Addition of Indole to Methyl 2-Chloro-2-cyclopropylideneacetate en Route to Spirocyclopropanated Analogues of Demethoxyfumitremorgine C and Tadalafil[‡]

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Indole readily added across the double bond of the highly reactive Michael acceptor methyl 2-chloro-2-cyclopropylideneacetate (**4**) to yield 2-chloro-2-(3′-indolylcyclopropyl)acetate **5** (85%) which was converted in two steps into the racemic tryptophan analogue **7** in 90% yield. This in turn was transformed by a condensation and Pictet–Spengler sequence into the spirocyclopropane analogues, **11**, **13** and **15**, of both the natural product (demethoxy)fumitremorgine C (**3b**, 3 steps, 11% yield) and the potent PDE-5 inhibitor Tadalafil (**2**, 3 steps, 71% yield) as well as the original lead structure with a hydantoin backbone (**1**, 2 steps, 79% yield).

Introduction

Lewis acid-catalyzed Michael addition of indoles onto Michael acceptors[1] provides interesting 3-substituted tryptophan analogues[2] and other indole derivatives.[3] Condensation of these with various aldehydes and subsequent Pictet−Spengler reaction[4] leads to 1-substituted tetrahydro-β-carbolines, a common heterocyclic skeleton in many indole alkaloids and their analogues, mostly with interesting biological activities.[5] Among these are the natural products demethoxyfumitremorgine C[6] (**3b**) and fumitremorgine C (**3a**) (Figure 1), both neurotoxic secondary metabolites isolated from the fermentation broth of *Aspergillus fumigatus* BM 939[7] that reverse multidrug resistance (MDR) which frequently occurs in cancer therapy,[8] as well as selective inhibitors of cyclic guanosine monophosphate (cGMP) type 5 specific phosphodiesterase (PDE 5), such as the commercial drug Tadalafil (Elli Lilly).[9]

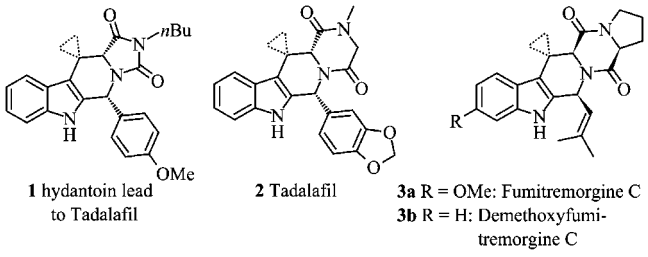

Figure 1. Biologically active tetrahydro-β-carboline derivatives and their spirocyclopropanated analogues.

In view of the fact that methyl 2-chloro-2-cyclopropylideneacetate (**4**) is a particularly reactive Michael acceptor and as such can favorably be employed as a building block for various conformationally restricted peptidomimetics,[10] it was straightforward to conceive a facile access to cyclopropane analogues of the hydantoin lead structure to Tadalafil,[11] Tadalafil itself,[12] as well as demethoxyfumitremorgine C (Figure 1).[13] We decided to execute this idea, not least because it was expected to demonstrate once again the enhanced tendency with which a suitable 1,1-disubstituted cyclopropane derivative undergoes ring closure due to an enforced favorable conformation just like the correspondingly substituted 2,2-disubstituted propane derivative.[14]

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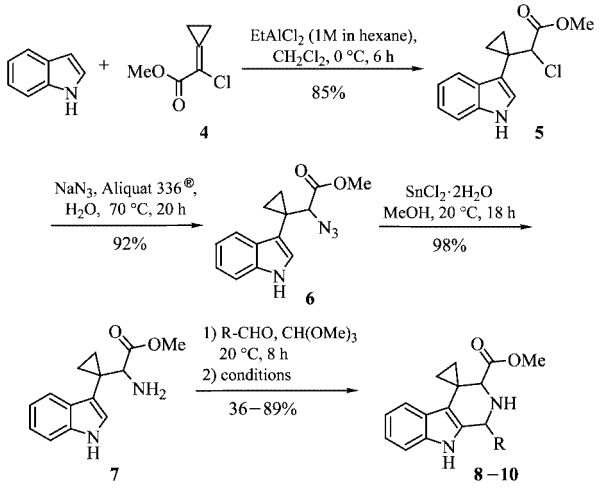
Results and Discussion

Indeed the potent Michael acceptor methyl 2-chloro-2-cyclopropylideneacetate (**4**), in the presence of ethylaluminum dichloride, rapidly underwent addition of indole to furnish **5** (85%). From here the cyclopropanated tryptophan methyl ester **7**[15] was prepared in two simple steps (Scheme 1), namely by nucleophilic substitution of the chloride in **5** under phase-transfer catalysis with sodium azide in water and subsequent reduction of the azido ester **6** with tin(II) chloride (overall yield 90%).

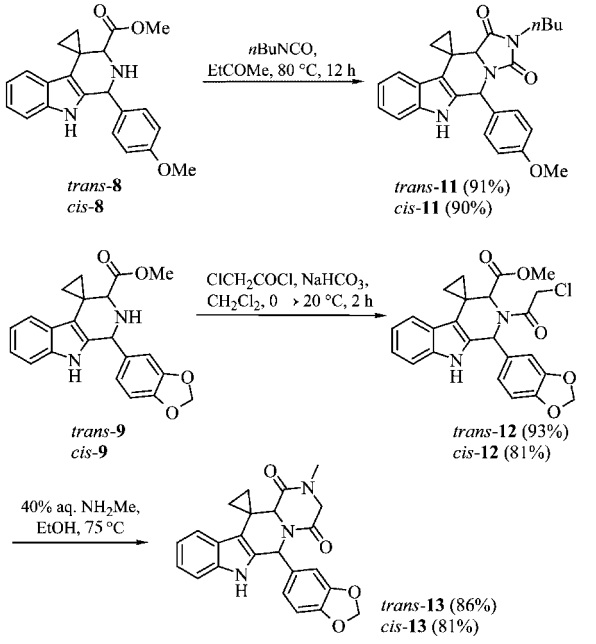


Scheme 1. Pictet–Spengler reactions of some tryptophan analogues derived from the Michael adduct of indole with methyl 2-chloro-2-(cyclopropylidene)acetate; for more details see Table 1.

Condensation of **7** with *p*-anisaldehyde or piperonal in trimethyl orthoformate almost quantitatively yielded the corresponding imine, which upon treatment with 4 equiv. of trifluoroacetic acid at 0 °C and subsequent stirring at 20 °C gave the tetrahydro-β-carbolines **8** and **9** in 87 (*cis*:*trans* = 1:1.7) and 89% (1:2.5) yields, respectively. The diastereomers in both cases could be separated by simple crystallization from EtOAc (**8**) or EtOAc/diethyl ether (**9**) (Scheme 1, Table 1). The relative configurations of each of the diastereomers **9** were assigned by NOE experiments and were used as a basis for the assignment of the relative configurations of the diastereomers **8**.

Under the same conditions the imine formed from **7** and prenal underwent complete decomposition.[16] An attempted cyclization by treatment with 20 equiv. of trifluoroacetic acid at −40 °C (0.2 M imine in $CHCl_3$) for 4 h according to a protocol of Bailey and co-workers[17] only led to complete recovery of the starting imine. However, at a slightly higher temperature and with a significantly extended reaction time (−30 °C, 63 h), tetrahydro-β-carboline **10** was obtained, albeit in only 36% yield. In this case only the *trans* diastereomer was isolated, whereas the corresponding non-cyclopropanated tetrahydro-β-carboline was reported to be formed predominantly as the *cis* diastereomer (6:1) with virtually the same moderate yield (36%).[16]

Treatment of the tetrahydrocarbolines *trans*-**8** and *cis*-**8** with *n*-butyl isocyanate in refluxing ethyl methyl ketone for 12 h led directly to the hydantoin lead structures *trans*-**11** (91%) and *cis*-**11** (90% yield) (Scheme 2).



Scheme 2. Formation of the spirocyclopropanated hydantoin lead structures of Tadalafil and Tadalafil itself (**11** and **13**, respectively).

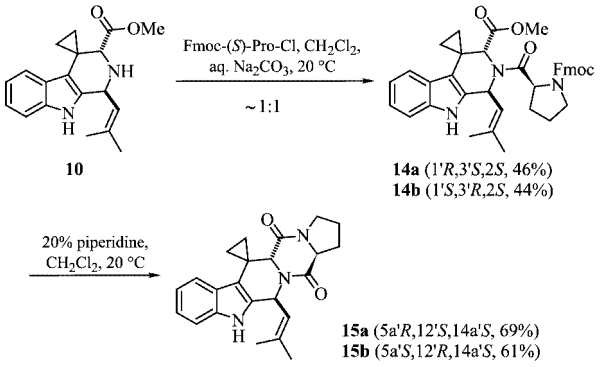
The tetrahydrocarboline derivatives *trans*-**9** and *cis*-**9** were acylated under Schotten–Baumann conditions with chloroacetyl chloride to provide the *N*-chloroacetyl derivatives *trans*-**12** (93%) and *cis*-**12** (81% yield), which upon reaction with methylamine in aqueous ethanol underwent nucleophilic substitution and subsequent ring-closing amide formation to give the spirocyclopropanated Tadalafil analogues *trans*-**13** (86%) and *cis*-**13** (81% yield).

