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Tandem Intramolecular Photocycloaddition−Retro-Mannich Fragmentation as a Route to Spiro[pyrrolidine-3,3′-oxindoles]. Total Synthesis of (±)-Coerulescine, (±)-Horsfiline, (±)-Elacomine, and (±)-6-Deoxyelacomine

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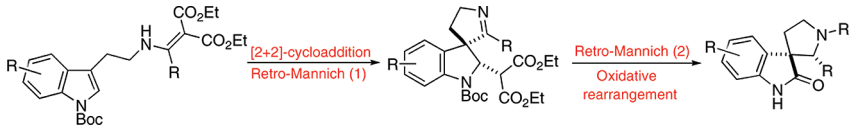

Irradiation of a tryptamine linked through its side-chain nitrogen to an alkylidene malonate residue results in an intramolecular [2 + 2] cycloaddition to the indole 2,3-double bond. The resultant cyclobutane undergoes spontaneous retro-Mannich fission to produce a spiro[indoline-3,3′-pyrrolenine] with relative configuration defined by the orientation of substituents in the transient cyclobutane. The tandem intramolecular photocycloaddition−retro-Mannich process, abbreviated as TIPCARM, leads to a spiropyrrolidine which is poised to undergo a second retro-Mannich fragmentation that expels the malonate unit and generates transiently an indolenine. The latter undergoes rearrangement to a β-carboline, which upon brominative oxidation undergoes further rearrangement to an oxindole. With tryptamine as starting material, the entire sequence leads to the alkaloid (±)-coerulescine. Starting from 5-methoxytryptamine, a parallel series affords (±)-horsfiline. Modification of the malonylidene unit to include an isobutyl substituent at C3 affords a photosubstrate which also undergoes the TIPCARM process. In this case, a 2′-isobutyl-substituted spiro[indoline-3,3′-pyrrolenine] results. This undergoes stereoselective hydride reduction to give a product with relative orientation at the spiro carbon and the new stereocenter bearing the isobutyl appendage corresponding to that of the alkaloid elacomine. From tryptamine, the sequence paralleling that leading to coerulescine and horsfiline terminates at 6-deoxyelacomine, whereas 6-methoxytryptamine as starting material affords (±)-elacomine itself.

Introduction

Photochemical [2 + 2] cycloaddition of an α,β-unsaturated carbonyl compound to an alkene followed by fragmentation of the resultant cyclobutane is a valuable strategy for building structural complexity from simple subunits.[1] The success of the method hinges not only on release of the >20 kcal/mol of strain energy embedded in the cyclobutane but also on deployment of functional groups around the four-membered ring that steers rupture in a desired direction.[2] De Mayo was the first to recognize the utility of this principle in his elegant construction of 1,4-dicarbonyl systems by irradiating an enolic β-diketone (**1**, X = O, Scheme 1) in the presence of an alkene.[3] Retro-aldol cleavage of the resultant cyclobutane **2** led via **3** to **4**. Numerous applications of this concept to the synthesis of novel substances have evolved from De Mayo's pioneering study.[4]

(1) Ho, T.-L. *Tactics of Organic Synthesis*; Wiley: New York, 1994; pp 138−144.
(2) (a) White, J. D.; Dillon, M. P.; Butlin, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 9673. (b) White, J. D.; Kim, J.; Drapela, N. *J. Am. Chem. Soc.* **2000**, *122*, 8665.
(3) De Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41.
(4) (a) Inter alia: Büchi, G.; Carlson, J. A.; Powell, J. E.; Tietze, L.-F. *J. Am. Chem. Soc.* **1973**, *95*, 540. (b) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532. (c) Oppolzer, W.; Godel, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2583. (d) Baker, R.; Sims, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3087. (e) Piers, E.; Abeysekera, B. F.; Herbert, D. J.; Suckling, I. D. *Can. J. Chem.* **1985**, *63*, 3418. (f) Disanayala, B. W.; Weedon, A. C. *Chem. Commun.* **1985**, 1282. (g) Seto, H.; Fujimoto, Y.; Tatsumo, T.; Yoshioka, H. *Synth. Commun.* **1985**, *15*, 1217. (h) Crimmins, M. T.; Gould, L. D. *J. Am. Chem. Soc.* **1987**, *109*, 6199.

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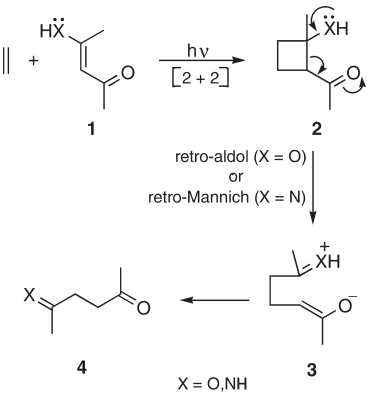
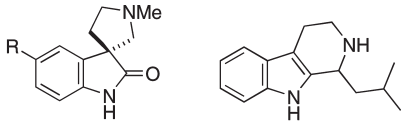
SCHEME 1



Vinylogous amides (enaminones, **1**, X = NH, Scheme 1) undergo photochemical cycloaddition to alkenes in a manner analogous to that of enolic β-diketones.[5] In this case, opening of the cyclobutane can occur via retro-Mannich cleavage to yield a 1,4-imino ketone. The intramolecular variant of this tandem photocycloaddition−retro-Mannich fragmentation (which we abbreviate as "TIPCARM") was first investigated by Schell[6] and subsequently was exploited broadly by Winkler who employed a TIPCARM strategy in several alkaloid syntheses.[7] Swindell also used a TIPCARM approach to construct a portion of the taxane skeleton.[8]



