Intramolecular Ritter Reactions of 2-(2-Cyanoethyl)tetrahydrocyclopenta-[*b*]indole and -carbazole Derivatives

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Intramolecular Ritter reactions of 2-(2-cyanoethyl)tetrahydrocyclopenta[*b*]indole and -carbazole derivatives, prepared by a sequence of two different α-substitutions and Grignard reactions of the indole-based ketones 4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one and 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one, were used as key steps in the construction of various tetracyclic lactam compounds.

Introduction

In previous work we reported the synthesis of hexahydroindenopyridines of type **1**.[1,2] These compounds can be regarded as conformationally constrained analogues of the NK_1-antagonists **2** (CP-96345),[3] and **3** (CP-99994),[4] in which the required 1,2-diamino-1-phenylethane pharmacophore is incorporated in a tricyclic ring system. Furthermore, similar tricyclic diamine compounds with suitable OH-substitution of the benzene moiety have been conceived as potential D_1-selective dopamine receptor ligands,[5] characterized by a conformationally constrained 2-(hydroxyphenyl)-2-phenethylamino pharmacophore.[6] Successful examples of this general approach in which restriction of the bioactive conformation results in improved binding affinity and selectivity are the highly potent and selective D_1 agonists **4** [(±)-*trans*-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[*a*]phenanthridine][7] and **5**,[8] in which the 2-(hydroxyphenyl)-2-phenethylamino dopamine pharmacophore is embedded in a polycyclic framework (Figure 1).

Since the indole moiety is found in many bioactive molecules, the indole analogues **6** of tricyclic diamines **1** were conceived as suitable target compounds of potential interest as neurotransmitters. For the construction of the six-membered nitrogen heterocycle of **6** we envisaged an approach (Scheme 1) similar to that used for tricyclic diamines **1**.[1] Thus, conversion of the indole-based propanenitrile precursors **7** into alcohols **8** and subsequent intramolecular Ritter reaction should provide access to the tetracyclic ester compounds **9** as key intermediates; on further transformation of the angular ester group these could give rise to conformationally constrained indole analogues of various neurotransmitters. Here we deal with the sequential application

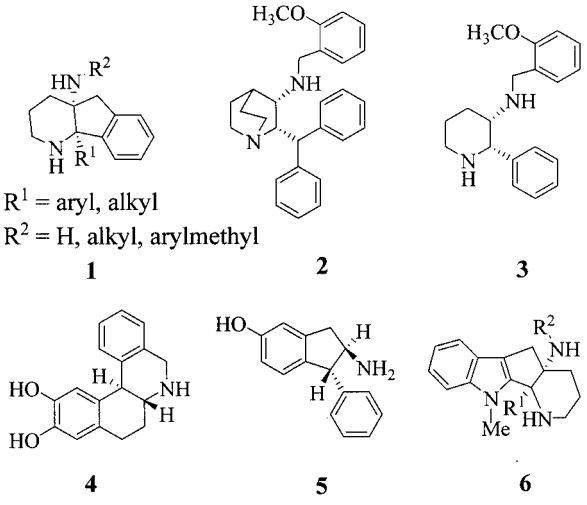
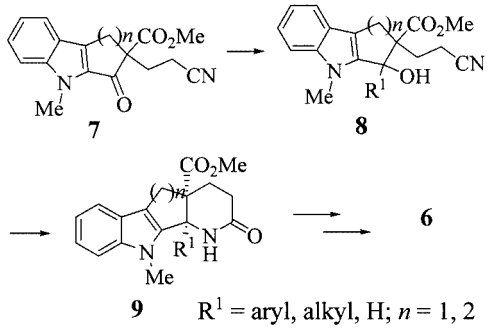


Figure 1. Structures of diamine model compounds and target compounds



Scheme 1. Planned conversion of indole-based precursors **7** into tetracyclic ester compounds **9**[2]

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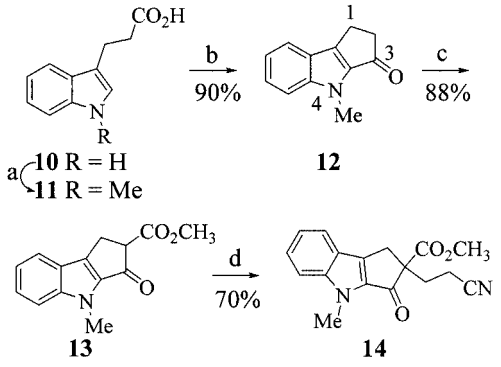
of Grignard and Ritter reactions to both five- and six-membered indole-based ketones **7**.

Results and Discussion

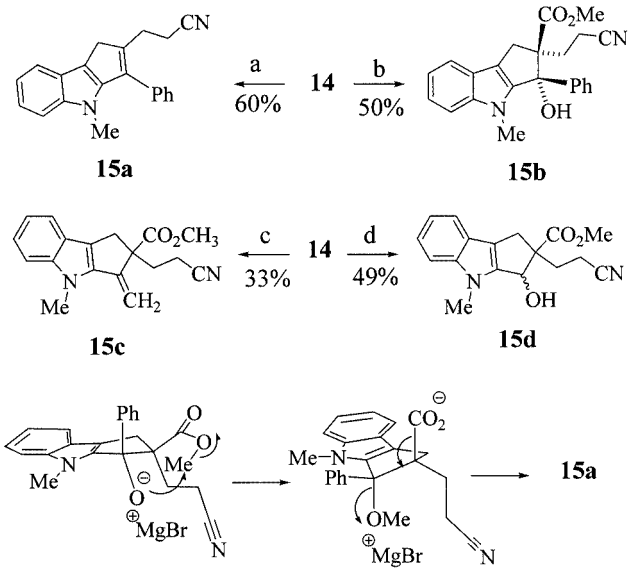
1. Grignard Reactions on Five- and Six-Membered β-Keto Esters

The starting five-membered ring ketone **12** [4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one] was prepared by *N*-methylation of 3-indolepropionic acid (**10**),[9,10] followed by acid-catalysed cyclisation of 3-(1-methyl-1*H*-indol-3-yl)propanoic acid (**11**).[11] Subsequent methoxycarbonylation of the electron-rich ketone **12** with dimethyl carbonate required use of a stronger base (KH) than that applied for the analogous conversion of 1-indanone (NaH).[1] Final Michael addition of β-keto ester **13** to acrylonitrile in *t*BuOH as a solvent and with *t*BuOK as a base catalyst afforded the required keto nitrile precursor **14** (Scheme 2).



Scheme 2. Reagents and conditions: (a) (i) KOH, MeI, acetone; (ii) KOH, H_2O, reflux; (b) PPA, toluene, 110 °C; (c) KH, $(CH_3O)_2CO$, 150 °C; (d) *t*BuOK, acrylonitrile, *t*BuOH

The Grignard reaction between β-keto ester **14** and freshly prepared phenylmagnesium bromide at −78 °C in THF afforded the cyclopentene product **15a** instead of the expected tertiary alcohol **15b**. Presumably, elimination is triggered by transfer of the methyl group of the ester to the vicinal O-anion centre, followed by expulsion of CO_2 and methoxide (Scheme 3). In view of the steric requirements imposed by the two bulky reaction centres, methyl transfer may proceed through an internal S_N2 attack of the O-anion in a six-membered transition state: for the main diastereoisomer with the OH and CO_2Me groups in a relative *trans* configuration (see below) this would involve a pseudo-equatorial orientation of the vicinal substituents, while subsequent elimination of the acid and methoxide could proceed via a diaxial orientation. Since this ester elimination reaction occurs to a much lower extent in the indanol analogues obtained from Grignard reactions of the corresponding indane β-keto esters,[1] this result may be attributed to the enhanced nucleophilic properties of the O-anion formed from indole keto ester **14**. In fact, when the Grignard reaction of indole keto ester **14** was carried out in Et_2O instead of THF, the expected diastereoisomeric alcohols **15b** were isolated as the only products with a *de* value of 26% for the (OH, CO_2Me) *trans*-disposed alcohol. No elimination product was detected under these conditions, although the yield of **15b** was lower (50%) than that obtained for the combined addition/elimination in THF (60%). Therefore, elimination probably may also proceed for the (OH, CO_2Me) *cis*-disposed alcohol if one takes the rather low *de* value observed in Et_2O into account. Again, suppression of the elimination reaction may be due to the decreased nucleophilicity of the *O*-anion, which forms a tighter ion pair with the MgX^+ counter-ion in the less polar ether solvent.