Tabelle 1. Pictet–Spengler reactions of some tryptophan analogues derived from the Michael adduct of indole with methyl 2-chloro-2-cyclopropylideneacetate.

Compound	R	Conditions	Yield[a] [%]
8	*p*-MeO-C_6H_4-	TFA, CH_2Cl_2, 0 → 25 °C, 15 h	87 (1:1.7)
9	piperonyl	TFA, CH_2Cl_2, 0 → 25 °C, 12 h	89 (1:2.5)
10	prenyl	TFA, CH_2Cl_2, −30 °C, 63 h	36 (1:99)

[a] The *cis*/*trans* diastereomeric ratio is given in parentheses.

To obtain the analogue of demethoxyfumitremorgine C, the tetrahydro-β-carboline **10** was condensed with Fmoc−(*S*)-Pro−Cl[18] to yield the two diastereomers **14a** (46%) and **14b** (44% yield) which were separated by column chromatography, but not fully characterized owing to their dynamic NMR behavior even at an elevated temperature (90 °C). Removal of the Fmoc-protecting group by treatment with piperidine led directly to the diketopiperazine targets **15a** and **15b** in enantiopure form (Scheme 3). However, they are both diastereomers (opposite configuration at C-1 and C-3, respectively) of natural (demethoxy)fumitremorgine C. The relative configuration of **15a** was proved by single-crystal X-ray structure analysis (Figure 2).[19]



Scheme 3. Condensation of the tetrahydro-β-carboline **10** with Fmoc-(*S*)-Pro-Cl and ring closure to the diketopiperazine targets **15a** and **15b**.

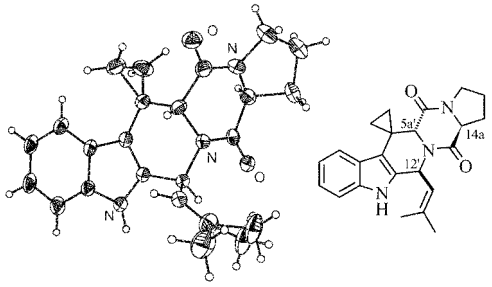


Figure 2. Relative configuration of **15a** according to an X-ray crystal structure analysis.[19]

Conclusions

In conclusion, addition of indole to methyl 2-chloro-2-cyclopropylideneacetate[20] in the presence of a Lewis acid occurs with great facility and yields a 1,1-disubstituted cyclopropane derivative which is well suited for transformation to cyclopropanated tryptophan analogues. These undergo Pictet−Spengler annelation to tetrahydro-β-carboline derivatives with greater efficiency than the corresponding non-cyclopropanated precursors (87% for **8** versus 62%[11] and 89% for **9** versus 61%[12]). The products can readily be converted into spirocyclopropanated analogues of interesting biologically active compounds by applying known methodology.

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers without further purification. All reactions in non-aqueous solvents were carried out by using standard Schlenk techniques under dry nitrogen. Solvents were purified and dried according to conventional methods prior to use; diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone. Solvents are abbreviated as follows: Py = pyridine, EtOAc = ethyl acetate, MEK = ethyl methyl ketone, MeOH = methanol, EtOH = ethanol. ^1H and ^{13}C NMR spectra were recorded at ambient temperature with a Bruker AM 250 instrument. Chemical shifts, δ, are given in ppm relative to solvent resonances (^1H: 7.26 ppm for chloroform; ^{13}C: 77.0 ppm for [D]chloroform), coupling constants, *J*, are given in Hertz. Characterization of the multiplicity of signals: s = singlet, br. s = broad singlet, d = doublet, t = triplet, m = multiplet. The multiplicities of the signals were determined by the DEPT technique: + = primary or tertiary (positive DEPT signal), − = secondary (negative DEPT signal), C_{quat} = quaternary carbon atoms. IR spectra were recorded with a Bruker IFS 66 spectrometer. Mass spectra were acquired on a Finnigan MAT 95 spectrometer. High-resolution mass spectra (HRMS) were obtained by preselected-ion peak matching at $R \approx 10000$ and are within ±2 ppm of the exact mass. Chromatographic separations were carried out on Merck Silica 60 (0.063−0.200 mm, 70−230 mesh ASTM). The dimensions of the columns used are given as "diameter × height of the silica column". TLC was performed with Machery−Nagel TLC Alugram® Sil G/UV_{254} plates; detection was under UV light at 254 nm and development with ninhydrin (100 mg of ninhydrin, 3 mL of concd. acetic acid in 100 mL of 1-butanol) or MOPS reagent (10% molybdophosphoric acid in ethanol). Melting points were obtained with a Büchi Dr. Tottoli apparatus; values are uncorrected. Elemental analyses were carried out by the Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen.

Methyl 2-Chloro-2-[1-(1*H*-indol-3-yl)cyclopropyl]acetate (5): Ethylaluminum dichloride (51.0 mL, 51.0 mmol, 1 M solution in hexane) was added to a solution of methyl 2-chloro-2-cyclopropylideneacetate[20] (4.40 g, 30.0 mmol) and indole (5.97 g, 51.0 mmol) in CH_2Cl_2 (150 mL) at 0 °C and the mixture was stirred at this temperature for 6 h. The mixture was carefully poured into an ice-cold saturated Na_2CO_3 solution (150 mL). Extraction of the aqueous phase with CH_2Cl_2 (3 × 200 mL), drying of the combined organic phases over $MgSO_4$, evaporation of the solvents and chromatographic purification of the residue on 80 g of silica gel (4.5 × 20 cm, R_f = 0.45, pentane/Et_2O, 5:1) yielded 6.70 g (85%) of **5** as a pale yellow oil. IR (film): $\tilde{\nu}$ = 3306, 3008, 2949, 1747, 1456, 1420, 1313, 1195, 1170, 1010 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.02−1.24 (m, 3 H, Cpr-H), 1.35−1.46 (m, 1 H, Cpr-H), 3.60 (s, 3 H, OCH_3), 4.31 (s, 1 H, 2-H), 7.06−7.38 (m, 4 H, 2′-H, 5′-H, 6′-H, 7′-H), 7.65−7.72 (m, 1 H, 4′-H), 8.00−8.14 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 13.6 (−, Cpr-C), 21.6 (C_{quat}, Cpr-C), 52.8 (+, OCH_3), 69.2 (+, C-2), 111.4 (+, C-7′), 113.9 (C_{quat}, C-3′), 118.9 (+, C-4′*), 119.4 (+, C-6′*), 121.8 (+, C-5′), 125.8 (+, C-2′), 127.2 (C_{quat}, C-3a′), 135.7 (C_{quat}, C-7a′), 169.2 (C_{quat}, C=O) ppm. MS (70 eV): *m/z* (%) = 265/263 (14/52) [M^+], 228 (100) [M^+ − Cl], 196 (73), 168 (35), [M^+ − Cl − CO_2Me − H], 130 (29), 83 (28). $C_{14}H_{14}ClNO_2$ (263.7): calcd. 263.0713 (correct HRMS).

Methyl 2-Azido-2-[1-(1*H*-indol-3-yl)cyclopropyl]acetate (6): A suspension of **5** (6.50 g, 24.7 mmol), NaN_3 (4.80 g, 73.9 mmol) and Aliquat 336® (12.4 g,12.4 mmol) in water (60 mL) was heated at 70 °C for 20 h. After cooling to 20 °C the reaction mixture was extracted with Et_2O (3 × 100 mL) and the combined organic phases were dried with Na_2SO_4. Removal of the solvent in vacuo and column chromatography of the residue on 80 g of silica gel (4.5 × 20 cm, R_f = 0.36, CH_2Cl_2/MeOH, 10:1) yielded 6.10 g (91%) of **6** as a slightly yellow oil. IR (KBr): $\tilde{\nu}$ = 3329, 2923, 2104, 1743, 1442, 1338, 1270, 1233, 1033, 746 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.00−1.18 (m, 3 H, Cpr-H), 1.24−1.42 (m, 1 H, Cpr-H), 3.68 (s, 3 H, OCH_3), 3.75 (s, 1 H, 2-H), 7.10−7.21 (m, 3 H, 2′-H, 5′-H, 6′-H), 7.33 (d, ^3J = 7.5 Hz, 1 H, 7′-H), 7.70 (d, ^3J = 7.5 Hz, 1 H, 4′-H), 8.00−8.14 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.9 (−, Cpr-C), 11.9 (−, Cpr-C), 20.1 (C_{quat}, Cpr-C), 52.4 (+, OCH_3), 69.2 (+, C-2), 111.4 (+, C-7′), 114.6 (C_{quat}, C-3′), 119.0 (+, C-4′*), 119.6 (+, C-6′*), 122.0 (+, C-5′), 125.3 (+, C-2′), 127.3 (C_{quat}, C-3a′), 135.8 (C_{quat}, C-7a′), 169.6 (C_{quat}, C=O) ppm. MS (70 eV): *m/z* (%) = 270 (71) [M^+], 228 (100) [$M^+ - N_3$], 196 (56), 183 (58) [$M^+ - N_2 - CO_2Me$], 168 (20) [$M^+ - N_3 - CO_2Me - H$], 156 (62), 129 (47), 117 (12). $C_{14}H_{14}N_4O_2$ (270.3): calcd. C 62.21, H 5.22; found C 62.12, H 5.33.

