Pd(0)-Catalyzed cross-coupling reactions of 2-indolylzinc halides. A convenient route to indolo[2,3-*a*]quinolizidines

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This work is dedicated to Prof. Marcial Moreno-Mañas on the occasion of his 60th birthday
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Abstract
The generation of 4-, 5-, and 6-methoxy-3-indolylzinc chlorides **3a-c** and their Pd(0)-catalyzed cross-coupling reactions with 2-halopyridines to give 4-, 5-, and 6-methoxy substituted 2-(2-pyridyl)indoles **4a-c** is reported. 2-(2-Pyridyl)indole **8** is converted to indolo[2,3-*a*]quinolizidine **15**. The key step is the regioselective cyclization on the indole 3-position of a thionium ion generated by Pummerer reaction from an appropriately substituted 2-(2-piperidyl)indole.

Keywords: Indoloquinolizidine, palladium(0), cross-coupling, Zinc, bromopyridine, Pummerer-reaction

Introduction

The indolo[2,3-*a*]quinolizidine ring system is often embedded in the structure of many naturally occurring compounds exhibiting a wide range of biological activities.[1] Although at the present time there is a plethora of synthetic strategies for the elaboration of indoloquinolizidine derivatives, most approaches have relied on the generation of the C_{12a}-C_{12b} bond from appropriate *N*-[2-(3-indolyl)ethyl]piperidines or the elaboration of the piperidine D ring in the last steps of the synthesis.[2]
In previous works[3] we have reported the preparation of 2-(2-pyridyl)indoles by Pd(0)-catalyzed cross-coupling[4] of 1-(benzenesulfonyl)-2-indolylzinc chloride and a variety of 2-chloro- and 2-bromopyridines bearing substituents of different electronic nature, and we have explored a procedure for their conversion into indoloquinolizidine derivatives.[3a,5] This approach involves the formation of the C_7-C_{7a} bond by intramolecular alkylation of the indole 3-position from a 2-(2-piperidyl)indole as the key step, a transformation for which no efficient methods had been described at the beginning of our studies. In this paper we report the generation of 4-, 5-, and 6-

methoxy substituted 2-indolylzinc chlorides[6] and their use in Pd(0)-catalyzed cross-coupling reactions leading to 2-(2-pyridyl)indoles bearing methoxy groups on the indole ring, which are of interest in the synthesis of hydroxy or methoxy substituted indoloquinolizidine alkaloids such as those depicted in Figure 1. Additionally, we report an efficient conversion of 2-(2-pyridyl)indole **9** to methyl indolo[2,3-*a*]quinolizidine-2-carboxylate **15**, thus establishing the usefulness of our method for preparing indoloquinolizidines.

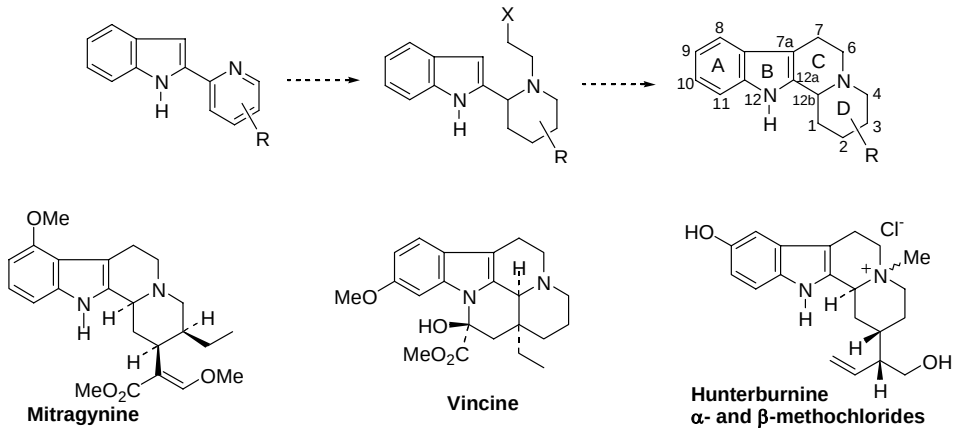
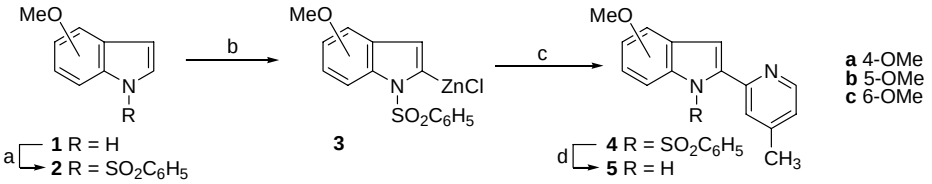