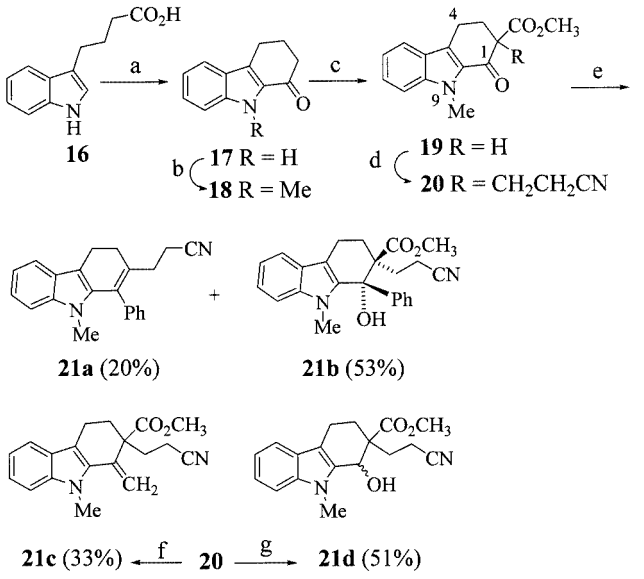
Scheme 3. Reagents and conditions: (a) PhMgBr, THF, −78 °C; (b) PhMgBr, Et_2O, −78 °C, *de* = 26%.; (c) MeMgBr, THF, −78 °C; (d) $NaBH_4$, MeOH, phosphate buffer pH = 7, *de* = 12%

Treatment of β-keto ester **14** with methylmagnesium bromide in THF furnished another alkene compound **15c**, corresponding to elimination of the tertiary alcohol but not the ester group. Since the ester is retained a different mechanism must apply, such as the formation of a stabilised carbocation upon workup of the reaction mixture. Conversely, such a stabilised carbocation cannot be an intermediate in the conversion of tertiary alcohol **15b** into cyclopentene **15a**, as it is shown further on that the carbocations formed in the acid-catalysed Ritter reactions of **15b** and **15c** did not lose their ester groups.

Finally, reduction of β-keto ester **14** with $NaBH_4$ produced a mixture of the diastereoisomeric secondary alcohols **15d** (Scheme 3).

In a manner analogous to that described for the conversion of 3-indolepropionic acid (Scheme 2), 3-indolebutyric acid **16** was first converted into the corresponding six-membered ring ketone **18**, which was further transformed into the 2-cyanoethyl keto ester **20** (Scheme 4). In this case *N*-methylation was carried out on the intermediate six-membered ketone 17,[11] which could easily be isolated by column chromatography, in contrast to the more polar *N*-unmethylated analogue of the five-membered ring ketone **12**. A subsequent Grignard reaction with phenylmagnesium

bromide at −78 °C in THF now produced a mixture of alkene **21a** and the isomerically pure (OH, CO_2Me) *trans*-disposed alcohol **21b**, while treatment with methylmagnesium bromide furnished methylene compound **21c**. Reduction of **21** with $NaBH_4$ finally afforded the epimeric alcohols **21d**.

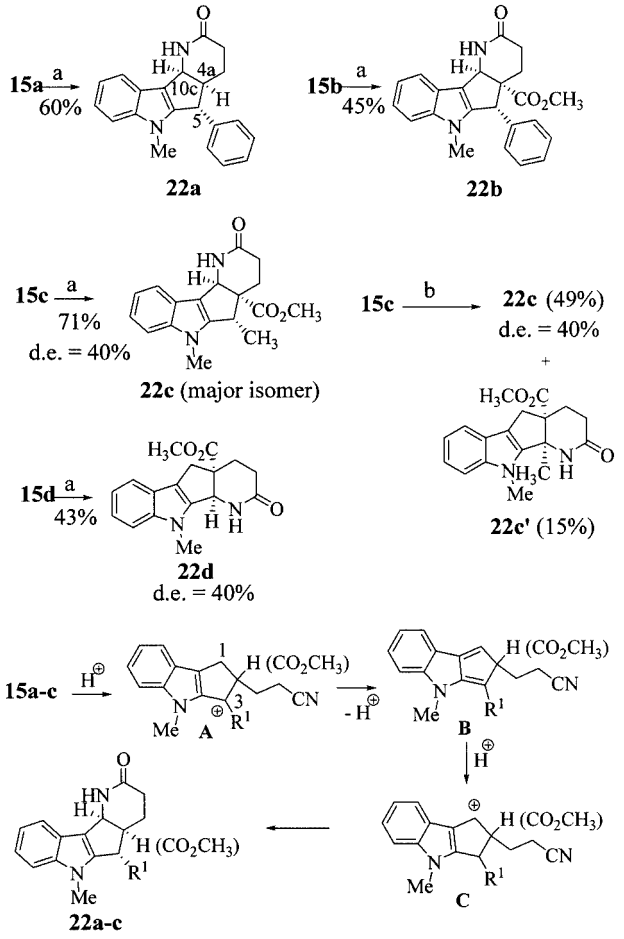


Scheme 4. Reagents and conditions: (a) PPA, toluene, 110 °C, 85%; (b) KOH, MeI, acetone, 65%; (c) KH, $(CH_3O)_2CO$, 150 °C, 74%; (d) *t*BuOK, acrylonitrile, *t*BuOH, 73%; (e) PhMgBr, THF, −78 °C; (f) MeMgBr, THF, −78 °C; (g) $NaBH_4$, MeOH, *de* = 30%

2. Ritter Reactions

Both the alkene **15a** and the tertiary alcohol **15b** were treated with methanesulfonic acid in chlorobenzene at 100 °C to effect cyclisation by an intramolecular Ritter reaction, which involves attack of the nitrile group on a stabilised carbocation intermediate (Scheme 5).[12,13] However, ring closure did not occur at the expected 3-position but rather at the 1-position of the tetrahydrocyclopenta[*b*]indole ring system. Apparently the initially formed benzylic cation **A** transforms into a more stable 3-indolylmethyl type cation **C**: this probably proceeds through loss of a proton at the 1-position to generate an *ortho*-quinodimethane intermediate **B**.

When methylene compound **15c** was subjected to the same reaction conditions (i.e., heating with methanesulfonic acid in chlorobenzene at 100 °C), ring closure again occurred exclusively at the 1-position, yielding **22c** as a mixture of diastereoisomers (*de* = 40%). Under less drastic conditions (use of methanesulfonic acid at room temperature), however, a mixture of lactams **22c** and **22c′** (ring closure at the 3-position) was obtained. Finally, the Ritter reaction of secondary alcohol **15d** resulted in exclusive ring closure at the 3-position. In this case direct attack of the nitrile group on the more reactive carbocation **A** is enhanced over isomerisation into **C** as there is no substituent in the 3-position to retard cyclisation. Thus, the steric hindrance exerted by substituents in the 3-position (i.e., phenyl in **15a** and **15b** and methyl in **15c**) may account for the transformation of cation **A** into **C**, which, especially at higher temperatures, occurs more rapidly than the ring closure in the 3-position.



Scheme 5. Reagents and conditions: (a) CH_3SO_3H, PhCl, 100 °C; (b) CH_3SO_3H, as solvent, room temp.

The relative stereochemistries of the lactams obtained from the Ritter reactions were revealed by ^1H NMR analysis. Thus, compound **22a** can be assigned as (10c,4a)-*cis*, (4a,5)-*trans* on the basis of NOE correlations observed in its ^1H NMR spectrum. A NOE between H-4a and H-10c reveals a *cis* fusion of the tetracyclic lactam system. The *trans* relationship between H-5 and H-4a is demonstrated by a NOE between H-5 and one of the 4-methylene protons, while the other 4-methylene proton correlates with H-4a (Figure 2).

Compounds **22b**, **22c**, **22c′** and **22d** were characterized in a similar manner by NOESY analysis. In all cases, ring fusion proceeds diastereoselectively in *cis* fashion, due to the favourable *syn* attack of the nitrile on the planar cation intermediate. Compound **22c** was isolated as a mixture of diastereoisomers with a *de* of 40%. NOE difference analysis of this mixture revealed that, in the major isomer, the 5-methyl is *cis* to proton H-10c and hence also to the ester group. Indeed, on irradiation at the respective resonance frequencies corresponding to the 5-methyl group of each isomer, the

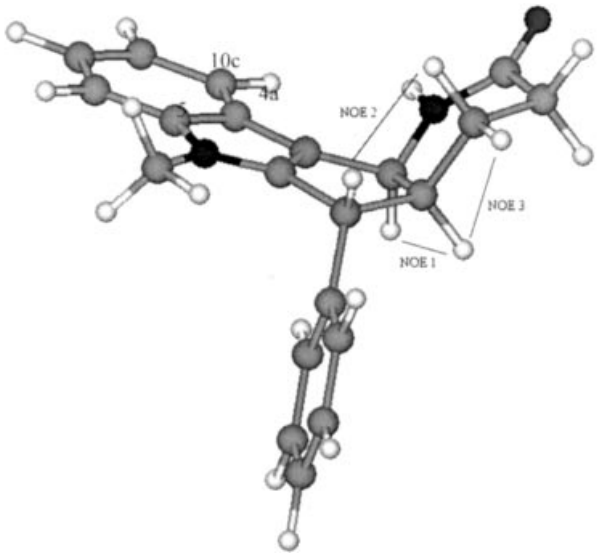
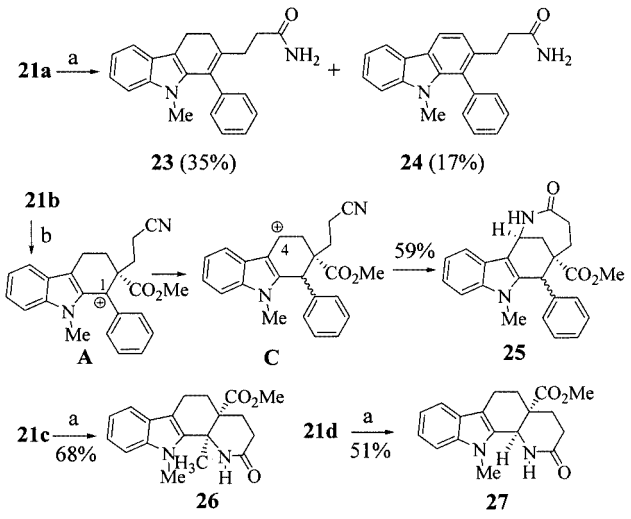


Figure 2. NOE correlations in the ^{1}H NMR spectrum of lactam **22a**



Scheme 6. Reagents and conditions: (a) CH_3SO_3H, PhCl, 100 °C; (b) CH_3SO_3H, as solvent, room temp.

