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Regioselective 1,3-Dipolar Cycloaddition Reactions of Unsymmetrical Münchnones (1,3-Oxazolium-5-olates) with 2- and 3-Nitroindoles. A New Synthesis of Pyrrolo[3,4-*b*]indoles

Gordon W. Gribble,* Erin T. Pelkey, Wendy M. Simon and Hernando A. Trujillo

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

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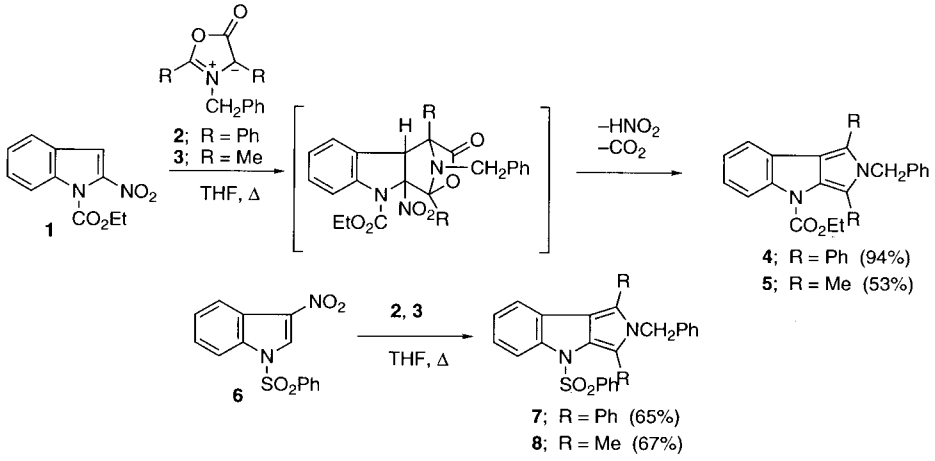
Abstract—The unsymmetrical mesoionic münchnones **13** (3-benzyl-2-methyl-4-phenyl-1,3-oxazolium-5-olate) and **14** (3-benzyl-4-methyl-2-phenyl-1,3-oxazolium-5-olate) react with the *N*-protected 2- and 3-nitroindoles **1** (ethyl 2-nitroindole-1-carboxylate), **6** (3-nitro-1-(phenylsulfonyl)indole), and **17** (ethyl 3-nitroindole-1-carboxylate) in refluxing THF to afford in good to excellent yields the pyrrolo[3,4-*b*]indoles **15** (2-benzyl-1-methyl-3-phenyl-4-carboethoxy-2,4-dihydropyrrolo[3,4-*b*]indole), **16** (2-benzyl-3-methyl-1-phenyl-4-carboethoxy-2,4-dihydropyrrolo[3,4-*b*]indole), **18** (2-benzyl-1-methyl-3-phenyl-4-(phenylsulfonyl)-2,4-dihydropyrrolo[3,4-*b*]indole), and **19** (2-benzyl-3-methyl-1-phenyl-4-(phenylsulfonyl)-2,4-dihydropyrrolo[3,4-*b*]indole). In several cases the regiochemistry, which is opposite to that predicted by FMO theory, is very high and leads essentially to a single pyrrolo[3,4-*b*]indole; e.g., **6**+**13**→**19** in 74% yield.

Pyrrolo[3,4-*b*]indoles are valuable synthetic analogues of indole-2,3-quinodimethanes and there is great interest in their synthesis and subsequent chemistry, particularly that involving cycloaddition reactions leading to carbazoles, carbolines, and related natural products.[1] Following the inaugural synthesis of a pyrrolo[3,4-*b*]indole by Welch,[2] subsequent syntheses of this ring system were reported by Sha,[3–5] Kreher,[6,7] Srinivasan,[8] Snyder,[9] and ourselves.[10,11]

In our pursuit of a simple, one-step synthesis of pyrrolo-[3,4-*b*]indoles,[10,11] we recently reported the 1,3-dipolar cycloaddition reaction of mesoionic münchnones (1,3-oxazolium-5-olates) **2** and **3** with both 2- and 3-nitroindoles (**1** and **6**) to give in one operation the corresponding pyrrolo[3,4-*b*]indoles **4**, **5**, **7**, **8** as shown in Scheme 1.[12] This reaction is presumed to involve formation of a cycloadduct that loses the elements of nitrous acid and carbon



Scheme 1.

Keywords: münchnone; 2-nitroindole; 3-nitroindole; 1,3-dipolar cycloaddition; 1,3-oxazolium-5-olates; pyrrolo[3,4-*b*]indole.
* Corresponding author. Tel.: +1-603-646-2501; fax: +1-603-646-3946; e-mail: grib@dartmouth.edu

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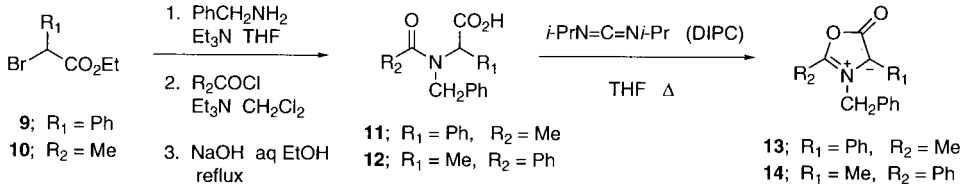
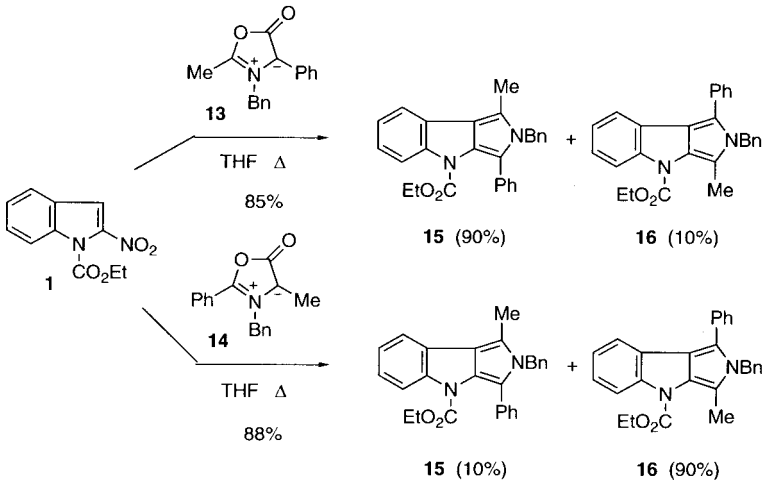


Scheme 2.