Methyl 2-Amino-2-[1-(1*H*-indol-3-yl)cyclopropyl]acetate (7): Tin(II) chloride dihydrate (9.90 g, 43.9 mmol) was added to a solution of **6** (6.00 g, 22.2 mmol) in MeOH (80 mL) and the solution was stirred at 20 °C for 18 h. After removal of the solvent in vacuo, the residue was taken up in CH_2Cl_2 (150 mL), the solution extracted with saturated Na_2CO_3 solution (100 mL), the aqueous layer re-extracted with CH_2Cl_2 (3 × 150 mL), the combined organic phases dried with $MgSO_4$, the solvents removed, and the residue purified by column chromatography on 100 g of silica gel (3 × 30 cm, R_f = 0.30, CH_2Cl_2/MeOH, 10:1) to yield 5.22 g (98%) of **7** as a pale yellow solid (m.p. 127 °C). IR (KBr): $\tilde{\nu}$ = 3348 (NH), 3136, 2986, 2945, 2919, 1736 (C=O), 1584, 1435, 1199, 1015, 919, 741 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.85−1.09 (m, 3 H, Cpr-H), 1.21−1.29 (m, 1 H, Cpr-H), 1.65 (s, 2 H, NH_2), 3.08 (s, 1 H, 2-H), 3.65 (s, 3 H, OCH_3), 7.07−7.20 (m, 3 H, 2′-H, 5′-H, 6′-H), 7.31 (d, ^3J = 7.7 Hz, 1 H, 7′-H), 7.70 (d, ^3J = 7.7 Hz, 1 H, 4′-H), 8.21−8.33 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 11.6 (−, Cpr-C), 12.2 (−, Cpr-C), 22.2 (C_{quat}, Cpr-C), 51.8 (+, OCH_3), 62.6 (+, C-2), 111.3 (+, C-7′), 115.3 (C_{quat}, C-3′), 119.3 (+, C-4′*), 119.5 (+, C-6′*), 122.0 (+, C-5′), 124.9 (+, C-2′), 127.8 (C_{quat}, C-3a′), 135.9 (C_{quat}, C-7a′), 174.7 (C_{quat}, C=O) ppm. MS (70 eV): *m/z* (%) = 244 (28) [M^+], 215 (12), 185 (38) [$M^+ - CO_2Me$], 168 (25), 156 (100), 129 (42), 117 (9). $C_{14}H_{16}N_2O_2$ (244.3): calcd. C 68.83, H 6.60; found C 68.65, H 6.84.

Methyl 1′-(4-Methoxyphenyl)-2′,3′,4′,9′-tetrahydrospiro[cyclopropane-1,4′-1*H*-β-carboline]-3′-carboxylate (8): *p*-Anisaldehyde (694 mg, 5.10 mmol) was added to a solution of **7** (1.22 g, 5.00 mmol) in trimethyl orthoformate (25 mL) and the solution was stirred at 20 °C for 8 h. After removal of the volatiles in vacuo and dissolving of the residue in CH_2Cl_2 (25 mL) at 0 °C trifluoroacetic acid (2.24 g, 19.6 mmol) was added over a period of 5 min, and the resulting red solution was stirred at 25 °C for 15 h. Dilution with saturated aqueous $NaHCO_3$ (20 mL), extraction of the aqueous phase with CH_2Cl_2 (2 × 25 mL), washing of the combined organic phases with brine (50 mL), drying over $MgSO_4$ and column chromatography of the residue on 50 g of silica gel (3 × 15 cm, R_f = 0.54, Et_2O) yielded 1.57 g (87%) of crude **8** as a mixture of *cis* and *trans* diastereomers (1:1.7). Crystallization from EtOAc yielded the *trans* diastereomer (830 mg, 46%) as a colorless solid, m.p. 190 °C. The residue from the mother liquor contained the *cis* and *trans* diastereomers in a ratio of 5:1, m.p. 91−98 °C. ***trans*-8:** IR (KBr): $\tilde{\nu}$ = 3393, 3171, 2956, 1725, 1514, 1246, 1178, 1027 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.06−1.12 (m, 2 H, Cpr-H), 1.4−1.48 (m, 1 H, Cpr-H), 1.80−1.88 (m, 1 H, Cpr-H), 2.20−2.81 (br. s, 1 H, NH), 3.44 (s, 1 H, CH), 3.70 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 5.52 (s, 1 H, CH), 6.84−6.90 (m, 2 H, aryl-H), 6.94−7.12 (m, 2 H, aryl-H), 7.16−7.42 (m, 4 H, aryl-H), 7.55 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.7 (−, Cpr-C), 13.6 (−, Cpr-C), 20.0 (C_{quat}, Cpr-C), 51.8 (+, OCH_3), 54.2 (+, OCH_3), 55.3 (+, CH), 62.2 (+, CH), 111.2 (+, aryl-C), 111.5 (C_{quat}, aryl-C), 114.1 (+, 2 C, aryl-C), 118.8 (+, aryl-C), 119.3 (+, aryl-C), 121.4 (+, aryl-C), 124.5 (C_{quat}, aryl-C), 130.0 (+, 2 C, aryl-C), 133.3 (C_{quat}, aryl-C), 134.8 (C_{quat}, aryl-C), 136.0 (C_{quat}, aryl-C), 159.5 (C_{quat}, aryl-C), 172.7 (C_{quat}, C=O) ppm. MS (70 eV): *m/z* (%) = 362 (100) [M^+], 303 (75) [$M^+ - CO_2Me$], 195 (50), 168 (18), 121 (22). $C_{22}H_{22}N_2O_3$ (362.4): calcd. C 72.91, H 6.12, N 7.73; found C 72.83, H 6.05, N 7.58. ***cis*-8:** IR (KBr): $\tilde{\nu}$ = 3394, 3004, 2950, 1734, 1512, 1457, 1251, 1174, 1030 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.86−0.91 (m, 1 H, Cpr-H), 1.04−1.40 (m, 2 H, Cpr-H), 1.68−1.80 (m, 1 H, Cpr-H), 2.21−2.80 (br. s, 1 H, NH), 3.46 (s, 1 H, CH), 3.74 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.23 (s, 1 H, CH), 6.84−6.92 (m, 2 H, aryl-H), 6.94−7.12 (m, 2 H, aryl-H), 7.16−7.42 (m, 4 H, aryl-H), 7.52 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 9.0 (−, Cpr-C), 11.8 (−, Cpr-C), 20.2 (C_{quat}, Cpr-C), 51.8 (+, OCH_3), 55.3 (+, CH), 57.1 (+, OCH_3), 62.5 (+, CH), 111.3 (+, aryl-C), 113.4 (C_{quat}, aryl-C), 114.3 (+, 2 C, aryl-C), 118.8 (+, aryl-C), 119.5 (+, aryl-C), 121.6 (+, aryl-C), 124.5 (C_{quat}, aryl-C), 129.8 (+, 2 C, aryl-C), 132.1 (C_{quat}, aryl-C), 135.9 (C_{quat}, aryl-C), 159.7 (C_{quat}, aryl-C), 170.9 (C_{quat}, C=O) ppm. MS (70 eV): *m/z* (%) = 363/362 (20/100) [M^+], 303 (75) [$M^+ - CO_2Me$], 302 (35), 195 (50), 168 (18), 121 (22). $C_{22}H_{22}N_2O_3$ (362.4): calcd. C 72.91, H 6.12, N 7.73; found C 72.49, H 5.98, N 7.61.