NOE diff. signals detected for the major isomer were those for H-5 and H-10c, whereas only the H-5 signal remained for the minor isomer.

When the Ritter reaction was applied to the six-membered 2-cyanoethyl-substituted carbazole alcohols, it was to be expected that cyclisation at the 4-position of the rearranged 3-indolylmethyl type cation **C** to form a bridged ring system should be less likely to occur. Indeed, treatment of alkene **21a** with methanesulfonic acid in chlorobenzene at 100 °C did not result in ring closure, but instead yielded the amides **23** and **24**. However, treatment of ester **21b** with methanesulfonic acid at room temperature afforded a 1:1 mixture of the diastereoisomeric bridged compounds **25** resulting from intramolecular attack of the nitrile group at the 4-position in rearranged cation **C**. The two diastereoisomers of **25** were separated by column chromatography and their structures were assigned by ^{1}H NMR NOESY analysis. On the other hand, compounds **21c** and **21d** were converted into lactams **26** and **27**, corresponding to direct cyclisation of cation **A** generated at the 1-position. Presumably, the benzylic cation **A** formed from **21b** is less reactive towards attack of the nitrile, due both to the stabilising effect of the phenyl group and to its larger steric hindrance compared to a methyl group or hydrogen.

Conclusion

Intramolecular Ritter reactions of 2-cyanoethyl-substituted indole-based alcohols, encompassing cyclopentene- or cyclohexene-fused ring moieties, were used as key steps in the construction of lactam compounds serving as precursors to conformationally constrained indole analogues of NK-1 and dopamine receptor ligands. When phenyl groups are present in the tertiary alcohol positions of the tricyclic cyclopenta[*b*]indole and carbazole substrates, acidic Ritter reaction conditions result in rearrangement of the original benzylic cations to form stable 3-indolylmethyl-type cations and concomitant ring closure at that site. While cyclopenta[*b*]indole **15c**, with a 3-methyl substituent, reveals competitive cyclisation at the 1- and 3-positions, the corresponding carbazole **21c** and the secondary alcohols **15d** and **21d** exclusively undergo ring closure at the original cation site.

Experimental Section

General Remarks: Infrared spectra were recorded with a Perkin−Elmer 1600 Fourier transform spectrometer. Mass spectra were run with a Hewlett−Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For the NMR spectra (δ, ppm) a Bruker AMX 400 and a Bruker Avance 300 spectrometer were used. For column chromatography 70−230 mesh silica 60 (E.M. Merck) was used as the stationary phase. All reagents and solvents were of commercial quality. THF, Et_2O and toluene were dried with sodium and distilled before use. Some signals in the ^{1}H NMR spectrum of compound **15b** and the ^{13}C NMR spectra of compounds **15c**, **21a**, **21b**, **15b**, **15d**, **22b**, **24** are lacking due to the spectral complexity (e.g., overlapping signals or the presence of an isomeric mixture).

3-(1-Methyl-1*H*-indol-3-yl)propanoic Acid (11): KOH (1.78 g, 31.7 mmol) and MeI (1.64 mL, 26.5 mmol) were added at 0 °C to a solution of indolepropanoic acid (1.0 g, 5.3 mmol) in acetone (50 mL). The mixture was stirred at room temperature for 4 h, and the solvent was evaporated. The residue was dissolved in water (100 mL), and KOH (1.48 g, 26.4 mmol) was added. After having been heated at reflux for 2 h, the mixture was made acidic with HCl (6N). The precipitate was filtered off and washed with heptane. The product was purified by crystallization from CH_2Cl_2/heptane. Yield: 95%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1710 (s, C=O). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.04 (s, 1 H, CO_2H), 7.52 (d, J = 8 Hz, 1 H, H-arom.), 7.36 (d, J = 8 Hz, 1 H, H-arom.), 7.13 (t, J = 8 Hz, 1 H, H-arom.), 7.03 (s, 1 H, H-arom.), 7.01 (t, J = 8 Hz, 1 H, H-arom.), 3.72 (s, 3 H, NCH_3), 2.92 (t, J = 8 Hz, 2 H, $CH_2CH_2CO_2H$), 2.57 (t, J = 8 Hz, 2 H, CH_2CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 174.1, 136.6, 127.2, 126.6,

121.0, 118.4, 118.3, 112.7, 109.5, 34.6, 32.2, 20.1 ppm. MS (EI): *m/z* (%) = 203 (47) [$M^{\cdot+}$], 185 (3) [$M^{\cdot+} - H_2O$], 144 (100) [$M^{\cdot+} - CH_2CO_2H$]; exact mass calculated for $C_{12}H_{13}NO_2$: 203.0946; found 203.0941.

General Procedure for the Synthesis of 4-Methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (12) and 2,3,4,9-Tetrahydro-1*H*-carbazol-1-one (17): Compound **11** (1 g, 4.95 mmol) or 4-(3-indolyl)butyric acid **16** (4.95 mmol) was added to a solution of polyphosphoric acid (PPA) (7.24 g, 73.91 mmol) in toluene (50 mL). The mixture was stirred at 110 °C for 4 h, and ice-water (100 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 7:3).

4-Methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (12): Yield: 95%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1970 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 8, 1 Hz, 1 H, H-arom.), 7.42 (dt, *J* = 8, 1 Hz, 1 H, H-arom.), 7.35 (dd, *J* = 8, 1 Hz, 1 H, H-arom.), 7.17 (dt, *J* = 8, 1 Hz, 1 H, H-arom.), 3.92 (s, 3 H, NCH_3), 3.06 (m, 2 H, H^2), 2.98 (m, 2 H, H^1) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 145.0, 144.8, 138.9, 126.8, 123.1, 121.7, 120.2, 110.9, 41.2, 30.0, 19.6 ppm. MS (EI): *m/z* (%) = 185 (100) [$M^{\cdot+}$], 157 (53) [$M^{\cdot+}$ − CO], 142 (13) [$M^{\cdot+}$ − CH_3 − CO]; exact mass calculated for $C_{12}H_{11}NO$: 185.0841; found 185.0837.

2,3,4,9-Tetrahydro-1*H*-carbazol-1-one (17): Yield: 85%. IR (NaCl, cm^{-1}): $\tilde{\nu}$ = 3284 (m, NH), 2930 (s, CH_2), 1637 (s, CO). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.86 (s, 1 H, NH), 7.66 (d, *J* = 8 Hz, 1 H, H-arom.), 7.51 (d, *J* = 8 Hz, 1 H, H-arom.), 7.38 (ddd, *J* = 8, 7, 1 Hz, 1 H, H-arom.), 7.15 (ddd, *J* = 8, 7, 1 Hz, 1 H, H-arom.), 3.03 (t, *J* = 6 Hz, 2 H, H^2), 2.71 (t, *J* = 7 Hz, 2 H, H^4), 2.27 (m, 2 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.2, 138.5, 131.6, 130.0, 127.4, 126.3, 121.8, 120.8, 113.0, 38.8, 24.4, 21.8 ppm. MS (EI) *m/z* (%) = 185 (100) [$M^{\cdot+}$], 156 (35) [$M^{\cdot+}$ − CHO], 143 (19) [$M^{\cdot+}$ − CH_2CO], 129 (77) [$M^{\cdot+}$ − CH_2CH_2CO], 77 (10) [$C_6H_5^+$]; exact mass calculated for $C_{12}H_{11}NO$: 185.0841; found 185.0841.

9-Methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (18): KOH (1.64 g, 29.0 mmol) and MeI (1.5 mL, 24.0 mmol) were added at 0 °C to a solution of **17** (1.8 g, 10.0 mmol) in acetone (100 mL). The mixture was stirred at room temperature for 2 h, and was then acidified with HCl (6N). The aqueous layer was extracted three times with CH_2Cl_2, the combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 1:1). Yield: 82%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2932 (s, CH_2), 1646 (s, CO). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8 Hz, 1 H, H-arom.), 7.40 (m, 2 H, H-arom.), 7.13 (ddd, *J* = 8,7,1 Hz, 1 H, H-arom.), 4.07 (3, s, NCH_3), 3.02 (t, *J* = 6 Hz, 2 H, H^2), 2.65 (t, *J* = 6 Hz, 2 H, H^4), 2.22 (q, *J* = 6 Hz, 2 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.7, 140.1, 130.8, 129.6, 127.0, 125.1, 121.7, 120.4, 110.6, 40.4, 31.9, 25.2, 22.2 ppm. MS (EI) *m/z* (%) = 199 (100) [$M^{\cdot+}$], 170 (40) [$M^{\cdot+}$ − CHO], 157 (22) [$M^{\cdot+}$ − CH_2CO], 143 (56) [$M^{\cdot+}$ − CH_2CH_2CO], 77 (7) [$C_6H_5^+$]; exact mass calculated for $C_{13}H_{13}NO$: 199.0997; found 199.0996.