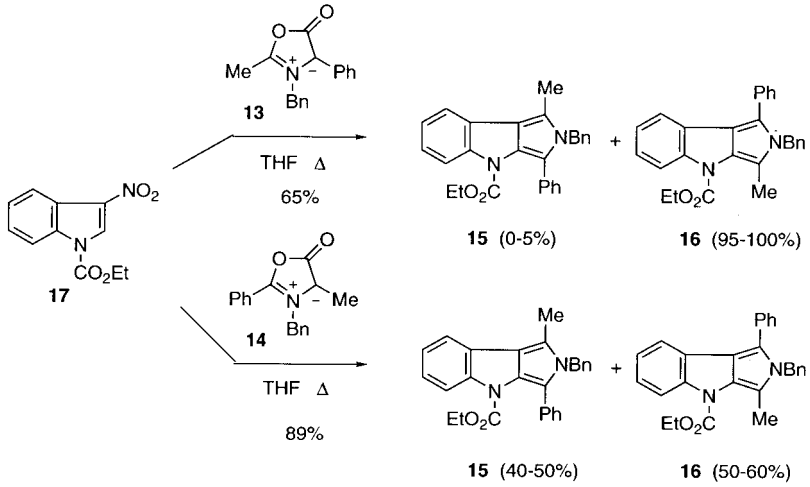


Scheme 3.

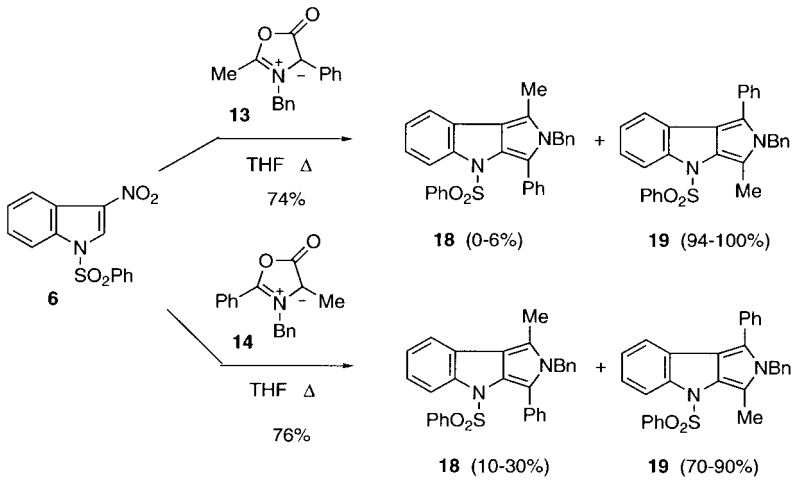
dioxide to afford the pyrrolo[3,4-*b*]indole in good to excellent yield.

We now describe 1,3-dipolar cycloaddition reactions of 2- and 3-nitroindoles with the unsymmetrical münchnones **13** (3-benzyl-2-methyl-4-phenyl-1,3-oxazolium-5-olate) and **14** (3-benzyl-4-methyl-2-phenyl-1,3-oxazolium-5-olate), which were generated in situ as shown in Scheme 2 from the *N*-acylamino acids **11** and **12**, respectively, using diisopropylcarbodiimide (DIPC) as the dehydrating agent.[13] Compounds **11** and **12** were synthesized from ethyl α-bromophenylacetate (**9**) and ethyl α-bromopropionate (**10**), respectively, by a sequence of benzylamine alkylation, acylation with acetyl or benzoyl chloride, and saponification.

The reactions of 2-nitroindole **1**[14] with münchnones **13** and **14** are highly regioselective and afford pyrroloindoles **15** and **16** as reasonably stable crystalline solids in excellent yields (Scheme 3). The isomer ratios were determined by ^{1}H NMR peak integration of the crude products before chromatography. The products **15** and **16** were separated by flash chromatography, fully characterized, and distinguished by an NOE between the C-3 methyl protons and the carboethoxy methyl protons in **16** but not in **15**. Moreover, the chemical shift of the carboethoxy protons indicates



Scheme 4.



Scheme 5.

pronounced shielding by the C-3 phenyl group in **15** but not in **16**. Thus, in the carboethoxy group the methylene protons appear at 3.8 ppm and the methyl protons appear at 0.8 ppm, compared with 4.5 ppm and 1.5 ppm, respectively, for the corresponding protons in **16**.

Perhaps surprisingly, the expected regioselectivity from frontier molecular orbital (FMO) theory is not observed, and the major product, **15** and **16**, respectively, from each reaction with 2-nitroindole **1** derives from the presumed positive end of the 1,3-dipole (C-2) bonding with the electron-deficient indole C-3 position and the presumed negative site (enolate carbon) of the 1,3-dipole (C-3) bonding with the electron-rich indole C-2 position of **1**. These FMO-based predictions are discussed later.