***trans*-2′-Butyl-10′-(4-methoxyphenyl)-3a′,4′,9′,10′-tetrahydrospiro[cyclopropane-1,4′-(2′,9′,11′-triazacyclopenta[*b*]fluorene)]-1′,3′-dione (*trans*-11):** *n*-Butyl isocyanate (31 mg, 313 μmol) was added to a solution of *trans*-**8** (100 mg, 276 μmol) in MEK (5 mL) and the mixture was stirred at 80 °C for 12 h. The solvent was removed in vacuo, and the residue purified by chromatography on 15 g of silica (3 × 15 cm, R_f = 0.35, pentane/Et_2O, 1:1) to yield 108 mg (91%) of *trans*-**11** as a colorless solid, m.p.178 °C. IR (KBr): $\tilde{\nu}$ = 3309, 2959, 2933, 2866, 1761, 1708, 1512, 1457, 1249, 1174, 1078 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 8 Hz, 3 H, CH_3), 1.08−1.42 (m, 4 H, Cpr-H), 1.55−1.62 (m, 3 H, CH_2), 1.92−2.04 (m, 1 H, CH_2), 3.40−3.52 (m, 2 H, NCH_2), 3.77 (s, 3 H, OCH_3), 4.48 (s, 1 H, CH), 6.3 (s, 1 H, CH), 6.80−6.91 (m, 2 H, aryl-H), 7.04−7.5 (m, 6 H, aryl-H), 8.04 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 7.8 ppm (−, Cpr-C), 11.7 (−, Cpr-C), 13.6 (+, CH_3), 18.9 (−, CH_2), 19.9 (−, Cpr-C), 30.1 (−, CH_2), 38.5 (−, NCH_2), 51.1 (+, OCH_3), 55.3 (+, CH), 56.4 (+, CH), 111.5 (+, aryl-C), 113.3 (−, aryl-C), 114.4 (+, 2 C, aryl-C), 119.0 (+, aryl-C), 120.0 (+, aryl-C), 122.4 (+, aryl-C), 123.9 (−, aryl-C), 129.6 (+, 2 C, aryl-C), 131.1 (−, aryl-C), 131.4 (−, aryl-C), 136.8 (−, aryl-C), 154.7 (−, aryl-C), 159.9 (−, C=O), 170.0 (−, C=O) ppm. MS (70 eV): *m/z* (%) = 430/429 (30/100) [M^+], 322 (35), 301 (10), 195 (10). $C_{26}H_{27}N_3O_3$ (429.5): calcd. C 72.71, H 6.34, N 9.78; found C 72.57, H 6.32, N 9.57.

***cis*-2′-Butyl-10′-(4-methoxyphenyl)-3a′,4′,9′,10′-tetrahydrospiro[cyclopropane-1,4′-(2′,9′,11′-triazacyclopenta[*b*]fluorene)]-1′,3′-dione (*cis*-11):** *n*-Butyl isocyanate (158 mg, 1.60 mmol) was added to a solution of **8** (480 mg, 1.33 mmol, *cis*:*trans* = 5:1) in MEK (20 mL) and the mixture was stirred at 80 °C for 12 h. Evap-

oration of the solvents and chromatographic purification of the residue on 20 g of silica (3 × 15 cm, pentane/Et_2O, 1:2) yielded 84 mg (89% from the starting *trans* diastereomer) of *trans*-**11** (R_f = 0.71) and 426 mg (90%) of *cis*-**11** (R_f = 0.30), the latter as a colorless solid, m.p. 104−105 °C. IR (KBr): $\tilde{\nu}$ = 3290, 2961 2933, 2871, 1766, 1702, 1512, 1447, 1331, 1244, 1173, 1063 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 8 Hz, 3 H, CH_3), 1.12−1.38 (m, 4 H), 1.55−1.62 (m, 2 H, CH_2), 1.85−2.04 (m, 2 H, CH_2), 3.40−3.52 (m, 2 H, NCH_2), 3.80 (s, 3 H, OCH_3), 4.65 (s, 1 H, CH), 5.84 (s, 1 H, CH), 6.85−6.91 (m, 2 H, aryl-H), 7.04−7.36 (m, 6 H, aryl-H), 7.52 (br. s, 2 H, aryl-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 7.1 (−, Cpr-C), 11.0 (−, Cpr-C), 13.6 (+, CH_3), 18.9 (−, CH_2), 19.9 (C_{quat}, Cpr-C), 30.0 (−, CH_2), 38.3 (−, NCH_2), 55.1 (+, OCH_3), 56.3 (+, CH), 60.5 (+, CH), 111.4 (+, aryl-C), 112.0 (C_{quat}, aryl-C), 114.1 (+, 2 C, aryl-C), 119.0 (+, aryl-C), 119.9 (+, aryl-C), 122.2 (+, aryl-C), 124.0 (C_{quat}, aryl-C), 129.1 (+, 2 C, aryl-C), 130.7 (C_{quat}, aryl-C), 134.3 (C_{quat}, aryl-C), 136.9 (C_{quat}, aryl-C), 154.7 (C_{quat}, aryl-C), 159.5 (C_{quat}, C=O), 169.1 (C_{quat}, C=O) ppm. MS (70 eV): *m*/*z* (%) = 430/429 (30/100) [M^+], 322 (38), 301 (10), 223 (10) 195 (10). $C_{26}H_{27}N_3O_3$ (429.5): calcd. C 72.71, H 6.34, N 9.78; found C 72.45, H 6.29, N 9.81.

Methyl 1′-(1,3-Benzodioxol-5-yl)-2′,3′,4′,9′-tetrahydrospiro[cyclopropane-1,4′-(1*H*-β-carboline)]-3′-carboxylate (9): Piperonal (750 mg, 5.00 mmol) was added to a solution of **7** (1.22 g, 5.00 mmol) in trimethyl orthoformate (25 mL) and the solution was stirred at 25 °C for 8 h. After removal of the volatiles in vacuo the residue was taken up in CH_2Cl_2 (30 mL), at 0 °C trifluoroacetic acid (2.28 g, 20.0 mmol) was added over a period of 5 min and the solution was stirred at 25 °C for 12 h. Dilution with CH_2Cl_2 (50 mL), addition of saturated aqueous $NaHCO_3$ (25 mL), extraction of the aqueous phase with CH_2Cl_2 (2 × 30 mL), drying of the combined organic phases over $MgSO_4$, evaporation of the solvents and column chromatography of the residue on 50 g of silica gel (3 × 15 cm, R_f = 0.40, pentane/Et_2O, 2:1) yielded 1.67 g (89%) of crude **9** as a mixture of the *cis* and *trans* diastereomers (1:2.5). Crystallization from EtOAc/pentane yielded the *trans* diastereomer (980 mg, 52%) as a colorless solid, m.p. 190 °C. The residue from the mother liquor contained the *cis* and *trans* diastereomers in a ratio of 3:1, m.p. 79−85 °C. ***trans*-9:** IR (KBr): $\tilde{\nu}$ = 3271, 2972, 2892, 1740, 1487, 1354, 1238, 1111, 1038 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.06−1.12 (m, 2 H, Cpr-H), 1.38−1.42 (m, 1 H, Cpr-H), 1.80−1.82 (m, 1 H, Cpr-H), 2.20 (br. s, 1 H, NH), 3.42 (s, 1 H, CH), 3.71 (s, 3 H, OCH_3), 5.61 (s, 1 H, CH), 5.94 (s, 2 H, CH_2), 6.72−6.92 (m, 3 H, aryl-H), 6.96−7.14 (m, 2 H, aryl-H), 7.18−7.38 (m, 2 H, aryl-H), 7.60 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.7 (−, Cpr-C), 13.6 (−, Cpr-C), 15.2 (C_{quat}, Cpr-C), 51.7 (+, CH_3), 54.6 (+, CH), 62.3 (+, CH), 101.1 (−, CH_2), 108.1 (+, aryl-C), 108.9 (+, aryl-C), 111.2 (+, aryl-C), 111.5 (C_{quat}, aryl-C), 118.8 (+, aryl-C), 119.4 (+, aryl-C), 121.4 (+, aryl-C), 122.0 (+, aryl-C), 124.5 (C_{quat}, aryl-C), 134.3 (C_{quat}, aryl-C), 135.5 (C_{quat}, aryl-C), 136.1 (C_{quat}, aryl-C), 147.5 (C_{quat}, aryl-C), 148.0 (C_{quat}, aryl-C), 172.9 (C_{quat}, C=O) ppm. MS (70 eV): *m*/*z* (%) = 376 (100) [M^+], 359 (20), 317 (64) [M^+ − CO_2Me], 195 (10), 168 (18). $C_{22}H_{20}N_2O_4$ (376.4): calcd. C 70.20, H 5.36, N 7.44; found C 69.90, H 5.60, N 7.55. ***cis*-9:** IR (KBr): $\tilde{\nu}$ = 3302, 3013, 2890, 2773, 1735, 1697, 1487, 1443, 1248, 1039 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.85−0.92 (m, 1 H, Cpr-H), 1.38−1.42 (m, 2 H, Cpr-H), 1.72−1.80 (m, 1 H, Cpr-H), 3.10 (br. s, 1 H, NH), 3.75 (s, 3 H, CH_3), 4.28 (s, 1 H, CH), 5.20 (s, 1 H, CH), 5.96 (s, 2 H, CH_2), 6.72−6.94 (m, 3 H, aryl-H), 6.98−7.14 (m, 2 H, aryl-H), 7.18−7.38 (m, 2 H, aryl-H), 7.55 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.7 (−, Cpr-C), 13.6 (−, Cpr-C), 20.0 (C_{quat}, Cpr-C), 51.8 (+, CH_3), 54.2 (+, CH), 62.2 (+, CH), 101.4 (−, CH_2), 108.2 (+, aryl-C), 111.2 (+, aryl-C), 111.5 (C_{quat}, aryl-C), 114.1 (+, aryl-C), 118.8 (+, aryl-C), 119.3 (+, aryl-C), 121.4 (+, aryl-C), 124.5 (C_{quat}, aryl-C), 130.0 (+, aryl-C), 133.3 (C_{quat}, aryl-C), 134.2 (C_{quat}, aryl-C), 134.8 (C_{quat}, aryl-C), 136.0 (C_{quat}, aryl-C), 159.5 (C_{quat}, aryl-C), 172.7 (C_{quat}, C=O) ppm. MS (70 eV): *m*/*z* (%) = 376 (100) [M^+], 359 (20), 317 (64) [M^+ − CO_2Me], 315 (20), 289 (12), 195 (10), 168 (18). $C_{22}H_{20}N_2O_4$ (376.4): calcd. C 70.20, H 5.36, N 7.44; found C 70.48, H 5.56, N 7.13.