General Procedure for the Synthesis of Methyl 4-Methyl-3-oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indole-2-carboxylate (13) and Methyl 9-Methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (19): A solution of **12** (1 g, 5.4 mmol) or **18** (5.4 mmol) in dimethyl carbonate (50 mL) was added dropwise at 0 °C to a mixture of KH (35% dispersion in mineral oil, 1.4 g, 11.9 mmol) in dimethyl carbonate (70 mL). The mixture was heated at reflux temperature (150 °C) for 1 h, and ice-water (100 mL) was then added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, heptane/ethyl acetate, 7:3).

Methyl 4-Methyl-3-oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indole-2-carboxylate (13): Yield: 88%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1736.4 (s, C=O), 1676.9 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 8, 1 Hz, 1 H, H-arom.), 7.41 (ddd, *J* = 9, 8, 1 Hz, 1 H, H-arom.), 7.32 (dd, *J* = 8, 1 Hz, 1 H, H-arom.), 7.17 (ddd, *J* = 9, 8, 1 Hz, 1 H, H-arom.), 3.97 (dd, *J* = 7, 3 Hz, 1 H, H^2), 3.86 (s, 3 H, OCH_3), 3.78 (s, 3 H, NCH_3), 3.39 (dd, *J* = 17, 3 Hz, 1 H, H^1), 3.24 (dd, *J* = 17, 7 Hz, 1 H, H^1) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.1, 170.0, 145.3, 144.1, 137.0, 127.3, 122.6, 121.8, 120.4, 110.9, 57.8, 52.5, 29.9, 24.2 ppm. MS (EI) *m/z* (%) = 243 (75) [$M^{\cdot+}$], 211 (24) [$M^{\cdot+}$ − MeOH], 183 (100) [$M^{\cdot+}$ − HCO_2CH_3]; exact mass calculated for $C_{14}H_{13}NO_3$: 243.0895; found 243.0892.

Methyl 9-Methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (19): Yield: 74%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2958 (s, CH_2), 1737 (s, CO), 1666 (s, CO). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8 Hz, 1 H, H-arom.), 7.36 (ddd, *J* = 8, 7, 1 Hz, 1 H, H-arom.), 7.32 (d, *J* = 8 Hz, 1 H, H-arom.), 7.09 (ddd, *J* = 8, 7, 1 Hz, 1 H, H-arom.), 3.95 (s, 3 H, OCH_3), 3.77 (s, 3 H, NCH_3), 3.59 (dd, *J* = 9, 4 Hz, 1 H, H^2), 3.05 (m, 1 H, H^4), 2.90 (m, 1 H, H^4), 2.52 (m, 1 H, H^3), 2.37 (m, 1 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.1, 171.4, 140.6, 129.8, 128.7, 126.6, 121.7, 120.7, 119.6, 111.8, 56.5, 51.8, 32.9, 31.0, 30.3 ppm. MS (EI) *m/z* (%) = 257 (100) [$M^{\cdot+}$], 226 (5) [$M^{\cdot+}$ − OCH_3], 198 (93) [$M^{\cdot+}$ − CO_2CH_3], 183 (28) [$M^{\cdot+}$ − CO_2CH_3 − CH_3]; exact mass calculated for $C_{15}H_{15}NO_3$: 257.1052; found 257.1055.

General Procedure for the Synthesis of 14 and 20: *t*BuOK (0.18 g, 1.6 mmol) and acrylonitrile (0.84 mL, 12.7 mmol) were added to a solution of **13** (1.5 g, 6.4 mmol) or **19** (6.4 mmol) in *t*BuOH (100 mL). The mixture was stirred at room temperature for 3 h, and water (70 mL) was then added. The aqueous layer was extracted three times with CH_2Cl_2, the combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/ethyl acetate, 19:1).

Methyl 2-(2-Cyanoethyl)-4-methyl-3-oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indole-2-carboxylate (14): Yield: 70%. IR (NaCl, cm^{-1}): $\tilde{\nu}$ = 2246 (w, CN), 1733 (s, C=O), 1691 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 9, 1 Hz, 1 H, H-arom.), 7.47 (dt, *J* = 9, 1 Hz, 1 H, H-arom.), 7.38 (dd, *J* = 9, 1 Hz, 1 H, H-arom.), 7.21 (dt, *J* = 9, 1 Hz, 1 H, H-arom.), 3.91 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 3.58 (d, *J* = 17 Hz, 1 H, H^1), 3.10 (d, *J* = 17 Hz, 1 H, H^1), 2.56 (m, 2 H, CH_2CN), 2.42 (m, 2 H, CH_2CH_2CN) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9, 171.1, 145.7, 143.0, 136.7, 127.9, 122.6, 122.0, 120.5, 119.8, 111.2, 64.0, 52.9, 31.4, 30.7, 30.2, 13.0 ppm. MS (EI) *m/z* (%) = 296 (100) [$M^{\cdot+}$], 256 (15) [$M^{\cdot+}$ − CH_2CN], 236 (38) [$M^{\cdot+}$ − HCO_2CH_3], 196 (61) [$M^{\cdot+}$ − HCO_2CH_3 − CH_2CN]; exact mass calculated for $C_{17}H_{16}N_2O_3$: 296.1161; found 296.1161.

Methyl 2-(2-Cyanoethyl)-9-methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (20): Yield: 73%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2243 (w, CN), 1727 (s, C=O), 1660 (s, C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8 Hz, 1 H, H-arom.), 7.40 (ddd, *J* = 8, 7, 1 Hz, 1 H, H-arom.), 7.36 (d, *J* = 8 Hz, 1 H, H-arom.), 7.15 (ddd, *J* = 8, 7, 1 Hz, 1 H, H-arom.), 4.05 (s, 3 H, OCH_3), 3.72 (s, 3 H, NCH_3), 3.08 (t, *J* = 6 Hz, 2 H, H^4), 2.63 (m, 3 H, $1H^3$ +$2CH_2CN$), 2.30 (m, 3 H, $1H^3$ +$2CH_2CH_2CN$) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 188.3, 172.2, 140.9, 129.7, 129.0, 126.7, 122.8, 121.9, 120.7, 119.9, 111.9, 85.1, 52.2, 31.1, 29.3, 19.2, 17.5, 13.9 ppm. MS (EI) *m/z* (%) = 310 (100) [$M^{\cdot+}$], 256 (74) [$M^{\cdot+}$ − CH_2CH_2CN], 251 (75) [$M^{\cdot+}$ − CO_2CH_3], 224 (83) [$M^{\cdot+}$ − CH_2CH_2CN − MeOH], 197 (15) [$M^{\cdot+}$ − MeOH − CO_2 − CH=CHCN], 182 (13) [$M^{\cdot+}$ − MeOH − CO_2 − CH=CHCN − CH_3]; exact mass calculated for $C_{18}H_{18}N_2O_3$: 310.1317; found 310.1320.

General Procedure for the Synthesis of 15a, 21a and 21b: Bromobenzene (2.7 mL, 26 mmol) was added dropwise under argon to a stirred mixture of magnesium turnings (0.8 g, 23 mmol) and a iodine crystal in dry THF (50 mL). The mixture was heated at reflux for 1 h, and was then cooled to −78 °C and a solution of **14** (4.3 g,15 mmol) or **20** (15 mmol) in THF (100 mL) was added. The reaction mixture was allowed to come to room temperature overnight (16 h), and NH_4Cl (satd. aq. solution, 150 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/ethyl acetate, 19:1).

3-(4-Methyl-3-phenyl-1,4-dihydrocyclopenta[*b*]indol-2-yl)propanenitrile (15a): Yield: 60%. IR (NaCl, cm^{-1}): $\tilde{\nu}$ = 2250 (w, CN). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.58 (m, 9 H, H-arom.), 3.41 (s, 2 H, H^1), 3.40 (s, 3 H, NCH_3), 2.75 (t, *J* = 7 Hz, 2 H, CH_2CN), 2.48 (t, *J* = 7 Hz, 2 H, CH_2CH_2CN) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 141.0, 129.2, 128.6, 128.5, 128.0, 125.1, 123.7, 120.1, 119.6, 118.0, 115.1, 109.8, 33.5, 30.6, 25.4, 18.1 ppm. MS (EI) *m/z* (%) = 298 (39) [$M^{\cdot+}$], 258 (100) [$M^{\cdot+}$ − CH_2CN], 243 (15) [$M^{\cdot+}$ − CH_2CH_2CN]; exact mass calculated for $C_{21}H_{18}N_2$: 298.1471; found 298.1469.