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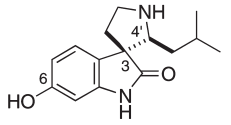
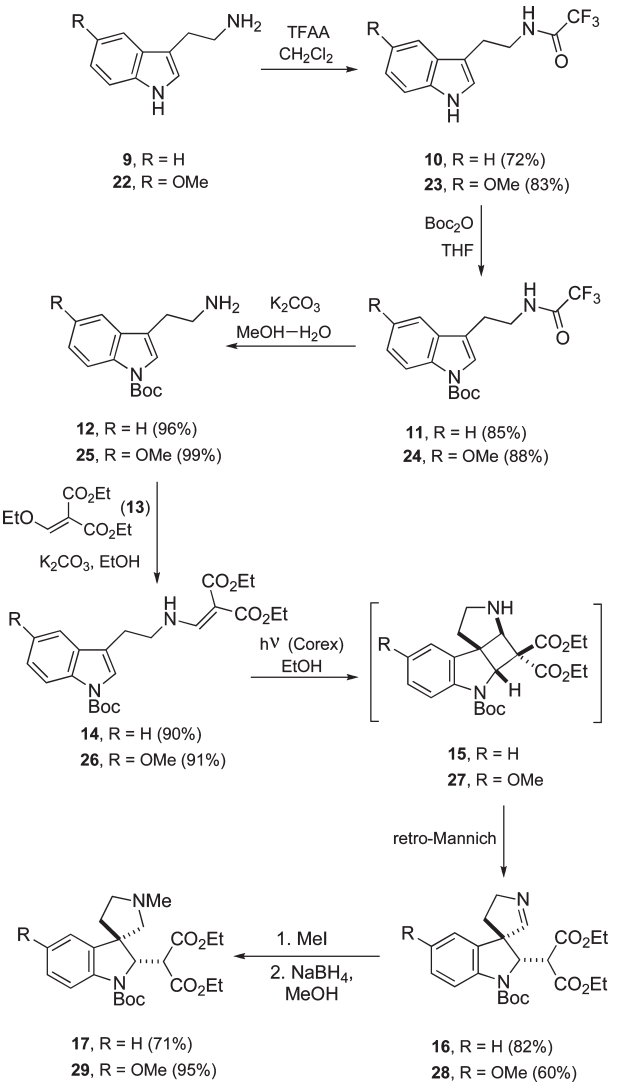

8, Elacomine

Recently, we showed that the 2,3-double bond of an indole can serve as the alkene partner in intramolecular photocycloaddition with a β-amino alkylidenemalonate.[9] Subsequent retro-Mannich fragmentation of the formed cyclobutane led to a spiro[pyrrolinoindoline] skeleton. We now report that extrapolation of our TIPCARM sequence can include a second retro-Mannich fragmentation, "[TIPCA-(RM)$_2$]", which expels a malonate residue used for the initial photoaddition step. This second fragmentation, when followed by rearrangement of the resulting spiroindolenine to a β-carboline and then oxidation, provides access to alkaloids of the spiro[pyrrolidine-3,3′-oxindole] class. The method has

SCHEME 2



now been applied to syntheses of oxindole alkaloids (±)-coerulescine (**5**) from the blue canary grass *Phalaris coerulescens*[10] and to (±)-horsfiline (**6**), first isolated from the Malaysian medicinal plant *Horsfildea superba* Warb.[11] It has been further extended to the β-carboline alkaloid **7** found in the shrub *Elaeagnus commutata* Bernh[12] and to the 4′-substituted spiro[pyrrolidine-3,3′-oxindole] alkaloid (±)-elacomine (**8**), also from *E. commutata*.[13] There has been strong interest in the synthesis of spiro[pyrrolidine-3,3′-oxindoles],[14] especially horsfiline (**6**), due to their structural relationship to the cell cycle inhibitors spirotryprostatins A and B.[15]

(5) Cantrell, T. S. *Tetrahedron* **1971**, *27*, 1227.
(6) Schell, F. M.; Cook, P. M. *J. Org. Chem.* **1984**, *49*, 4067.
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(9) White, J. D.; Ihle, D. C. *Org. Lett.* **2006**, *8*, 1081.
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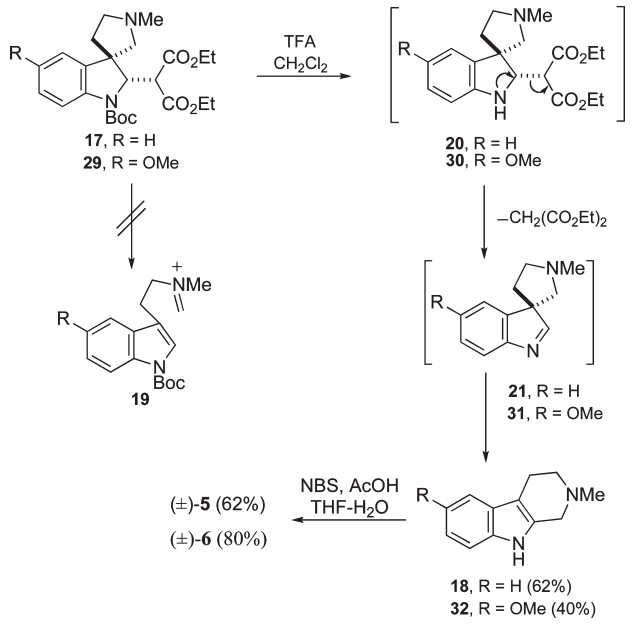
(11) Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.
(12) Slywka, G. W. A.; Locock, R. A. *Tetrahedron Lett.* **1969**, 4635.
(13) James, M. N. G.; Williams, G. J. B. *Can. J. Chem.* **1972**, *50*, 2407.
(14) Reviews: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.
(15) Cui, C.-B.; Kakeya, J.; Osada, J. *Tetrahedron* **1996**, *52*, 12651.

SCHEME 3



Results and Discussion

(±)-Coerulescine (5) and (±)-Horsfiline (6). For the synthesis of **5**,[16] tryptamine (**9**) was first converted to trifluoroacetamide **10** before protection of the indole nitrogen as Boc derivative **11** (Scheme 2). Removal of the trifluoroacetyl group and condensation of the liberated amine **12** with diethyl β-ethoxymethylidenemalonate (**13**)[17] afforded photo substrate **14**. Irradiation of **14** in EtOH with a 450 W medium-pressure mercury lamp through a Corex filter (50% transmission at 290 nm)[18] led via cycloadduct **15** and in situ retro-Mannich fragmentation to spiropyrrolenine **16** in good yield. Although formation of **16** was more rapid when **14** was irradiated through a Vycor filter (90% transmission at 280 nm), decomposition of the product complicated purification in this case. No reaction occurred when **14** was irradiated through Pyrex glass (20% transmission at 290 nm). These experiments confirm that the photocycloaddtion step in our TIPCARM sequence is sensitive to the energy of the incident radiation.

