Oxidative Cleavage of Indole δ-Lactones with *m*-Chloroperbenzoic Acid: First Synthesis of Spiroindolin-2-one γ-Lactones

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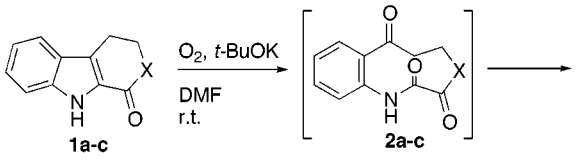
In a previous study dealing with the preparation of quinolones annelated at the 2,3-positions to a γ-lactam and a γ-imide, we described the one-pot synthesis of pyrrolo[3,4-*b*]quinoline-3,9-diones (quinolone γ-lactams) **3a**,**b** from 2,3,4,9-tetrahydropyrido[3,4-b]indol-1-ones (indole δ-lactams) **1a**,**b** via nonisolated ketoamides **2a**,**b** (Scheme 1).[1] Under the same conditions (O_2, *tert*-BuOK), the corresponding quinolone γ-lactone **3c** could not be obtained from the 3,4-dihydropyrano[3,4-*b*]indol-1(9*H*)-one (indole δ-lactone) **1c**.

Another possible route to prepare such unknown quinolone γ-lactones is a two-step procedure, i.e., oxidation of **1** to a nine-membered ring ketoamide **2** and subsequent cyclization in alkaline medium. Various methods of oxidative cleavage of the 2,3-double bond of the indole nucleus such as ozonolysis[2] or oxidation by sodium periodate[3] or by O_2/Pt[4] were attempted without success using indole δ-lactones **1c** and **4a** as starting material.

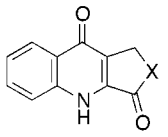
In this paper, we report the unexpected results obtained in the course of this project by oxidation of *N*-substituted indole δ-lactones **4** with *m*-chloroperbenzoic acid (*m*-CPBA).

Oxidation of 2,3-disubstituted indoles with peracids is well-known. [5] Hino has reported that treatment of tetrahydrocarbazole with *m*-CPBA (1 equiv, −60 °C in CH_2Cl_2) afforded hydroxy-4a*H*-carbazole as the major product. [6] The latter hydroxyindolenine could be oxidized in good yield to the corresponding ketoamide by either perbenzoic acid [4] or *m*-CPBA in the presence of a small amount of H_2SO_4.[6] Protonated hydroxyindoline facilitates the addition of peracid to the C=N double bond, and the ketoamide is obtained by subsequent cleavage. [6] On the other hand, *m*-CPBA oxidation at −40 °C of aristoteline, a piperidino-indole alkaloid, gave the corresponding hydroxyindolenine in 94% yield. When the same reaction was performed at 25 °C, the hydroxyindolenine was obtained as the major product (57%) beside 21% of ketoamide and two spiro derivatives as byproducts (9% of spiroindolin-3-one and 3% of spiroindolin-2-one). [7] Moreover, ketoamides have been prepared by *m*-CPBA oxidation of a tetrahydrobenzo[*b*][1,8]naphthyridin-5(7*H*)-one [8] and of *N*-methylazetopyridoindoles. [9]

Scheme 1

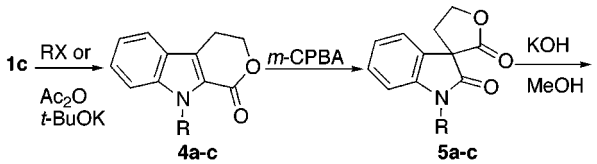


a : X = *N*-benzyl ; b : X = *N*-n-butyl ; c : X = O

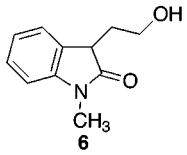


3 a-b 70%
c 0%

Scheme 2



a : R = methyl ; b : R = 2,4-dinitrophenyl ; c : R = acetyl



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In light of these results, we have attempted the oxidative cleavage of the indole 2,3 double bond according to Kurihara's experimental conditions [9] (*m*-CPBA, room temperature in CH_2Cl_2) with *N*-substituted indole δ-lactones **4a**−**c**. The expected ketoamides were not obtained, but instead new heterocycles were formed to which the structures of 4,5-dihydrospiro[furan-3(2*H*),3′-indole]-2,2′-(1′*H*)-diones (spiroindolin-2-one γ-lactones) **5a**−**c** were attributed (Scheme 2). The reaction proceeded in the same manner but faster when performed in 1,2-dichloroethane at reflux instead of using CH_2Cl_2 at room temperature (1 h instead of 2 days in the case of **5a**).