3-(9-Methyl-1-phenyl-4,9-dihydro-3*H*-carbazol-2-yl)propanenitrile (21a): Yield: 20%. IR (NaCl, cm^{-1}): $\tilde{\nu}$ = 2246 (w, CN). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (dt, *J* = 6, 1 Hz, 1 H, H-arom.), 7.50 (m, 3 H, H-arom.), 7.36 (dt, *J* = 6, 1 Hz, 2 H, H-arom.), 7.19 (m, 3 H, H-arom.), 3.03 (s, 3 H, NCH_3), 3.02 (m, 2 H, H^4), 2.58 (m, 4 H, H^3, CH_2CH_2CN), 2.43 (m, 2 H, CH_2CN) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.2, 130.0, 128.9, 128.7, 126.3, 125.9, 123.5, 122.7, 120.4, 120.2, 119.7, 119.6, 118.9, 110.9, 109.7, 109.2, 32.0, 29.5, 20.5, 19.6, 16.8 ppm.

Methyl (1*R,2*R**)-2-(2-Cyanoethyl)-1-hydroxy-9-methyl-1-phenyl-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (21b):** Yield: 53%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3420 (b, OH), 2246 (w, CN), 1704 (s, C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8 Hz, 1 H, H-arom.), 7.43−7.18 (m, 8 H, H-arom.), 6.10 (s, 1 H, OH), 3.86 (s, 3 H, OCH_3), 3.51 (s, 3 H, NCH_3), 3.05 (ddd, *J* = 17, 6, 2 Hz, 1 H, H^4), 2.95 (ddd, *J* = 17, 11, 6 Hz, 1 H, H^4), 2.76 (ddd, *J* = 17, 9, 6 Hz, 1 H, CH_2CN), 2.47 (ddd, *J* = 17, 9, 7 Hz, 1 H, CH_2CN), 2.32 (ddd, *J* = 14, 6, 2 Hz, 1 H, H^3), 2.19 (ddd, *J* = 14, 11, 6 Hz, 1 H, H^3), 1.95 (ddd, *J* = 15, 9, 7 Hz, 1 H, CH_2CH_2CN), 1.86 (ddd, *J* = 15, 9, 6 Hz, 1 H, CH_2CH_2CN) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.9, 140.9, 138.9, 137.9, 130.1, 128.5, 126.3, 122.6, 120.7, 120.0, 119.6, 119.2, 115.9, 110.8, 109.8, 78.9, 55.1, 54.1, 53.3, 31.3, 30.8, 19.2, 14.4 ppm. MS (EI) *m/z* (%) = 388 (100) [$M^{\cdot+}$], 371 (8) [$M^{\cdot+}$ − OH], 312 (10) [$M^{\cdot+}$ − OH − CO_2CH_3], 105 (90,) [$C_6H_5CO^+$], 77 (63) [$C_6H_5^+$]; exact mass calculated for $C_{24}H_{24}N_2O_3$: 388.1787; found 388.1793.

Methyl 2-(2-Cyanoethyl)-3-hydroxy-4-methyl-3-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole-2-carboxylate (15b): Bromobenzene (2.7 mL, 26 mmol) was added dropwise to a stirred mixture of magnesium turnings (0.8 g, 23 mmol) and an iodine crystal in dry Et_2O (50 mL) under argon. After having been heated at reflux temperature for 1 h, the mixture was cooled to −78 °C, and a solution of **14** (4.3 g, 15 mmol) in dry Et_2O (100 mL) was added. The stirred reaction mixture was allowed to come to room temperature overnight (16 h), and NH_4Cl (satd. aq. solution, 150 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/ethyl acetate, 19:1). Yield: 50%; mixture of diastereoisomers, *de* = 26%. IR (NaCl, cm^{-1}): $\tilde{\nu}$ = 2247 (w, CN), 1732 (s, C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73−7.22 (m, 18 H major, minor isomer, H-arom.), 4.15 (dd, *J* = 11, 3 Hz, 1 H major isomer, CH_2CH_2CN), 4.00 (dd, *J* = 11, 3 Hz, 1 H minor isomer, CH_2CH_2CN), 3.85 (dd, *J* = 16, 4 Hz, 1 H minor isomer, CH_2CN), 3.80 (s, 3 H major isomer, NCH_3), 3.70 (dd, *J* = 16, 4 Hz, 1 H major isomer, CH_2CN), 3.55 (s, 3 H minor isomer, NCH_3), 3.18 (s, 3 H major isomer, OCH_3), 3.07 (s, 3 H minor isomer, OCH_3), 3.31−2.18 (m, 4 H, $2CH_2CH_2CN$ major, minor isomer + $2CH_2CN$ major, minor isomer + 4 H^1 major, minor isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5, 139.3, 130.4, 130.3, 130.0, 129.3, 128.3, 127.9, 127.8, 126.5, 126.3, 126.2, 125.6, 125.5, 125.1, 124.1, 121.6, 121.5, 121.4, 121.3, 120.9, 120.8, 119.4, 118.9, 110.9, 110.8, 53.0, 52.6, 52.3, 43.4, 40.6, 40.5, 30.6, 30.2, 30.0, 29.9, 25.6, 25.1 ppm MS (EI): *m/z* (%) = 374 (24) [$M^{\cdot+}$], 248 (100) [$M^{\cdot+}$ − CH_2CN − HCO_2CH_3 − C_2H_4], 235 (93) [$M^{\cdot+}$ − CH_2CH_2CN − CO_2CH_3 − C_2H_2], 105 (65) [$C_6H_5CO^+$], 77 (38) [$C_6H_5^+$]; exact mass calculated for $C_{23}H_{22}N_2O_3$: 374.1630; found 374.1634.

General Procedure for the Synthesis of 15c and 21c: MeMgBr (22 wt-% in THF, 7.82 mL, 23 mmol) was added at −78 °C under argon to a stirred solution of **14** (4.3 g, 15 mmol) or **20** (15 mmol) in dry THF (100 mL). After further reaction at room temperature for 16 h, NH_4Cl (satd. aq. solution, 150 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/ethyl acetate, 19:1).

Methyl 2-(2-Cyanoethyl)-4-methyl-3-methylene-1,2,3,4-tetrahydrocyclopenta[*b*]indole-2-carboxylate (15c): Yield: 33%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2244 (w, CN), 1722 (s, C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8 Hz, 1 H, H-arom.), 7.29 (m, 2 H, H-arom.), 7.13 (ddd, *J* = 8, 6, 2 Hz, 1 H, H-arom.), 5.44 (d, *J* = 1 Hz, 1 H, $=CH_2$), 5.05 (d, *J* = 1 Hz, 1 H, $=CH_2$), 3.84 (s, 3 H, NCH_3), 3.74 (s, 3 H, OCH_3), 3.56 (d, *J* = 16 Hz, 1 H, H^3), 2.84 (d, *J* = 16 Hz, 1 H, H^3), 2.34 (m, 4 H, CH_2CH_2CN, CH_2CN) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 174.5, 144.1, 143.9, 141.1, 124.2, 123.7, 123.4, 120.3, 120.2, 119.9, 110.0, 102.6, 61.3, 53.1, 34.4, 33.2, 31.1, 13.2 ppm. MS (EI) *m/z* (%) = 294 (70) [$M^{\cdot+}$], 254 (100) [$M^{\cdot+}$ − CH_2CN], 241 (25) [$M^{\cdot+}$ − CH_2=CHCN], 235 (13) [$M^{\cdot+}$ − CO_2CH_3], 194 (58) [$M^{\cdot+}$ − HCO_2CH_3 − CH_2CN]; exact mass calculated for $C_{18}H_{18}N_2O_2$: 294.1368; found 294.1362.

Methyl 2-(2-Cyanoethyl)-9-methyl-1-methylene-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (21c): Yield: 33%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2242 (w, CN), 1717 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8 Hz, 1 H, H-arom.), 7.28 (m, 2 H, H-arom.), 7.12 (ddd, *J* = 8, 6, 1 Hz, 1 H, H-arom.), 5.50 (s, 1 H, $=CH_2$), 5.08 (s, 1 H, $=CH_2$), 3.85 (s, 3 H, NCH_3), 3.74 (s, 3 H, OCH_3), 3.04 (dt, *J* = 17, 6 Hz, 1 H, H^4), 2.83 (ddd, *J* = 17, 9, 6 Hz, 1 H, H^4), 2.57 (m, 2 H, $1H^3$ +$1CH_2CN$), 2.43 (ddd, *J* = 17, 10, 6 Hz, 1 H, CH_2CN), 2.28 (ddd, *J* = 14, 10, 6 Hz, 1 H, CH_2CH_2CN), 2.19 (ddd, *J* = 14, 10, 6 Hz, 1 H, CH_2CH_2CN), 2.00 (dt, *J* = 14, 6 Hz, 1 H, H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 139.8, 138.0, 137.7, 125.9, 123.3, 119.6, 119.5, 119.0, 113.0, 109.5, 109.4, 52.7, 52.3, 32.4, 31.0, 30.3, 18.2, 13.5 ppm. MS (EI) *m/z* (%) = 308

(93) [$M^{\cdot+}$], 277 (7) [$M^{\cdot+} - OCH_3$], 248 (28) [$M^{\cdot+} - HCO_2CH_3$], 220 (13) [$M^{\cdot+} - HCO_2CH_3 - C_2H_4$], 195 (23) [$M^{\cdot+} - CH_2CH_2CN - CO_2CH_3$], 167 (100) [$M^{\cdot+} - CH_2CH_2CN - CO_2CH_3 - C_2H_4$], 77 (14) [$C_6H_5^+$]; exact mass calculated for $C_{19}H_{20}N_2O_2$: 308.1525; found 308.1536.