Figure 1

Results and Discussion

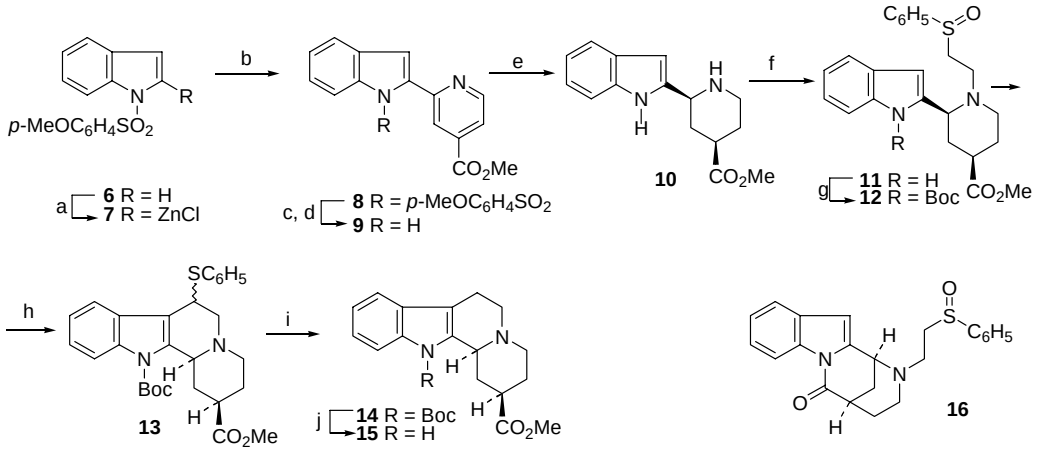
The required 4-, 5-, and 6-methoxyindoles **1a-c** were prepared by the procedure of Batcho and Leimgruber,[7] from the corresponding methylnitroanisole derivatives. A subsequent sulfonylation was carried out under phase-transfer conditions[8] to give the protected methoxyindoles **2a-c** in excellent yields. Regioselective litiation of **2a-c** with LDA, followed by transmetalation with anhydrous $ZnCl_2$ afforded 2-indolylzinc chlorides **3a-c**, which were allowed to react with 2-bromo-4-methylpyridine in the presence of Pd(0) in refluxing THF. The best conditions were found to be the use of 0.1 equivalent of $Pd(PPh_3)_4$ with respect to the 2-halopyridine. In this manner, methoxy-2-(2-pyridyl)indoles 4a-c were isolated in 64%, 65%, and 80% yield, respectively. Finally, the deprotected methoxy-2-(2-pyridyl)indoles **5a-c** were obtained in good yields by treatment of **4a-c** under alkaline conditions. The new methoxy substituted 2-indolylzinc halides **3a-c** reported here can be useful intermediates for the synthesis of indole derivatives.



Reagents and conditions: (a) $ClSO_2C_6H_5$, $(n\text{-Bu})_4N{\cdot}HSO_4$, NaOH, H_2O, C_6H_6, 25 ºC, overnight (**2a**, 98%; **2b**, 85%; **2c**, 92%); (b) LDA, THF, 0 ºC, 30 min, then $ZnCl_2$, 25 ºC, 30 min; (c) 2-bromo-4-methylpyridyne, $Pd[P(C_6H_5)_3]_4$, THF, reflux, 4 h (**4a**, 64%; **4b**, 65%; **4c**, 80%); (d) NaOH, EtOH, H_2O, reflux, 12 h (**5a**, 85%; **5b**, 93%; **5c**, 87%).

Scheme 1

On the other hand, as an extension of our previous work on the use of the Pummerer[9] reaction in electrophilic cyclizations on the indole 3-position,[3a,10] we describe here the synthesis of indoloquinolizidine **15** from pyridylindole **9**. This compound was prepared in 85% overall yield by palladium(0)-catalyzed cross-coupling reaction of 2-indolylzinc chloride **7** and methyl 2-chloropyridine-4-carboxylate, followed by alkaline hydrolysis of the resulting protected pyridylindole **8** and reesterification of the corresponding acid. As expected, catalytic hydrogenation of **9** stereoselectively afforded the 2,4-*cis* indolylpiperidine **10**. Incorporation of the (phenylsulfinyl)ethyl chain on the piperidine nitrogen was carried out by refluxing a methanolic solution of **10** and phenyl vinyl sulfoxide. In this way, compound **11** was obtained in 89% yield as a mixture of isomers at the sulfur atom. In previous studies[3a] we concluded that protection of the indole nitrogen with an electron-withdrawing group constitutes an essential requirement for the success of the closure of the indoloquinolizidine C ring by electrophilic attack on the indole 3-position of a thionium ion generated by the Pummerer reaction.



Scheme 2

Reagents and conditions: (a) LDA, THF, 0 ºC, 30 min, then $ZnCl_2$; (b) methyl 2-chloropyridine-4-carboxylate, $PdCl_2(PPh_3)_2$, DIBAH, THF, reflux (89%); (c) NaOH, EtOH, H_2O, reflux, 12 h, (96%); (d) HCl, anh. MeOH, reflux, 3 h (98%); (e) H_2, PtO_2, AcOH (65%); (f) $C_6H_5S(O)CH=CH_2$, MeOH, reflux, 24 h (89%); (g) $(Boc)_2O$, DMAP, CH_2Cl_2, 25 ºC, 10 h; (85%) (h) TMSOTf, DIPEA, CH_2Cl_2, 25 ºC, 15 min (84%); (i) Bu_3SnH, AIBN, C_6H_6, reflux, 3 h (75%); (j) HCO_2H, 25 ºC, 24 h (96%).