The formation of two spiro structures **5** and **9** could be considered (Scheme 3). The presence in the ^{13}C NMR spectra of a new quaternary carbon (≈56 ppm) in addition to two carbonyl signals (172−174 ppm) are in agreement with mass spectrometry data. The two carbonyl absorptions in the IR spectra at 1757−1781 cm^{-1} and 1720−1727 cm^{-1} are typical of γ-lactone and lactam, respectively. This hypothesis is also corroborated by a complex ABXY pattern in the ^1H NMR spectra accounting for the lactone ring ethano protons (2.70, 2.90, 4.65, and 4.80

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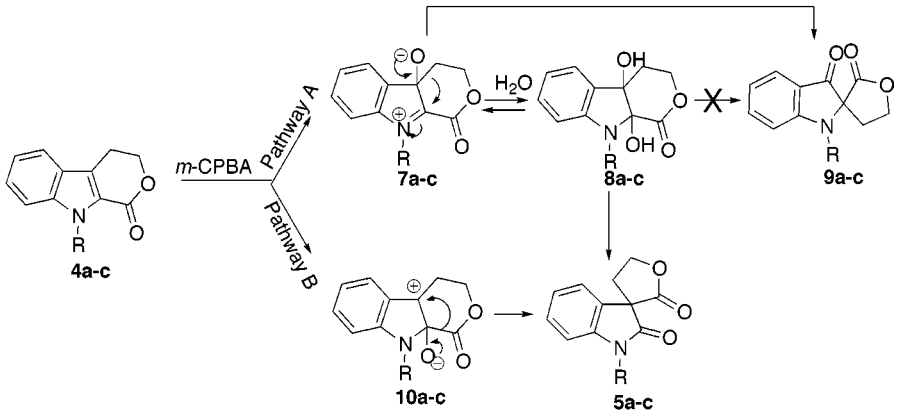
Scheme 3



a : R = methyl ; b : R = 2,4-dinitrophenyl ; c : R = acetyl

ppm for **5a**). According to Güller, [10] spiroindolin-3-one and -2-one can be distinguished because the former shows a benzylic carbonyl near 200 ppm in the ^{13}C NMR and a quaternary C-2 near 80 ppm, but the latter shows a lactam carbonyl near 180 ppm and a quaternary C-3 near 60 ppm. Moreover, compounds **9a** and **9c** are known[11] and their melting points are significantly different from those of our *N*-methyl and *N*-acetyl spiro derivatives. Thus, the spiro-2,2′ structure **9** could be disregarded. The spiro 3,3′ structure **5** was definitely assigned by the chemical transformation of **5a** into the known 3-(2-hydroxyethyl)-1-methyloxindole **6** [12] by heating in KOH−MeOH (Scheme 2). The opening of the lactone ring is followed by a facile decarboxylation of the *β*-amido acid.

To our knowledge, no 4,5-dihydrospiro[furan-3(2*H*),3′-indole]-2,2′(1′*H*)-dione has been previously described in the literature. Despite the absence of subsequent acidic or alkaline medium and workup in neutral conditions, the yields in **5a**−**c** are moderate on account of the instability of their lactone rings. The presence of other derivatives was not detected by TLC in the reaction medium.

This spiroannelation is rather surprising since carbocyclic spiroindolin-2-ones are usually obtained either by action of *tert*-butyl hypochlorite,[13] NBS,[14] and OsO_4[15] and subsequent acidic treatment or by $Pb(OAc)_4$ oxidation followed by an akaline treatment. [16]

The rearrangement of hydroxyindolenine in acidic medium to spiroindolin-2-one as the minor derivative besides spiroindolin-3-one was interpreted by Güller[10] in terms of hydratation of the protonated indolenine. Accordingly, indoliminium salt **7** (Scheme 3) should be in equilibrium with the hydrated form **8**, the resulting diol could undergo a pinacol type rearrangement to give **5** and **9**. On the other hand, Zhang[17] has demonstrated that the first step of the dimethyldioxirane oxidation of *N*-acetyl-2,3-dialkylindoles is the formation of 2,3-epoxides which rearrange to indolinones. The ratio of indolin-2-one and -3-one is interpreted in terms of ring opening via a carbocation intermediate. A stabilized benzylic carbocation leads to the pinacol-rearranged indolin-2-one as the major product. According to Hino,[6] the products obtained by *m*-CPBA oxidation of 2,3-disubstituted indole might derive from 2,3-epoxide or 3-hydroxyindolenine as the first intermediate.