Treatment of **16** with methyl iodide gave a methiodide which was reduced with sodium borohydride to saturated spiro[pyrrolidinoindoline] **17**. Removal of Boc protection from **17** with trifluoroacetic acid under more strenuous conditions than those used previously[9] resulted in a second, spontaneous retro-Mannich fragmentation in which diethyl malonate was expelled to afford the known β-carboline **18**[19] (Scheme 3). β-Carbolines such as **18** are conventionally prepared by Pictet–Spengler condensation of a tryptamine with an aldehyde[20] or by Bischler–Napieralski cyclization of a tryptamide followed by reduction.[21] Our observation that removal of the Boc group from **17** was necessary in order to trigger the second retro-Mannich process argues against a pathway to **18** via indole **19** followed by Pictet–Spengler cyclization. More likely, **20** leads transiently to spiroindolenine **21**, and it is this species that rearranges spontaneously in acid to **18**. Oxidation of **18** with *N*-bromosuccinimide in aqueous acetic acid following a protocol first published by Lawson and Withrop and further developed by van Tamelen as a general route to oxindoles[22,23] gave (±)-coerulescine (**5**). The same oxidative rearrangement of **18** was recently accomplished by Danishefsky in his synthesis of (±)-(**5**).[24] Our overall yield of **5** for the nine steps from tryptamine (**9**) was 11%.

A sequence parallel to that shown in Schemes 2 and 3 but departing from 5-methoxytryptamine (**22**) and proceeding via **23**, **24**, and **25** led to (±)-horsfiline (**6**) in an overall yield of 12% (Scheme 3). The photocycloaddition–retro-Mannich sequence from **26** via **27** to **28** was both slower and less efficient than the analogous conversion of **14** to **16**, probably due to partial quenching of the photoexcited malonylidene unit of **26** by the methoxy substituted indole. On the other hand, the combined *N*-methylation and borohydride reduction of **28** resulted in more efficient preparation of **29** than of **17**. Subsequent steps from **29** to (±)-horsfiline (**6**) proceeded via **30** and **31** to β-carboline **32** which was brominatively oxidized to the racemic alkaloid. The structures of (±)-**5** and (±)-**6** were confirmed by comparison of their ^{1}H and ^{13}C NMR spectra with published spectra of coerulescine[16b] and horsfiline,[16i] respectively.

(±)-Elacomine (8). The isobutyl substituent located at C4′ in elacomine presented our TIPCA(RM)$_2$ strategy with two new challenges. Since we wished to bring the isobutyl appendage into our synthetic sequence at an early stage, the first goal involved incorporation of that substituent into the aminomalonylidene portion of our photo substrate. A second issue concerned the new stereocenter at C4′ and specifically whether it would be oriented correctly with respect to the adjacent spiro carbon at C3. Some precedent for both of these operations existed in our previous work,[9] but it was unclear whether the more sterically demanding isobutyl group would impose a constraint on the photocycloaddition step of TIPCARM which would now generate a more highly congested cyclobutane intermediate. Our solution to the first of these tasks was straightforward and required only acylation of diethyl malonate with isovaleryl chloride followed by *O*-methylation of **34**[25] to provide **35** (Scheme 4).

We chose initially to test our approach to **8** in the context of 6-deoxyelacomine (**36**, Scheme 6). Although this

(16) The first synthesis of **5** appears to have been an adventitious one recorded by Kuehne; Kuehne, M. E.; Roland, D. M.; Hafter, R *J. Org. Chem.* **1978**, *43*, 3705. For subsequent syntheses of **5** and/or **6**, see: (a) Kuehne, M. E.; Roland, D. M.; Hafter, R. *Heterocycles* **1994**, *38*, 725. (b) Pellegrini, C.; Strässler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. (c) Lakshmaiah, G.; Kawabata, G.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699. (d) Kumar, U. K. S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193. (e) Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447. (f) Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117. (g) Chang, M.-Y.; Pai, C.-L.; Kung, Y.-H. *Tetrahedron Lett.* **2005**, *46*, 8463. (h) Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287. (i) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027.

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(20) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151.

(21) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.

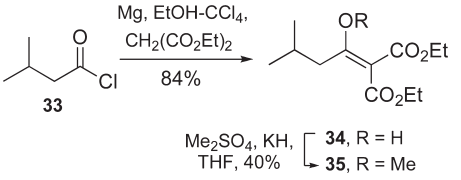
(22) Lawson, W. B.; Withrop, B. *J. Org. Chem.* **1961**, *26*, 263.

(23) van Tamelen, E. E.; Yardley, J. P.; Miyano, M.; Hinshaw, W. B. *J. Am. Chem. Soc.* **1969**, *91*, 7333.

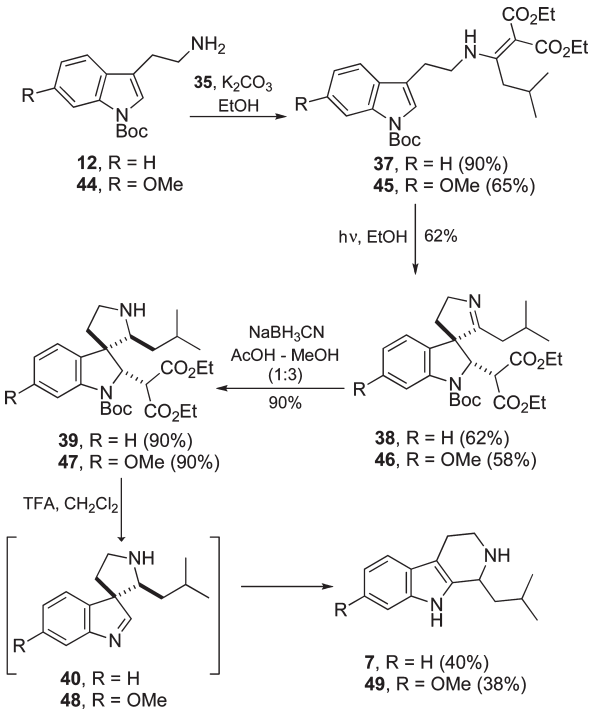
(24) Li, C.; Chan, C.; Heimann, A.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1444.

(25) Huffman, J. W.; Garg, S. P.; Cecil, J. H. *J. Org. Chem.* **1966**, *31*, 1276.