Methyl *trans*-1′-(1,3-Benzodioxol-5-yl)-2′-(2-chloroacetyl)-2′,3′,4′,9′-tetrahydrospiro[cyclopropane-1,4′-(1*H*-β-carboline)]-3′-carboxylate (*trans*-12): Chloroacetyl chloride (372 mg, 3.30 mmol) was added to a mixture of *trans*-**9** (619 mg, 1.65 mmol) and 1 N Na_2CO_3 (8.25 mL, 8.25 mmol) in CH_2Cl_2 (30 mL) at 0 °C, the mixture was stirred at 20 °C for 2 h, diluted with CH_2Cl_2 (25 mL) and washed with a saturated $NaHCO_3$ solution (20 mL). Drying over $MgSO_4$, evaporation of the solvents and chromatographic purification of the residue on 25 g of silica (1.5 × 20 cm, R_f = 0.40, pentane/Et_2O, 1:2) yielded 697 mg (93%) of *trans*-**12** as a colorless solid, m.p. 118 °C. IR (KBr): $\tilde{\nu}$ = 3302, 2890, 1739, 1662, 1487, 1444, 1394, 1240, 1039 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.06−1.12 (m, 1 H, Cpr-H), 1.24−1.30 (m, 1 H, Cpr-H), 1.52−1.64 (m, 1 H, Cpr-H), 2.18−2.26 (m, 1 H, Cpr-H), 3.65 (s, 3 H, OCH_3), 3.74−4.15 (m, 3 H, CH_2,CH), 5.81−5.93 (m, 2 H, CH_2), 6.12 (s, 1 H, CH), 6.72−6.80 (m, 1 H, aryl-H), 6.86−7.00 (m, 2 H, aryl-H), 7.02−7.28 (m, 3 H, aryl-H), 7.40−7.51 (m, 1 H, aryl-H), 8.60 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.3 (−, Cpr-C), 15.3 (−, Cpr-C), 19.5 (C_{quat}, Cpr-C), 43.1 (−, CH_2), 52.8 (+, OCH_3), 57.6 (+, CH), 62.2 (+, CH), 101.2 (−, CH_2), 106.4 (C_{quat}, aryl-C), 107.3 (+, aryl-C), 108.6 (+, aryl-C), 111.5 (+, aryl-C), 118.4 (+, aryl-C), 118.8 (C_{quat}, aryl-C), 119.3 (+, aryl-C), 121.4 (+, aryl-C), 124.5 (+, aryl-C), 135.0 (C_{quat}, 2 C, aryl-C), 136.2 (C_{quat}, 2 C, aryl-C), 149.2 (C_{quart}, aryl-C), 169.4 (C_{quart}, C=O), 171.8 (C_{quat}, C=O) ppm. MS (70 eV): *m*/*z* (%) = 454/452 (22/63) [M^+], 417 (36) [M^+ − Cl], 375 (100) [M^+ − $COCH_2Cl$], 315 (40), 195 (20). $C_{24}H_{21}ClN_2O_5$ (452.9): calcd. C 63.65, H 4.67, N 6.19; found C 63.82, H 4.92, N 5.96.

Methyl *cis*-1′-(1,3-Benzodioxol-5-yl)-2′-(2-chloroacetyl)-2′,3′,4′,9′-tetrahydrospiro[cyclopropane-1,4′-(1*H*-β-carboline)]-3′-carboxylate (*cis*-12): Chloroacetyl chloride (452 mg, 4.00 mmol) was added to a mixture of *cis*-**9** (752 mg, 2.00 mmol, mixture of *cis*/*trans* = 3:1) and 1 N Na_2CO_3 (10.0 mL, 10.0 mmol) in CH_2Cl_2 (25 mL) at 0 °C, the mixture was stirred at 20 °C for 2 h, diluted with CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ solution (20 mL). Drying over $MgSO_4$, evaporation of the solvents and chromatographic purification on 25 g of silica (1.5 × 20 cm, R_f = 0.51, pentane/Et_2O, 1:1) yielded 551 mg (81% from pure *cis*-**9**) of *cis*-**12** as a colorless solid, m.p. 125−132 C. IR (KBr): $\tilde{\nu}$ = 3295, 2891, 1738, 1670, 1486, 1395, 1040 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.86−0.92 (m, 1 H, Cpr-H), 0.96−1.15 (m, 1 H, Cpr-H), 142−1.58 (m, 1 H, Cpr-H), 2.05−2.21 (m, 1 H, Cpr-H), 3.58 (s, 3 H, OCH_3), 3.92−4.10 (m, 3 H, CH_2,CH), 5.78−5.95 (m, 2 H, CH_2), 6.08 (s, 1 H, CH), 6.63−6.76 (m, 1 H, aryl-H), 6.82−7.13 (m, 4 H, aryl-H), 7.21−7.40 (m, 2 H, aryl-H), 7.82 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 10.2 (−, Cpr-C), 15.1 (−, Cpr-C), 19.6 (−, Cpr-C), 43.3 (−, CH_2), 52.7 (+, OCH_3), 57.7 (+, CH), 64.1 (+, CH), 101.3 (−, CH_2), 106.4, (−, aryl-C), 108.7 (+, aryl-C), 107.4 (+, aryl-C), 111.4 (+, aryl-C), 118.8 (−, aryl-C), 119.2 (−, aryl-C), 119.8 (+, aryl-C), 122.1 (+, aryl-C), 124.2 (+, aryl-C), 136.3 (−, 2 C, aryl-C), 136.8 (−, 2 C, aryl-C), 147.5 (−, aryl-C), 166.2 (−, C=O), 171.5 (−, C=O) ppm. MS (70 eV): *m*/*z* (%) = 454/452 (30/79) [M^+], 417 (48) [M^+ − Cl], 375 (100) [M^+

− $COCH_2Cl$], 315 (46), 195 (20). $C_{24}H_{21}ClN_2O_5$ (452.9): calcd. C 63.65, H 4.67, N 6.19; found C 63.90, H 5.31, N 6.16.

***trans*-6′-(1,3-Benzodioxol-5-yl)-2′-methyl-2′,3′,6′,7′,12′,12a′-hexahydrospiro[cyclopropane-1,12′-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole]1′,4′-dione (*trans*-13):** A solution of *trans*-**12** (596 mg, 1.32 mmol) and methylamine (1 mL, 40% in H_2O) in EtOH (25 mL) was heated at 75 °C for 16 h. All volatiles were removed in vacuo, the residue was dissolved in CH_2Cl_2 (30 mL), the solution washed with water (20 mL) and dried with $MgSO_4$. Evaporation of the solvent and chromatographic purification of the residue on 25 g of silica (1.5 × 20 cm, R_f = 0.23, pentane/Et_2O, 1:2) yielded 470 mg (86%) of *trans*-**13** as a colorless solid, m.p. > 250 °C. IR (KBr): $\tilde{\nu}$ = 3299, 2888, 1664, 1488, 1330, 1236, 1036, 935 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.70−0.78 (m, 1 H, Cpr-H), 1.24−1.32 (m, 1 H, Cpr-H), 1.54−1.82 (m, 2 H, Cpr-H), 2.98 (s, 3 H, CH_3), 3.86−4.20 (m, 2 H, CH_2), 4.56 (s, 1 H, CH), 5.32 (s, 1 H, CH), 5.95 (s, 2 H, CH_2), 6.68−6.82 (m, 3 H, aryl-H), 6.96−7.20 (m, 2 H, aryl-H), 7.28−7.39 (m, 2 H, aryl-H), 8.12 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 8.2 ppm (−, Cpr-C), 11.2 (−, Cpr-C), 21.0 (C_{quat}, Cpr-C), 33.5 (+, CH_3), 51.5 (−, CH_2), 53.4 (+, CH), 56.8 (+, CH), 101.3 (−, CH_2), 108.3 (C_{quat}, aryl-C), 109.1 (+, aryl-C), 111.5 (+, aryl-C), 113.6 (+, aryl-C), 118.9 (C_{quat}, aryl-C), 120.0 (+, aryl-C), 122.4 (+, aryl-C), 122.5 (+, aryl-C), 123.9 (+, aryl-C), 130.4 (C_{quat}, aryl-C), 131.4 (C_{quat}, aryl-C), 136.5 (C_{quat}, aryl-C), 148.0 (C_{quat}, aryl-C), 148.2 (C_{quat}, aryl-C), 162.9 (C_{quat}, C=O), 163.0 (C_{quat}, C=O) ppm. MS (70 eV): *m*/*z* (%) = 415 (100) [M^+], 315 (15), 289 (48). $C_{24}H_{21}N_3O_4$ (415.5): calcd. 415.1532 (correct HRMS).