Although the formation of epoxide was not proven for *m*-CPBA oxidation, the mechanism described for the transformation of the indole-lactones **4** in pathway B (Scheme 3) may be the more probable one. Indeed, the other process (pathway A) would led to a mixture of indolinones **5** and **9** as published in other series. Benzylic carbocation **10** is more stable than indolinium **7** which is destabilized by the presence of the lactone function. Consequently, the carbocation **10** is exclusively formed and the transposition occurred at the benzylic position to give the indolin-2-one **5**.

It is noteworthy that the indole-lactone **1c** is not oxidized in the above conditions. The difference in reactivity between *N*-substituted and unsubstituted indoles can be interpreted in terms of tautomerism that leads to a decreasing enamine character of the indole (Figure 1).

It should also be noted that *m*-CPBA oxidation of the *N*-(4-methoxyphenyl) substituted indole-lactam **11** did not furnish a spiro derivative but a mixture of the two oxindoles **12** and **13** which were easily separated by column chromatography (Scheme 4). Two possibilities can be considered for the formation of **12**: either the reaction starts by oxidation, transposition into spirolactone, hydrolysis of the lactone, and then decarboxylation or the first step is the hydrolysis of the *δ*-lactone ring of **11**, and then oxidation, transposition, and decarboxylation. Diol **13** probably results from further oxidation of the enol form of **12** and subsequent deshydratation.

The difference in reactivity between derivatives **4** and **11** may be interpreted in terms of difference in the

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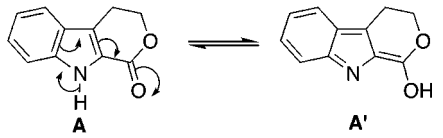
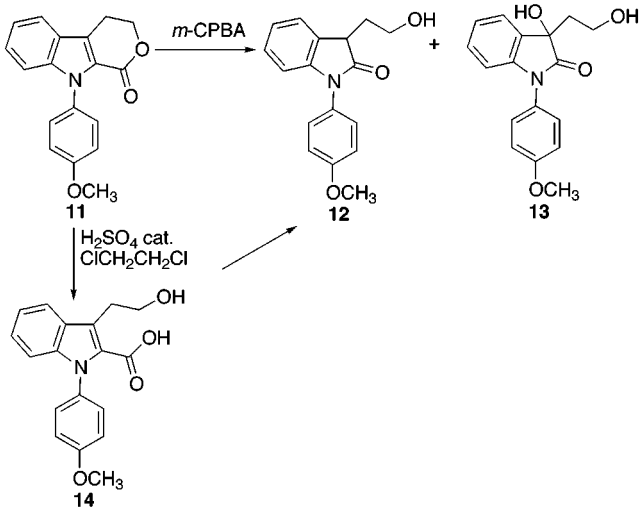


Figure 1.

Scheme 4



stability of their lactone functions under the reaction conditions. Contrary to the *N*-methyl derivative **4a** (no reaction after 1 h), lactone **11** is a quite labile compound which is hydrolyzed in 10 min in refluxing 1,2-dichloroethane in the presence of a small amount of H_2SO_4. The resulting acid-alcohol **14**, treated with *m*-CPBA, provided the two derivatives **12** and **13**. The instability of **11** in acidic medium could justify the occurrence of the pathway via **14**. When the reaction was carried out for an additional 18 h, it was possible to isolate **13** as a single product in 58% yield. Consequently, the *m*-CPBA oxidation of *N*-substituted-3-(2-hydroxyethyl)indole-2-carboxylic acids may be an interesting route for the synthesis of *N*-substituted-3-hydroxy-3-(2-hydroxyethyl)oxindoles. To our knowledge, only the *N*-unsubstituted derivative has been prepared from isatin in six steps and in 50% overall yield. [18] However, the utility of this method is limited by the availability of isatins.

