Studies on the synthesis of *Strychnos* indole alkaloids from 2-(3-indolyl)piperidine derivatives. A new synthetic entry to the indolo[3,2-*a*]quinolizidine system

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This work is dedicated to Prof. Enrique Meléndez on the occasion of his 70th birthday

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Abstract

The attempted elaboration of the pentacyclic skeleton of *Strychnos* indole alkaloids by a Pummerer-initiated sequential closure of C and E rings from a 2-(3-indolyl)piperidine-4-acetate derivative bearing a 2-(phenylsulfinyl)ethyl chain on the piperidine nitrogen is described. An indolo[3,2-*a*]quinolizidine, resulting from the direct attack of the intermediate thionium ion on the 2 position of the heterocycle, is obtained instead.

Keywords: Indoloquinolizidine, Pummerer reaction, palladium(0)-cross coupling, electrophilic substitution on indoles, *Strychnos* alkaloids

Introduction

In previous papers we have described the preparation of 2-(2-indolyl)- and 2-(3-indolyl)piperidine derivatives from the corresponding 2-(indolyl)pyridines, which were efficiently obtained by palladium(0)-catalyzed heteroarylation of 2- and 3-indolylzinc chlorides with 2-halopyridines. These indolylpiperidines have served as synthetic precursors of indolo[2,3-*a*]quinolizidines and alkaloids of the uleine group.[1] In order to explore new synthetic applications of 2-(3-indolyl)piperidine derivatives, we devised a synthetic approach to the pentacyclic skeleton of *Strychnos* indole alkaloids[2] involving the sequential closure of C and E rings in a single synthetic step from a 2-(3-indolyl)piperidine-4-acetate derivative bearing a functionalized two-carbon chain on the piperidine nitrogen atom (Figure 1).

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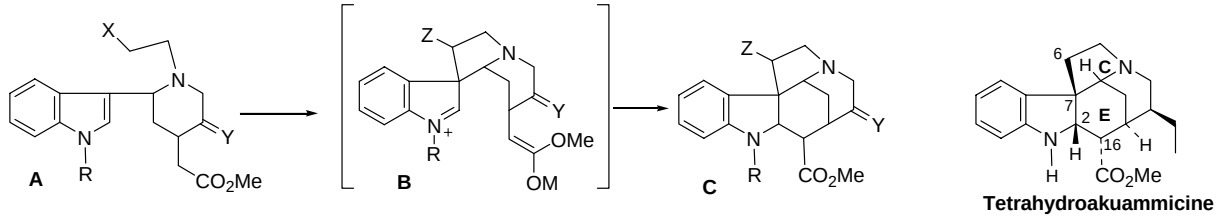


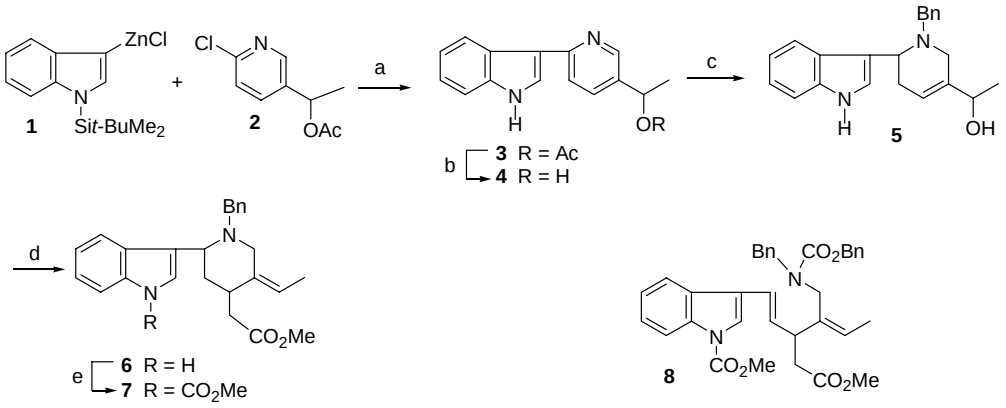
Figure 1

For this purpose, taking into account our previous experience[1,3] in the incorporation of the tryptamine two-carbon atoms, present in many indole alkaloids, by intramolecular alkylation of the indole 3-position from *N*-[2-(phenylsulfinyl)ethyl] indolylpiperidine derivatives, we selected the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-promoted[4] Pummerer[5] reaction of sulfoxide **A** (X = $S(O)C_6H_5$; R = CO_2Me, Y = CHMe). Thus, the intramolecular attack on the indole 3-position by the thionium ion generated in the Pummerer reaction would afford an intermediate *N*-acyl spiroindoleninium salt **B** (Z = SC_6H_5, R = CO_2Me), which could be trapped by the *O*-silyl ketene acetal (M = $SiMe_3$) formed *in situ* under the reaction conditions [TMSOTf and diisopropylethylamine (DIPEA)].[6] Two possible mechanistic pathways have been proposed for the electrophilic substitution in 3-substituted indoles:[7] either the direct attack at the indole 2-position or the attack at the 3-position of the indole ring followed by rearrangement of the resulting indolenine intermediate. However, the studies conducted by Jackson,[8] as well as the numerous mechanistic studies about the Pictet-Spengler[9] and Bischler-Napieralski[10] reactions, have provided a substantial amount of evidence in support of the spiroindolenine intermediate.[11] Furthermore, several reports have described the intramolecular trapping of the spiroindoleninium intermediate by a nucleophilic residue to furnish polycyclic spiroindolines.[12,13] In this context, it is worth mentioning that sequential treatment of *N*-(2-hydroxyethyl)-2-(1-benzenesulfonyl-3-indolyl)piperidine-4-acetate **A** (X = OH; R = $SO_2C_6H_5$; Y = H, Et) with *t*-BuOK and $BF_3{\cdot}Et_2O$ affords a mixture of the alkaloid tetrahydroakuammicine and the indolo[2,3-*a*]quinolizidine resulting from the rearrangement of the intermediate spiroindolenine,[14] which would corroborate the feasibility of our synthetic route to *Strychnos* alkaloids.