This protecting group not only blocks the indole nitrogen but also diminishes the nucleophilic character of the indole nucleus, thus avoiding the formation of both undesired *N*-regioisomers[3a,11] and byproducts coming from the attack of the indole ring upon the oxysulfonium intermediate[12] initially formed in the Pummerer reaction. The *N*-Boc derivative **12** was obtained in good yield by treatment of **11** with di-*t*-butyl dicarbonate and DMAP in dichloromethane. It is worth mentioning that when this transformation was attempted by treating compound **11** with methyl cyanoformate and sodium hydride, tetracycle **16** was formed in 50% yield instead of the desired compound **12**. Sulfoxide **12** was subjected to the Pummerer reaction by treatment with TMSOTf and DIPEA in dichloromethane at room temperature. This reaction afforded the desired indoloquinolizidine **13** in 84% yield as a mixture of epimers at C_7. Finally, elimination of the phenylsulfanyl group by treatment of **13** with tributyltin hydride and AIBN, followed by hydrolysis of the Boc group with formic acid, provided indoloquinolizidine **15**[13] in excellent yield.

In conclusion, a convenient route to indolo[2,3-*a*]quinolizidines involving, as the key steps, a palladium(0)-catalyzed cross-coupling reaction between a 2-indolylzinc derivative and a 2-halopyridine and a Pummerer cyclization on the indole 3-position of a 2-(2-piperidyl)indole has been developed.

Experimental Section

General Procedures. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded on either a Varian Gemini 200 operating at 200 MHz for ^1H and 50.3 MHz for ^{13}C, or a Varian Gemini 300 operating at 300 MHz for ^1H and 75.5 MHz for ^{13}C. Chemical shifts are reported in values ppm relative to TMS as internal reference. IR spectra were recorded on a FTIR Perkin-Elmer 1600 spectrometer with samples prepared either as KBr pellets or thin films on NaCl salt plates, and only noteworthy absorptions are listed. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with aqueous potassium permanganate solution. Column chromatography was carried out on SiO_2 (silica gel 60, SDS, 70-200 microns). Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 35-70 microns). All reagents were purchased from Aldrich or Fluka and were used without further purification. Tetrahydrofuran was distilled from sodium/benzophenone. Solvents for chromatography were distilled at atmospheric pressure prior

to use and dried using standard procedures. All reactions were performed under argon or nitrogen. Drying of the organic extracts during the work-up of reactions was performed over Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

General procedure for the preparation of protected methoxyindoles 2a-c
Tetrabutylammonium hydrogen sulfate (27 mg, 78 mmol) and a 50% aqueous NaOH solution (8 mL) were added to a vigorously stirred solution of **1a-c** (1.0 g, 6.8 mmol) in benzene (20 mL). After 5 min, a solution of benzenesulfonyl chloride (1.3 mL, 10.2 mmol) in benzene (10 mL) was added, and the mixture was stirred at room temperature overnight. The benzene layer was separated, washed with water, dried, and concentrated to give, after flash chromatography (3:2 CH_2Cl_2:hexane), compounds **2a-c**.

1-(Benzenesulfonyl)-4-methoxyindole (2a). 98% yield; mp 77-78 ºC (lit.[14] 79-80 ºC); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.88 (s, 3H), 6.64 (d, *J* = 8 Hz, 1H), 6.77 (dd, *J* = 3.7, 0.7 Hz, 1H), 7.23 (t, *J* = 8 Hz, 1H), 7.38-7.70 (m, 4H), 7.47 (d, *J* = 3.7 Hz, 1H), 7.60 (d, *J* = 8 Hz, 1H), 7.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 55.4, 103.5, 106.3, 106.4, 121.0, 124.7, 125.7, 126.7 (2 C), 129.2 (2 C), 133.8, 136.0, 138.2, 153.1.

1-(Benzenesulfonyl)-5-methoxyindole (2b). 85% yield; mp 94-95 ºC (lit.[15] 98-99 ºC); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.81 (s, 3H), 6.59 (d, *J* = 3.6 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 7.39-7.56 (m, 3H), 7.52 (d, *J* = 3.6 Hz, 1H), 7.83-7.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 55.6, 103.6, 109.4, 113.7, 114.3, 126.6 (2 C), 127.0, 129.1 (2 C), 129.5, 131.7, 133.7, 138.0, 156.4.

1-(Benzenesulfonyl)-6-methoxyindole (2c). 92% yield; mp 138-139 ºC (lit.[15] 140-142 ºC); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, 3 H), 6.58 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 3.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1 H), 7.87 (d, *J*=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 55.7, 97.9, 109.1, 112.5, 124.4, 125.0, 125.1, 126.6 (2 C), 129.1 (2 C), 133.7, 135.9, 138.3, 157.9.

General procedure for the preparation of methoxy-2-(2-pyridyl)indoles 4a-c
A solution of LDA (1.34 mL of a 1.5 M solution in cyclohexane, 2.0 mmol) was slowly added to a solution of indoles **2a-c** (500 mg, 1.83 mmol) in anhydrous THF (3 mL) at 0 ºC, and the resulting mixture was stirred for 30 min at this temperature. Then, a solution of anhydrous $ZnCl_2$ (330 mg, 2.0 mmol) in THF (4.5 mL) was added, and the stirring was continued for 30 min at 25 ºC. In a separate flask, a solution of 2-bromo-4-methylpyridine (210 mg, 1.22 mmol) in anhydrous THF (1.5 mL) was added to a solution of tetrakis(triphenylphosphine)palladium(0) (141 mg, 0.12 mmol) in THF (4.5 mL), and the mixture was stirred at 25 ºC for 10 min. The resulting solution was transferred via canula to the solution of methoxyindolylzinc chloride **3a-c** prepared above and the mixture was heated at reflux for 4 h, cooled, and poured into saturated

aqueous Na_2CO_3. The aqueous phase was extracted with Et_2O, and the organic extracts were concentrated to give a residue, which was purified by flash chromatography (CH_2Cl_2).