***cis*-6′-(1,3-Benzodioxol-5-yl)-2′-methyl-2′,3′,6′,7′,12′,12a′-hexahydrospiro[cyclopropane-1,12′-pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole]1′,4′-dione (*cis*-13):** A solution of *cis*-**12** (226 mg, 500 μmol) and methylamine (0.4 mL, 40% in H_2O) in EtOH (10 mL) was heated at 75 °C for 16 h. The volatiles were removed in vacuo, the residue was dissolved in CH_2Cl_2 (20 mL), washed with water (10 mL) and dried with $MgSO_4$. Evaporation of the solvents and chromatographic purification of the residue on 20 g of silica (1.5 × 20 cm, R_f = 0.40, pentane/Et_2O, 1:1) yielded 168 mg (81%) of *cis*-**13** as a colorless solid, m.p. > 250 °C. IR (KBr): $\tilde{\nu}$ = 3245, 2890, 1668, 1489, 1465, 1332, 1040 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.10−1.16 (m, 2 H, Cpr-H), 1.36−1.40 (m, 1 H, Cpr-H), 1.72−1.78 (m, 1 H, Cpr-H), 3.01 (s, 3 H, CH_3), 3.85−4.20 (m, 2 H, CH_2), 4.52 (s, 1 H, CH), 5.22 (s, 1 H, CH), 5.98 (s, 2 H, CH_2), 6.71−6.84 (m, 3 H, aryl-H), 6.96−7.20 (m, 2 H, aryl-H), 7.26−7.38 (m, 2 H, aryl-H), 8.12 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 8.2 (−, Cpr-C), 11.2 (−, Cpr-C), 21.0 (C_{quat}, Cpr-C), 33.5 (+, CH_3), 51.5 (−, CH_2), 53.4 (+, CH), 56.8 (+, CH), 101.3 (−, CH_2), 108.3 (C_{quat}, aryl-C), 109.1 (+, aryl-C), 111.5 (+, aryl-C), 113.6 (+, aryl-C), 118.9 (C_{quat}, aryl-C), 120.0 (+, aryl-C), 122.4 (+, aryl-C), 122.5 (+, aryl-C), 123.9 (+, aryl-C), 130.4 (C_{quat}, aryl-C), 131.4 (C_{quat}, aryl-C), 136.5 (C_{quat}, aryl-C), 148.0 (C_{quat}, aryl-C), 148.2 (C_{quat}, aryl-C), 162.9 (C_{quat}, C=O), 163.0 (C_{quat}, C=O) ppm. MS (70 eV): *m*/*z* (%) = 416 (32), 415 (100) [M^+], 315 (15), 289 (50), 274 (10). $C_{24}H_{21}N_3O_4$ (415.5): calcd. C 69.39, H 5.10, N 10.11; found C 69.12, H 5.09, N 9.91.

Methyl 1′-(2-Methylpropenyl)-2′,3′,4′,9′-tetrahydrospiro[cyclopropane-1,4′-(1*H*-β-carboline)]-3-carboxylate (10): 3-Methylcrotonaldehyde (prenal) (1.44 g, 17.2 mmol) was added to a solution of **7** (3.81 g, 15.6 mmol) in trimethyl orthoformate (70 mL) at 0 °C, and the mixture was stirred at this temperature for 12 h. Removal of the volatiles in vacuo yielded 4.80 g (15.5 mmol, 99%) of raw imine[21] as a colorless solid, m.p. 152 °C. TFA (11.4 g, 100 mmol) was added to a solution of the raw imine (1.55 g, 5.00 mmol) in CH_2Cl_2 (25 mL) at −30 °C, and the mixture was stirred at this temperature for 63 h. Then 2 N NaOH solution (60 mL) was added, the phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (10 mL) and dried with $MgSO_4$. Evaporation of the solvents and chromatographic purification of the residue on 100 g of silica (4 × 30 cm, R_f = 0.48, Et_2O/EtOAc, 50:1) yielded 556 mg (36% yield) of **10** as a red oil. IR (film): $\tilde{\nu}$ = 3387 (NH), 3175, 3058, 2950, 1734 (C=O), 1457, 1376, 1258, 1194, 1110, 1016, 741 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.94−0.99 (m, 1 H, Cpr-H), 1.05−1.13 (m, 1 H, Cpr-H), 1.24−1.32 (m, 1 H, Cpr-H), 1.80 (s, 3 H, CH_3), 1.82−1.86 (m, 1 H, Cpr-H), 1.88 (s, 3 H, CH_3), 2.31−2.48 (br. s, 1 H, NH), 3.32 (s, 1 H, 3′-H), 3.63 (s, 3 H, OCH_3), 5.23 (d, ^3J = 9.1 Hz, 1 H, 1′-H), 5.31 (d, ^3J = 9.1 Hz, 1 H, 1′′-H), 6.98 (m_c, 1 H, 6′-H), 7.06 (m_c, 1 H, 7′-H), 7.25 (d, ^3J = 8.2 Hz, 1 H, 8′-H), 7.31 (d, ^3J = 8.2 Hz, 1 H, 5′), 7.64−7.70 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.3 (−, Cpr-C), 14.1 (−, Cpr-C), 18.2 (+, CH_3), 19.8 (C_{quat}, Cpr-C), 25.8 (+, CH_3), 47.9 (+, C-1′), 51.6 (+, OCH_3), 63.3 (+, C-3′), 109.8 (C_{quat}, C-4a′), 111.0 (+, C-8′), 118.6 (+, C-5′*), 119.1 (+, C-7′*), 121.0 (+, C-6′), 124.5 (+, C-1′′), 124.8 (C_{quat}, C-4b′), 135.2 (C_{quat}, C-9a′), 135.7 (C_{quat}, C-8a′), 137.3 (C_{quat}, C-2′′), 173.1 (C_{quat}, C=O) ppm. MS (70 eV): *m*/*z* (%) = 310 (100) [M^+], 295 (14), 251 (48) [$M^+ - CO_2Me$], 223 (16), 195 (32), 180 (8), 167 (14). $C_{19}H_{22}N_2O_2$ (310.4): calcd. C 73.52, H 7.14, N 9.03; found C 73.54, H 6.90, N 8.89.

Methyl 2′-[1-(9*H*-Fluoren-9-ylmethoxycarbonyl)pyrrolidin-2-ylcarbonyl]-1′-(2-methylpropenyl)-2′,3′,4′,9′-tetrahydrospiro[cyclopropane-1,4′-(1*H*-β-carboline)]-3′-carboxylate (14a) and (14b): Fmoc-(*S*)-Pro−Cl (520 mg, 1.46 mmol) was added to a solution of **10** (301 mg, 970 μmol) in CH_2Cl_2 (20 mL) at 20 °C. After 2 min, aqueous 1 N Na_2CO_3 (15 mL, 15 mmol) was added. After stirring for 4 h, the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were washed with brine (10 mL) and dried with $MgSO_4$. Evaporation of the solvent and chromatographic purification of the residue on 35 g of silica (3 × 20 cm, pentane/EtOAc, 1:1) yielded 282 mg (46%) of **14a** (R_f = 0.52) as a yellow solid, m.p. 183 °C, and 266 mg (44%) of **14b** (R_f = 0.27) as a yellow solid, m.p. 174 °C.