Results and Discussion

For the preparation of the required 2-(3-indolyl)piperidine-4-acetate derivative **6** we envisaged a synthetic route involving as the key steps a cross-coupling reaction for the generation of the 2-(3-indolyl)pyridine moiety and a Johnson-Claisen rearrangement[15] for the incorporation of the acetate chain at the piperidine 4-position. Thus, 3-(2-pyridyl)indole **3** was obtained in 72% yield by palladium(0)-catalyzed cross-coupling reaction of 3-indolylzinc chloride **1** with 2-chloropyridine **2**, followed by desilylation of the indole nitrogen with tetrabutylammonium fluoride (TBAF) (Scheme 1). Methanolysis of acetate **3** afforded alcohol **4** in good yield, which

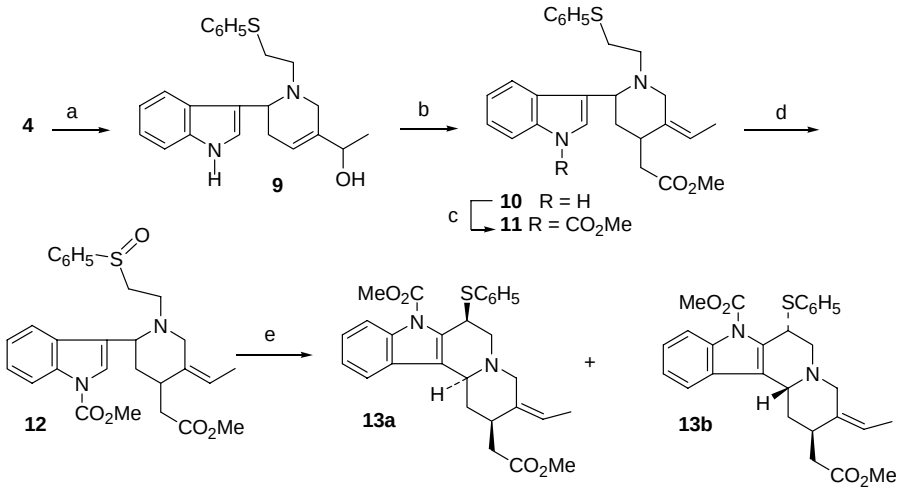
on treatment with benzyl bromide followed by $NaBH_4$ reduction of the resulting pyridinium salt gave 2-(3-indolyl)tetrahydropyridine **5** as a nearly equimolecular mixture of epimers.[16] Johnson–Claisen rearrangement of the allylic alcohol **5** with methyl orthoacetate gave access to 2-(3-indolyl)piperidine-4-acetate **6** in 72% yield as a mixture of 2,4 *cis* and *trans* isomers, which could not be separated. Unfortunately, all attempts to remove the benzyl protecting group from compound **6** or from its *N*-(methoxycarbonyl)indole derivative **7** by catalytic hydrogenation resulted in failure, the reduction of the ethylidene side chain being the only process observed. On the other hand, treatment of compound **7** with benzyl chloroformate in refluxing dichloromethane afforded compound **8** as the only identifiable product, whereas no reaction was observed at room temperature. Compound **8** is probably formed by cleavage of the N-C_2 bond from the intermediate *N*-acyl ammonium salt, with the assistance of the indole, to generate a 3-alkylideneindoleninium salt, which undergoes deprotonation.



Scheme 1. Reagents and conditions: (a) $Pd[P(C_6H_5)_3]_4$, DIBAH, THF, reflux, 4 h, then TBAF, THF, 25 ^oC, 15 min, 72%; (b) K_2CO_3, MeOH, 25 ^oC, 1 h, 95%; (c) BrBn, C_6H_6-acetone, reflux, 24 h, then $NaBH_4$, MeOH, 25 ^oC, 12 h, 67%; (d) $CH_3C(OMe)_3$, dimethoxyethane, pivalic acid, reflux, 48 h, 64%; (e) $NCCO_2Me$, DMAP, CH_3CN, reflux, 5 h, 91%.

