J* = 2.0 Hz, 1 H, Meldrum CH), 7.01 (t, *J* = 8.0 Hz, 1 H, indole 5-H), 7.08 (t, *J* = 8.0 Hz, 1 H, indole 6-H), 7.34 (d, *J* = 8.0 Hz, 1 H, indole 7-H), 7.62 (d, *J* = 8.0 Hz, 1 H, indole 4-H), 10.98 (s, 1 H, NH), 12.22 (br s, 1 H, COOH). – ¹³C NMR ([D₆]DMSO): δ = 27.1 (CH₃), 27.8 (CH₃), 31.9 (CH), 38.7 (CH₂), 50.6 (Meldrum CH), 105.1 (Meldrum acetonide carbon), 111.5 (indole C-7), 113.8 (indole C-3), 118.7, 119.2, 121.2, 123.9 (indole C-2), 126.8 (indole C-3a), 135.7 (indole C-7a), 165.8 (Meldrum C=O), 165.9 (Meldrum C=O), 173.3 (acid C=O). – C₁₇H₁₇N₁O₆: Mr = 331.32. – MS (EI); *m/z* (%): 229 (59) [M⁺ – CH₃COCH₃ – CO₂], 201 (10), 170 (15), 143 (100), 115 (26).

Dimethyl 3-(1H-Indol-3-yl)pentanedioate (14): To a solution of **12** (100 mg, 0.30 mmol) in CH₃CN (50 mL) was added ethyldiisopropylamine (0.53 mL, 3.02 mmol). The solution was stirred at 50 °C for 3 d. The solvent was evaporated and Et₂O (50 mL) was added to the residue. To the suspension was added an excess of diazomethane. Dissolution gradually occurred on vigorous stirring. The mixture was stirred for 10 h at room temperature, then concentrated under reduced pressure to give a brown residue which, after crystallization in MeOH, gave 72 mg (0.26 mmol, 87% yield) of white crystals. – M.p. 124 °C. – UV: λ_{max} = 203 nm, 221, 274, 281, 291. – IR (KBr): ν = 3403 cm⁻¹, 2953, 1732, 1458, 1435, 1340, 1279, 1175, 1011, 745. – ¹H NMR (CDCl₃): δ = 2.82 (d, *J* = 6.5 Hz, 4 H, CH₂), 3.60 (s, 6 H, OCH₃), 3.99 (t, *J* = 6.5 Hz, 1 H, CH), 6.98 (d, *J* = 2.0 Hz, 1 H, indole 2-H), 7.09 (t, *J* = 8.0 Hz, 1 H, indole 5-H), 7.15 (t, *J* = 8.0 Hz, 1 H, indole 6-H), 7.30 (d, *J* = 8.0 Hz, 1 H, indole 7-H), 7.62 (d, *J* = 8.0 Hz, 1 H, indole 4-H), 8.50 (br s, 1 H, indole NH). – ¹³C NMR (CDCl₃): δ = 29.9 (CH), 39.8 (CH₂), 51.4 (OCH₃), 111.3 (indole C-7), 117.1 (indole C-3), 118.7, 119.2, 121.2 (indole C-2), 121.7, 126.0 (indole C-3a), 136.3 (indole C-7a), 172.6 (ester C=O). – C₁₅H₁₇N₁O₄: Mr = 275.31. – MS (EI); *m/z* (%): 275 (43) [M⁺], 244 (10), 215 (20), 202 (100), 170 (20), 160 (70), 143 (55), 115 (30). – HRMS: calcd. 275.1154; found 275.1163.