SCHEME 4



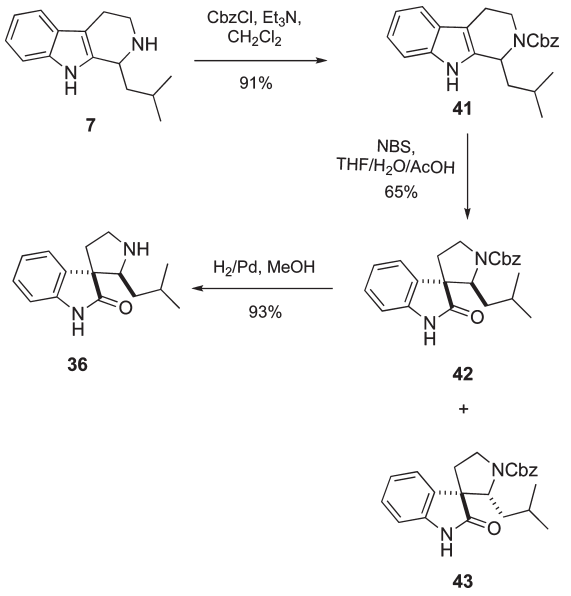
SCHEME 5



substance has not been found in Nature, we foresaw that our route would pass through the known alkaloid **7**, a substance previously obtained by Borschberg in the course of his synthesis of (±)-elacomine.[26] Correlation would provide assurance that our TIPCA(RM)$_2$ strategy was applicable to elacomine itself. First, *N*-Boc tryptamine **12** was condensed under basic conditions with **35** to furnish photo substrate **37** in excellent yield (Scheme 5). Irradiation of **37** under conditions previously used for photolysis of **14** and **26** led directly to spiropyrrolenine **38** which was immediately subjected to reduction with sodium cyanoborohydride. Our expectation based on steric grounds was that hydride would be delivered to imine **38** from the face opposite the C2 branched indoline substituent and our prediction was confirmed with the isolation of **39** as a single stereoisomer in high yield. Exposure of spiropyrrolidine **39** to trifluoroacetic acid removed Boc protection from *N*1 and led spontaneously to retro-Mannich expulsion of the malonate residue to produce transiently spiroindolenine **40** and then β-carboline **7**. The spectral properties of **7** matched those reported by Borschberg,[26] and data for the hydrochloride of **7** agreed with those reported by Slywka and Locock for the corresponding salt of the alkaloid isolated from *E. commutata*.[12]

(26) Pellegrini, C.; Weber, M.; Borschberg, H.-J. *Helv. Chim. Acta* **1996**, *79*, 151.

SCHEME 6



The presence of a secondary amine in **7** prevented its direct conversion to an oxindole, as was executed successfully with **18** and **32**, and therefore, **7** was protected as its carbobenzyloxy derivative **41** (Scheme 6). Treatment of **41** with NBS in an aqueous medium containing THF and acetic acid gave **42** and **43**. After separation by chromatography, hydrogenolysis of **42** gave (±)-6-deoxyelacomine (**36**).

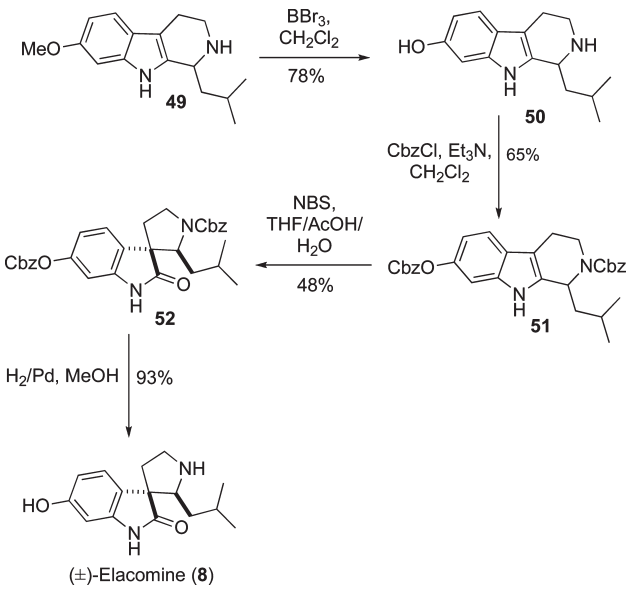
For the synthesis of (±)-elacomine (**8**), we chose *N*-protected 6-methoxytryptamine **44** as our starting material with the expectation that judicious timing of the methyl ether cleavage would need to be made at some point in the sequence. Tryptamine derivative **44** was prepared by a known route from indole[27] and was condensed with **35** to furnish photo substrate **45**. Irradiation of **45** gave **46** and subsequent reduction to **47** followed by retro-Manich fission via **48** yielded β-carboline **49** in a process that closely paralleled the sequence from **12** to **7**. However, in attempting to advance **49** toward elacomine (**8**), it became clear that unmasking the hydroxyl group of the alkaloid as a final step was problematic. Consequently, we chose **49** as the more opportune substrate for accomplishing this transformation and when **49** was reacted with boron tribromide at low temperature it gave β-carboline **50** in satisfactory yield. Protection of both the amine and hydroxyl substituent of **50** as bis-carbobenzyloxy derivative **51** followed by brominative oxidation and rearrangement produced oxindole **52**. Final hydrogenolysis then yielded (±)-elacomine (**8**) (Scheme 7). The ^{1}H and ^{13}C NMR spectra of (±)-**8** were identical to corresponding spectra of the racemic alkaloid published by Horne.[28]

In summary, a photocycloaddition−retro-Mannich sequence applied to tryptamine systems provides a new entry to spiro[pyrrolidino-3,3′-indolines] and thus to corresponding oxindole alkaloids found in Nature. Although a malonyl unit present in the photosubstrate is subsequently expelled in

(27) (a) Teranishi, K.; Nakatsuka, K.; Goto, T. *Synthesis* **1994**, 1018. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.

(28) Miyake, F.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2004**, *6*, 711.

SCHEME 7



a second retro-Mannich fragmentation after spiro[pyrrolinoindoline] formation, retention of the malonyl function would afford opportunities for accessing more complex alkaloid skeletons including those of the *Strychnos* family. This aspect of our TIPCARM strategy will be the subject of a future study.

Experimental Section

General Methods. Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^1H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent.