(5a′*R*,12′*S*,14a′*S*)-1′,2′,3′,5a′,6′,11′,12′,14a′-Octahydro-12′-(2-methyl-1-propenyl)-5′*H*,14′*H*-spiro[cyclopropane-1,6′-pyrrolo[1′′,2′′:4′,5′]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole]-5′,14′-dione (15a): Piperidine (3 mL) was added to a solution of **14a** (260 mg, 413 μmol) in CH_2Cl_2 (15 mL) at 20 °C and the mixture stirred for 1 h. Evaporation of the solvent and chromatographic purification of the residue on 35 g of silica (3 × 20 cm, R_f = 0.28, pentane/EtOAc, 1:1) yielded 107 mg (69%) of **15a** as a slightly yellow solid, m.p. 215 °C. $[\alpha]_D^{20}$ = +164.6 (*c* = 0.35, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3282 (NH), 3064, 2965, 2880, 1657 (C=O), 1440, 1332, 1296, 1261, 1148, 1077, 1016, 741 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.84−0.93 (m, 1 H, Cpr-H), 1.26−1.35 (m, 1 H, Cpr-H), 1.48−1.57 (m, 1 H, Cpr-H), 1.65−1.80 (m, 1 H, Cpr-H), 1.75 [s, 3 H, CH=C(CH_3)$_2$], 1.91 [s, 3 H, CH=C(CH_3)$_2$], 1.96−2.05 (m, 3 H, 1′-H, 2′-H), 2.41−2.46 (m, 1 H, 1′-H), 3.52−3.75 (m, 2 H, 3′-H), 4.14−4.20 (m, 1 H, 14a′-H), 4.77 (s, 1 H, 5a′-H), 5.49 [d, ^3J = 8.6 Hz, 1 H, CH=C(CH_3)$_2$], 6.55 (d, ^3J = 8.6 Hz, 1 H, 12′-H), 6.97−7.11 (m, 2 H, 8′-H, 9′-H), 7.23−7.31 (m, 2 H, 7′-H, 10′-H), 8.42 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 7.6 (−, Cpr-C), 11.3 (−, Cpr-C), 18.7 [+, CH=C(CH_3)$_2$], 20.3 (C_{quat}, Cpr-C), 22.1 (−, C-2′), 25.8 [+, CH=C(CH_3)$_2$], 29.7 (−, C-1′), 45.6 (−, C-3′), 47.3 (+, C-12′), 58.5 (+, C-5a′), 60.5 (+, C-14a′), 110.9 (C_{quat}, C-6a′), 111.3 (+, C-10′), 118.6 (+, C-7′), 119.6

(+, C-8′), 120.5 (+, C-9′), 121.7 [+, CH=C(CH$_3$)$_2$], 124.0 (C$_{quat}$, C-6b′), 133.9 (C$_{quat}$, C-11a′), 136.2 [C$_{quat}$, CH=C(CH$_3$)$_2$], 139.7 (C$_{quat}$, C-10a′), 162.2 (C$_{quat}$, C-5′), 166.1 (C$_{quat}$, C-14′) ppm. MS (70 eV): *m*/*z* (%) = 375 (100) [M$^+$], 320 (8), 278 (14), 167 (11), 70 (16), 41 (16). $C_{23}H_{25}N_3O_2$ (375.5): calcd. 375.1947 (correct HRMS).

X-ray Crystal Structure Analysis of 15a: Formula $C_{23}H_{25}N_3O_2$, M = 375.5, colorless crystal, temperature 133(2) K, λ = 0.71073 Å, monoclinic, $P2_1$, unit cell dimensions a = 8.4619(9) Å, α = 90°, b = 11.0894(10) Å, β = 98.896(8)°, c = 12.7990(13) Å, γ = 90°, V = 1186.6(2) Å^3, $\rho_{calcd.}$ = 1.170 g·cm^{-3}. Absorption coefficient 0.183 mm^{-1}, F(000) 442. θ range for data collection 1.61−24.63°. Index ranges $-9 \le h \le 9$, $-12 \le k \le 12$, $-14 \le l \le 14$. Reflections collected/unique 5853/3371 [R(int) = 0.0407]. Observed reflections 3122 [$I \ge 2\sigma(I)$]. Completeness to θ = 24.63−97.7. Refinement method: full-matrix least-squares on F^2. Data/restraints/parameters 3371/1/289. Goodness-of-fit on F^2 1.068. Final R indices [$I \ge 2\sigma(I)$], R = 0.0725, wR^2 = 0.2199; R indices (all data) R = 0.0772, wR^2 = 0.2260. Absolute structure parameter −0.2(3). Largest diff. peak and hole, 0.899 and −0.379 e·Å^{-3}. CCDC-247926 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

(5a′*S*,12′*R*,14a′*S*)-1′,2′,3′,5a′,6′,11′,12′,14a′-Octahydro-12′-(2-methyl-1-propenyl)-5′*H*,14′*H*-spiro[cyclopropane-1,6′-pyrrolo[1′′,2′′:4′,5′]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole]-5′,14′-dione (15b): Piperidine (2 mL) was added to a solution of **14b** (184 mg, 292 μmol) in CH_2Cl_2 (10 mL) at 20 °C and the mixture was stirred for 2 h. Evaporation of the solvent and chromatographic purification of the residue on 25 g of silica (2.5 × 20 cm, R_f = 0.17, pentane/EtOAc, 1:1) yielded 67.4 mg (61%) of **15b** as a slightly yellow solid, m.p. 227 °C. $[\alpha]_D^{20}$ = −5.0 (c = 0.30, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3314 (NH), 2965, 2939, 1649 (C=O), 1455, 1303, 1145, 741 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.59−0.66 (m, 1 H, Cpr-H), 1.18−1.25 (m, 1 H, Cpr-H), 1.64−1.71 (m, 1 H, Cpr-H), 1.74 [s, 3 H, CH=C(CH$_3$)$_2$], 1.78−2.07 (m, 4 H, Cpr-H, 1′-H, 2′-H), 1.89 [s, 3 H, CH=C(CH$_3$)$_2$], 2.37−2.43 (m, 1 H, 1′-H), 3.24−3.33 (m, 1 H, 3′-H), 3.81−3.91 (m, 1 H, 3′-H), 4.05 (dd, ^3J = 5.9, 10.8 Hz, 1 H, 14a′-H), 4.67 (s, 1 H, 5a′-H), 5.47 [d, ^3J = 8.6 Hz, 1 H, CH=C(CH$_3$)$_2$], 6.64 (d, ^3J = 8.6 Hz, 1 H, 12′-H), 6.97 (t, ^3J = 7.9 Hz, 1 H, 8′-H), 7.05 (t, ^3J = 7.9 Hz, 1 H, 9′-H), 7.23 (d, ^3J = 7.9 Hz, 1 H, 10′-H), 7.33 (d, ^3J = 7.9 Hz, 1 H, 7′-H), 8.42 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.1 (−, Cpr-C), 11.6 (−, Cpr-C), 18.8 [+, CH=C(CH$_3$)$_2$], 21.7 (C$_{quat}$, Cpr-C), 22.2 (−, C-2′), 25.8 [+, CH=C(CH$_3$)$_2$], 29.7 (−, C-1′), 44.3 (−, C-3′), 46.7 (+, C-12′), 58.6 (+, C-5a′), 59.4 (+, C-14a′), 111.2 (C$_{quat}$, C-6a′), 111.3 (+, C-10′), 118.8 (+, C-7′), 119.6 (+, C-8′), 121.0 (+, C-9′), 121.6 [+, CH=C(CH$_3$)$_2$], 124.1 (C$_{quat}$, C-6b′), 133.1 (C$_{quat}$, C-11a′), 136.4 [C$_{quat}$, CH=C(CH$_3$)$_2$], 139.4 (C$_{quat}$, C-10a′), 161.9 (C$_{quat}$, C-5′), 164.3 (C$_{quat}$, C-14′) ppm. MS (ESI, MeOH): *m*/*z* (%) = 398 (89) [M$^+$ + Na], 773 (100) [2 M + Na$^+$]. $C_{23}H_{25}N_3O_2$ (375.5): calcd. 375.1947 (correct HRMS).

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[1] [1a] P. López-Alvarado, S. García-Granda, C. Álvarez-Rúa, C. Avendaño, *Eur. J. Org. Chem.* **2002**, 1702−1707. [1b] P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, J. Sebastião, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3317−3324. [1c] J. H. Poupaert, J. Bukuru, A. Gozzo, *Monatsh. Chem.* **1999**, *130*, 929−932. [1d] M.-F. Hsieh, P. D. Rao, C.-C. Liao, *Chem. Commun.* **1999**, 1441−1442. [1e] X.-L. Li, Y.-M. Wang, T. Matsuura, J.-B. Meng, *J. Heterocycl. Chem.* **1999**, *36*, 697−701. [1f] S. Peng, E. Winterfeldt, *Liebigs Ann. Chem.* **1990**, 319−322. [1g] P. E. Harrington, M. A. Kerr, *Synlett* **1996**, 1047−1048. [1h] M. Bandini, P. G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva, A. Umani-Ronchi, *J. Org. Chem.* **2002**, *67*, 3700−3704.