1-(Benzenesulfonyl)-4-methoxy-2-(4-methyl-2-pyridyl)indole (4a). 64% yield; IR (KBr): 3450, 1607, 1369, 1103, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.42 (s, 3H), 3.83 (s, 3H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.96 (s, 1H), 7.13 (dm, *J* = 5.2 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.32 (tm, *J* = 7.8 Hz, 1 H), 7.43 (t, *J* = 7.8, 1.2 Hz, 1H), 7.48 (br s, 1H), 7.73 (dm, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 8.52 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 21.1, 55.4, 104.5, 108.8, 111.8, 120.7, 123.9, 126.2, 126.7, 127.0 (2 C), 128.6 (2 C), 133.5, 137.3, 139.1, 139.5, 146.5, 148.5, 151.2, 153.1.

1-(Benzenesulfonyl)-5-methoxy-2-(4-methyl-2-pyridyl)indole (4b). 65% yield; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.44 (s, 3H), 3.80 (s, 3H), 6.80 (d, *J* = 0.9 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.16 (dm, *J* = 5.1 Hz, 1H), 7.30 (tm, *J* = 7.8 Hz, 1H), 7.43 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.53 (m, 1H), 7.60 (dm, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 8.54 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 21.1, 55.5, 103.6, 114.1, 115.6, 117.4, 124.2, 127.0 (2 C), 127.2, 128.2, 128.6 (2 C), 132.6, 133.5, 136.6, 142.2, 146.5, 148.6, 151.0, 157.1.

1-(Benzenesulfonyl)-6-methoxy-2-(4-methyl-2-pyridyl)indole (4c). 80% yield; IR (film): 3350, 1610, 1371, 1176, 591cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.43 (s, 3H), 3.91 (s, 3H), 6.78 (d, *J* = 0.9 Hz, 1H), 6.86 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.12 (dm, *J* = 5.2 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.33 (tm, *J* = 7.5 Hz, 1H), 7.50 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.52 (m, 1H), 7.65 (dm, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 8.51 (dd, *J* = 5.2, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 21.0, 55.8, 100.7, 113.4, 115.1, 121.7, 123.8, 124.2, 126.8, 126.9 (2 C), 128.5 (2 C), 133.5, 137.0, 139.4, 140.1, 146.4, 148.5, 151.2, 158.3.

General procedure for the preparation of methoxy-2-(2-pyridyl)indoles 5a-c

A solution of compounds **4a-c** (250 mg, 0.66 mmol) in EtOH (40 mL) and 10% aqueous NaOH (4 mL) was heated at reflux for 12 h. The resulting mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (15 mL). The organic solution was washed with water and aqueous Na_2CO_3, dried, concentrated, and the resulting residue was purified by flash chromatography (CH_2Cl_2).

4-Methoxy-2-(4-methyl-2-pyridyl)indole (5a). 85% yield; IR (film): 3162, 1610, 1247, 1105, 771 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.37 (s, 3H), 3.98 (s, 3H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 5.1 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.14 (s, 1H), 7.64 (s, 1H), 8.36 (d, *J* = 5.1 Hz, 1H), 10.25 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 20.9, 55.1, 98.1, 99.3, 104.7, 120.0, 120.7, 122.9, 123.7, 135.0, 139.0, 148.0, 148.3, 150.2, 153.4; Anal. Calcd for $C_{15}H_{14}N_2O \cdot 2/3\ H_2O$: C, 71.96; H, 6.18; N, 11.19. Found: C, 71.94; H, 5.75; N, 10.79.

5-Methoxy-2-(4-methyl-2-pyridyl)indole (5b). 93% yield; mp 115-116 °C; IR (film): 3150, 1606, 1225, 801 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.42 (s, 3H), 3.88 (s, 3H), 6.88 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.95 (m, 1H), 7.00 (dm, *J* = 5.1 Hz, 1H), 7.11 (d. *J* = 2.3 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.63 (m, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 10.0 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 21.1, 55.7, 100.0, 102.2, 112.1, 113.6, 120.5, 123.1, 129.4, 131.8, 137, 147.7, 148.7,

150.2, 154.3; Anal. Calcd for $C_{15}H_{14}N_2O \cdot 1/2\ H_2O$: C, 72.85; H, 6.11; N, 11.33. Found: C, 72.41; H, 5.92; N, 11.76.

6-Methoxy-2-(4-methyl-2-pyridyl)indole (5c). 87% yield; mp 145-146 °C; IR (KBr): 3418, 1603, 1261, 816 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.34 (s, 3H), 3.74 (s, 3H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.76 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.90 (m, 1H), 6.93 (dm, *J* = 5.1 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.56 (br s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 10.5 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 21.1, 55.4, 94.2, 100.5, 110.4, 120.2, 121.6, 122.6, 123.3, 135.9, 137.6, 147.7, 148.5, 150.5, 157.0; Anal. Calcd for $C_{15}H_{14}N_2O \cdot 1/4\ H_2O$: C, 74.21; H, 6.02; N, 11.54. Found: C, 74.46; H, 5.83; N, 11.40.