Routine monitoring of reactions was performed using silica gel on aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on 230−400 mesh silica gel.

Air- and/or moisture-sensitive reactions were performed under inert atmosphere conditions. Reactions requiring rigorously anhydrous conditions were performed under a blanket of argon in glassware dried in an oven at 150 °C or by flame and then cooled under argon. Dry THF and dichloromethane were obtained from commercial solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-2,2,2-trifluoroacetamide (10).** To a solution of tryptamine (**9**, 1.00 g, 6.24 mmol) in CH_2Cl_2 (56 mL) containing pyridine (5.6 mL) at 0 °C under argon was added dropwise trifluoroacetic anhydride (920 μL, 6.60 mmol). After 5 min, the cold bath was removed, and the mixture was stirred at rt for 2 h. The mixture was diluted with CH_2Cl_2, and the solution was washed with satd aq $NaHCO_3$, aq NH_4Cl, and H_2O. The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes/EtOAc 3:1) afforded **10** as a colorless oil (944 mg, 72%): IR (neat) 3406, 1701, 1560, 1173, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.10 (t, $J = 6.7$ Hz, 2H), 3.73 (dd, $J = 6.5$, 6.4 Hz, 2H), 7.08 (d, $J = 2.3$ Hz, 1H), 7.18 (t, $J = 7.8$ Hz, 1H), 7.27 (t, $J = 8.0$ Hz, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 8.12 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 40.1, 111.4, 111.8, 118.5, 119.8, 122.2, 122.6, 127.0, 136.5; HRMS calcd for $C_{12}H_{11}N_2F_3O$ m/z 256.0824, found 256.0820.

***tert*-Butyl 3-(2-(2,2,2-Trifluoroacetamido)ethyl)-1*H*-indole-1-carboxylate (11).** To a solution of **10** (1.00 g, 3.90 mmol) in THF (39.0 mL) was added Boc_2O (916 mg, 4.68 mmol) followed by DMAP (24.0 mg, 5 mol %). The solution was warmed to 40 °C for 1 h and then was diluted with CH_2Cl_2 and washed with H_2O. The solution was dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes/EtOAc 10:1) gave **11** as a colorless oil (1.25 g, 85%): IR (neat) 3314, 2982, 1723, 1566, 1462, 1380, 1168, 1086, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 9H), 3.05 (t, $J = 6.7$ Hz, 2H), 3.61 (dd, $J = 6.5$, 6.4 Hz, 2H), 6.60 (bs, 1H), 7.22 (t, $J = 7.8$ Hz 1H), 7.34 (t, $J = 8.0$ Hz 1H), 7.42 (s, 1H), 7.52 (d, $J = 7.8$ Hz 1H), 8.15 (d, $J = 7.8$ Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 28.2, 39.6, 83.2, 115.5, 116.5, 118.6, 122.7, 123.4, 124.8, 128.5, 129.3, 135.1, 149.0; HRMS calcd for $C_{17}H_{19}N_2F_3O_3$ m/z 356.1348, found 356.1360.

Diethyl 2-((2-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)ethylamino)-methylene)malonate (14). To a solution of **11** (700 mg, 1.85 mmol) in MeOH−H_2O (18.5 mL, 70:30) was added K_2CO_3 (900 mg) in one portion. The mixture was stirred for 48 h and then was poured into H_2O and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo to afford crude **12** as a pale yellow oil (880 mg, 96%). This material was used without further purification in the next reaction.

To a solution of **12** obtained above (880 mg, 3.02 mmol) and diethyl ethoxymethylenemalonate (**13**, 345 μL, 3.44 mmol) in EtOH (3 mL) was added K_2CO_3 (520 mg, 3.94 mmol), and the mixture was stirred at rt for 5 h. The resulting yellow solution, which contained a small amount of white solid, was poured into H_2O (50 mL) and was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo to afford crude **14** as a yellow oil. The crude product was purified by chromatography on silica gel (hexanes/EtOAc 4:1) to give pure **14** as a pale yellow solid (1.37 g, 90%): mp 58 °C; IR (KBr) 3276, 3192, 3112, 3057, 2979, 2935, 2901, 1734, 1653, 1616, 1456, 1375, 1258, 1217, 1154, 1088, 1033, 802, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, $J = 6.7$ Hz, 3H), 1.31 (t, $J = 6.7$ Hz, 3H), 1.66 (s, 9H), 2.98 (t, $J = 6.8$ Hz, 2H), 3.63 (q, $J = 5.9$ Hz, 2H), 4.13 (q, $J = 6.9$ Hz, 2H), 4.21 (q, $J = 6.9$ Hz, 2H), 7.24 (m, 1H), 7.33 (m, 1H), 7.41 (s, 1H), 7.47 (m, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 8.14 (d, $J = 7.9$ Hz, 1H), 9.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.4, 26.8, 28.1, 49.3, 59.6, 59.8, 83.5, 89.8, 113.2, 116.1, 124.3, 130.6, 135.5, 149.5, 156.0, 165.9, 169.2; HRMS calcd for $C_{23}H_{31}N_2O_6$ m/z 431.2182, found 431.2163.

Diethyl 2-(1-(*tert*-Butoxycarbonyl)-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-2-yl)malonate (16). A degassed solution of **14** (200 mg, 0.47 mmol) in EtOH (100 mL) was irradiated with a 450 W medium-pressure mercury lamp through a Corex filter for 12 h. The solution was concentrated in vacuo, and the resulting yellow oil was purified by chromatography on silica gel (hexanes/EtOAc 1:1) to afford **16** as a pale yellow oil (164 mg, 82%): IR (neat) 2978, 2936, 2863, 1733, 1700, 1481, 1381, 1305, 1283, 1253, 1165, 1033, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.57 (s, 9H), 1.99 (ddd, $J = 12.8$, 6.8, 6.8 Hz, 1H), 2.30 (ddd, $J = 12.8$, 6.8, 6.8 Hz, 1H), 3.85 (m, 2H), 3.99 (t, $J = 6.4$ Hz, 2H), 4.15 (m, 2H), 4.22 (d, $J = 6.4$ Hz, 2H), 4.96 (bs, 1H), 6.80 (dt, $J = 7.6$, 1.2 Hz, 1H), 6.95 (dt, $J = 7.6$, 1.2 Hz, 1H), 7.18 (dt, $J = 7.8$, 1.2 Hz, 1H), 7.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 13.8, 28.4, 42.1, 52.6, 59.9, 60.0, 61.6, 64.1, 67.8, 115.5, 122.6, 123.5, 128.6, 134.7, 140.2, 166.5, 166.9, 167.0; HRMS calcd for $C_{23}H_{30}N_2O_6$ m/z 430.2104, found 430.2115.