The difficulties encountered in the removal of the *N*-benzyl group from **6** or **7** made us go back in the synthetic sequence and incorporate the functionalized two-carbon chain on the piperidine nitrogen atom at an early stage of the synthesis. Thus, compound **4** was treated with 2-iodoethyl phenyl sulfide and the resulting pyridinium salt was subsequently reduced with sodium borohydride to give the desired tetrahydropyridine **9** as a mixture of stereoisomers (Scheme 2). Johnson–Claisen rearrangement of the allylic alcohol **9** satisfactorily gave the 2-(3-indolyl)piperidine-4-acetate **10** as a nearly equimolecular mixture of *cis* and *trans* isomers. On the grounds of our previous experience in the Pummerer reaction on indole derivatives,[1c,3] we decided to prepare compound **11**, which bears an electron-withdrawing protecting group on the indole nitrogen. Moreover, acylation of the indole nitrogen could facilitate the closure of the E ring, since a highly reactive *N*-acyliminium intermediate **B** (Figure 1, R = CO_2Me) would be generated after the attack of the thionium ion on the indole 3-position. Compound **11** was

obtained by treatment of **10** with methyl cyanoformate and 4-(dimethylamino)pyridine (DMAP) in refluxing acetonitrile. Chemoselective oxidation of sulfide **11** with 3-chloroperbenzoic acid (*m*-CPBA) was carried out from the corresponding trifluoroacetate salt at low temperature in order to avoid oxidation of the nitrogen and double bond functions. In this way, sulfoxide **12** was isolated in 72% yield. Finally, treatment of **12** with excess (4 equiv) TMSOTf and DIPEA in dichloromethane at room temperature gave tetracyclic indolo[3,2-*a*]quinolizidine **13** as a nearly equimolecular mixture of isomers **13a** and **13b** in 42% yield. Neither the desired pentacyclic compound with the *Strychnos* skeleton nor the corresponding indolo[2,3-*a*]quinolizidine resulting from the rearrangement of the presumed spiroindoleninium intermediate could be detected, which clearly indicates that the electrophilic attack of the thionium ion generated from sulfoxide **12** under Pummerer conditions does not take place at the indole 3-position but directly at the 2-position of the heterocycle. This result can be accounted for by considering previous studies by Casnati[17] who has shown that the alkylation of 3-substituted indoles can occur by direct attack at the 2-position of the indole when very reactive electrophiles are involved.



Scheme 2. Reagents and conditions: (a) $ICH_2CH_2SC_6H_5$, MeOH, reflux, overnight, then $NaBH_4$, MeOH, 25 °C, 4 h, 45%; (b) $CH_3C(OMe)_3$, dimethoxyethane, pivalic acid, reflux, 48 h, 69%; (c) $NCCO_2Me$, DMAP, CH_3CN, reflux, 5 h, 74%; (d) TFA, CH_2Cl_2, 0 °C, 30 min, then MCPBA, CH_2Cl_2, -60°C, 2 h, 72%; (e) TMSOTf, DIPEA, CH_2Cl_2, 0 °C, 1.5 h, 42%.

It is worth mentioning that the conversion of indole alkaloids of the indolo[2,3-*a*]quinolizidine type into the corresponding indolo[3,2-*a*]quinolizidine derivatives ("inverted" alkaloids) has been described previously by sodium borohydride reduction of the corresponding pseudoindoxyl analogs followed by treatment of the product under acidic conditions.[18]

Conclusions

In summary, the electrophilic attack of the thionium ion generated by Pummerer rearrangement of the sulfoxide present in 2-(3-indolyl)-*N*-2-(phenylsulfinyl)ethylpiperidine derivatives such as **12**, takes place directly on the unsubstituted indole 2-position affording an indolo[3,2-a]quinolizidine system.

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 ^{1}H and 50.3 MHz for ^{13}C, or a Varian Gemini 300 operating at 300 MHz for ^{1}H 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.

5-(1-Acetoxyethyl)-2-(3-indolyl)pyridine (3). A solution of *t*-BuLi (7.6 mL of a 1.7 M solution in pentane, 13.0 mmol) was slowly added to a solution of 3-bromo-1-(*tert*-butyldimethylsilyl)indole (2.0 g, 6.45 mmol) in anhydrous THF (5 mL) at -78 ºC, and the resulting mixture was stirred for 10 min at this temperature. Then, a solution of anhydrous $ZnCl_2$ (886 mg, 6.5 mmol) in THF (4 mL) was added, and the stirring was continued for 30 min at 25 ºC. In a separate flask, a solution of $Pd[P(C_6H_5)_3]_4$ (499 mg, 0.43 mmol) in anhydrous THF (16 mL) was added to a solution of chloropyridine **2** (862 mg, 4.32 mmol) in THF (8 mL), and the mixture was stirred at room temperature for 10 min. The resulting solution was transferred via cannula to the solution of indolylzinc **1** in THF prepared as described above, and the mixture was heated at reflux for 4 h, cooled, and poured into saturated aqueous Na_2CO_3. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried, filtered, and concentrated to give a residue, which was subjected to desilylation without further purification. A 1.0 M solution of tetrabutylammonium fluoride (6.5 mL, 6.5 mmol) was added to a solution of

the above reaction mixture in anhydrous THF (22 mL), and the mixture was stirred for 15 min at room temperature. The solution was poured into saturated aqueous Na_2CO_3, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and concentrated. The residue was chromatographed (gradient from 2:3 AcOEt-hexane to AcOEt) to give pure indolylpyridine **3** (741 mg, 72%). IR (KBr) 3300, 1731, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.61 (d, *J* = 6.6 Hz, 3 H), 2.1 (s, 3 H), 5.94 (q, *J* = 6.6 Hz, 1 H), 7.27 (m, 2 H), 7.41 (m, 1 H), 7.70 (m, 2 H), 7.77 (d, *J* = 2.6 Hz, 1 H), 8.32 (m, 1 H), 8.61 (br s, 1 H), 8.67 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2 (CH_3), 21.7 (CH_3), 70.3 (CH), 111.6 (CH), 116.3 (C), 120.2 (CH), 120.5 (CH), 120.7 (CH), 122.3 (CH), 125.0 (CH), 125.1 (C), 133.1 (C), 134.5 (CH), 136.9 (C), 147.4 (CH), 154.7 (C), 170.3 (C); mp 98-99 °C (Et_2O-hexane). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.89; H, 5.74; N, 10.00.