In conclusion, we have described the first synthesis of 4,5-dihydrospiro[furan-3(2*H*),3′-indole]-2,2′(1′*H*)-diones. Moreover, a new synthesis of 3-hydroxy-3-(2-hydroxyethyl)oxindoles has been achieved.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. *m*-CPBA (70−75% purity) was purchased from Acros and used without further purification.

9-Methyl-3,4-dihydropyrano[3,4-*b*]indol-1(9*H*)-one 4a. To a solution of indole-lactone **1c**[19] (187 mg, 1 mmol) in THF (10 mL) were added *tert*-BuOK (123 mg, 1.1 mmol) and then methyl iodide (0.125 mL, 2 mmol). The reaction mixture was stirred for 1 h at room temperature. After the solvent has been removed by evaporation, the residue was triturated with water, filtered off, dried, and recrystallized from ethanol to give **4a** (191 mg, 95%). mp 104 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ: 3.10 (t, 2H, J = 5 Hz), 4.00 (s, 3H), 4.55 (t, 2H, J = 5 Hz), 7.15 (t, 1H, J = 8 Hz), 7.40 (t, 1H, J = 8 Hz), 7.55 (d, 1H, J = 8 Hz), 7.60 (d, 1H, J = 8 Hz); ^{13}C NMR (DMSO-d_6) δ: 22.0, 32.1, 69.9, 108.1, 112.1, 121.4, 122.2, 123.1, 123.8, 124.0, 127.2, 149.2. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.94; H, 5.50; N, 6.65.

9-(2,4-Dinitrophenyl)-3,4-dihydropyrano[3,4-*b*]indol-1(9*H*)-one 4b. A mixture of indole-lactone **1c** (187 mg, 1 mmol), K_2CO_3 (138 mg, 1 mmol), and 2,4-dinitrofluorobenzene (0.5 mL) was heated at 140 °C for 6 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The crude product was purified by chromatography on silica gel (ligroin/AcOEt 8.5:1.5) and then recrystallization from ethanol to give 310 mg (88%) of pure **4b**: mp 208 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ: 3.20 (t, 2H, J = 8 Hz), 4.65 (t, 2H, J = 8 Hz), 7.05 (d, 1H, J = 8 Hz), 7.25 (t, 1H, J = 8 Hz), 7.35 (t, 1H, J = 8 Hz), 7.65 (d, 1H, J = 8 Hz), 7.75 (d, 1H, J = 8 Hz), 8.55 (dd, 1H, J = 8 and 2 Hz), 9.00 (d, 1H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.5, 68.8, 110.5, 121.6, 122.8, 125.0, 127.1, 128.0, 128.3, 132.1, 136.8, 138.4, 139.3, 145.9, 146.8, 159.5. Anal. Calcd for $C_{17}H_{11}N_3O_6$: C, 57.80; H, 3.14; N, 11.89. Found: C, 57.50; H, 2.99; N, 11.49.

9-Acetyl-3,4-dihydropyrano[3,4-*b*]indol-1(9*H*)-one 4c. To a solution of indole-lactone **1c** (500 mg, 2.67 mmol) in THF (5 mL) were added *tert*-BuOK (448 mg, 4 mmol) and Ac_2O (0.38 mL, 4 mmol). The reaction mixture was stirred for 30 min at room temperature and then poured into water. After extraction with CH_2Cl_2, the crude product was purified by chromatography on silica gel (CH_2Cl_2) to yield 400 mg (65%) of **4c**: mp 144 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ: 2.65 (s, 3H), 3.10 (t, 2H, J = 6 Hz), 4.60 (t, 2H, J = 6 Hz), 7.25 (t, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz), 7.50 (t, 1H, J = 8 Hz), 8.35 (d, 1H, J = 8 Hz). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.03; H, 4.96; N, 6.01.