1-(*tert*-Butoxycarbonyl)-2-(1,3-diethoxy-1,3-dioxopropan-2-yl)-1′-methyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrol]-1′-ium Iodide. A mixture of methyl iodide (1.10 mL, 2.00 mmol) and **16** (380 mg, 0.88 mmol) was stirred for 48 h. The resulting yellow solution was concentrated in vacuo, and the residual solid was dried under high vacuum to afford iodide as a pale yellow solid (475 mg, 94%): IR (KBr) 3444, 2979, 2935, 1716, 1483, 1382, 1287, 1256, 1162, 1032, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.61 (s, 9H), 2.75 (m, 2H), 3.52 (m, 1H), 3.87 (m, 1H), 4.14 (s, 2H), 4.22 (m, 2H), 4.39 (m, 2H), 4.95 (bs, 1H), 4.97 (ddd, $J = 13.6$, 7.2, 7.2 Hz, 1H), 7.10 (t, $J = 7.6$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 7.40 (bs, 1H), 7.85 (bs, 1H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 13.9, 27.2, 28.3, 39.8, 44.1, 60.3, 62.4, 63.0, 67.6, 83.6, 115.2, 124.8, 126.1, 129.2, 130.4, 139.5, 151.4, 167.5, 168.3, 178.4. This material was used without further purification in the next reaction.

Diethyl 2-(1-(*tert*-Butoxycarbonyl)-1′-methylspiro[indoline-3,3′-pyrrolidine]-2-yl)malonate (17). To a solution of iodide obtained above (500 mg, 0.873 mmol) in MeOH (10 mL) was added $NaBH_4$ (50.0 mg, 1.32 mmol) in one portion. The solution was stirred for 3 h, after which satd aq NH_4Cl was added. The mixture was concentrated by removing solvent in vacuo, and the residue was extracted with EtOAc (3×5 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2/MeOH 20:1) gave **17** as a colorless oil (268 mg, 71%): IR (neat) 3048, 2978, 2938, 2838, 2780, 1733, 1708, 1602, 1481, 1387, 1280, 1254, 1168, 1039, 868, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, $J = 7.2$ Hz, 3H), 1.20 (t, $J = 7.2$ Hz, 3H), 1.55 (s, 9H), 1.85 (ddd, $J = 12.8$, 8.0, 8.0 Hz, 1H), 2.18 (ddd, $J = 12.8$, 8.0, 4.0, 1H), 2.56 (s, 3H), 2.70 − 3.10 (m, 3H), 3.31 (m, 1H), 3.75 − 4.00 (m, 3H), 4.11 (m, 2H), 4.99 (d, $J = 4.8$ Hz, 1H), 7.00 (t, $J = 7.6$, 1H), 7.15 (t, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 7.7$ Hz, 1H), 7.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 13.9, 28.4, 28.4, 43.7, 54.6, 60.1, 60.6, 61.8, 69.4, 115.2, 123.6, 127.9, 167.6; HRMS calcd for $C_{24}H_{34}N_2O_6$ m/z 446.2417, found 446.2493.

2-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (18). To a solution of **17** (200 mg, 0.45 mmol) in CH_2Cl_2 was added TFA (1.60 mL), and the solution was stirred for 24 h. Saturated aq Na_2CO_3 was added, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2/MeOH 50:1) gave **18** as a colorless oil (53.4 mg, 62%): IR (neat) 3411, 2927, 2851, 1674, 1457, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 2.85 (m, 4H), 3.58 (s, 2H), 7.13 (m, 2H), 7.30 (m, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.95(bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ31.9, 45.2, 52.0, 52.9, 107.7, 110.9, 118.0, 119.3, 121.4, 127.1, 131.2, 136.2; HRMS calcd for $C_{12}H_{14}N_2$ m/z 186.1157, found 186.1159.

(±)-Coerulescine (5). To a solution of **18** (33 mg, 0.18 mmol) in THF−H_2O−AcOH (1 mL, 1:1:1.5) was added NBS (18 mg, 0.09 mmol). The mixture was stirred for 15 min at rt, after which satd aq $NaHCO_3$ was added and the mixture was extracted with EtOAc−Et_3N (6:1, 3×5 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2/MeOH 50:1) afforded **5** as a colorless oil (21 mg, 62%): IR (neat) 3225, 1712, 1626, 1470, 1190, 1108, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (m, 1H), 2.45(m, 1H), 2.51 (s, 3H), 2.80 (m, 2H), 2.91 (m, 1H), 3.08 (m, 1H), 6.91 (d, $J = 7.6$ Hz, 1H), 7.08 (dt, $J = 7.6$, 1.1 Hz, 1H), 7.23 (dt, $J = 7.6$, 1.2 Hz, 1H), 7.41 (d, $J = 7.2$ Hz, 1H), 8.29 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.0, 41.9, 53.7, 56.8, 66.4, 109.4, 122.9, 123.4, 127.8, 136.3, 140.0, 182.7; HRMS calcd for $C_{12}H_{14}N_2O$ m/z 202.1106, found 202.1108.

2,2,2-Trifluoro-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)acetamide (23). To a solution of 5-methoxytryptamine (**22**, 100 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) containing pyridine (1 mL) at 0 °C under argon was added dropwise trifluoroacetic anhydride (78 μL, 0.55 mmol). After 5 min, the cold bath was removed, and the mixture was stirred at rt for 2 h. The mixture was diluted with CH_2Cl_2, and the solution was washed with satd aq $NaHCO_3$, aq NH_4Cl, and H_2O. The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes/EtOAc 3:1) yielded **23** as a colorless oil (125 mg, 83%): IR (neat) 3335, 1701, 1489, 1216, 1173, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.04 (t, $J = 6.7$, 2H), 3.71 (dd, $J = 6.3$, 6.3 Hz, 2H), 3.91 (s, 3H), 6.39 (bs, 1H), 6.91 (dd, $J = 8.8$, 2.6 Hz 1H), 7.05 (dd, $J = 8.3$, 2.1 Hz, 2H), 7.29 (d, $J = 8.5$ Hz 1H), 8.02 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 40.0, 55.9, 100.1, 111.5, 112.2, 112.8, 123.0, 154.3; HRMS calcd for $C_{13}H_{14}N_2F_3O_2$ m/z 287.1007, found 287.1011.