Similarly, reaction of 1-carboethoxy-3-nitroindole (**17**)[11,15] with münchnone **13** also affords nearly exclusively the '*anti*-FMO' product **16**, whereas münchnone **14** with **17** gives **15** and **16** in nearly equal amounts (Scheme 4).[16]

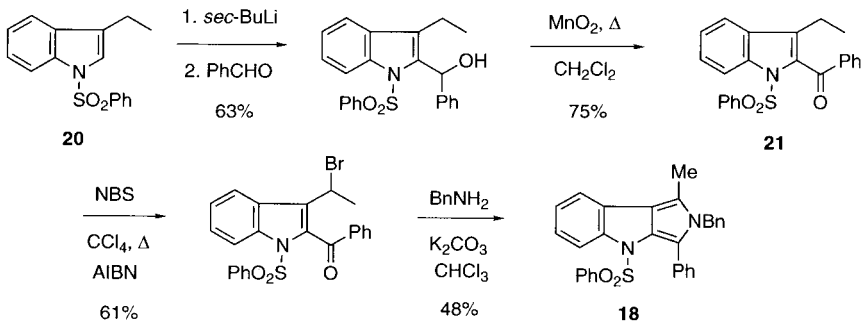
Reactions of 3-nitro-1-(phenylsulfonyl)indole (**6**)[11,15] with münchnones **13** and **14** have also been investigated (Scheme 5). The former cycloaddition reaction proceeds to give exclusively the *anti*-FMO pyrroloindole **19** in good yield. However, reaction of **6** with münchnone **14** yields pyrroloindoles **18** and **19**, with the FMO product **19** somewhat favored.

The structure of the major isomer **19** was confirmed by X-ray crystallography.[17] This isomer shows deshielding of the C-3 methyl protons (2.66 ppm) relative to that chemical shift in the minor isomer **18** (2.33 ppm), presumably due to the phenylsulfonyl group. The structure of the minor isomer **18** was confirmed by independent synthesis (Scheme 6) using the general method of Srinivasan.[18] Lithiation of indole **20**[19] and quenching with benzaldehyde, followed by oxidation yielded ketone **21**.[19] Bromination and amination afforded **18**, identical with the minor isomer obtained from **6** and **14** in Scheme 5.

An electron-withdrawing group on the indole nitrogen appears to be required for these cycloadditions to occur, since, for example, 1-methyl-3-nitroindole fails to react with münchnone **14** after 24 h of reflux in THF or digylme; at most, $<1\%$ of products are formed.

We performed AM1 calculations through Spartan, and these FMO predictions are consistent with the fact that the observed cycloaddition regiochemistry is generally '*anti*-FMO'. The HOMO/LUMO energies are listed in Table 1, and Scheme 7 depicts the coefficients for the favored HOMO (münchnone)+LUMO (nitroindole) interaction.

Thus, a comparison of the HOMO–LUMO energies (Table 2) predicts that the 1,3-dipolar cycloaddition should involve the HOMO of the münchnone (1,3-dipole) interacting with



Scheme 6.

Table 1. AM1 Calculation results performed through SPARTAN

cpd	Energies, eV HOMO	LUMO
1	−9.512	−1.247
6	−9.536	−1.562
17	−9.514	−1.141
13	−7.674	−0.423
14	−7.743	−0.683

Table 2. Comparison of LUMO–HOMO energy differences, eV (energy values are taken from Table 1)

Reaction	*E* (LUMO nitroindole)−*E* (HOMO münchnone), eV	*E* (LUMO münchnone)−*E* (HOMO nitroindole), eV	ΔeV
1+**3**	6.428	8.089	1.661
1+**14**	6.497	8.829	2.332
6+**13**	6.112	9.113	3.001
6+**14**	6.181	8.853	2.672
17+**13**	6.533	9.091	2.558
17+**14**	6.602	8.831	2.229

the LUMO of the nitroindole (dipolarophile). These energy differences are lower by 1.7–3.0 eV than the reverse situation involving the LUMO of the münchnone and the HOMO of the nitroindole. However, in only one case is the FMO-predicted regiochemistry realized to any extent. The reaction of 3-nitroindole **6** with münchnone **14** gives a preponderance of pyrroloindole **19** over the isomeric **18** (Scheme 5). The reaction of 3-nitroindole **17** with münchnone **14** gives perhaps a slight excess of the FMO-product **16** (Scheme 4).

One feature of the regiochemistry is that in every case but one the major or exclusive product is the one where the phenyl group of the münchnone is *syn* to the nitro group in the indole (Schemes 3–5). This may suggest a favorable transition state π-interaction between the phenyl ring of the münchnone and the nitro group leading to the observed regiochemistry that is *anti*-FMO, or it may simply be a consequence of a highly nonsynchronous transition state where bond making between the methyl ring carbon of the münchnone and the electron-deficient carbon of the nitroindole double bond precedes, for steric reasons, bond making involving the phenyl ring carbon of the münchnone. Another interesting possibility is that there is a favorable interaction between the 'enolate' oxygen of the münchnone and the nitrogen of the nitro group. Transition state calculations may help to answer this question. Clearly, further work is needed to understand the regiochemistry observed in these reactions.

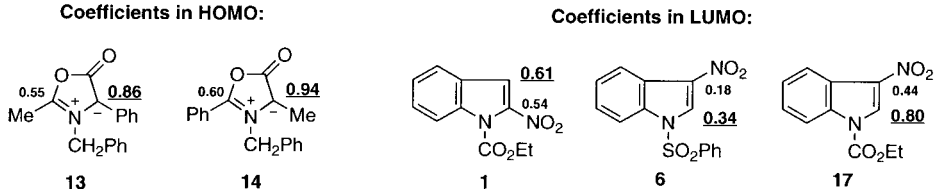
Other workers who have explored unsymmetrical münchnone cycloaddition reactions have encountered similar vagaries in the regiochemical outcome.[20–25] However, in some cases the regiochemistry can be satisfactorily explained with ab initio molecular orbital calculations.[24]

In summary, the reaction of 2- and 3-nitroindoles with münchnones **13** and **14** can be highly regioselective to afford 1,3-disubstituted pyrrolo[3,4-*b*]indoles in one operation. The factors governing the regiochemical outcome are unclear but probably reflect a combination of electronic, steric, and possibly dipole interactions. In any event, simple FMO theory fails to account for the observed regiochemistry. Moreover, the exact mechanism and sequence of nitrous acid and carbon dioxide loss remains to be established, and we are continuing our work in this area.