4-(1H-Indol-3-yl)pyrrolidin-2-one (15a): To a solution of **12** (550 mg, 1.66 mmol) in CH₃CN (50 mL) was added ethyldiisopropylamine (2.89 mL, 16.60 mmol). The solution was stirred at 50 °C for 3 d. The solvent was evaporated and the residue was dissolved in *t*BuOH (50 mL). The solution was heated to 50 °C, and diphenylphosphoryl azide (0.36 mL, 1.66 mmol) was added. The mixture was stirred at this temperature for 2 d. The solvent was evaporated and column chromatography (eluent: EtOAc/MeOH, 100:2) gave 73 mg (0.37 mmol, 22% yield) of white crystals. – M.p. 163 °C. – UV: λ_{max} = 221 nm, 281, 290. – IR (KBr): ν = 3406 cm⁻¹, 3260, 1680, 1431, 1339, 1267, 1103, 743. – ¹H NMR ([D₆]DMSO): δ = 2.40 (dd, *J* = 9.0, 17.0 Hz, 1 H, CH₂CO), 2.60 (dd, *J* = 9.0, 17.0 Hz, 1 H, CH₂CO), 3.32 (t, *J* = 8.0 Hz, 1 H, CH₂NH), 3.73 (t, *J* = 8.0 Hz, 1 H, CH₂NH), 3.85 (m, 1 H, CH), 7.01 (t, *J* = 8.0 Hz, 1 H, indole 5-H), 7.11 (t, *J* = 8.0 Hz, 1 H, indole 6-H), 7.24 (d, *J* = 2.0 Hz, 1 H, indole 2-H), 7.38 (d, *J* = 8.0 Hz, 1 H, indole 7-H), 7.58 (d, *J* = 8.0 Hz, 1 H, indole 4-H), 7.71 (s, 1 H, lactam NH), 10.92 (s, 1 H, indole NH). – ¹³C NMR ([D₆]DMSO): δ = 31.9 (CH), 37.4, 48.2, 111.7 (indole C-7), 116.1 (indole C-3), 118.6, 118.7, 121.3, 121.7, 126.4 (indole C-3a), 136.8 (indole C-7a), 176.6 (C=O). – C₁₂H₁₂N₂O₁: Mr = 200.20. – MS (EI); *m/z* (%):

200 (70) [M⁺], 170 (10), 143 (100), 115 (35). – HRMS: calcd. 200.0949; found 200.0996.

Benzyl 4-(1H-Indol-3-yl)-2-oxopyrrolidine-1-carbamate (15b): A solution of **7b** (0.50 g, 1.15 mmol) in absolute ethanol was refluxed for 1.5 h. The mixture was concentrated to dryness and purified twice by column chromatography on silica gel (eluent: CH₂Cl₂/MeOH, 9.5:0.5) to give 240 mg (0.62 mmol, 63% yield) of a colorless solid. – M.p. 163 °C. – UV: λ_{max} = 216 nm, 281, 290. – IR (KBr): ν = 3345 cm⁻¹, 2927, 1780, 1709, 1456, 1281, 1103, 1028, 745. – ¹H NMR ([D₆]DMSO): δ = 2.80 (dd, *J* = 8.9, 16.9 Hz, 1 H, CH₂CO), 2.95 (dd, *J* = 7.7, 16.9 Hz, 1 H, CH₂CO), 3.80 (m, 2 H, CH & CH₂N), 4.25 (t, *J* = 6.6 Hz, 1 H, CH₂N), 5.25 (s, 2 H, CH₂Ph), 7.01 (t, *J* = 8.0 Hz, 1 H, indole 5-H), 7.11 (t, *J* = 8.0 Hz, 1 H, indole 6-H), 7.28 (d, *J* = 2.0 Hz, 1 H, indole 2-H), 7.30–7.50 (m, 6 H, H_{arom}), 7.62 (d, *J* = 8.0 Hz, 1 H, indole 4-H), 10.98 (br s, 1 H, NH). – ¹³C NMR ([D₆]DMSO): δ = 28.2 (CH), 39.3, 52.2, 67.1 (CH₂Ph), 111.8 (indole C-7), 114.4 (indole C-3), 118.7, 118.8, 121.5, 121.9, 126.3 (indole C-3a), 127.9 (Ph), 128.2 (Ph), 128.6 (Ph), 136.0, 136.7, 151.1 (carbamate C=O), 173.2 (lactam C=O). – C₂₀H₁₈N₂O₃. – MS (EI); *m/z* (%): 334 (45) [M⁺], 200 (18), 143 (100), 130 (10), 115 (15). – HRMS: calcd. 334.1317; found 334.1304.