5-(1-Hydroxyethyl)-2-(3-indolyl)pyridine (4). A mixture of acetate **3** (0.83 g, 2.96 mmol) and K_2CO_3 (1.23 g, 8.9 mmol) in absolute MeOH (8 mL) was stirred for 1 h at room temperature. The solvent was eliminated under vacuum, and the residue was dissolved in CH_2Cl_2, washed with brine, dried, filtered, and concentrated. The residue was chromatographed (AcOEt) to give pure alcohol **4** (670 mg, 95%). IR (KBr) 3168, 1601 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 1.50 (d, *J* = 6.5 Hz, 3 H), 4.89 (q, *J* = 6.5 Hz), 7.25 (m, 2 H), 7.54 (dm, *J* = 7.2 Hz, 1 H), 7.87 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.89 (s, 1 H), 7.92 (dd, *J* = 8.3, 2.2 Hz, 1 H), 8.21 (dm, *J* = 7.8 Hz, 1 H), 8.62 (m, 1 H); ^{13}C NMR (CD_3OD, 75 MHz) δ 25.3 (CH_3), 68.5 (CH), 112.7 (CH), 116.9 (C), 121.2 (CH), 121.3 (CH), 122.0 (CH), 123.1 (CH), 126.2 (CH), 126.6 (C), 135.7 (CH), 138.7 (C), 139.3 (C), 147.6 (CH), 155.7 (C); mp 176 °C (MeOH). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.63; H, 5.91; N, 11.83.

1-Benzyl-5-(1-hydroxymethyl)-2-(3-indolyl)-1,2,3,6-tetrahydropyridine (mixture of isomers) (5). Benzyl bromide (1.1 mL, 9.26 mmol) was added to a solution of indolylpyridine **4** (940 mg, 3.95 mmol) in a 2:1 mixture of anhydrous benzene and acetone (9 mL), and the solution was refluxed for 24 h. The mixture was concentrated under vacuum, and the resulting pyridinium salt was washed with anhydrous Et_2O, dried, and dissolved in MeOH (40 mL). The solution was cooled to 0 °C, $NaBH_4$ (625 mg, 16.5 mmol) was added, and the stirring was continued at room temperature for 12 h. The solvent was eliminated under vacuum, and the residue was dissolved in a 1:1 mixture of Et_2O-H_2O (100 mL). K_2CO_3 (600 mg) was added, and the resulting mixture was stirred for 1 h. The aqueous layer was washed with Et_2O, and the combined organic extracts were dried, filtered, and concentrated. The residue was chromatographed (Et_2O) to give the tetrahydropyridine **5** (878 mg, 67%) as a 55:45 mixture of isomers (calculated by ^1H NMR), which could not be separated. IR (film) 3000, 1455, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, mixture of epimers) δ 1.26 (d, *J* = 6.4 Hz, 3 H), 1.27 (d, *J* = 6.4 Hz, 3 H), 1.60 (br s, 1 H each isomer); 2.40-2.58 (m, 1 H each isomer); 2.62-2.58 (m, 1 H each isomer), 2.94 (dm, *J* = 16.6 Hz, 1 H each isomer), 3.15 (d, *J* = 16.6 Hz, 1 H), 3.17 (d, *J* = 13.0 Hz, 1 H), 3.22 (d, *J* = 13.0 Hz, 1 H), 3.226 (d, *J* = 16.6 Hz, 1 H), 3.77 (d, *J* = 13.0 Hz, 1 H), 3.79 (d, *J* = 13.0 Hz, 1 H), 4.02 (dd, *J* = 8.5, 5.0 Hz, 1 H), 4.07 (dd, *J* = 8.0, 5.5 Hz, 1 H), 4.21 (q, *J* = 6.4 Hz, 1 H each isomer), 5.84 (br s, 1 H each isomer), 7.10-7.37 (m), 7.36 (d, *J* = 7.8 Hz, 1 H each isomer), 7.87 (m), 8.15 (br s); ^{13}C NMR ($CDCl_3$, 75 MHz, mixture of epimers) δ 21.8 (CH_3), 21.9 (CH_3), 32.6 (CH_2), 32.8

(CH_2), 50.0 (CH_2), 50.3 (CH_2), 55.2 (CH), 55.4 (CH), 58.8 (CH_2), 58.9 (CH_2), 69.7 (CH), 70.0 (CH), 111.1 (2 CH), 116.5 (2 C), 118.8 (2 CH), 119.3 (2 CH), 119.7 (2 CH), 121.9 (2 CH), 122.3 (CH), 122.4 (CH), 126.7 (2 CH), 127.1 (2 C), 128.0 (4 CH), 129.1 (2 CH), 129.2 (2 CH), 136.1 (2 C), 138.8 (C), 139.0 (C), 139.6 (C), 139.8 (C). Exact mass Calcd for $C_{22}H_{24}N_2O$: 332.1888. Found: 332.1880.