Methyl 2-[1-(*p*-methoxybenzenesulfonyl)-2-indolyl]pyridine-4-carboxylate (8). A solution of LDA (51.3 mL, 1.5 M in cyclohexane, 77 mmol) was slowly added to a solution of sulfonylindole **6**[16] (20 g, 70 mmol) in anhydrous THF (100 mL) at 0 ºC, and the resulting mixture was stirred for 30 min at this temperature. Then, a solution of anhydrous $ZnCl_2$ (10.5 g, 77 mmol) in THF (170 mL) was added, and the stirring was continued for 30 min at 25 ºC. In a separate flask, a solution of dichlorobis(triphenylphosphine)palladium(II) (0.7 g, 1 mmol) and DIBAH (2 mL, 1.0 M solution in hexane, 2.0 mmol) in THF (40 mL) was stirred at 25 ºC for 5 min, and then a solution of methyl 2-chloropyridine-4-carboxylate[17] (8.6 g, 50 mmol) in anhydrous THF (60 mL) was added. The stirring was continued at 25 ºC for 10 min. The resulting solution was transferred via canula to the solution of methoxyindolylzinc chloride **7** prepared above and the mixture was heated at reflux for 4 h, cooled, and poured into saturated aqueous Na_2CO_3. The aqueous phase was extracted with Et_2O, and the organic extracts were concentrated to give a residue, which, after purification by flash chromatography (CH_2Cl_2), afforded pure 2-(2-pyridyl)indole **8** (18.8 g, 89%): mp 126-127 ºC (Et_2O); IR (KBr): 1732, 1595, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ 3.75 (s, 3H), 3.99 (s, 3H), 6.77 (dm, *J* = 9.1 Hz, 2H), 6.90 (s, 1H), 7.26 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (ddd, *J* = 8.5, 7.5, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.57 (dm, *J* = 9.1 Hz, 2H), 7.90 (dd, *J* = 5.1, 1.6 Hz, 1 H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.27 (br s, 1H), 8.84 (d, *J* = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 52.7, 55.4, 113.8 (2 C), 115.8, 116.3, 121.4, 122.0, 124.4, 125.4, 125.5, 128.4, 129.2 (2 C), 130.3, 136.9, 138.2, 140.2, 149.5, 152.5, 163.5, 165.3; Anal. Calcd for $C_{22}H_{18}N_2O_5S$: C, 62.55; H, 4.30; N, 6.63; S, 7.59. Found: C, 62.23; H, 4.18; N, 6.46; S, 7.60.

Methyl 2-(2-indolyl)pyridine-4-carboxylate (9). A solution of compound **8** (1.8 g, 4.27 mmol) in EtOH (200 mL) and 10% aqueous NaOH (25 mL) was heated at reflux for 12 h, cooled, concentrated, and the residue treated with 10% aqueous H_2SO_4 (10 mL). The resulting precipitate was filtered, washed with water, and dried to give acid 2-(2-indolyl)pyridine-4-carboxylic (0.98 g, 96%) as a white solid: mp 286-289 °C (H_2O); IR (KBr): 3300, 1713, 1620 cm^{-1}; ^1H NMR (DMSO, 200 MHz): δ 7.01 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.25 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 4.8 Hz, 1H), 8.35 (s, 1H), 8.79 (d, *J* = 4.8 Hz, 1H), 11.8 (br s, 1 H); ^{13}C NMR (DMSO, 50.3 MHz): 101.8, 112.4, 119.0, 119.9, 121.2 (2 C), 123.0, 128.6, 136.7, 137.7, 139.5, 150.6, 151.7, 166.5; Anal. Calcd for $C_{14}H_{10}N_2O_2 \cdot 1/2\ H_2O$: C, 68.01; H, 4.48; N, 11.33. Found: C, 68.36; H, 4.05; N, 11.33. A

solution of this acid (0.76 g, 3.2 mmol) in a saturated HCl methanolic solution (100 mL) was heated at reflux under stirring for 3 h. The solution was cooled and concentrated under reduced pressure, and the resulting residue was taken up with saturated aqueous $NaHCO_3$ (10 mL). The precipitate was filtered and dried to give compound **9** (0.79 g, 98%) as a white solid: mp 160-161 °C (CH_2Cl_2); IR (film): 3370, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.01 (s, 3H), 7.14 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.15 (s, 1H), 7.24 (ddd, *J* = 8.0, 7.0, 1.4 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.70 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.33 (dd, *J* = 1.6, 1.0 Hz, 1H), 8.70 (dd, *J* = 4.8, 1.0 Hz, 1H), 9.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 52.7, 101.7, 111.4, 119.3, 120.2, 120.7, 121.3, 123.5, 128.9, 135.9, 136.7, 137.9, 149.7, 151.3, 165.4; Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.11. Found: C, 71.03; H, 4.79; N, 10.94.