Ethyl Hydrogen 2-[2-[(Benzyl)(benzyloxycarbonyl)amino]-1-(1H-indol-3-yl)ethyl]malonate (16): A solution of **7c** (4.15 g, 7.89 mmol) in EtOH (40 mL) was stirred under nitrogen for 48 h at 60 °C. The solvent was evaporated, the residue was dissolved in Et₂O (75 mL) and extracted with 5% NaHCO₃ solution (4 × 50 mL). The combined aqueous extracts were carefully acidified with 10% HCl solution, and the resulting suspension was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (2 × 100 mL), dried, and concentrated to give 3.61 g of **16** as a brown solid (7.02 mmol, 90% yield). – M.p. 136 °C. – UV: λ_{max} = 203 nm, 217, 282, 292. – IR (film): ν = 3389 cm⁻¹, 3061, 3034, 2982, 1730, 1694, 1456, 1427, 1227, 1177, 741. – ¹H NMR (CDCl₃): δ = 0.80 (t, *J* = 7.0, 1.5 H, CH₃), 1.18 (t, *J* = 7.0, 1.5 H, CH₃), 3.65–3.95 (m, 4 H), 4.05–4.40 (m, 4 H), 4.90–5.12 (m, 2 H, OCH₂), 6.80–7.55 (m, 15 H, H_{arom}), 8.08 (s, 0.5 H, NH), 8.12 (s, 0.5 H, NH), 9.30 (br s, 1H, CO₂H). – ¹³C NMR (CDCl₃): δ = 13.4 (CH₃), 13.9 (CH₃), 49.0, 50.6, 50.7, 54.8 (CH), 55.4 (CH), 61.5 (COOCH₂CH₃), 61.9 (COOCH₂CH₃), 67.5 (CO₂CH₂Ph), 67.6 (CO₂CH₂Ph), 111.2 (indole C-7), 111.3 (indole C-7), 112.7 (indole C-3), 112.8 (indole C-3), 118.9, 119.0, 119.6, 122.1, 123.3, 127.2, 127.4, 127.5, 127.6, 127.7, 128.0, 128.4, 136.1, 136.2, 136.5, 137.4, 137.6, 156.9 (carbamate C=O), 168.3 (ester C=O), 169.0 (ester C=O), 171.1 (acid C=O), 171.3 (acid C=O). – C₃₀H₃₀N₂O₆. Mr = 514.56. – MS (EI); *m/z* (%) = 470 (55) [M⁺ – CO₂], 229 (45), 216 (100), 143 (90). – HRMS: calcd. 470.2202; found 470.2205.

Ethyl 4-[(Benzyl)(benzyloxycarbonyl)amino]-2-[(benzyloxycarbonyl)amino]-3-(1H-indol-3-yl)butyrate (17): To a solution of **16** (3.59 g, 6.98 mmol) in dry toluene (49 mL) was added triethylamine (1.46 mL, 10.47 mmol) and diphenylphosphoryl azide (2.26 mL, 10.47 mmol), under nitrogen. The reaction mixture was stirred for 1 h at 50 °C, then refluxed for 0.5 h. Benzyl alcohol (1.08 mL, 10.47 mmol) was added, and the mixture was refluxed for 12 h. The solvent was evaporated, and the residue was dissolved in EtOAc (150 mL). The solution was washed with 5% NaHCO₃ solution (3 × 100 mL), 5% citric acid solution (3 × 100 mL), and brine (2 × 100 mL), then dried (Na₂SO₄), and concentrated. The residue was purified by column chromatography on silica gel (eluent: EtOAc/hexane, 2:8) to give 2.78 g (4.49 mmol, 63% yield) of a light yellow solid. – M.p. 50 °C. – UV: λ_{max} = 224 nm, 276, 281, 290. – IR (film): ν = 3325 cm⁻¹, 3063, 3034, 1722, 1699, 1497, 1234, 1062,

741. – ¹H NMR (CDCl₃): δ = 1.05 (t, *J* = 7.0 Hz, 3 H, CH₃), 3.30–5.20 (m, 12 H), 6.80–7.55 (m, 21 H), 8.12 (s, 0.5 H, indole NH), 8.25 (s, 0.5 H, indole NH). – ¹³C NMR (CDCl₃): δ = 13.8, 13.9, 36.3, 37.1, 38.2, 38.8, 47.0, 48.2, 48.6, 49.5, 50.4, 51.1, 55.2, 56.4, 61.5, 61.7, 66.7, 67.0, 67.2, 67.7, 110.5, 110.6, 113.0, 111.3, 118.3, 118.7, 119.5, 122.1, 127.2, 127.4, 127.6, 127.8, 128.0, 128.1, 128.4, 128.5, 136.0, 136.1, 136.8, 137.4, 156.4 (carbamate C=O), 156.7 (carbamate C=O), 171.5 (ester C=O). – C₃₇H₃₇N₃O₆. – MS (EI); *m/z* (%) = 619 (2) [M⁺], 511 (45), 383 (100). – HRMS: calcd. 619.2682; found 619.2665.