Methyl 1-benzyl-5(*Z*)-ethylidene-2-(3-indolyl)-4-piperidineacetate (mixture of isomers) (6). Methyl orthoacetate (1.5 mL, 11.9 mmol) and pivalic acid (13 mg, 0.12 mmol) were added to a solution of tetrahydropyridine **5** (400 mg, 1.2 mmol, mixture of epimers) in anhydrous dimethoxyethane (7 mL), and the mixture was heated at reflux for 48 h. The solvent was eliminated under reduced pressure, the residue was dissolved in CH_2Cl_2, and the solution was washed with saturated aqueous Na_2CO_3, dried, filtered, and concentrated. The resulting residue was chromatographed (1:3 AcOEt-hexane) to give compound **6** (300 mg, 64%) as a nearly equimolecular mixture of isomers, which could not be efficiently separated. IR (film) 1728, 742 cm^{-1}; *cis* isomer: ^1H NMR ($CDCl_3$, 300 MHz, most significant signals from an enriched fraction) δ 1.47 (d, *J* = 6.6 Hz, 3 H), 2.25 (dd, *J* = 14.7, 7.4 Hz, 1 H), 2.34 (d, *J* = 12.5 Hz, 1 H), 2.98 (d, *J* = 13.4 Hz, 1 H), 3.65 (s, 3 H), 3.80 (dd, *J* = 11.2, 2.2 Hz, 1 H), 3.84 (d, *J* = 12.5 Hz, 1 H), 3.96 (d, *J* = 13,4 Hz, 1 H), 5.13 (q, *J* = 6.6 Hz, 1 H), 7.10-7.40 (m, 9 H), 7.95 (m, 1 H), 8.10 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.6 (CH_3), 36.8 (CH_2), 39.0 (CH), 41.8 (CH_2), 51.6 (CH_3), 52.9 (CH_2), 58.8 (CH_2), 61.2 (CH), 111.1 (CH), 114.6 (CH), 118.4 (C), 119.2 (CH), 120.2 (CH), 122.0 (CH), 126.4 (CH), 128.0 (2 CH), 128.5 (2 CH), 128.8 (C), 135.9 (C), 137.5 (C), 138.8 (C), 173.6 (C); *trans* isomer: ^1H NMR ($CDCl_3$, 300 MHz, most significant signals from an enriched fraction) δ 1.43 (d, *J* = 6.6 Hz, 3 H), 3.08 (d, *J* = 13.4 Hz, 1 H), 3.60 (d, *J* = 13.0 Hz, 1 H), 3.65 (s, 3 H), 3.95 (d, *J* = 13.4 Hz, 1 H), 3.97 (m, 1 H), 5.38 (q, *J* = 6.6 Hz, 1 H), 7.10-7.40 (m, 9 H), 7.95 (m, 1 H), 8.10 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.7 (CH_3), 37.9 (CH_2), 38.5 (CH_2), 39.6 (CH), 48.0 (CH_2), 51.5 (CH_3), 55.8 (CH), 58.5 (CH_2), 111.1 (CH), 118.4 (C), 119.2 (CH), 119.6 (CH), 120.1 (CH), 122.0 (CH), 126.5 (CH), 128.0 (2 CH), 128.6 (2 CH), 128.8 (C), 136.4 (C), 137.5 (C), 139.7 (C), 173.1 (C). Exact mass Calcd for $C_{25}H_{28}N_2O_2$: 388.2150. Found: 388.2144.

Methyl 1-benzyl-5(*Z*)-ethylidene-2-(1-methoxycarbonyl-3-indolyl)-4-piperidineacetate (mix ture of isomers) (7). Methyl cyanoformate (178 μL, 2.24 mmol) and 4-(dimethylamino)pyridine (35 mg, 0.29 mmol) were added to a solution of compound **6** (100 mg, 0.26 mmol, mixture of epimers) in acetonitrile (2 mL), and the mixture was heated at reflux for 5 h, cooled, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with brine, dried, filtered, and concentrated. The residue was chromatographed (7:3 hexane-AcOEt) to give compound **7** (105 mg, 91%). ^1H NMR ($CDCl_3$, 300 MHz, most significant signals from a mixture of isomers) δ 1.42 (d, *J* = 6.6 Hz, 3 H), 1.45 (d, *J* = 6.6 Hz, 3 H), 1.95 (ddd, *J* = 12.6, 3.8, 3.5 Hz, 1 H), 2.24 (dd, *J* =14.8, 6.6 Hz, 1H), 2.32 (d, *J* = 11.5 Hz, 1 H), 2.58 (dd, *J* = 14.8, 7.6 Hz, 1 H), 2.95 (m, 1H), 3.00 (d, *J* = 13.4 Hz, 1 H), 3.09 (d, *J* = 13.4 Hz, 1 H), 3.58 (d, *J* = 13.2 Hz, 1 H), 3.64 (s, 3 H), 3.65 (s, 3 H), 3.75 (dd, *J* = 11.5, 2.8 Hz, 1 H), 3.82 (d, *J* = 12.4 Hz, 1 H), 3.88 (d, *J* = 13.4 Hz, 1 H each isomer), 4.01 (s, 3 H), 4.02 (s, 3 H), 5.14 (q, *J* = 6.6 Hz, CH), 5.38 (q, *J* = 6.6 Hz, 1 H); 7.10-7.39 (m), 7.60 (d, *J* = 6.5 Hz, 1 H each