Methyl *cis*-2-(2-indolyl)piperidine-4-carboxylate (10). A solution of pyridylindole **9** (4.0 g, 16 mmol) in glacial acetic acid (50 mL) was shaken at 25 ºC under hydrogen in the presence of PtO_2 (600 mg). The catalyst was removed by filtration, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and the solution was washed with saturated aqueous Na_2CO_3, dried, filtered, and concentrated under reduced pressure. Column chromatography (95:3:2 Et_2O:acetone:DEA) of the residue afforded pure piperidine **10** (2.68 g, 65%): mp 116-117°C (Et_2O); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.63 (qd, *J* = 12.5, 4.2 Hz, 1H), 1.68-1.80 (m, 2H), 1.98 (dm, *J* = 13.2 Hz, 1 H), 2.29 (dm, *J* = 12.9 Hz, 1H), 2.60 (tt, *J* = 12.3, 3.8 Hz, 1H), 2.83 (td, *J* = 12.5, 2.7 Hz, 1H), 3.26 (ddd, *J* = 12.5, 4.1, 2.4 Hz, 1H), 3.70 (s, 3H), 3.91 (dd, *J* = 11.3, 2.5 Hz, 1H), 6.35 (d, *J* = 1.0 Hz, 1H), 7.03-7.16 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 28.6, 35.1, 41.7, 45.9, 51.7, 54.3, 98.6, 110.7, 119.5, 120.2, 121.5, 127.9, 135.6, 140.7, 175.0; Anal. Calcd for $C_{15}H_{18}N_2O_2 \cdot 1/2\ H_2O$: C, 67.40; H, 7.16; N, 10.85. Found: C, 67.00; H, 7.20; N, 10.54.

Methyl *cis*-2-(2-indolyl)-1-[2-(phenylsulfinyl)ethyl]piperidine-4-carboxylate (11). A solution of indolylpiperidine **10** (1.11 g, 4.3 mmol) and phenyl vinyl sulfoxide (980 mg, 6.4 mmol) in MeOH (15 mL) was heated at reflux for 24 h. The mixture was cooled, concentrated, and the residue was chromatographed (20:1 Et_2O:MeOH) to give two epimeric sulfoxides **11** (1.57 g, 89%). Major epimer (1,15 g, higher Rf): mp 162-163 ºC (CH_2Cl_2); IR (film): 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.89-2.12 (m, 3H), 2.18 (ddd, *J* = 13.2, 4.1, 2.9 Hz, 1H), 2.25 (ddd, *J* = 12.3, 11.5, 2.8 Hz, 1H), 2.37 (ddd, *J* = 13.1, 6.4, 2.7 Hz, 1H), 2.55 (tt, *J* = 12.3, 4.1 Hz, 1H), 2.73-2.90 (m, 2H), 3.13 (ddd, *J* = 13.1, 9.7, 7.7 Hz, 1H), 3.34 (dt, *J* = 11.5, 3.3 Hz, 1H), 3.58 (dd, *J* = 11.4, 2.9 Hz, 1H), 3.66 (s, 3H), 6.32 (s, 1H), 7.06 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1,0 Hz, 1H), 7.43-7.62 (m, 7H), 9.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 27.8, 37.7, 41.6, 47.1, 51.3, 51.7, 54.8, 61.5, 100.2, 111.7, 119.3, 119.7, 121.3, 124.0, 128.1, 129.2 (2 C), 130.9, 136.7, 140.1, 143.9, 174.7; Anal. Calcd for $C_{23}H_{26}N_2O_3S$: C, 67.29; H, 6.38; N, 6.82; S, 7.81. Found: C, 67.19; H, 6.54; N, 6.78; S, 7.65. Minor isomer (0.42 g, lower Rf): mp 120-121 ºC (Et_2O); IR (KBr): 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.77 (qd, *J* = 12.3, 3.9 Hz, 1H), 1. 92 (t, *J* = 12.2 Hz, 1H), 1.90 (masked, 1H), 2.14 (ddd, *J* = 13.2, 3.8, 2.8 Hz, 1H), 2.28 (ddd, *J* = 12.3, 11.6, 2.6 Hz, 1H), 2.47 (tt, *J* = 12.3, 3.8 Hz, 1H), 2.52-2.92 (m, 4H), 3.21 (dt, *J* = 11.6, 3.3 Hz, 1H), 3.47 (dd, *J* = 11.4, 2.8 Hz, 1H), 3.66 (s, 3H), 6.30 (s, 1H), 7.09 (ddd, *J* = 8.0,

7.0, 1.0 Hz, 1H), 7.17 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.25-7.39 (m, 6H), 7.53 (d, *J* = 8.0 Hz, 1H), 9.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 27.6, 35.6, 41.3, 48.1, 51.7, 52.8, 54.8, 61.0, 100.8, 111.3, 119.5, 120.1, 121.6, 123.7 (2 C), 127.9, 128.9 (2 C), 130.7, 136.2, 139.3, 143.3, 174.8.