(±)-cis-3-Amino-1-benzyl-4-(1H-indol-3-yl)pyrrolidin-2-one (18a) and (±)-trans-3-Amino-1-benzyl-4-(1H-indol-3-yl)pyrrolidin-2-one (18b): To a solution of **17** (3.07 g, 4.96 mmol) in absolute ethanol (80 mL) was added 10% Pd/C (400 mg). The mixture was stirred under H₂ at atmospheric pressure at room temperature for 48 h. The suspension was filtered through Celite®, and the solvent was evaporated. The residue was purified twice by column chromatography on silica gel (eluent: CH₂Cl₂/MeOH/AcOH, 180:10:5) to give 0.57 g of **18a** as a light brown solid (1.87 mmol, 38% yield, less polar compound) and 0.56 g of **18b** as a white solid (1.84 mmol, 37% yield, more polar compound). Both were crystallized from MeOH to give analytically pure samples.

Compound 18a: M.p. 155 °C. – UV: λ_{max} = 207 nm, 218, 273, 283, 290. – IR (KBr): ν = 3235 cm⁻¹, 2934, 2874, 1684, 1495, 1456, 1261, 745. – ¹H NMR ([D₆]DMSO): δ = 1.31 (br s, 2 H, NH₂), 3.45 (dd, *J* = 5.0, 9.0 Hz, 1 H, CH₂NCH₂Ph), 3.59 (dd, *J* = 7.0, 9.0 Hz, 1 H, CH₂NCH₂Ph), 3.76 (d, *J* = 8.0 Hz, 1 H, CHNH₂), 3.88 (m, 1 H, CH), 4.48 (d, *J* = 12.0 Hz, 1 H, CH₂Ph), 4.58 (d, *J* = 12.0 Hz, 1 H, CH₂Ph), 6.98 (t, *J* = 8.0 Hz, 1 H, indole 5-H), 7.08 (s, 1 H, indole 2-H), 7.10 (t, *J* = 8.0 Hz, 1 H, indole 6-H), 7.25–7.40 (m, 6 H, H_{arom}), 7.53 (d, *J* = 8.0 Hz, 1 H, indole 4-H), 11.0 (s, 1 H, NH). – ¹³C NMR ([D₆]DMSO): δ = 35.3 (CH), 46.0 (CH₂Ph), 50.0 (CH₂), 55.6 (CHNH₂), 111.4 (indole C-3), 111.6 (indole C-7), 118, 7 (indole C-5), 118.9 (indole C-4), 121.3 (indole C-6), 123.2 (indole C-2), 127.3 (indole C-3a), 127.5 (Ph), 128.1 (Ph), 128.8 (Ph), 136.3 (indole C-7a), 137.1 (Ph), 175.3 (C=O). – C₁₉H₁₉N₃O. – MS (EI); *m/z* (%) = 305 (45) [M⁺], 288 (3) [M⁺ – NH₃], 248 (5), 171 (10), 158 (23), 143 (100), 130 (25), 115 (10). – HRMS: calcd. 305.1528; found 305.1497.