Experimental

General considerations

Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl before use. ^{1}H (300 MHz) and $^{13}C\{^{1}H\}$ NMR spectra (75 MHz) were obtained on a Varian Unity-300 NMR spectrometer. Chemical shifts are given as ppm downfield of TMS; coupling constants are in Hz. An asterisk after a chemical shift denotes a quaternary carbon. IR spectra were obtained as KBr pellets on a Perkin–Elmer 1600 FTIR spectrometer. UV–VIS spectra were obtained in ethanol on a HP-8451 diode array spectrophotometer; approximate ε values are reported in parentheses. Melting Points were obtained in nitrogen-filled capillaries on a Mel-Temp apparatus, and are uncorrected. Flash chromatography was performed using Flash silica obtained from Selecto Scientific; samples were generally adsorbed onto Celite prior to application to the column. *N*,*N*′-Diisopropylcarbodiimide (DIPC) was purchased from Aldrich. *N*-Benzyl-*N*-benzoylalanine, *N*-acetyl-*N*-benzyl-α-phenylglycine, *N*-benzyl-*N*-benzoyl-α-phenylglycine, were prepared as described in the literature. 2- and 3-Nitro-1-phenylsulfonylindole, 3-nitro-1-ethoxycarbonylindole, and 1-methyl-3-nitroindole were prepared as described in references 14 and 15. Low resolution mass spectra were also obtained from the Boston University School of Medicine Mass Spectrometry Resource, which is supported by NIH/NCRR Grant No. P41-RR10888 (to C. E. Costello). High-resolution mass spectrometry (HRMS) was performed at University of Illinois (Urbana—Champaign) mass spectrometry laboratory or by SOCAL Mass Spectrometry Facility at University of California (Riverside). Elemental analyses were performed by Atlantic Microlabs, Inc. (Norcross, GA).



Scheme 7.

Ethyl 2-nitroindole-1-carboxylate (1). To a 0°C stirred suspension of sodium hydride (152 mg, 6.00 mmol) in anhydrous DMF (20 mL) was added a solution of 2-nitroindole (486 mg, 3.00 mmol) dissolved in anhydrous DMF (20 mL) dropwise via syringe. The reaction mixture was stirred at 0°C for 1 h and then freshly distilled ethyl chloroformate (651 mg, 6.00 mmol) was added dropwise. The reaction mixture was allowed to slowly warm to rt and stirred stirred at rt for 12 h. The reaction mixture was poured into externally cooled distilled water (50 mL) and extracted with ether (3×80 mL). The combined organic extracts were washed with brine (200 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a brown oil (1 g) which was purified by flash chromatography (hexanes; 1:2 CH_2Cl_2/hexanes). The desired product **1** was obtained as an analytically pure orange powder (522 mg, 2.23 mmol, 74%): mp 55–57°C; R_f=0.65 (3:1 hexanes/CH_2Cl_2); IR (PTFE) 2983, 1746 (C=O), 1548, 1519, 1475, 1375, 1327, 1255, 1201, 1146, 1072, 1020, 943, 860, 842, 759 cm^{-1}; UV (EtOH) λ_{max} 218, 326 nm; ^1H NMR ($CDCl_3$) δ 8.03–8.07 (m, 1H), 7.69–7.71 (m, 1H), 7.54–7.60 (m, 1H), 7.44 (s, 1H), 7.35–7.40 (m, 1H), 4.50 (q, 2H, J=7.2 Hz), 1.43 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 149.6, 142.7, 136.8, 129.7, 124.9, 123.8, 115.0, 112.4, 111.5, 65.2, 14.0; MS m/z 235 (M^++1), 234 (M^+), 162, 145, 132 (100%), 115, 104, 89, 77, 63. HRMS calcd for $C_{11}H_{10}N_2O_4$ (M^+) 234.0641, found 234.0641. Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.46; H, 4.30; N, 11.96. Found: C, 56.54; H, 4.34; N, 11.85.

3-Nitroindole. To a 0°C stirred mixture of silver nitrate (10.2 g, 60.0 mmol) in acetonitrile (40 mL) was added a solution of benzoyl chloride (7.73 g, 55.0 mmol) dissolved in acetonitrle (20 mL) dropwise via addition funnel over 5 min. The benzoyl nitrate solution thus formed was added to a −10°C stirred solution of indole (5.86 g, 50.0 mmol) dissolved in acetonitrile (60 mL). The reaction mixture was stirred at −10°C for 1 h and then at rt for 30 min. The reaction mixture was then poured into externally cooled distilled water (300 mL) and extracted with acetate (8×150 mL). The combined organic extracts were washed with brine (1 L), dried over sodium sulfate, and concentrated in vacuo to give a dark purple amorphous solid (15 g) which was purified by flash chromatography (hexanes; 1:1 CH_2Cl_2/hexanes). The desired product was obtained as an orange amorphous solid (1.90 g, 11.7 mmol, 23%). Recrystallization (aq. EtOH) gave greenish crystals: mp 215–217°C; R_f=0.29 (CH_2Cl_2); IR (PTFE) 3223 (NH), 3125, 2924, 1504, 1444, 1377, 1322, 1277, 1238, 1211, 1151, 1128, 830, 748 cm^{-1}; UV (EtOH) λ_{max} 212, 234 (sh), 267 (sh), 350 nm; ^1H NMR (D_6-DMSO) δ 12.65 (br s, 1H), 8.65 (s, 1H), 8.07–8.10 (m, 1H), 7.55–7.58 (m, 1H), 7.30–7.38 (m, 2H); ^{13}C NMR (D_6-DMSO) δ 135.1, 130.5, 128.5, 124.2, 123.7, 119.8, 119.4, 113.4; MS m/z 163 (M^++1), 162 (M^+, 100%), 146, 132, 116, 104, 89, 77, 63.