Methyl 2-(2-Cyanoethyl)-3-hydroxy-4-methyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole-2-carboxylate (15d): $NaBH_4$ (0.046 g, 1.2 mmol) was added to a solution of **14** (0.36 g, 1.2 mmol) in a 3:1 mixture of MeOH/phosphate buffer (pH = 7, 50 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and NH_4Cl (satd. aq. solution, 50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/ethyl acetate, 19:1). Yield: 49%; mixture of diastereoisomers, *de* = 12%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3397 (b, OH), 2251 (w, CN), 1730 (s, C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47 (dd, J = 8, 1 Hz, 1 H, H-arom.), 7.33−7.06 (m, 3 H, H-arom.), 5.60 (d, J = 8 Hz, 0.56 H, H^1), 5.11 (d, J = 8 Hz, 0.44 H, H^1), 3.80 (s, 1.32 H, NCH_3), 3.76 (s, 1.68 H, NCH_3), 3.75 (s, 1.32 H, OCH_3), 3.72 (s, 1.68 H, OCH_3), 3.58 (d, J = 15 Hz, 0.44 H, H^3), 3.41 (d, J = 15 Hz, 0.56 H, H^3), 2.93 (d, J = 8 Hz, 1 H, OH), 2.87 (d, J = 15 Hz, 0.44 H, H^3), 2.72 (d, J = 15 Hz, 0.56 H, H^3), 2.57−2.17 (m, 4 H, CH_2CH_2CN) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 174.2, 144.2, 144.1, 143.6, 143.5, 142.5, 142.4, 142.2, 142.1, 123.7, 123.6, 122.6, 122.5, 120.2, 120.0, 119.7, 119.6, 117.7, 117.6, 110.5, 110.3, 64.1, 62.9, 53.1, 53.0, 33.7, 33.6, 30.9, 30.8, 30.3, 14.3, 14.1 ppm. MS (EI) *m*/*z* (%) = 298 (100) [$M^{\cdot+}$], 280 (9) [$M^{\cdot+} - H_2O$], 267 (7) [$M^{\cdot+} - OCH_3$], 198 (39) [$M^{\cdot+} - HCO_2CH_3 - CH_2CN$], 184 (12) [$M^{\cdot+} - HCO_2CH_3 - CH_2CH_2CN$], 77 (8) [$C_6H_5^+$]; exact mass calculated for $C_{17}H_{18}N_2O_3$: 298.1317; found 298.1315.

Methyl 2-(2-Cyanoethyl)-1-hydroxy-9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate (21d): $NaBH_4$ (0.06 g, 1.7 mmol) was added to a solution of **20** (0.53 g, 1.7 mmol) in methanol (50 mL). The mixture was stirred at room temperature for 1 h, and NH_4Cl (satd. aq. solution, 50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/ethyl acetate, 19:1). Yield: 51%; mixture of diastereoisomers, *de* = 30%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2945 (b, OH), 2244 (w, CN), 1726 (s, C=O) ppm. MS (EI) *m*/*z* (%) = 312 (35) [$M^{\cdot+}$], 294 (1) [$M^{\cdot+} - H_2O$], 281 (4) [$M^{\cdot+} - OCH_3$], 253 (6) [$M^{\cdot+} - CO_2CH_3$], 235 (6) [$M^{\cdot+} - CO_2CH_3 - H_2O$], 226 (6) [$M^{\cdot+} - H_2O - CH_2CH_2CN - CH_3$], 194 (8) [$M^{\cdot+} - H_2O - HCO_2CH_3 - CH_2CN$], 173 (100) [$M^{\cdot+} - CO_2CH_3 - CH_2CH_2CN - C_2H_2$]; exact mass calculated for $C_{18}H_{20}N_2O_3$: 312.1474; found 312.1464; **major Isomer:** (Methyl (1*S**,2*S**)-2-(2-cyanoethyl)-1-hydroxy-9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate): ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, J = 8 Hz, 1 H, H-arom.), 7.30 (d, J = 8 Hz, 1 H, H-arom.), 7.26 (dt, J = 8, 1 Hz, 1 H, H-arom.), 7.10 (dt, J = 8, 1 Hz, 1 H, H-arom.), 5.15 (d, J = 9 Hz, 1 H, H^1), 3.78 (s, 3 H, NCH_3), 3.64 (s, 3 H, OCH_3), 2.84 (ddd, J = 17, 6, 2 Hz, 1 H, H^4), 2.72 (ddd, J = 17, 11, 6 Hz, 1 H, H^4), 2.57 (ddd, J = 16, 9, 6 Hz, 1 H, CH_2CN), 2.41 (ddd, J = 16, 9, 6 Hz, 1 H, CH_2CN), 2.33−2.20 (m, 2 H, $1CH_2CH_2CN+1H^3$), 2.12 (ddd, J = 14, 9, 6 Hz, 1 H, CH_2CH_2CN), 1.86 (ddd, J = 14, 11, 6 Hz, 1 H, H^3), 1.66 (d, J = 9 Hz, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 137.9, 134.7, 125.8, 122.6, 119.4, 119.2, 119.1, 110.7, 109.3, 62.7, 52.2, 51.0, 31.7, 29.3, 26.9, 18.5, 12.6; **minor Isomer:** (Methyl (1*R**,2*S**)-2-(2-cyanoethyl)-1-hydroxy-9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylate): ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8 Hz, 1 H, H-arom.), 7.31 (d, J = 8 Hz, 1 H, H-arom.), 7.27 (t, J = 8 Hz, 1 H, H-arom.), 7.12 (t, J = 8 Hz, 1 H, H-arom.), 4.88 (d, J = 8 Hz, 1 H, H^1), 3.86 (s, 3 H, OCH_3), 3.80 (s, 3 H, NCH_3), 2.92 (ddd, J = 17, 6, 3 Hz, 1 H, H^4), 2.62 (ddd, J = 17, 11, 6 Hz, 1 H, H^4), 2.51 (d, J = 8 Hz, 1 H, OH), 2.44−2.22 (m, 3 H, $2CH_2CN$, 1 H^3), 2.14 (ddd, J = 15, 6, 3 Hz, 1 H, H^3), 2.05 (dt, J = 15, 7 Hz, 1 H, CH_2CH_2CN), 1.90 (ddd, J = 15, 9, 7 Hz, 1 H, CH_2CH_2CN) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 138.0, 133.0, 125.7, 122.7, 119.3, 119.0, 118.7, 110.0, 109.3, 67.4, 52.5, 52.0, 29.4, 28.5, 22.8, 17.4, 13.5 ppm.

General Procedure A for the Ritter Reaction with CH_3SO_3H and Chlorobenzene at 100 °C: The alcohol or alkene (5 mmol) was dissolved in a chlorobenzene/CH_3SO_3H mixture (1:1, 20 mL). The mixture was stirred at 100 °C for 4 h, and ice-water (50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, eluent: see data of individual compounds).

General Procedure B for the Ritter Reaction with CH_3SO_3H at Room Temperature: The alcohol or alkene (5 mmol) was dissolved in CH_3SO_3H (20 mL) at 0 °C. The mixture was stirred at room temperature for 8 h, and ice-water (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated. The residue was purified by column chromatography (silica gel, eluent: see data of individual compounds).

(4a*R,5*R**,10c*R**)-6-Methyl-5-phenyl-3,4,4a,5,6,10c-hexahydropyrido[2′,3′:3,4]cyclopenta[1,2-*b*]indol-2(1*H*)-one (22a):** Eluent: CH_2Cl_2/ethyl acetate, 1:1; yield: 17% by procedure B, 60% by procedure A. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1664 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, J = 8 Hz, 1 H, H-arom.), 7.34−7.13 (m, 8 H, H-arom.), 6.22 (s, 1 H, NH), 5.18 (d, J = 7 Hz, 1 H, H^{10c}), 4.29 (d, J = 5 Hz, 1 H, H^5), 3.32 (s, 3 H, NCH_3), 3.15 (m, 1 H, H^{4a}), 2.50 (m, 1 H, H^3), 2.39 (m, 1 H, H^3), 2.16 (m, 1 H, H^4), 2.06 (m, 1 H, H^4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 146.3, 142.1, 141.8, 129.1, 127.4, 122.6, 121.5, 121.4, 120.1, 118.9, 118.2, 109.9, 53.4, 52.9, 49.6, 30.5, 29.4, 24.1 ppm. MS (EI) *m*/*z* (%) = 316 (100) [$M^{\cdot+}$], 258 [$M^{\cdot+} - CH_2CONH_2$], 245 (27) [$M^{\cdot+} - CH_2{=}CHCONH_2$]; exact mass calculated for $C_{21}H_{20}N_2O$: 316.1576; found 316.1574.