Compound 18b: M.p. 185 °C. – UV: λ_{max} = 207 nm, 218, 273, 283, 290. – IR (KBr): ν = 3293 cm⁻¹, 2930, 2878, 1686, 1495, 1447, 1261, 741. – ¹H NMR ([D₅]pyridine): δ = 2.40 (br s, 2 H, NH₂), 3.45 (t, *J* = 8.5 Hz, 1 H, CH₂NCH₂Ph), 3.61 (t, *J* = 8.5 Hz, 1 H, CH₂NCH₂Ph), 3.69 (m, 1 H, CH), 4.10 (d, *J* = 9.0 Hz, 1 H, CHNH₂), 4.62 (d, *J* = 14.5 Hz, 1 H, CH₂Ph), 4.70 (d, *J* = 14.5 Hz, 1 H, CH₂Ph), 7.15–7.40 (m, 7 H, H_{arom}), 7.42 (d, *J* = 2.0 Hz, 1 H, indole 2-H), 7.58 (d, *J* = 8.0 Hz, 1 H, indole 7-H), 7.83 (d, *J* = 8.0 Hz, 1 H, indole 4-H), 12.03 (s, 1 H, NH). – ¹³C NMR ([D₆]DMSO): δ = 40.2 (CH), 46.0 (CH₂Ph), 49.5 (CH₂), 58.8 (CHNH₂), 111.7 (indole C-7), 113.6 (indole C-3), 118.5 (indole C-5), 119.0 (indole C-4), 121.2 (indole C-6), 122.4 (indole C-2), 126.8 (indole C-3a), 127.4 (Ph), 127.8 (Ph), 128.8 (Ph), 136.7, 137.0, 175.2 (C=O). – C₁₉H₁₉N₃O. – MS (EI); *m/z* (%) = 305 (40) [M⁺], 288 (2) [M⁺ – NH₃], 248 (5), 171 (10), 158 (20), 143 (100), 130 (25), 115 (10). – HRMS: calcd. 305.1528; found 305.1513.

(±)-(3aR*,5R*,10cR*)-2-Benzyl-5-phenyl-1,3a,4,5,6,10c-hexahydropyrrolo[3',4':5,6]pyrido[3,4-b]indol-3(2H)-one (19a) and (±)-(3aR*,5S*,10cR*)-2-benzyl-5-phenyl-1,3a,4,5,6,10c-hexahydropyrrolo[3',4':5,6]pyrido[3,4-b]indol-3(2H)-one (20a): To a suspension of **18a** (100 mg, 0.32 mmol) in CH₂Cl₂ (15 mL), containing activated molecular sieves (4 Å), was added benzaldehyde (50 μL,

0.49 mmol). The mixture was stirred at room temperature under nitrogen for 24 h. Trifluoroacetic acid (50 μ L, 0.66 mmol) was added and the mixture was stirred for 3 h, then washed with 5% NaHCO₃ solution (2 $\times$ 20 mL), and brine (2 $\times$ 20 mL), dried (Na₂SO₄), and concentrated to dryness. Column chromatography (eluent: EtOAc/hexane, 5:5) gave 37 mg (0.09 mmol, 29% yield) of white crystals of **19a** (less polar compound) and 37 mg (0.09 mmol, 29% yield) of white crystals of **20a** (more polar compound).

Compound 19a: M.p. 201 °C. – UV: $\lambda_{\max}$ = 206 nm, 220, 281, 290. – IR (KBr): ν = 3281 cm⁻¹, 2924, 1682, 1454, 1258, 698. – ¹H NMR (CDCl₃): δ = 2.40 (br s, 1 H, NH), 3.48 (t, J = 8.6 Hz, 1 H, CH₂NCH₂Ph), 3.61 (m, 1 H, CHCHNH), 3.79 (t, J = 7.9 Hz, 1 H, CH₂NCH₂Ph), 3.95 (d, J = 6.1 Hz, 1 H, CHCHNH), 4.41 (d, J = 14.9 Hz, 1 H, CH₂Ph), 4.60 (d, J = 14.9 Hz, 1 H, CH₂Ph), 5.15 (s, 1 H, CHPh), 7.00–7.40 (m, 14 H, H_{arom}), 7.55 (s, 1 H, indole NH). – ¹³C NMR (CDCl₃): δ = 31.0 (CH₂CH), 46.5 (NCH₂Ph), 52.1 (CH₂CH), 57.4 (NHCHPh), 58.5 (COCHNH), 107.6 (indole C-3), 111.1 (indole C-7), 118.0, 119.7, 121.9, 126.7 (indole C-3a), 127.5, 127.9, 128.5, 128.6, 128.7, 128.8, 135.7, 135.8, 136.2, 140.5, 173.6 (C=O). – C₂₆H₂₃N₃O₁. – MS (EI): m/z (%) = 393 (100) [M⁺], 316 (60), 245 (55), 219 (55), 169 (95). – HRMS: calcd. 393.1841; found 393.1838.