[2] [2a] C. Balsamini, G. Diamantini, A. Duranti, G. Spadoni, A. Tontini, *Synthesis* **1995**, 370−372. [2b] G. Spadoni, C. Balsamini, A. Bedini, E. Duranti, A. Tontini, *J. Heterocycl. Chem.* **1992**, *29*, 305−309.

[3] [3a] M.-Y. Chang, S.-T. Chen, N.-C. Chang, *Heterocycles* **2002**, *57*, 2321−2334. [3b] K. Yamada, F. Yamada, M. Somei, *Heterocycles* **2002**, *57*, 1231−1234. [3c] G. Galambos, P. Csókási, C. Szántay Jr., C. Szantay, *Liebigs Ann. Recl.* **1997**, 1969−1978. [3d] G. Galambos, P. Csókási, C. Szántay Jr., G. Czira, C. Szántay, *Heterocycles* **1994**, *38*, 1727−1732. [3e] M. Toyota, K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1* **1992**, 547−552. [3f] M. Somei, F. Yamada, H. Ohnishi, Y. Makita, M. Kuriki, *Heterocycles* **1987**, *26*, 2823−2828. [3g] E. Ciganek, E. M. Schubert, *J. Org. Chem.* **1995**, *60*, 4629−4634. [3h] A.-A. S. El-Ahl, *Synth. Commun.* **2000**, *30*, 2223−2231.

[4] For a review, see: E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797−1842.

[5] J. Li, T. Wang, P. Yu, A. Peterson, R. Weber, D. Soerens, D. Grubisha, D. Bennett, J. M. Cook, *J. Am. Chem. Soc.* **1999**, *121*, 6998−7010.

[6] Natural demethoxyfumitremorgine C has an $[\alpha]_D^{30}$ of 8.0 (c = 0.2, $CHCl_3$), cf. ref.[7c]

[7] [7a] C.-B. Cui, H. Kakeya, G. Okada, R. Onose, M. Ubukata, I. Takaheshi, K. Isono, H. Osada, *J. Antibiot.* **1995**, *48*, 1382−1384. [7b] C.-B. Cui, H. Kakeya, G. Okada, R. Onose, H. Osada, *J. Antibiot.* **1996**, *49*, 527−533. [7c] C.-B. Cui, H. Kakeya, H. Osada, *J. Antibiot.* **1996**, *49*, 534−540. [7d] C.-B. Cui, H. Kakeya, H. Osada, *J. Antibiot.* **1996**, *49*, 832−835. [7e] C.-B. Cui, H. Kakeya, H. Osada, *Tetrahedron* **1996**, *52*, 12651−12666. [7f] C.-B. Cui, H. Kakeya, H. Osada, *Tetrahedron* **1997**, *53*, 59−72.

[8] S. K. Rabindran, H. He, M. Singh, E. Brown, K. I. Collins, T. Annable, L. M. Greenberger, *Cancer Res.* **1998**, *58*, 5850−5858.

[9] W. E. Pullman, S. J. Whitaker, A61 K31/4985, **2003**; Lilly Icos LLC. Pr.: WO2000US11129, **2000**.

[10] [10a] M. Limbach, M. Es-Sayed, A. de Meijere, unpublished results. [10b] V. N. Belov, C. Funke, T. Labahn, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem.* **1999**, 1345−1356.

[11] A. Dougan, P. Grondin, C. Ruault, A.-C. Le Monnier de Gouville, H. Coste, J. Kirilovsky, F. Hyafil, R. Labaudinière, *J. Med. Chem.* **2003**, *46*, 4525−4532.

[12] A. Dougan, P. Grondin, C. Ruault, A.-C. Le Monnier de Gouville, H. Coste, J. M. Linget, J. Kirilovsky, F. Hyafil, R. Labaudinière, *J. Med. Chem.* **2003**, *46*, 4533−4542.

[13] [13a] P. D. Bailey, P. J. Cochrane, K. Lorenz, I. P. Collier, D. P. J. Pearson, G. M. Rosair, *Tetrahedron Lett.* **2001**, *42*, 113−115. [13b] T. Gan, J. M. Cook, *Tetrahedron Lett.* **1997**, *38*, 1301−1304. [13c] K. M. Depew, S. J. Danishefsky, N. Rosen, L. Sepp-Lorenzino, *J. Am. Chem. Soc.* **1996**, *118*, 12463−12464.

[14] This so-called Thorpe−Ingold effect had originally been attributed to an angle enlargement, see: [14a] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc.* **1915**, *107*, 1080−1106. [14b] C. K. Ingold, *J. Chem. Soc.* **1921**, *119*, 305. It was later shown that the major influence stems from the conformational preference of such a system, see: [14c] M. E. Jung, M. Kiankarimi, *J.*

Org. Chem. **1998**, *63*, 2968−2974. [14d] M. E. Jung, J. Gervay, *J. Am. Chem. Soc.* **1991**, *113*, 224−232.

[15] The corresponding 2-amino-2-[1-(1*H*-indol-3-yl)cylopropyl]-acetic acid has already been described, see: D. C. Horwell, M. J. McKiernan, S. Osborne, *Tetrahedron Lett.* **1998**, *39*, 8729−8732.

[16] Problems with the cyclization of prenaldimines have also been observed by others, see: D. M. Harrison, R. B. Sharma, *Tetrahedron* **1993**, *49*, 3165−3184.

[17] [17a] P. D. Bailey, S. P. Hollinshead, N. R. Mc Lay, K. Morgan, S. J. Palmer, S. N. Prince, C. D. Reynolds, S. D. Wood, *J. Chem. Soc., Perkin Trans. 1* **1993**, 431−439. [17b] P. D. Bailey, M. H. Moore, K. M. Morgan, D. I. Smith, J. M. Vernon, *Tetrahedron Lett.* **1994**, *35*, 3587−3588. [17c] H. Wang, A. Ganesan, *Tetrahedron Lett.* **1997**, *38*, 4327−4328.

[18] L. A. Carpino, B. J. Cohen, K. E. Stephens Jr., S. Y. Sadat-Aalaee, J.-H. Tien, D. C. Langridge, *J. Org. Chem.* **1986**, *51*, 3732−3734.

[19] On the basis of the known absolute configuration of the employed (*S*)-proline and the assumption that it did not racemize during incorporation, this depicts the overall absolute configuration as well.

[20] [20a] T. Liese, F. Seyed-Mahdavi, A. de Meijere, *Org. Synth.* **1990**, *69*, 148−153. [20b] For an advanced synthesis of **4** see: M. Limbach, S. Dalai, A. de Meijere, *Adv. Synth. Catal.* **2004**, *346*, 760−766.

[21] In this case the imine was isolated before cyclization. Experimental data: methyl [1-(1*H*-indol-3-yl)cyclopropyl][(3-methylbut-2-enylidene)amino]acetate. IR (KBr): $\tilde{\nu}$ = 3129, 3087, 3012, 2920, 2881, 1745 (C=O), 1652, 1611, 1434, 1344, 1198, 1162, 1082, 739 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.83−1.09 (m, 3 H, Cpr-H), 1.13−1.19 (m, 1 H, Cpr-H), 1.88 (s, 6 H, CH_3), 3.56 (s, 3 H, OCH_3), 3.80 (s, 1 H, 2-H), 6.11 (d, ^3J = 9.4 Hz, 1 H, 2′-H), 7.06−7.17 (m, 3 H, 2′′-H, 5′′-H, 6′′-H), 7.30 (d, ^3J = 7.0 Hz, 1 H, 7′′-H), 7.69 (d, ^3J = 7.0 Hz, 1 H, 4′′-H), 8.06 (d, ^3J = 9.4 Hz, 1 H, 1′-H), 8.07−8.18 (br. s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ = 10.3 ppm (−, Cpr-C), 10.4 (−, Cpr-C), 18.7 (+, CH_3), 21.6 (C_{quat}, Cpr-C), 26.7 (+, CH_3), 51.8 (+, OCH_3), 79.7 (+, C-2), 111.2 (+, C-7′′), 116.9 (C_{quat}, C-3′′), 119.2 (+, C-4′′*), 119.4 (+, C-6′′*), 121.6 (+, C-5′′), 125.2 (+, 2 C, C-2′′, C-2′), 127.6 (C_{quat}, C-3a′′), 135.9 (C_{quat}, C-7a′′), 148.7 (C_{quat}, C-3′), 161.6 (C_{quat}, C-1′), 172.3 (C_{quat}, C=O) ppm. MS (70 eV): *m*/*z* (%) = 310 (12) [M^+], 251 (100) [$M^+ - CO_2Me$], 212 (6), 196 (12), 183 (4), 168 (13), 156 (30), 129 (15). $C_{19}H_{22}N_2O_2$ (310.4): calcd. C 73.52, H 7.14, N 9.03; found C 73.19, H 7.15, N 8.91.

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