3-Nitro-1-(phenylsulfonyl)indole (6). To a 0°C stirred suspension of sodium hydride (152 mg, 6.02 mmol) suspended in anhydrous DMF (15 mL) was added a solution of 3-nitroindole (811 mg, 5.00 mmol) dissolved in anhydrous DMF (15 mL) dropwise via an addition funnel. The resulting reddish-purple solution was stirred at 0°C for 30 min and then neat benzenesulfonyl chloride (1.06 g, 6.00 mmol) was added dropwise via syringe. The reaction mixture was stirred at rt for 10 h and then poured into cooled distilled water (50 mL) and ether (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (2×60 mL). The combined organic layers were washed with distilled water (150 mL), brine (150 mL), and dried over sodium sulfate. Removal of solvent in vacuo gave a crude purple solid (1.5 g) which was purified by flash chromatography (hexanes; 1:1 CH_2Cl_2/hexanes). The desired product **6** was obtained as a white powder (1.30 g, 4.30 mmol, 86%) with spectral data (^1H NMR) consistent with that reported: mp 131–133°C; R_f=0.50 (1:1 CH_2Cl_2/hexanes); IR (KBr) 3118, 3061, 1583, 1540, 1477, 1443, 1385 (SO_2), 1296, 1267, 1223, 1183, 1137, 1089, 956, 823, 752 cm^{-1}; UV (EtOH) λ_{max} 210, 236, 270 (sh), 278 (sh), 324 nm; ^1H NMR ($CDCl_3$) δ 8.58 (s, 1H), 8.23–8.27 (m, 1H), 8.00–8.05 (m, 3H), 7.46–7.69 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 137.0, 135.4, 133.8, 133.5, 130.1, 128.0, 127.6, 127.1, 126.2, 122.0, 121.5, 113.8; MS m/z 302 (M^+), 286, 191, 165, 141, 125, 103, 77 (100%), 62.

Ethyl 3-nitroindole-1-carboxylate (17). To a 0°C stirred suspension of sodium hydride (152 mg, 6.00 mmol) in DMF (15 mL) was added a solution of 3-nitroindole (486 mg, 3.00 mmol) dissolved in DMF (15 mL). The reaction mixture was stirred at 0°C for 2 h and then freshly distilled ethyl chloroformate (434 mg, 4.00 mmol) was added and the reaction mixture was allowed to slowly warm to rt and then stirred for 18 h. The reaction mixture was poured into externally cooled distilled water (50 ml) and extracted with ether (4×60 mL). The combined organic extracts were washed with brine (200 mL) and dried over sodium sulfate. Removal of solvent in vacuo gave a brown amorphous solid (0.8 g) which was purified by flash chromatography (hexanes; 1:1 CH_2Cl_2/hexanes). The desired product **17** was obtained as a white amorphous solid (350 mg, 1.50 mmol, 50%, mp 124–126°C). Recrystallization (1:4 CH_2Cl_2/hexanes) gave **17** as a white powder: mp 129–130°C; R_f=0.27 (1:2 CH_2Cl_2/hexanes); IR (PTFE) 3173, 2977, 1762 (C=O), 1551, 1494, 1450, 1368, 1336, 1302, 1254, 1209, 1142, 1077, 1030, 767 cm^{-1}; UV (EtOH) λ_{max} 216, 242, 330 nm; ^1H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.24–8.29 (m, 2H), 7.47–7.50 (m, 2H), 4.60 (q, 2H, J=7.2 Hz), 1.55 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 149.9, 134.5, 133.2, 127.7, 127.0, 125.9, 121.7, 121.0, 115.7, 65.2, 14.5; MS m/z 235 (M^++1), 234 (M^+, 100%), 175, 162, 132, 116, 103, 90, 76, 62. Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.34; H, 4.35; N, 12.05.

Ethyl 2-(benzylamine)propionate. To a 0°C stirred solution of benzylamine (11.8 g, 0.11 mol, 12.0 mL), and triethylamine (11.1 g, 0.11 mol, 15.3 mL) dissolved in THF (30 mL), was added a solution of ethyl 2-bromopropionate (**10**) (18.1 g, 0.10 mol, 13.0 mL), dissolved in THF (30 mL) dropwise via addition funnel over the period of 30 min. The reaction mixture was stirred at 0°C for 2 h and then at rt for 45 h. The mixture was filtered through a plug of Celite and washed with THF (20 mL). The filtrate was concentrated in vacuo. Ether (100 mL) was added to the solution. The white milky product was concentrated in vacuo and the residue was dissolved in ethyl acetate. The usual workup and concentration in vacuo gave a yellow oil.

Fractional distillation under reduced pressure gave 13.5 g (65%): bp 124–125°C (3 Torr); ^{1}H NMR ($CDCl_3$) δ 7.33–7.34 (m, 5H), 4.20 (q, 2H, J=7.2 Hz), 3.66–3.84 (m, 2H), 3.38 (q, 1H, J=6.9 Hz), 1.86 (bs, 1H), 1.31 (t, 3H, J=7.2 Hz), 1.28 (d, 3H, J= 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 176.0, 140.0, 128.6, 128.4, 127.3, 60.9, 56.2, 52.2, 19.3, 14.5.

***N*-Benzoyl-*N*-benzylalanine ethyl ester.** To a 0°C stirred solution of ethyl 2-(benzylamine)propionoate (11.9 g, 0.057 mol) dissolved in CH_2Cl_2 (100 mL) in a 250 mL 3-necked flask was added neat triethylamine (6.39 g, 0.063 mol) followed by the dropwise addition of benzoyl chloride (8.48 g, 0.060 mol) via addition funnel over the period of 2 h. The solution was left at rt for 44 h. The reaction mixture was partitioned between methylene chloride and 10% HCl. This mixture was then washed with 10% HCl. After usual workup 17.9 g (100%) of solid product remained, which was utilized without further purification in the next reaction.