Compound 20a: M.p. 195 °C. – UV: $\lambda_{\max}$ = 205 nm, 220, 283, 290. – IR (KBr): ν = 3297 cm⁻¹, 2928, 2861, 1688, 1454, 1285, 1117, 743, 700. – ¹H NMR (CDCl₃): δ = 2.70 (br s, 1 H, NH), 3.51 (d, J = 9.6 Hz, 1 H, CH₂NCH₂Ph), 3.63 (dd, J = 6.0, 9.6 Hz, 1 H, CH₂NCH₂Ph), 3.99 (t, J = 6.6 Hz, 1 H, CHCHNH), 4.13 (d, J = 7.0 Hz, 1 H, CHCHNH), 4.16 (d, J = 14.9 Hz, 1 H, CH₂Ph), 4.61 (d, J = 14.9 Hz, 1 H, CH₂Ph), 5.28 (s, 1 H, CHPh), 6.95–7.40 (m, 14 H, H_{arom}), 7.60 (s, 1 H, indole NH). – ¹³C NMR (CDCl₃): δ = 30.4 (CH₂CH), 46.7 (NCH₂Ph), 49.6 (CH₂CH), 53.8 (NHCHPh), 57.9 (COCHNH), 108.0 (indole C-3), 111.2 (indole C-7), 118.0, 119.6, 121.8, 126.2 (indole C-3a), 127.3, 127.6, 128.4, 128.5, 128.7, 128.9, 135.7, 136.1, 136.5, 140.7, 173.1 (C=O). – C₂₆H₂₃N₃O₁. – MS (EI): m/z (%) = 393 (100) [M⁺], 376 (30), 302 (30), 285 (25), 245 (80), 219 (20), 169 (85). – HRMS: calcd. 393.1841; found 393.1820.

X-ray Analysis of 18b:^[16,17] C₁₉H₁₉ON₃ (M_r = 305.38), orthorhombic, $P2_12_12_1$, a = 8.490(2), b = 9.358(2), c = 20.262(4) Å, V = 1609.7(6) Å³, Z = 4, D_x = 1.260 Mg·m⁻³, λ (Mo- K_α) = 0.71073 Å, μ = 0.746 cm⁻¹, $F(000)$ = 648, T = 294 K. The sample (0.30 $\times$ 0.30 $\times$ 0.35 mm) was studied with an automatic diffractometer CAD4 ENRAF-NONIUS with graphite-monochromatized Mo- K_α radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection [$2\theta_{\max}$ = 50°, scan $\omega/2\theta$ = 1, $t_{\max}$ = 60 s, hkl range: h 0,10, k 0,11, l 0,25 intensity controls without appreciable decay (0.3%)] gave 1922 reflections, of which 1375 independent with $I > 2\sigma(I)$. After Lorentz and polarization corrections, the structure was solved using SHELXS-86, which revealed the non-hydrogen atoms of the molecule. After anisotropic refinement, the hydrogen atoms were found with a difference Fourier analysis (between 0.40 and 0.25 e Å⁻³). The whole structure was refined by full-matrix, least-squares techniques [use of F magnitude; x, y, z, β_{ij} for C, O and N atoms and x, y, z for H atoms; 266 variables and 1375 observations; $w = 1/\sigma(F_o)^2 = [\sigma^2(I) +$

$(0.04F_o)^2]^{-1/2}$] with the resulting $R = 0.043$, $R_w = 0.042$ and $S_w = 0.724$ (residual $\Delta\rho \leq 0.17$ e Å⁻³). Atomic scattering factors from International Tables for X-ray Crystallography, 1974. The calculations were performed with a Silicon Graphics Indy R4600 computer with the MOLEN package (Enraf–Nonius, 1990) and SHELXS-86 (Sheldrick, 1985).

Acknowledgments

This work was financed by the ADIR Company (Laboratoires Servier) and by the CNRS (Centre National de la Recherche Scientifique), to which our gratitude is expressed. Special thanks are due to Dr. Csaba Nemes for helpful discussions and to Christelle Berteaux for her collaboration.

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Received March 8, 2000
[O00119]