Preparation of Spiroindolin-2-one γ-Lactones 5 from Indole Lactones 4. A solution of *m*-CPBA (1.5 g) in 1,2-dichloroethane (20 mL), which had been previously dried over Na_2SO_4, was added to a solution of indole lactone **4** (2.5 mmol) in 1,2-dichloroethane (30 mL). The reaction mixture was refluxed either for 1 h (compound **4a**,**c**) or for 5 h (compound **4b**). After being cooled to room temperature, the reaction mixture was filtered off, and the resulting solution was purified by chromatographies on alumina (CH_2Cl_2) and then on silica gel (CH_2Cl_2). A recrystallization from methanol afforded pure indole lactones **5**.

1′-Methyl-4,5-dihydrospiro[furan-3(2*H*),3′-indole]-2,2′-(1′*H*)-dione 5a: yield: 52%; mp 141 °C (MeOH); IR (KBr) 1757, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.70 (m, 1H), 2.90 (m, 1H); 3.25 (s, 3H), 4.65 (m, 1H), 4.80 (m, 1H), 6.90 (d, 1H, J = 8 Hz), 7.15 (t, 1H, J = 8 Hz), 7.25 (d, 1H, J = 8 Hz), 7.40 (t, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ: 26.6, 33.4, 55.5, 66.7, 108.8, 122.8, 123.3, 127.6, 129.6, 144.2, 172.9, 173.2; MS (CI): *m*/*z* 218 $[MH]^+$, 235 $[MNH_4]^+$. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.71; H, 5.44; N, 6.08.

1′-(2,4-Dinitrophenyl)-4,5-dihydrospiro[furan-3(2*H*),3′-indole]-2,2′(1′*H*)-dione 5b: yield: 50%; mp 210 °C dec (MeOH); IR (KBr) 1769, 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.80 (m, 1H), 3.05 (m, 1H), 4.65 (m, 1H), 4.85 (m, 1H), 6.80 (d, 1H, J = 8 Hz), 7.25−7.40 (m, 3H), 7.95 (d, 1H, J = 9 Hz), 8.65 (dd, 1H, J = 9 and 2 Hz), 9.05 (d, 1H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ: 34.1, 55.9, 66.8, 109.2, 121.9, 124.1, 125.3, 127.6, 128.7, 129.9, 130.9, 132.8, 142.0, 145.5, 147.1, 171.8, 172.0; MS (CI): *m*/*z* 387 $[MNH_4]^+$. Anal. Calcd for $C_{17}H_{11}N_3O_7$: C, 55.29; H, 3.00; N, 11.38. Found: C, 55.54; H, 3.14; N, 11.22.

1′-Acetyl-4,5-dihydrospiro[furan-3(2*H*),3′-indole]-2,2′-(1′*H*)-dione 5c: yield: 52%; mp 138 °C (MeOH); IR (KBr) 1781, 1745, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.60−2.75 (m, 4H), 3.00 (m, 1H), 4.65 (m, 1H), 4.85 (m, 1H), 7.25 (m, 2H), 7.40 (t, 1H, J = 8 Hz), 8.30 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ: 26.5, 34.4, 56.4, 66.7, 117.0, 122.4, 125.9, 126.6, 130.0, 140.7, 170.2, 171.8, 174.2; MS (CI): *m*/*z* 246 $[MH]^+$, 263 $[MNH_4]^+$. Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.48; H, 4.63; N, 5.55.

3-(2-Hydroxyethyl)-1-méthyl-1,3-dihydro-2*H*-indol-2-one 6. A mixture of compound **5a** (100 mg, 0.46 mmol) and NaOH (37 mg, 0.92 mmol) in methanol (5 mL) was refluxed for 5 min. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The

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crude product was purified by chromatography on silica gel (CH_2Cl_2/CH_3OH 9.8: 0.2) to yield 72 mg (82%) of **6** as oil. The spectroscopic data were consistent with the structure of the product.[12]

9-(4-Methoxyphenyl)-3,4-dihydropyrano[3,4-*b*]indol-1(9*H*)-one 11. A mixture of indole lactone **1c** (500 mg, 2.67 mmol), 4-bromoanisole (0.4 mL, 3.2 mmol), K_2CO_3 (400 mg, 3.6 mmol), and CuO (13 mg, 0.16 mmol) in DMF (4 mL) was refluxed for 24 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The crude product was purified by chromatography on silica gel (CH_2Cl_2) to yield 525 mg (67%) of pure oily **11**: ^{1}H NMR ($CDCl_3$) δ: 3.05 (t, 2H, J = 8 Hz), 3.82 (s, 3H), 3.95 (t, 2H, J = 8 Hz), 6.95 (d, 2H, J = 8 Hz), 7.10−7.20 (m, 2H), 7.35 (d, 2H, J = 8 Hz), 7.40 (d, 1H, J = 8 Hz), 7.62 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ: 28.6, 55.5, 62.5, 110.4, 112.6, 114.6, 119.0, 119.7, 122.3, 125.6, 126.5, 128.4, 132.6, 136.5, 158.0.