***N*-Benzoyl-*N*-benzylalanine (12).** To a solution of *N*-benzoyl-*N*-benzylalanine ethyl ester (17.9 g, 0.057 mol) dissolved in ethanol (60 mL) and distilled water (20 mL) was added freshly crushed sodium hydroxide (4.56 g, 0.114 mol). The reaction mixture was heated to reflux for 6 h and then stirred at rt for 64 h. The aqueous solution was treated with water (100 mL) and ethyl acetate (100 mL). The organic layer was separated and washed with 1.0 M NaOH (2×100 mL). The aqueous layers were acidified with HCl to pH 2 with ice added and external cooling. The acidic solution was extracted with ethyl acetate (2×200 mL). After the usual workup the resulting yellow oil was dissolved in ether (40 mL). After gravity filtration and refrigeration, the product crystallized out. The resulting crystals were dried in vacuo to a yield 8.2 g (50%): mp 139–140°C; ^{1}H NMR (D_6-DMSO) δ 12.78 (bs, 1H), 7.25–7.46 (m, 10H), 4.13–5.08 (m, 3H), 1.28–1.36 (m, 3H). For major rotamer ^{13}C NMR (D_6-DMSO) δ 172.4, 171.0, 137.5, 136.3, 129.6, 128.5, 128.2, 127.3, 126.9, 126.2, 54.9, 52.8, 14.5.

2-Benzyl-3-methyl-1-phenyl-4-(phenylsulfonyl)-2,4-dihydropyrrolo[3,4-*b*]indole (19) and 2-benzyl-1-methyl-3-phenyl-4-(phenylsulfonyl)-2,4-dihydropyrrolo[3,4-*b*]indole (18). *a. From n-benzyl-n-benzoylalanine (12).* A solution of 3-nitro-1-(phenylsulfonyl)indole (**6**) (296 mg, 0.98 mmol) and *N*-benzyl-*N*-benzoylalanine (0.86 g, 3.0 mmol, 3.0 equiv.) in THF (30 mL) was treated with DIPC (0.47 mL, 3.0 mmol, 3.0 equiv.). The resulting yellow mixture was refluxed under nitrogen for 24 h, cooled, poured into saturated aqueous $NaHCO_3$ (25 mL), and extracted with ether (2×25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 mL), dried over brine and $MgSO_4$, and evaporated. ^{1}H NMR of the crude product showed a 70:30 mixture of **19** and **18**. Flash chromatography (2:1 hexanes/CH_2Cl_2) of the residue gave **19** (241 mg beige crystals, 73%) followed by **18** (120 mg orange oil, 85%). An analytical sample of **19** was recrystallized from CH_2Cl_2 to give colorless blocks: mp: 171–172°C; ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J=8.3 Hz 1H), 7.57 (m, 2H), 7.44 (tt, J=8.1, 1.5 Hz, 1H), 7.2–7.4 (m, 12H), 7.08 (td, J=7.0, 1.0 Hz, 1H), 6.39 (m, 2H), 5.31 (s, 2H, CH_2), 2.66 (s, 3H, CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 144.4*, 138.8*, 136.2*, 133.3, 132.0*, 129.3*, 128.9 (2C), 128.8 (2C), 128.3*, 127.6, 127.3, 127.2 (2C), 126.4*, 125.5 (2C), 125.0, 124.6, 122.6*, 119.3, 117.6, 177.3*, 114.1*, 48.3, 11.4; IR (KBr) 1630 m, 1354 vs, 1176 vs cm^{-1}; UV–VIS (CH_2Cl_2, 2×10^{-5} M) 230 (10,000), 268 (6000), 332 (4000) nm; UV–VIS (EtOH): 208, 220 sh, 266, 330 nm. Anal. Calcd for $C_{30}H_{24}N_2O_2S$: C, 75.61; H, 5.07; N, 5.88; S, 6.73. Found: C, 75.73; H, 5.09; N, 5.93; S, 6.73.

An analytical sample of isomer **18** was recrystallized from MeOH/CH_2Cl_2. Mp: 157–158°C; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 1H), 7.2–7.6 (m, 16H), 6.72 (m, 2H), 5.02 (s, 2H, CH_2), 2.33 (s, 3H, CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 143.9*, 138.9*, 136.5*, 133.2, 132.3*, 131.7 (2C), 128.9 (2C), 128.4 (2C), 128.2, 128.1 (2C), 127.8*, 127.3, 127.2 (2C), 126.7*, 125.5 (2C), 124.7, 124.5, 119.5, 117.8*, 117.6, 117.2*, 116.4*, 48.0, 12.0; IR (KBr) 1631 m, 1602 m, 1365 vs, 1349 s, 1176 vs cm^{-1}; UV–VIS (EtOH): 208, 262, 303 (sh) nm. Anal. Calcd for $C_{30}H_{24}N_2O_2S$: C, 75.61; H, 5.07; N, 5.88; S, 6.73. Found: C, 75.64; H, 5.09; N, 5.92; S, 6.75.

b. From n-acetyl-n-benzyl-α-phenylglycine (11): A solution of 3-nitro-1-phenylsulfonylindole (299 mg, 0.99 mmol) and *N*-acetyl-*N*-benzyl-α-phenylglycine (**11**) (826 mg, 3.0 mmol, 3 equiv.) in THF (30 mL) was treated with DIPC (0.47 mL, 3.0 mmol, 3.0 equiv.). The resulting yellow solution was heated at reflux for 23 h. Saturated aqueous $NaHCO_3$ (30 mL) was added to the cooled mixture, which was extracted with ether (2×0 mL). The combined organic extracts were washed with water (3×30 mL), dried over brine (20 mL) and $MgSO_4$, and evaporated. The ^{1}H NMR of the crude product showed a 94:6 ratio of **19** and **18**. Chromatography on alumina (basic, activity III) with hexanes/CH_2Cl_2 (5:1) gave **19** as a yellow solid (356 mg, 74%).