***tert*-Butyl 5-Methoxy-3-(2-(2,2,2-trifluoroacetamido)ethyl)-1*H*-indole-1-carboxylate (24).** To a solution of **23** (120 mg, 0.42 mmol) in THF (5 mL) was added Boc_2O (98 mg, 0.50 mmol) followed by DMAP (2.5 mg, 5 mol %). The solution was stirred at 40 °C for 1 h and then was diluted with CH_2Cl_2 and washed with H_2O. The solution was dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (hexanes/EtOAc 10:1) afforded **24** as a colorless oil (150 mg, 88%): IR (neat) 2941, 1723, 1481, 1388, 1126, 1081, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (s, 9H), 2.97 (t, $J = 6.7$ Hz, 2H), 3.71 (dd, $J = 6.6$, 6.6 Hz, 2H), 3.94 (s, 3H), 6.39 (bs, 1H), 6.98 (dd, $J = 8.2$, 2.4 Hz 2H), 7.29 (s, 1H), 8.02 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 28.2, 39.6, 55.8, 101.3, 113.4, 116.3, 124.0, 156.0; HRMS calcd for $C_{18}H_{21}N_2F_3O_4$ m/z 386.1453, found 386.1470.

***tert*-Butyl 3-(2-Aminoethyl)-5-methoxy-1*H*-indole-1-carboxylate (25).** To a solution of **24** (130 mg, 0.318 mmol) in MeOH−H_2O (70:30, 5 mL) was added K_2CO_3 (250 mg) in one portion. The mixture was stirred at rt for 48 h and was poured into H_2O. The mixture was extracted with CH_2Cl_2, and the extract was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to afford virtually pure **25** as a pale yellow oil (99 mg, 99%): IR (neat) 2921, 1723, 1478, 1385, 1265, 1009, 792 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 9H), 3.18 (bs, 2H), 3.25 (bs, 2H), 3.84 (s, 3H), 6.90 (dd, $J = 7.8$, 3.0 Hz, 1H), 7.06 (s, 1H), 7.52 (s, 1H), 7.95 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 29.7, 39.6, 55.9, 101.3, 113.4, 116.3, 156.0; HRMS calcd for $C_{16}H_{23}N_2O_3$ m/z [M + 1] 291.1709, found 291.1701.

Diethyl 2-((2-(1-(*tert*-Butoxycarbonyl)-5-methoxy-1*H*-indol-3-yl)ethylamino)methylene)malonate (26). To a solution of **25** (100 mg, 0.32 mmol) and diethyl ethoxymethylenemalonate (**13,** 37 μL, 0.35 mmol) in EtOH (3 mL) was added K_2CO_3 (55 mg, 0.40 mmol). The mixture was stirred at rt for 5 h, and the resulting yellow solution was poured into H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL), and the combined extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to afford a yellow oil which was purified by chromatography on silica gel (hexanes/EtOAc 4:1) to give **26** as a pale yellow oil (134 mg, 91%): IR (neat) 2970, 1728, 1658, 1609, 1472, 1385, 1265, 1157, 1075, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 6H), 1.66 (s, 9H), 2.97 (t, $J = 6.8$ Hz, 2H), 3.64 (dd, $J = 6.8$, 6.8 Hz, 2H), 3.86 (s, 3H), 4.15 (q, $J = 7.3$ Hz, 2H), 4.22(q, $J = 7.3$ Hz, 2H), 6.93 (m, 2H), 7.39 (s, 1H), 7.90 (d, $J = 8.0$ Hz, 1H), 8.04 (m, 1H), 9.26 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.4, 26.8, 28.2, 49.4, 55.7, 59.6, 59.8, 83.5, 89.8, 101.4, 113.2, 116.0, 116.2, 124.2, 130.7, 149.3, 155.9, 159.8, 166.0, 169.2; HRMS calcd for $C_{24}H_{32}N_2O_7$ m/z 460.2210, found 460.2216.

Diethyl 2-(1-(*tert*-Butoxycarbonyl)-5-methoxy-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-2-yl)malonate (28). A degassed solution of **26** (100 mg, 0.21 mmol) in EtOH (100 mL) was irradiated with a 450 W medium-pressure mercury lamp through a Corex

filter for 12 h. The solution was concentrated in vacuo, and the resulting yellow oil was purified by chromatography on silica gel (hexanes/EtOAc 1:1) to give **28** as a pale yellow oil (60 mg, 60%): IR (neat) 2970, 1734, 1494, 1385, 1282, 1162, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.59 (s, 9H), 2.05 (m, 1H), 2.32 (m, 1H), 3.75 (3H, s), 3.94 (m, 2H), 4.02 (dt, $J = 6.9$, 2.2 Hz, 2H), 4.20 (m, 4H), 4.99 (bs, 1H), 6.40 (d, $J = 2.6$ Hz, 1H), 6.75 (dd, $J = 8.8$, 2.5 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 13.9, 28.4, 42.0, 55.7, 60.1, 61.6, 61.9, 68.0, 108.4, 113.5, 116.1, 156.3, 166.5, 166.9; HRMS calcd for $C_{24}H_{32}N_2O_7$ m/z 460.2210, found 460.2213.

1-(*tert*-Butoxycarbonyl)-2-(1,3-diethoxy-1,3-dioxopropan-2-yl)-5-methoxy-1′-methyl-4′,5′dihydrospiro[indoline-3,3′-pyrrol]-1′-ium Iodide. A mixture of methyl iodide (370 mg, 2.60 mmol) and **32** (60 mg, 0.130 mmol) was stirred for 48 h. The resulting pale yellow solution was concentrated in vacuo, and the residue was dried under high vacuum to afford crude **33**. The crude product was used for the next step without purification.