Methyl (4a*S,5*S**,10c*S**)-6-Methyl-2-oxo-5-phenyl-1,3,4,5,6,10c-hexahydropyrido[2′,3′:3,4]cyclopenta[1,2-*b*]indole-4a(2*H*)-carboxylate (22b):** Eluent: CH_2Cl_2/ethyl acetate, 1:1; yield: 45% by procedure A. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3433 and 3182 (s, NH), 1725 (s, C=O), 1671 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8 Hz, 1 H, H-arom.), 7.26−7.13 (m, 6 H, H-arom.), 6.98 (d, J = 2 Hz, 1 H, NH), 6.93 (m, 2 H, H-arom.), 5.85 (d, J = 2 Hz, 1 H, H^{10c}), 4.37 (s, 1 H, H^5), 3.35 (s, 3 H, NCH_3), 3.22 (s, 3 H, OCH_3), 2.65 (dt, J = 9, 5 Hz, 1 H, H^4), 2.38 (m, 2 H, $1H^4 + 1H^3$), 2.24 (dt, J = 13, 5 Hz, 1 H, H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 171.9, 142.7, 141.7, 137.5, 128.4, 127.9, 122.9, 121.7, 120.1, 118.8, 117.5, 109.9, 63.3,56.0, 55.5, 51.8, 30.5, 30.3, 29.4 ppm. MS (EI) *m*/*z* (%) = 374 (68) [$M^{\cdot+}$], 359 (13) [$M^{\cdot+} - CH_3$], 343 [$M^{\cdot+} - OCH_3$], 325 (24) [$M^{\cdot+} - OCH_3 - H_2O$], 315 (100) [$M^{\cdot+} - CO_2CH_3$]; exact mass calculated for $C_{23}H_{22}N_2O_3$: 374.1630; found 374.1633.

Methyl (4a*S,5*R**,10c*S**)-5,6-Dimethyl-2-oxo-1,3,4,5,6,10c-hexahydropyrido[2′,3′:3,4]cyclopenta[1,2-*b*]indole-4a(2*H*)-carboxylate (22c):** Eluent: CH_2Cl_2/ethyl acetate, 1:1; yield: 49% by procedure B, 71% by procedure A; mixture of diastereoisomers, *de* = 40%. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3182 (m, NH), 1726 (s, C=O), 1697 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, J = 7 Hz, 1 H, H-arom.), 7.27 (d, J = 7 Hz, 1 H, H-arom.), 7.20 (t, J = 7 Hz, 1 H, H-arom.), 7.13 (t, J = 7 Hz, 1 H, H-arom.), 6.83 (s, 0.7 H, NH), 6.63 (s, 0.3 H, NH), 5.67 (d, J = 3 Hz, 0.7 H, H^{5a}), 5.46 (d, J = 3 Hz, 0.3 H, H^{5a}), 3.84 (s, 2.1 H, OCH_3), 3.80 (s, 0.9 H, OCH_3), 3.74 (m, 0.3 H, H^1), 3.72 (s, 0.9 H, NCH_3), 3.68 (s, 2.1 H, NCH_3), 3.27 (q, J = 7 Hz, 0.7 H, H^1), 2.48−2.03 (m, 4 H, H^2, H^3), 1.50 (d, J = 7 Hz, 0.9 H, CH_3), 1.22 (d, J = 7 Hz, 2.1 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 173.1, 172.6, 171.7, 145.3, 144.8, 141.6, 141.3, 123.1, 122.8, 121.4, 121.3, 120.0, 118.5, 118.3, 115.4, 115.2, 109.7, 109.6, 60.8, 59.9, 56.7, 55.8, 52.6, 52.4, 42.8, 40.4, 30.6, 30.3,29.5, 29.2, 29.1, 24.0, 16.6, 14.6 ppm. MS (EI) *m*/*z* (%) = 312 (100) [$M^{\cdot+}$], 297 (38) [$M^{\cdot+}$ − CH_3], 256 (40) [$M^{\cdot+}$ − CO − C_2H_4], 253 (98) [$M^{\cdot+}$ − CO_2CH_3], 225 (32) [$M^{\cdot+}$ − HCO_2CH_3 − H_2O], 197 (24) [$M^{\cdot+}$ − CO_2CH_3 − CO − C_2H_4], 182 (23) [$M^{\cdot+}$ − CO_2CH_3 − HNCO − C_2H_4]; exact mass calculated for $C_{18}H_{20}N_2O_3$: 312.1474; found 312.1474.

Methyl (4a*R,10b*S**)-10,10b−Dimethyl-2-oxo-1,3,4,5,10,10b-Hexahydropyrido[3′,2′:4,5]cyclopenta[1,2-*b*]indole-4a(2*H*)-carboxylate (22c′):** Eluent: CH_2Cl_2/ethyl acetate, 1:1; yield: 15% by procedure B. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3443 (m, NH), 1732 (s, C=O), 1659 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H, NH), 7.49 (d, J = 8 Hz, 1 H, H-arom.), 7.29 (d, J = 8 Hz, 1 H, H-arom.), 7.22 (dt, J = 8, 1 Hz, 1 H, H-arom.), 7.12 (dd, J = 8, 1 Hz, 1 H, H-arom.), 3.82 (s, 3 H, OCH_3), 3.76 (s, 3 H, NCH_3), 3.63 (d, J = 15 Hz, 1 H, H^5), 2.83 (d, J = 15 Hz, 1 H, H^5), 2.57 (m, 1 H, H^3), 2.29 (m, 3 H, 1 × H^3 , 2 × H^4), 1.85 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 173.8, 173.7, 144.3, 141.6, 123.5, 121.6, 119.6, 119.2, 113.2, 109.7, 63.1, 59.8, 52.1, 33.5, 31.0, 29.9, 28.8, 24.4 ppm. MS (EI) *m*/*z* (%) = 312 (100) [$M^{\cdot+}$], 297 (60) [$M^{\cdot+}$ − CH_3], 284 (15) [$M^{\cdot+}$ − CO], 255 (96) [$M^{\cdot+}$ − NCO − CH_3], 237 (15) [$M^{\cdot+}$ − HCO_2CH_3 − CH_3], 223 (26) [$M^{\cdot+}$ − CO_2CH_3 − C_2H_4 − H_2]; exact mass calculated for $C_{18}H_{20}N_2O_3$: 312.1474; found 312.1462.

Methyl (4a*R,10b*S**)-10-Methyl-2-oxo-1,3,4,5,10,10b-hexahydropyrido[3′,2′:4,5]cyclopenta[1,2-*b*]indole-4a(2*H*)-carboxylate (22d):** Eluent: ethyl acetate; yield: 43% by procedure A. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1731 (s, C=O), 1666 (s, C=O). ^1H (300 MHz, $CDCl_3$): δ = 7.51 (d, J = 8 Hz, 1 H, H-arom.), 7.27−7.06 (m, 3 H, H-arom.), 6.91 (s, 1 H, NH), 5.42 (s, 1 H, H^{10b}), 3.79 (s, 3 H, NCH_3), 3.65 (s, 3 H, OCH_3), 3.53 (d, J = 16 Hz, 1 H, H^5), 2.99 (d, J = 16 Hz, 1 H, H^5), 2.43−2.02 (m, 4 H, H^3, H^4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 173.3, 142.5, 141.9, 123.3, 121.7, 120.4, 118.7, 117.2, 110.1, 57.6, 56.7, 53.2, 35.8, 31.2, 30.9, 29.2 ppm. MS (EI) *m*/*z* (%) = 298 (100) [$M^{\cdot+}$], 283 (40) [$M^{\cdot+}$ − CH_3], 242 (72) [$M^{\cdot+}$ − CO − C_2H_4], 239 (44) [$M^{\cdot+}$ − CO_2CH_3], 227 (12) [$M^{\cdot+}$ − HNCO − C_2H_4]; exact mass calculated for $C_{17}H_{18}N_2O_3$: 298.1317; found 298.1316.

3-(9-Methyl-1-phenyl-4,9-dihydro-3*H*-carbazol-2-yl)propanamide (23): Eluent: ethyl acetate; yield: 35% by procedure A. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3402 (m, $CONH_2$), 1651 (s, C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54−7.04 (m, 9 H, H-arom.), 5.76 (s, 1 H, NH), 5.37 (s, 1 H, NH), 2.96 (s, 3 H, NCH_3), 2.90 (m, 2 H, H^4), 2.53 (m, 4 H, H^3, $CH_2CH_2CONH_2$), 2.31 (m, 2 H, CH_2CONH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 138.9, 138.6, 136.9, 136.4, 131.3, 130.2, 129.3, 129.2, 128.7, 127.8, 125.9, 121.4, 119.7, 118.6, 110.4, 109.6, 35.5, 31.9, 30.2, 29.9, 20.5 ppm. MS (EI) *m*/*z* (%) = 330 (100) [$M^{\cdot+}$], 285 (5) [$M^{\cdot+}$ − $HCONH_2$], 272 (42) [$M^{\cdot+}$ − CH_2CONH_2], 258 (88) [$M^{\cdot+}$ − $CH_2CH_2CONH_2$]; exact mass calculated for $C_{22}H_{22}N_2O$: 330.1732; found 330.1732.