Methyl *cis*-2-[1-(*tert*-butoxycarbonyl)-2-indolyl]-1-[2-(phenylsulfinyl)ethyl]-piperidine-4-carboxylate (12). A mixture of **11** (200 mg, 0.49 mmol, mixture of epimers), DMAP (10 mg, 0.08 mmol), and di-*tert*-butyl dicarbonate (229 mg, 1.05 mmol) in anhydrous CH_2Cl_2 (4 mL) was stirred at 25 ºC for 10 h. The resulting mixture was concentrated and the residue was chromatographed (12:1 Et_2O:MeOH) to give pure compound **12** as a mixture of epimers (211 mg, 85%). Higher Rf epimer: mp 131-132 °C (Et_2O); IR (KBr): 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.71 (s, 9H), 1.66-1.84 (m, 2H), 1.92 (dm, *J* = 12.3 Hz, 1H), 2.28 (dm, *J* = 12.5 Hz, 1H), 2.43 (td, *J* = 12.2, 2.5 Hz, 1H), 2.45-2.59 (m, 2H), 2.65-2.70 (m, 2H), 3.12 (dt, *J* = 13.4, 7.9 Hz, 1H), 3.21 (dt, *J* =12.3, 3.0 Hz, 1H), 3.67 (s, 3H), 4.37 (dd, *J* =7.4, 1.1 Hz, 1H), 6.68 (s, 1H), 7.27 (ddd, *J* = 8.4, 7.4. 1.4 Hz, 1H), 7.29-7.35 (m, 3H), 7.42-7.49 (m, 3H), 8.04 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 26.8, 28.2, 34.3, 41.6, 45.9, 51.6, 52.7, 55.4, 58.8, 84.2, 107.9, 115.3, 120.5, 122.6, 123.5 (2 C), 123.7, 128.8 (2 C), 130.5, 136.2, 142.4, 143.7, 150.3, 174.8; Anal. Calcd for $C_{28}H_{34}N_2O_5S$: C, 65.86; H, 6.71; N, 5.49; S, 6.28. Found: C, 66.01; H, 6.85; N, 5.50; S, 6.16. Lower Rf epimer: mp 113-114 °C (hexane-Et_2O); IR (KBr): 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.67 (s, 9H), 1.68 (masked, 1 H), 1.80 (qd, *J* = 12.2, 3.8 Hz, 1H), 1.98 (dm, *J* = 12.2 Hz, 1H), 2.29 (dm, *J* = 12.2 Hz, 1H), 2.33 (td, *J* = 12.2, 2.5 Hz, 1H), 2.47 (tt, *J* = 12.3, 2.5 Hz, 1H), 2.58 (m, 1H), 2.77-2.91 (m, 3H), 3.24 (dt, *J* = 11.6, 3.3 Hz, 1H), 3.65 (s, 3H), 4.25 (dd, *J* = 11.0, 2.5 Hz, 1H), 6.63 (s, 1H), 7.20-7.30 (m, 5H), 7.35-7.40 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 27.7, 28.1, 36.3, 41.4, 47.1, 51.5, 52.8, 54.4, 59.2, 84.2, 107.9, 115.4, 120.3, 122.6, 123.5 (2 C), 128.7 (2 C), 130.6, 136.0, 142.9, 143.1, 150.1, 174.6.

5-Oxo-1-[2-(phenylsulfinyl)ethyl]-2,6-methano[1,4]diazocino[1,2-*a*]indole (16). Methyl cyanoformiate (66 mg, 0.78 mmol) was added to a solution of compound **11** (320 mg, 0.78 mmol) and TMEDA (100 μL) in anhydrous THF (5 mL) containing NaH (100 mg of a 45-50% dispersion in mineral oil) and the mixture was stirred at 25 °C. After 8 h, water was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a residue, which, after purification by column chromatography (gradient from Et_2O to 10:1 Et_2O:MeOH), afforded pure diazocinoindole **16** (150 mg, 50%) as an oil: IR (film): 1704, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02-2.06 (m, 3H), 2.11 (dt, *J* = 12.9, 3.0 Hz, 1H), 2.29 (dt, *J* = 12.9, 3.0 Hz, 1H), 2.62-2.74 (m, 2H), 2.78 (m, 1H), 2.92-3.60 (m, 3H), 3.92 (t, *J* = 3.0 Hz, 1H), 6.16 (s, 1H), 7.23-7.34 (m, 2H), 7.47-7.60 (m, 4H), 7.68 (m, 2H), 8.43 (dd, *J* = 7.6, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 29.1, 31.7, 38.0, 46.0, 47.6, 50.8, 54.7, 107.3, 116.3, 120.4, 124.0, 124.0 (2 C), 124.8, 129.2 (2 C), 131.0, 133.4, 134.5, 143.8, 171.7; Anal. Calcd for $C_{22}H_{22}N_2O_2S\cdot 1/2\ H_2O$: C, 69.37; H, 6.55; N, 6.74; S, 7.72. Found: C, 69.09; H, 6.42; N, 6.77; S, 7.82.

Methyl *cis*-12-(*tert*-Butoxycarbonyl)-7-(phenylsulfanyl)indolo[2,3-*a*]quinolizidine-2-carboxylate (13). TMSOTf (305 μL, 1.7 mmol) was added to a solution of sulfoxide **12** (190 mg, 0.37 mmol, mixture of