isomer), 7.95 (d, J = 7.0 Hz, 1 H each isomer), 8.18 (d, J = 7.5 Hz, 1 H each isomer); ^{13}C NMR ($CDCl_3$, 75 MHz, signals of *cis* isomer from an enriched fraction): δ 12.5 (CH_3), 36.7 (CH_2), 38.7 (CH), 40.6 (CH_2), 51.4 (CH_3), 52.5 (CH_2), 53.6 (CH_3), 58.6 (CH_2), 60.9 (CH), 115.0 (CH), 119.8 (CH), 120.8 (CH) 122.6 (CH), 122.9 (CH), 123.7 (C), 124.6 (CH), 126.5 (CH), 127.9 (2 CH), 128.4 (2 CH), 128.5 (C), 135.8 (C), 137.0 (C), 139.5 (C), 151.3 (C), 172.8 (C); ^{13}C NMR ($CDCl_3$, 75 MHz, most significant signals of *trans* isomer): δ 12.6 (CH_3), 37.2 (CH_2), 37.7 (CH_2), 39.2 (CH), 47.6 (CH_2), 51.5 (CH_3), 53.6 (CH_3), 55.8 (CH), 58.3 (CH_2).

5-(1-Hydroxyethyl)-2-(3-indolyl)-1-[2-(phenylsulfanyl)ethyl]-1,2,3,6-tetrahydropyridine (mixture of isomers) (9). 2-(Phenylthio)ethyl iodide (554 mg, 2.1 mmol) was added to a solution of indolylpyridine **4** (200 mg, 0.84 mmol) in absolute MeOH (1.3 mL), and the mixture was heated at reflux overnight. The mixture was concentrated, dried under vacuum, and washed with anhydrous Et_2O. The resulting pyridinium salt was redissolved in absolute MeOH (8 mL), cooled to 0 °C, and treated with $NaBH_4$ (130 mg, 3.44 mmol). The mixture was stirred for 4 h at room temperature and concentrated. The resulting residue was dissolved in a 1:1 mixture of Et_2O-H_2O (21 mL), K_2CO_3 (127 mg) was added, and the mixture was stirred for 1 h. The aqueous layer was washed with Et_2O, and the combined ethereal layers were dried, filtered, and concentrated. The residue was chromatographed (Et_2O) to give the tetrahydropyridine **9** (142 mg, 45%) as a 5:4 mixture of isomers. IR (film) 3409, 1455, 1438, 1069 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, most significant signals of a mixture of isomers) δ 1.32 (d, J = 6.4 Hz, 3 H), 1.34 (d, J = 6.4 Hz, 3 H), 3.15 (m, 1 H), 3.20 (m, 1 H), 3.37 (d, J = 16.0 Hz, 1 H), 3.52 (d, J = 16.0 Hz, 1 H), 3.94 (dd, J = 8.7, 4.7 Hz, 1 H), 4.02 (dd, J = 7.7, 5.0 Hz, 1 H), 4.30 (m, 1 H each isomer), 5.82 (br s, 1 H each isomer), 6.92-7.07 (m), 7.12 (t, J = 7.5 Hz, 1 H each isomer), 7.21 (t, J = 7.5 Hz, 1 H each isomer), 7.35 (d, J = 7.5 Hz, 1 H each isomer), 7.77 (d, J = 7.5 Hz, 1 H), 7.80 (d, J = 7.5 Hz, 1 H), 8.20 (br s, 1 H each isomer); ^{13}C NMR ($CDCl_3$, 75 MHz, major epimer) δ 21.8 (CH_3), 30.6 (CH_2), 32.8 (CH_2), 50.4 (CH_2), 53.4 (CH_2), 55.3 (CH), 70.4 (CH), 111.2 (CH), 116.6 (C), 119.5 (CH), 1119.8 (CH), 120.2 (CH), 122.1 (CH), 122.3 (CH), 125.2 (CH), 126.8 (C), 128.0 (2 CH), 128.6 (2 CH), 136.2 (C), 139.4 (C), 139.5 (C); ^{13}C NMR ($CDCl_3$, 75 MHz, minor epimer) δ 21.6 (CH_3), 30.8 (CH_2), 32.6 (CH_2), 50.3 (CH_2), 53.2 (CH_2), 54.8 (CH), 70.0 (CH), 111.2 (CH), 116.3 (C), 119.5 (CH), 119.8 (CH), 120.2 (CH), 122.1 (CH), 122.2 (CH), 125.3 (CH), 126.9 (C), 128.2 (2 CH), 128.6 (2 CH), 136.1 (C), 139.4 (C), 139.5 (C). Exact mass Calcd for $C_{23}H_{26}N_2OS$: 378.1765. Found: 378.1754.

Methyl 5(*Z*)-ethylidene-2-(3-indolyl)-1-[2-(phenylsulfanyl)ethyl]-4-piperidineacetate (mixture of isomers) (10). Operating as described for **6**, starting from tetrahydropyridine **9** (370 mg, 0.98 mmol, mixture of epimers), 4-piperidineacetate **10** (292 mg, 69%) was obtained after chromatography (7:3 hexane-AcOEt) as a mixture of *cis* and *trans* isomers, which could not be separated. IR (film) 3300, 1600, 1450, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, most significant signals from a mixture of isomers) δ 1.66 (d, J = 6.5 Hz, 3 H), 1.73 (d, J = 6.5 Hz, 3 H), 1.92 (d, J = 12.5 Hz, 1 H), 2.56 (dd, J = 14.4, 7.5 Hz, 1 H), 3.65 (s, 3 H), 3.67 (s, 3 H), 3.77 (d, J = 13.2 Hz, 1 H), 3.78 (dd, J = 11.5, 2.8 Hz, 1 H), 3.83 (dd, J = 11.5, 2.8 Hz, 1 H), 4.03 (d, J = 12.0 Hz, 1 H each isomer), 5.20 (q, J = 6.8 Hz, 1 H), 5.43 (q, J = 6.8 Hz, 1 H), 6.90-7.00 (m), 7.10 (t, J = 7.5 Hz, 1 H each isomer), 7.20 (t, J = 7.5 Hz, 1 H each isomer), 7.35 (d, J = 7.5 Hz, 1 H each