2-Benzyl-3-methyl-1-phenyl-4-carboethoxy-2,4-dihydropyrrolo[3,4-*b*]indole (16) and 2-benzyl-1-methyl-3-phenyl-4-carboethoxy-2,4-dihydropyrrolo[3,4-*b*]indole (15). *a. From n-benzyl-n-benzoylalanine (12) and 1-carboxyethyl-3-nitroindole*. A solution of 1-carboethoxy-3-nitroindole (**17**) (236 mg, 1.3 mmol) and *N*-benzyl-*N*-benzoylalanine (**12**) (857 mg, 3.6 mmol, 2.8 equiv.) in THF (25 mL) was treated with DIPC (0.47 mL, 3.0 mmol, 2.4 equiv.) at rt. The resulting mixture was heated at reflux for 24 h, cooled to rt, poured into saturated aqueous $NaHCO_3$ (25 mL), and extracted with ether (3×25 mL). The combined extracts were washed with water (4×25 mL), dried over brine (25 mL) and Na_2SO_4, and evaporated. ^{1}H NMR of the residue showed a 60:40 ratio of **16** and **15**. Flash chromatography (2:1 hexanes/CH_2Cl_2) gave the mixed product isomers as a red oil (270 mg, 53%). On dissolution of this oil in hexanes and chilling, **16** precipitated as a yellow powder. An analytical sample of each isomer was prepared by recrystallization from CH_2Cl_2/hexanes. **16**: mp: 175–176°C; ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J=8.1 Hz, 1H), 7.2–7.6 (m, 11H), 7.09 (t, J=7.6 Hz, 1H), 6.94 (d, J=7.1 Hz, 2H), 5.26 (s, 2H, CH_2Ph), 4.49 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 2.54 (s, 3H, CCH_3), 1.47 (t, J=7.1 Hz, 3H, CH_2CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 152.4*, 139.1, 132.7*, 132.2*, 129.6 (2C), 129.1 (2C), 129.0 (2C), 127.6, 127.5*, 127.3, 125.8 (2C), 125.0, 124.5 (2C), 123.0,

122.3*, 119.2, 116.8. 116.1*, 111.4*, 62.7, 48.6, 14.9, 12.3. One quaternary carbon could not be located unambiguously. IR (KBr) 1707 vs, 1638 m, 1601 m, 1452 m, 1419 m cm^{-1}; UV–VIS (EtOH, 1×10^{-4} M) 208 (10,000), 268 (4000), 294 (2000, sh), 336 (2000) nm. Anal. Calcd for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N, 6.86. Found: C, 79.42; H, 5.88; N, 6.81. 15: colorless needles, mp: 122–123°C; ^1H NMR ($CDCl_3$) δ 8.32 (m, 1H), 7.67 (m, 1H), 7.24 (m, 10H), 6.82 (d, J=7.6 Hz, 2H), 4.98 (s, 2H, CH_2Ph), 3.74 (q, J=7.1 Hz, 2H, CH_2CH_3), 2.47 (s, 3H, CCH_3), 0.78 (t, J=7.1 Hz, 3H, CH_2CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 152.1*, 142.9*, 138.9*, 134.3, 132.1 (2C), 128.8 (2C), 127.6, 127.5 (2C), 127.3*, 127.2, 125.8 (2C), 124.7*, 124.4, 123.1, 119.2, 117.5, 116.4, 115.0*, 114.9*, 61.6, 48.2, 14.2, 12.1. One quaternary carbon could not be unambiguously located. IR (KBr) 1707 vs, 1639 s, 1601 m, 1451 s, 1414 vs cm^{-1}; UV–VIS (EtOH, 8×10^{-5} M) 208 (20,000), 252 (10,000), 273 (8000, sh), 309 (4000), 317 (3000, sh) nm. Anal. Calcd for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N, 6.86. Found: C, 79.33; H, 5.94; N, 6.85.

*b. From n-acetyl-n-benzyl-α-phenylglycine (**11**) and 1-carboxyethyl-3-nitroindole.* A solution of 1-carboethoxy-3-nitroindole (**17**) (430 mg, 1.8 mmol, 2.8 equiv.) in THF (12 mL) was treated with DIPC at rt. The resulting yellow mixture was refluxed for 24 h under nitrogen, then cooled. Crystalline diisopropylurea was removed by filtration, the filtrate poured into saturated aqueous $NaHCO_3$ (15 mL), and the mixture extracted with ether (3×15 mL), dried over brine and $MgSO_4$, and evaporated. Flash chromatography of the residue (1:1 CH_2Cl_2/hexanes) left a yellow solid (145 mg) containing unreacted indole and a 95:5 mixture of **16** and **15** (48 mg, 19%, estimated by NMR).

*c. From n-benzyl-n-benzoylalanine (**12**) and 1-carboxyethyl-2-nitroindole*. A rt solution of 1-carboxyethyl-2-nitroindole (**1**) (117 mg, 0.50 mmol) and *N*-benzyl-*N*-benzoylalanine (**12**) (428 mg, 1.5 mmol) in THF (15 mL) was treated with DIPC (0.234 mL, 1.5 mmol, 3.0 equiv.). The mixture was refluxed with stirring for 30 h, cooled to rt, filtered through Celite, and concentrated. Flash chromatography of the residue (2:1 hexanes/CH_2Cl_2) provided **16** (173 mg, 80%), mp 162–163°; ^1H and $^{13}C\{^1H\}$ NMR spectra as described above.

*d. From n-acetyl-n-benzyl-α-phenylglycine (**11**) and 1-carboxyethyl-2-nitroindole.* A rt solution of 1-carboxyethyl-2-nitroindole (**1**) (117 mg, 0.50 mmol) and *N*-acetyl-*N*-benzyl-α-phenylglycine (**11**) (438 mg, 1.50 mmol, 3 equiv.) was treated with DIPC (0.234 mL, 1.5 mmol, 3.0 equiv.). The mixture was refluxed for 23 h, cooled to rt, and filtered through Celite. The filtrate was washed with brine, dried over Na_2SO_4, and evaporated. The residue was recrystallized from EtOH to give **15** (80 mg. 39%). ^1H and $^{13}C\{^1H\}$ NMR spectra as reported above.