epimers) and DIPEA (300 μL, 1.7 mmol) in anhydrous CH_2Cl_2 (1.5 mL), and the mixture was stirred at 25 ºC for 15 min. The solution was poured into aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to afford a residue, which, after chromatography (1:1 AcOEt:hexane), gave two epimeric indoloquinolizidines **13** (155 mg, 84%). Higher Rf epimer (α-SC_6H_5, 105 mg 57%): mp 167-168 °C (Et_2O); IR (KBr): 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.60-1.87 (m, 3H), 1.68 (s, 9H), 2.22 (dm, *J* = 13.5 Hz, 1H), 2.67 (tt, *J* = 12.2, 3.8 Hz, 1H), 2.86 (dd, *J* = 12.2, 2.7 Hz, 1H), 3.14-3.30 (m, 2H), 3.51 (dd, *J* = 12.2, 3.8 Hz, 1H), 3.66 (s, 3H), 4.50 (dd, *J* =11.0, 2.0 Hz, 1H), 4.61 (dd, *J* = 3.8, 2.7 Hz, 1H), 7.22-7.38 (m, 5H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.65 (dd, *J* = 7.3, 1.5 Hz, 1H), 8.13 (dd, *J* = 7.2, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 23.2, 27.9, 28.2, 41.8, 42.5, 50.1, 51.7, 53.9, 56.2, 84.2, 114.3, 115.8, 119.0, 122.8, 124.3, 127.1, 127.8, 129.0 (2 C), 131.9 (2 C), 136.0, 136.6, 138.4, 149.8, 174.9; Anal. Calcd for $C_{28}H_{32}N_2O_4S$: C, 68.27; H, 6.55; N, 5.69; S, 6.51. Found: C, 68.20; H, 6.68; N, 5.62; S, 6.35. Lower Rf epimer (β-SC_6H_5, 50 mg 27%): oil; IR (film): 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (ddd, *J* = 12.0, 12.0, 10.5 Hz, 1H), 1.67 (s, 9H), 1.75-1.90 (m, 2H), 2.40 (dm, *J* = 12.0 Hz, 1H), 2.57 (tt, *J* = 12.0, 4.2 Hz, 1H), 2.73 (td, *J* = 12.0, 3.5 Hz, 1H), 3.02-3.10 (m, 2H), 3.20 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.67 (s, 3H), 3.85 (d, *J* = 10.5 Hz, 1H), 4.43 (m, 1H), 7.22-7.30 (m, 5H), 7.42-7.47 (m, 2H), 7.77 (dd, *J* = 7.3, 1.5 Hz, 1H), 8.09 (dd, *J* = 7.2, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 26.0, 28.1, 31.6, 41.9, 42.6, 51.7, 54.2, 55.7, 58.7, 84.2, 115.4, 115.8, 119.6, 122.8, 124.2, 127.2, 127.9, 128.8 (2 C), 132.8 (2 C), 135.2, 136.8, 138.4, 150.0, 174.9.

Methyl *cis*-12-(*tert*-butoxycarbonyl)indolo[2,3-*a*]quinolizidine-2-carboxylate (14). A mixture of sulfide **13** (180 mg, 0.37 mmol, mixture of epimers), Bu_3SnH (300 μL, 1.12 mmol), and AIBN in benzene (20 mL) was heated at reflux for 3 h. The mixture was concentrated, and the residue was purified by column chromatography (Et_2O) affording pure indoloquinolizidine **14** (105 mg, 75%): mp 148-149 °C (hexane-Et_2O); IR (film): 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.65 (ddd, *J* = 12.1, 12.1, 10.9 Hz, 1H), 1.68 (s, 9H), 1.79 (dm, *J* = 12.1 Hz, 1H), 1.90 (qd, *J* = 12.1, 4.2 Hz, 1H), 2.42 (dm, *J* =12.6 Hz, 1H), 2.66 (tt, *J* = 12.1, 4.1 Hz, 1H), 2.73-2.85 (m, 3H), 2.94 (td, *J* = 12.6, 3.3 Hz, 1H), 3.12-3.19 (m, 1H), 3.20 (ddd, *J* = 12.6, 4.1, 2.2 Hz, 1H), 3.68 (s, 3H), 4.10 (br d, *J* = 10.9 Hz, 1H), 7.18-7.30 (m, 2H), 7.40 (dd, *J* = 7.0, 1.0 Hz, 1H), 8.10 (dd, *J* = 7.4, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 22.2, 24.9, 28.2, 30.4, 42.0, 46.7, 51.7, 54.4, 58.1, 83.8, 115.5, 116.0, 117.9, 122.6, 124.0, 129.1, 136.2, 136.7, 150.2, 175.1; Anal. Calcd for $C_{22}H_{28}N_2O_4 \cdot 3/2H_2O$: C, 64.22; H, 7.46; N, 6.80. Found: C, 64.52; H, 7.16; N, 6.80.

Methyl *cis*-indolo[2,3-*a*]quinolizidine-2-carboxylate (15). Compound **14** (65 mg, 0.17 mmol) was dissolved in formic acid (10 mL), and the solution was stirred at 25 ºC for 24 h. The resulting mixture was concentrated, and the residue dissolved in CH_2Cl_2. The organic solution was washed with 10% aqueous Na_2CO_3, dried, and concentrated to give a residue, which was chromatographed (9:1 Et_2O:MeOH) affording pure compound **15**[13] (46 mg, 96%): ^1H NMR ($CDCl_3$, 300 MHz): δ 1.71 (q, *J* = 12.3 Hz, 1H), 1.89 (qd, *J* = 12.3, 4.2 Hz, 1H), 2.03 (dm, *J* = 12.3 Hz, 1H), 2.33-2.44 (m, 2H), 2.51 (tt, *J* = 12.3, 3.8 Hz, 1H), 2.60 (td, *J* = 11.0, 4.7 Hz, 1H), 2.71 (dm, *J* = 14.4 Hz, 1H), 2.92-3.14 (m, 3H), 3.20 (dd, *J* = 11.5, 1.8 Hz, 1H), 3.71 (s, 3H),

7.07-7.13 (m, 2H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 8.01 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 21.6, 28.1, 32.2, 41.4, 51.9, 52.9, 54.7, 59.1, 108.3, 110.8, 118.1, 119.3, 121.4, 127.2, 134.1, 136.0, 175.0.

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