3-(9-Methyl-1-phenyl-9*H*-carbazol-2-yl)propanamide (24): Eluent: ethyl acetate; yield: 17% by procedure A. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3341 (m, $CONH_2$), 1660 (s, C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, J = 8 Hz, 1 H, H-arom.), 8.02 (d, J = 8 Hz, 1 H, H-arom.), 7.50−7.36 (m, 6 H, H-arom.), 8.28 (d, J = 8 Hz, 1 H, H-arom.), 7.24 (d, J = 8 Hz, 1 H, H-arom.), 7.17 (d, J = 8 Hz, 1 H, H-arom.), 5.52 (s, 1 H, NH), 5.14 (s, 1 H, NH), 3.13 (s, 3 H, NCH_3), 2.86 (t, J = 7 Hz, 2 H, $CH_2CH_2CONH_2$), 2.38 (t, J = 7 Hz, 2 H, CH_2CONH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 142.4, 139.3, 138.6, 137.2, 131.3, 128.7, 128.3, 128.2, 128.0, 125.9, 120.4, 120.2, 119.9, 119.4, 109.0, 38.3, 32.2, 29.8 ppm. MS (EI) *m*/*z* (%) = 328 (100) [$M^{\cdot+}$], 284 (18) [$M^{\cdot+}$ − $CONH_2$], 270 (44) [$M^{\cdot+}$ − CH_2CONH_2], 255 (54) [$C_{19}H_{13}N^+$], 254 (56) [$C_{19}H_{12}N^+$]; exact mass calculated for $C_{22}H_{20}N_2O$: 328.1576; found 328.1580.

Bridged Compounds 25: Eluent: CH_2Cl_2/ethyl acetate, 1:1; yield: 57% by procedure B; a mixture of diastereoisomers (50:50) was separated. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3189 (m, NH), 1721 (s, C=O), 1653 (s, C=O) ppm. ppm. MS (EI) *m*/*z* (%) =388 (100) [$M^{\cdot+}$], 345 (6) [$M^{\cdot+}$ − HNCO], 329 (9) [$M^{\cdot+}$ − CO_2CH_3], 312 (17) [$M^{\cdot+}$ − CO_2CH_3 − NH_3], 286 (15) [$M^{\cdot+}$ − CO_2CH_3 − CONH], 220 (36) [$M^{\cdot+}$ − CO_2CH_3 − NHCO − C_6H_6]; exact mass calculated for $C_{24}H_{24}N_2O_3$: 388.1787; found 388.1785. **Isomer with Ph *trans* to Ester Group:** ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 8 Hz, 1 H, H-arom.), 7.37 (dt, J = 7, 1 Hz, 1 H, H-arom.), 7.25 (m, 5 H, H-arom.), 7.17 (dt, J = 7, 2 Hz, 1 H, H-arom.), 7.05 (d, J = 7 Hz, 1 H, H-arom.), 6.99 (d, J = 6 Hz, 1 H, NH), 5.05 (s, 1 H, H^5), 4.73 (t, J = 6 Hz, 1 H, H^{10c}), 3.78 (s, 3 H, OCH_3), 3.15 (s, 3 H, NCH_3), 2.81 (t, J = 6 Hz, 1 H, H^3), 2.70 (dd, J = 14, 6 Hz, 1 H, H^{11}), 2.37 (m, 2 H, H^{11}, H^3), 1.86 (m, 2 H, H^4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 176.2, 138.2, 138.1, 137.2, 129.6, 129.1, 128.6, 128.3, 127.7, 125.5, 122.0, 120.1, 118.2, 109.7, 109.3, 52.5, 50.7, 47.2, 43.4, 39.1, 33.5, 31.9, 25.7 ppm. **Isomer with Ph *cis* to Ester Group:** ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 8 Hz, 1 H, H-arom.), 4.76 (d, J = 6 Hz, NH), 7.21 (m, 5 H, H-arom.), 7.10 (ddd, J = 8, 7, 2 Hz, 1 H, H-arom.), 6.99 (m, 2 H, H-arom.), 4.87 (t, J = 6 Hz, 1 H, H-arom.), 4.26 (s, 1 H, H^5), 3.37 (s, 3 H, OCH_3), 3.26 (s, 3 H, NCH_3), 2.82 (dd, J = 15, 6 Hz, 1 H, H^{11}), 2.57 (m, 1 H, H^4), 2.42 (m, 2 H, H^3), 2.21 (d, J = 15 Hz, 1 H, H^{11}), 2.17 (m, 1 H, H^4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8, 174.5, 138.0, 137.8, 136.7, 129.3, 128.3, 127.5, 124.8, 121.9, 119.8, 118.6, 109.8, 109.0, 51.6, 51.0, 46.8, 42.9, 33.3, 33.0, 31.6, 29.3 ppm.

Methyl (4a*S,10b*S**)-11,11b−Dimethyl-2-oxo-1,2,3,4,5,6,11,11b-octahydro-4a*H*-pyrido[2,3-*a*]carbazole-4a-carboxylate (26):** Eluent: CH_2Cl_2/ethyl acetate, 1:1; yield: 68% by procedure A. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1882 (s, C=O), 1664 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H, NH), 7.49 (d, J = 8 Hz, 1 H, H-arom.), 7.32 (d, J = 8 Hz, 1 H, H-arom.), 7.26 (dt, J = 8, 1 H, H-arom.), 7.15 (t, J = 8 Hz, 1 H, H-arom.), 3.88 (s, 3 H, NCH_3), 3.82 (s, 3 H, OCH_3), 2.94 (dt, J = 16, 6 Hz, 1 H, H^6), 2.83 (ddd, J = 16, 10, 5 Hz, 1 H, H^6), 2.59 (m, 2 H, H^3), 2.26 (ddd, J = 14, 10, 6 Hz, 1 H, H^5), 2.15 (m, 2 H, H^4), 2.05 (ddd, J = 14, 14, 6 Hz, 1 H, H^5), 1.69 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 173.6, 138.0, 136.9, 125.6, 122.0, 119.2, 118.5, 109.0, 107.9, 56.7, 52.0, 48.9, 31.4, 29.0, 28.0, 26.1, 24.7, 21.2 ppm. MS (EI) *m*/*z* (%) = 326 (100) [$M^{\cdot+}$], 311 (61) [$M^{\cdot+}$ − CH_3], 268 (35) [$M^{\cdot+}$ − $COCH_2$], 253 (97) [$M^{\cdot+}$ − CO_2CH_3 − CH_3], 208 (39) [$M^{\cdot+}$ − HCO_2CH_3 − H_2NCOCH_2], 194 (26) [$M^{\cdot+}$ − HCO_2CH_3 − $H_2NCOCH_2CH_2$]; exact mass calculated for $C_{19}H_{22}N_2O_3$: 326.1630; found 326.1636.

Methyl (4a*R*,10b*R***)-11-Methyl-2-oxo-1,2,3,4,5,6,11,11b-octahydro-4a*H*-pyrido[2,3-*a*]carbazole-4a-carboxylate (27):** Eluent: CH_2Cl_2/MeOH, 19:1; yield: 51% by procedure A. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3189 and 3055 (s, CONH), 1731 (s, C=O), 1661 (s, C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 8 Hz, 1 H, H-arom.), 7.29 (d, J = 8 Hz, 1 H, H-arom.), 7.25 (t, J = 8 Hz, 1 H, H-arom.), 7.12 (t, J = 8 Hz, 1 H, H-arom.), 6.05 (s, 1H NH), 5.14 (s, 1 H, H^{11b}), 3.72 (s, 3 H, NCH_3), 3.63 (s, 3 H, OCH_3), 2.84 (ddd, J = 16, 6, 2 Hz, 1 H, H^6), 2.75 (ddd, J = 16, 11, 6 Hz, 1 H, H^6), 2.46 (ddd, J = 17, 6, 5 Hz, 1 H, H^3), 2.34 (ddd, J = 17, 10, 6 Hz, 1 H, H^3), 2.25 (ddd, J = 14, 10, 6 Hz, 1 H, H^4), 2.14 (ddd, J = 13, 6, 2 Hz, 1 H, H^5), 1.99 (m, 2 H, H^4, H^5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 170.5, 137.8, 132.1, 126.1, 122.5, 119.4, 118.9, 110.4, 109.3, 52.4, 48.8, 45.0, 30.8, 29.5, 27.7, 25.4, 18.6 ppm. MS (EI) m/z (%) = 312 (74) [$M^{\cdot+}$], 256 (36) [$M^{\cdot+} - CO - C_2H_4$], 253 (100) [$M^{\cdot+} - CO_2CH_3$], 197 (20) [$M^{\cdot+} - CO - CO_2CH_3 - C_2H_4$], 157 (26) [$M^{\cdot+} - CO - CO_2CH_3 - C_2H_4 - C_2H_2N$]; exact mass calculated for $C_{18}H_{20}N_2O_3$: 312.1474; found 312.1467.

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