3-Ethyl-2-(α-hydroxyphenylmethyl)-1-(phenylsulfonyl)-indole. To a −70°C stirred solution of 3-ethyl-1-(phenylsulfonyl)indole (**20**) (677 mg, 2.37 mmol) dissolved in THF (40 mL) was added a solution of *sec*-butyllithium (2.60 mmol, 1.3 M in cyclohexane, 2.00 mL) dropwise. The reaction mixture was stirred at −70°C for 3 h and then at 0°C for 3 h. The reaction mixture was recooled to −70°C and treated with freshly distilled benzaldehyde (378 mg, 3.56 mmol). The reaction mixture was stirred at −70°C and then at rt for 10 h and then was poured into a solution of saturated aqueous ammonium chloride (50 mL). The organic layer was separated and the aqueous layer was extracted with ether (2×60 mL). The combined organic extracts were washed with brine (150 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave an orange oil (1 g) which was purified by flash chromatography (hexanes; 3:1 CH_2Cl_2/hexanes). The desired product was obtained as a yellow oil (580 mg, 1.48 mmol, 63%) with spectral data (^1H NMR and ^{13}C NMR) consistent with that reported: R_f=0.56 (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.09–8.12 (m, 1H), 7.23–7.57 (m, 12H), 6.45–6.49 (m, 1H), 4.36 (d, 1H, J=10.2 Hz), 2.70–2.78 (m, 2H), 1.66 (br s, 1H), 1.18 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 142.3, 138.7, 137.0, 136.6, 133.8, 130.1, 129.2, 128.5, 127.3, 127.1, 126.8, 125.9, 125.7, 123.9, 119.8, 115.3, 67.0, 18.2, 15.0.

2-Benzoyl-3-ethyl-1-(phenylsulfonyl)indole (21). To a rt stirred solution of 3-ethyl-2-(α-hydroxyphenylmethyl)-1-(phenylsulfonyl)indole (387 mg, 1.00 mmol) dissolved in CH_2Cl_2 (25 mL) was added black MnO_2 (870 mg, 10.0 mmol) and the reaction mixture was heated to reflux for 11 h and then allowed to cool to rt. The mixture was filtered through celite and the filter plug was washed with CH_2Cl_2 (5×30 mL). The organic solution was washed with brine (150 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a tan amorphous solid which was purified by flash chromatography (hexanes; 1:1 CH_2Cl_2/hexanes). The desired product **21** was obtained as an off-white powder (290 mg, 0.749 mmol, 75%): mp 141–142°C (lit.[19] mp 142.5–143°C); R_f=0.77 (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.09–8.12 (m, 1H), 7.91–7.94 (m, 2H), 7.80–7.83 (m, 2H), 7.28–7.62 (m, 9H), 2.64 (q, 2H, J=7.5 Hz), 1.12 (t, 3H, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 189.8, 138.7, 136.9, 136.6, 134.0, 133.6, 133.3, 131.4, 130.6, 129.8, 129.0, 128.8, 127.5, 126.8, 124.6, 120.7, 115.7, 17.9, 14.8.

2-Benzoyl-3-(bromomethyl)-1-(phenylsulfonyl)indole. To a rt stirred solution of 2-benzoyl-3-ethyl-1-(phenylsulfonyl)indole (**21**) (217 mg, 0.560 mmol) and *N*-bromosuccinimide (110 mg, 0.620 mmol) dissolved in carbon tetrachloride (10 mL) was added AIBN (10 mg) and the reaction mixture was heated to reflux for 8 h. After cooling to 0°C, the succinimide which formed was separated by filtration. Removal of the solvent in vacuo gave a crude yellow amorphous solid (0.3 g). Recrystallization (ether/hexanes) gave the desired product as tan plates (160 mg, 0.343 mmol, 61%): mp 109–111°C (lit.[19]mp 112–114°C); R_f=0.67 (3:1 CH_2Cl_2/hexanes); ^1H NMR ($CDCl_3$) δ 8.09–8.12 (m, 1H), 7.86–7.96 (m, 5H), 7.34–7.66 (m, 8H), 5.19 (q, 1H, J=6.9 Hz), 2.04 (d, 3H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 189.5, 137.8, 136.8, 136.7, 134.4, 134.3, 129.9, 129.5, 129.3, 129.0, 128.9, 127.9, 127.6, 126.9, 124.4, 122.5, 115.4, 40.0, 26.5.

2,4-Dihydro-1-methyl-3-phenyl-2-benzyl-4-(phenylsulfonyl)pyrrolo[3,4-*b*]indole (18). To a rt stirred solution of 2-benzoyl-3-(α-bromoethyl)-1-(phenylsulfonyl)indole (47 mg, 0.10 mmol) and benzylamine (21 mg, 0.20 mmol) dissolved in chloroform (2 mL) was added potassium carbonate (55 mg, 0.40 mmol) and the reaction mixture was

stirred at rt for 10 h and then at reflux for 11 h. The reaction mixture was partitioned between chloroform (15 mL) and distilled water and acidified with a solution of HCl (2.0 M, 1 mL). The organic layer was separated and washed with brine (20 mL) and dried over sodium sulfate. Removal of the solvent in vacuo gave a green oil (0.1 g) which was purified by flash chromatography (hexanes; 1:2 CH_2Cl_2/hexanes). The desired product **18** was obtained as a green amorphous solid (23 mg, 0.048 mmol, 48%) identical (TLC, ^{1}H NMR) to the minor isomer obtained by the reaction of 3-nitro-1-(phenylsulfonyl)indole (**6**) and the münchnone derived by the cyclodehydration (DIPC) of *N*-benzyl-*N*-benzoylalanine: R_f=0.58 (1:1 CH_2Cl_2/hexanes).

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