isomer), 7.85 (dm, *J* = 7.5 Hz, 1 H each isomer), 8.15 (br s, 1 H each isomer); ^{13}C NMR ($CDCl_3$, 75 MHz, signals of *cis* isomer from an enriched fraction) δ 13.1 (CH_3), 30.5 (CH_2), 36.9 (CH_2), 38.9 (CH), 41.4 (CH_2), 51.6 (CH_3), 53.0 (CH_2), 53.2 (CH_2), 60.4 (CH), 111.1 (CH), 115.0 (CH), 118.0 (C), 119.4 (CH), 120.2 (CH), 122.1 (CH), 122.2 (CH), 125.0 (CH), 126.4 (C), 127.7 (2 CH), 128.6 (2 CH), 135.7 (C), 136.4 (C), 173.4 (C); ^{13}C NMR ($CDCl_3$, 75 MHz, *trans* isomer) δ 13.1 (CH_3), 30.6 (CH_2), 37.9 (CH_2), 38.1 (CH_2), 39.3 (CH), 48.6 (CH_2), 51.6 (CH_3), 53.1 (CH_2), 55.1 (CH). Anal. Calcd for $C_{26}H_{30}N_2O_2S\cdot1/2H_2O$: C, 67.65; H, 7.21; N, 6.11. Found: C, 67.99; H, 6.92; N, 6.06.

Methyl 5(*Z*)-ethylidene-2-[1-(methoxycarbonyl)-3-indolyl]-1-[2-(phenylsulfanyl)ethyl]-4-piperidine acetate (mixture of epimers) (11). Operating as described for **7**, starting from **10** (225 mg, 0.52 mmol, mixture of isomers), compound **11** (190 mg, 74%) was obtained as a mixture of *cis* and *trans* isomers after column chromatography (7:3 hexane-AcOEt). IR (film) 3950, 1737, 1455, 1258, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, most significant signals from a mixture of isomers) δ 1.65 (d, *J* = 6.6 Hz, 3 H), 1.72 (d, *J* = 6.6 Hz, 3 H), 1.87 (dm, *J* = 12.6 Hz, 1 H), 2.23 (dd, *J* = 14.1, 7.8 Hz, 1 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 3.76 (d, *J* = 12.3 Hz, 1 H), 3.77 (dd, *J* = 11.5, 2.8 Hz, 1 H), 3.80 (dd, *J* = 11.5, 2.8 Hz, 1 H), 3.90 (d, *J* = 12.3 Hz, 1 H), 4.00 (s, 3 H), 4.01 (s, 3 H), 5,20 (q, *J* = 6.6 Hz, 1 H), 5.43 (q, *J* = 6.6 Hz, 1 H), 6.80-7.00 (m), 7,24 (t, *J* = 7.5 Hz, 1 H each isomer), 7.36 (t, *J* = 7.5 Hz, 1 H each isomer), 7.44 (d, *J* = 7.5 Hz, 1 H each isomer), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.88 (d, *J* = 7.5 Hz, 1 H) 8.20 (d, *J* = 7.5 Hz, 1 H each isomer); ^{13}C NMR ($CDCl_3$, 75 MHz, signals of *cis* isomer from an enriched fraction) δ 12.9 (CH_3), 30.5 (CH_2), 36.6 (CH_2), 38.5 (CH), 40.1 (CH_2), 51.5 (CH_3), 52.7 (CH_2), 52.9 (CH_2), 53.5 (CH_3), 60.1 (CH), 114.9 (CH), 120.0 (CH), 122.6 (CH), 122.8 (CH), 123.0 (C), 124.6 (CH), 125.2 (CH), 127.8 (CH), 128.0 (2 CH), 128.3 (2 CH), 128.9 (C), 135.0 (C), 135.8 (C), 136.5 (C), 151.0 (C), 173.0 (C); ^{13}C NMR ($CDCl_3$, 75 MHz, *trans* isomer) δ 12.8 (CH_3), 30.7 (CH_2), 36.9 (CH_2), 37.7 (CH_2), 38.9 (CH), 48.2 (CH_2), 51.4 (CH_3), 52.8 (CH_2), 53.6 (CH_3), 55.0 (CH). Anal. Calcd for $C_{28}H_{32}N_2O_4S\cdot2/3H_2O$: C, 66.64; H, 6.66; N, 5.55. Found: C, 66.44; H, 6.34; N, 5.77.