***m*-CPBA Oxidation of the Indole Lactone 11**. Indole lactone **11** (500 mg, 1.7 mmol) was oxidized in the same manner as described for **4**, except that the mixture was refluxed for 30 min. After workup, purification of the crude product by flash chromatographies on alumina (CH_2Cl_2) and then on silica gel (CH_2Cl_2/ MeOH 9.8:0.2) provided **12** (70 mg, 15%) and **13** (180 mg, 35%) as oils.

3-(2-Hydroxyethyl)-1-(4-methoxyphenyl)-1,3-dihydroindol-2-one 12: IR (film) 3380, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.35 (m, 1H), 2.45 (m, 1H), 3.85 (dd, 1H, J = 5 and 8 Hz), 3.95 (s, 3H), 4.05 (t, 2H, J = 5 Hz), 6.85 (d, 1H, J = 8 Hz), 7.15 (d, 2H, J = 8 Hz), 7.20 (t, 1H, J = 8 Hz), 7.30 (t, 1H, J = 8 Hz), 7.45 (m, 3H); ^{13}C NMR ($CDCl_3$) δ: 33.3, 44.3, 55.4, 60.6, 109.3, 114.8, 122.8, 123.8, 126.7, 127.8, 128.3, 144.3, 159.1, 178.6; MS (EI): m/z 283 $[M]^+$; HRMS calcd for $C_{17}H_{17}NO_3$ 283.120 844, found 283.120 104.

3-Hydroxy-3-(2-hydroxyethyl)-1-(4-methoxyphenyl)-1,3-dihydroindol-2-one 13: IR (film) 3386, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.05 (m, 1H), 2.25 (m, 1H), 3.15 (bs, 1H, D_2O exch), 3.75 (s, 3H), 3.85 (t, 2H, J = 5 Hz), 4.70 (bs, 1H, D_2O exch), 6.75 (d, 1H, J = 8 Hz), 6.90 (d, 2H, J = 8 Hz), 7.00 (t, 1H, J = 8 Hz), 7.15 (t, 1H, J = 8 Hz), 7.20 (d, 2H, J = 8 Hz), 7.35 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ: 39.6, 55.4, 58.4, 76.1, 109.6, 114.8, 123.5, 124.1, 126.4, 127.8, 129.5, 130.1, 143.3, 159.2, 178.1; MS (EI): m/z 299 $[M]^+$; HRMS calcd for $C_{17}H_{17}NO_4$ 299.115 758, found 299.114 954.

3-(2-Hydroxyethyl)-1-(4-methoxyphenyl)indole-2-carboxylic acid 14. A solution of indole lactone **11** (100 mg, 0.34 mmol) in 1,2-dichloroethane (10 mL) was refluxed for 10 min in the presence of a small amount of concd H_2SO_4 . After the solvent has been removed by evaporation, the residue was triturated with water, filtered off, dried, and recrystallized from DMF to give **14** (82 mg, 78%): mp 208 °C (DMF); IR (KBr) 3404, 1677 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 3.25 (t, 2H, J = 7 Hz), 3.65 (t, 2H, J = 7 Hz), 3.85 (s, 3H), 6.95 (d, 1H, J = 8 Hz), 7.02 (d, 2H, J = 8 Hz), 7.15 (t, 1H, J = 8 Hz), 7.20 (m, 3H), 7.75 (d, 1H, J = 8 Hz); ^{13}C NMR (DMSO-d_6) δ: 29.8, 56.4, 62.8, 112.0, 115.3, 121.5, 121.8, 122.6, 126.7, 128.0, 128.2, 129.6, 132.7, 140.1, 163.7. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.26; H, 5.64; N, 4.40.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **5a**−**c**, **12**, **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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