Methyl 5(*Z*)-ethylidene-2-[1-(methoxycarbonyl)-3-indolyl]-1-[2-(phenylsulfinyl)ethyl]-4-piperidine acetate (mixture of isomers) (12). TFA (38 µL, 0.49 mmol) was added to a solution of sulfide **11** (190 mg, 0.38 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C, and the mixture was stirred for 30 min. The temperature was lowered to – 60 °C, a solution of *m*-CPBA (79 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (3 mL) was slowly added, and the stirring was continued for 2 h. Then, solid K_2CO_3 (0.5 g) was added, and the mixture was stirred for 2 h at room temperature, filtered, washed with brine, and concentrated. Column chromatography (Et_2O) of the residue afforded sulfoxide **12** (142 mg, 72%) as a mixture of S=O and 2,4-*cis/trans* isomers. IR (film) 3400, 1596, 1578, 1459, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, most significant signals); δ 1.63 (d, *J* = 6.6 Hz, 3 H), 1.67 (d, *J* = 6.6 Hz, 3 H), 1.70 (d, *J* = 6.6 Hz, 3 H), 1.73 (d, *J* = 6.6 Hz, 3 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 3.65 (s, 3 H), 3.66 (s, 3 H), 4.03 (s, corresponding to 4 OCH_3), 5.23 (q, *J* = 6.6 Hz, corresponding to 2 =CH), 5.43 (c, *J* = 6.6 Hz, corresponding to 2 =CH). Anal. Calcd for $C_{28}H_{32}N_2O_5S\cdot1/2H_2O$: C, 64.97; H, 6.43; N, 5.41. Found: C, 64.95; H, 6.32; N, 5.41.

Methyl 3(*Z*)-ethylidene-8-(methoxycarbonyl)-7-(phenylsulfanyl)indolo[3,2-*a*]quinolizidine-2-acetate (13). Diisopropylethylamine (DIPEA) (130 μL, 0.76 mmol) and trimethylsilyl triflate (140 μL, 0.76 mmol) were added to a 0 °C cooled solution of sulfoxide **12** (100 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (8 mL), and the mixture was stirred at room temperature for 1 h 30 min. The resulting reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$, dried, filtered, and concentrated. The residue, after purification by chromatography (9:1 CH_2Cl_2-AcOEt), afforded quinolizidine **13** (40 mg, 42 %) as a mixture of isomers **13a** and **13b**, which could not be separated. MS *m/e* (relative intensity): 490 (M^+, 8), 381 (M^+ - C_6H_5S, 100), 307 (21), 227 (27), 168 (21), 110 (21); *cis* isomer: ^{1}H NMR ($CDCl_3$, 500 MHz, assigned by HSQC and COSY experiments): δ 1.41 (q, *J* = 12.5 Hz, 1 H, H-1), 1.54 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.14 (dm, *J* = 12.5 Hz, 1 H, H-1), 2.64 (dd, *J* = 14.5, 8.0 Hz, 1 H, C*H*$_2$CO), 2.74 (dd, *J* = 14.5, 8.2 Hz, 1 H, C*H*$_2$CO), 2.76 (dd, *J* = 12.3, 3.3 Hz, 1 H, H-6), 2.85 (m, 1 H, H-2), 3.40 (d, *J* = 11.5 Hz, H-4), 3.42 (dd, *J* = 12.3, 3.6 Hz, 1 H, H-6), 3.62 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.81 (d, *J* = 11.5 Hz, 1 H, H-4), 4.25 (dd, *J* = 12.5, 3.5 Hz, 1 H, H-12c), 4.99 (br s, 1 H, H-7), 5.46 (q, *J* = 6.8 Hz, 1 H, =CH), 7.21-7.46 (m, 8 H, Ar), 8.11 (d, *J* = 7.5 Hz, H-9). ^{13}C NMR ($CDCl_3$, 75 MHz, assigned by HSQC experiments): δ 12.7 (CH_3), 36.2 (C-1), 37.8 (*C*H$_2$CO), 38.5 (C-2), 45.0 (C-7), 51.5 (OCH_3), 52.0 (C-6), 53.5 (OCH_3), 54.6 (C-4), 54.9 (C-12c), 115.6 (C-12b), 115.7 (C-9), 116.0 (=CH), 118.6 (C-12), 123.0 (C-11), 124.8 (C-10), 127.0 (C-12a), 127.1 (C-*p*), 128.9 (C-*m*), 131.7 (C-*o*), 136.0 (C-3), 151.7 (C=O), 172.7 (C=O). *trans* isomer: ^{1}H NMR ($CDCl_3$, 500 MHz, assigned by HSQC and COSY experiments): δ 1.60 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.94 (m, 2 H, H-1), 2.22 (dd, *J* = 15.5, 7.0 Hz, 1 H, C*H*$_2$CO), 2.61 (dd, *J* = 15.5, 6.5 Hz, 1 H, C*H*$_2$CO), 2.73 (dd, *J* = 12.0, 5.0 Hz, 1 H, H-6), 2.85 (m, 1 H, H-2), 3.50 (dd, *J* = 12.0, 3.6 Hz, 1 H, H-6), 3.56 (m, 2 H, H-4), 3.65 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.20 (dd, *J* = 12.0, 3.0 Hz, 1 H, H-12c), 4.99 (br s, 1 H, H-7), 5.25 (q, *J* = 6.8 Hz, 1 H, =CH), 7.21-7.46 (m, 8 H, Ar), 8.11 (d, *J* = 7.5 Hz, H-9). ^{13}C NMR ($CDCl_3$, 75 MHz, most significant signals assigned by HSQC experiments): δ 13.0 (CH_3), 32.9 (C-1), 36.9 (*C*H$_2$CO), 40.1 (C-2), 45.2 (C-7), 49.8 (C-4), 50.3 (C-12c), 51.5 (OCH_3), 52.4 (C-6), 53.5 (OCH_3), 121.5 (=CH), 135.5 (C-3), 151.7 (C=O), 173.0 (C=O).

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