Diethyl 2-(1-(*tert*-Butoxycarbonyl)-5-methoxy-1′-methylspiro-[indoline-3,3′-pyrrolidine]-2-yl)malonate (29). To a solution of crude iodide obtained above in MeOH (1 mL) was added $NaBH_4$ (7.4 mg, 0.20 mmol) in one portion. The solution was stirred for 3 h, after which satd aq NH_4Cl was added. The solvent was evaporated, the residue was extracted with EtOAc (3×10 mL), and the combined extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 20:1) to give **29** as a colorless oil (57 mg, 95% from **32**): IR (neat) 2976, 2832, 1734, 1707, 1494, 1391, 1255, 1162, 1037, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.59 (s, 9H), 1.97 (bs, 2H), 2.22 (bs, 1H), 2.46 (bs, 3H), 2.90 (m, 3H), 3.20 (bs, 1H), 3.80 (s, 3H), 3.94 (m, 3H), 4.16 (m, 2H), 5.00 (bs, 1H), 6.71 (dd, $J = 9$, 3 Hz, 1H), 6.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.7, 13.9, 28.4, 54.7, 55.8, 61.5, 61.6, 69.6, 115.9, 127.9, 167.2; HRMS calcd for $C_{25}H_{36}N_2O_7$ m/z 476.2522, found 476.2525.

6-Methoxy-2-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (32). To a solution of **29** (150 mg, 0.33 mmol) in CH_2Cl_2 was added TFA (200 μL), and the solution was stirred for 24 h. Aqueous Na_2CO_3 was added, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2/MeOH 50:1) afforded **32** as a colorless oil (28 mg, 40%): IR (neat) 3462, 2943, 2829, 1483, 1456, 1216, 1151, 835, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 2.84 (s, 4H), 3.58 (s, 2H), 3.87 (s, 3H), 6.80 (dd, $J = 8.7$, 2.4 Hz, 1H), 6.95 (d, $J = 2.4$ Hz, 1H), 7.18 (d, $J = 8.7$ Hz, 1H), 7.94(bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 45.5, 52.3, 53.0, 55.3, 100.4, 107.8, 111.0, 111.4, 113.8, 127.6, 131.2, 154.0; HRMS calcd for $C_{13}H_{16}N_2O$ m/z 216.1263, found 216.1269.

(±)-Horsfiline (6). To a solution of **32** (16.0 mg, 0.073 mmol) in THF−H_2O−AcOH (1 mL, 1:1:1.5) was added NBS (14 mg, 0.078 mmol), and the mixture was stirred for 15 min at rt. Aqueous $NaHCO_3$ was added, and the solution was extracted with a mixture of EtOAc and Et_3N (6:1, 3×5 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2/MeOH 50:1) afforded **6** as a colorless oil (13.5 mg, 80%): IR (neat) 3232, 2943, 2834, 1707, 1483, 1304, 1200, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (m, 1H), 2.42 (m, 1H), 2.47 (s, 3H), 2.75 (m, 1H), 2.87 (d, $J = 1.6$ Hz, 1H), 2.91 (m, 1H), 3.03 (m, 1H), 3.82 (s, 3H), 6.74 (dd, $J = 8.4$, 2.3 Hz, 1H), 6.77 (m, 1H), 7.05 (d, $J = 2.5$ Hz, 1H), 7.59 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 38.2, 41.8, 54.1, 55.9, 56.7, 66.5, 109.6, 110.4, 112.4, 133.1, 137.7, 156.2; HRMS calcd for $C_{13}H_{16}N_2O_2$ m/z 232.1212, found 232.1219.

Diethyl 2-(3-Methylbutanoyl)malonate (34). In a round-bottom flask were placed Mg (1.25 g, 51.3 mmol), absolute EtOH (1.25 mL), and CCl_4 (0.05 mL). A small portion of a solution of diethyl malonate (7.8 mL, 50 mmol) in EtOH (4 mL) was added, and the mixture was gently warmed until H_2 evolution began. The remaining solution of diethyl malonate in EtOH was added at such a rate that the exothermic reaction proceeded vigorously but under control. When the reaction moderated, the flask was cooled in ice−water, and Et_2O (30 mL) was added. The mixture was heated again on a water bath until no further H_2 was evolved. The mixture was cooled to rt, and a solution of isovaleryl chloride (**33**, 6.5 mL, 51.5 mmol) in Et_2O (20 mL) was added slowly. The mixture was refluxed for 15 min and cooled to rt, and dilute acetic acid (10% in water w/v) was added slowly until the pH was approximately 7. The mixture was extracted with Et_2O, and the extracts were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by chromatography on silica gel (hexanes/EtOAc 20:1) to yield **34** as a colorless liquid (10.3 g, 84%): IR (neat) 2964, 1738, 1645, 1599, 1241, 1085, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (dd, $J = 6.7$, 3.4 Hz, 6 H), 1.31 (m, 6 H), 2.15 (m, 1 H), 2.33 (d, $J = 6.8$ Hz, 1 H), 2.50 (d, $J = 6.8$ Hz, 1 H), 4.26 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.0, 22.3, 23.9, 48.4, 62.1, 67.2, 168.2, 201.9 ; HRMS calcd for $C_{12}H_{20}O_5$ m/z 244.1311, found 244.1315.

Diethyl 2-(1-Methoxy-3-methylbutylidene)malonate (35). To a solution of **34** (1.00 g, 4.11 mmol) in THF (20 mL) at 0 °C was added KH (329 mg, 8.2 mmol) slowly. The mixture was warmed to rt and was stirred for 30 min. Dimethyl sulfate (0.77 mL, 8.2 mmol) was added dropwise, and the mixture was stirred for 24 h at rt. Aqueous NH_4Cl was added, the mixture was extracted with Et_2O, and the extracts were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (hexanes/EtOAc 10:1) to give **35** as a colorless oil (410 mg, 40%): IR (neat) 2961, 1735, 1710, 1614, 1213, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, $J = 6.6$ Hz, 6 H), 1.29 (m, 6 H), 1.98 (m, 1 H), 2.77 (d, $J = 7.4$ Hz, 2 H), 3.78 (s, 3 H), 4.17 (q, $J = 7.1$ Hz, 2 H), 4.24 (q, $J = 7.1$ Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.3, 27.7, 35.6, 56.2, 60.4, 61.0, 109.5, 165.0, 173.2; HRMS calcd for $C_{13}H_{22}O_5$ m/z 258.1467, found 258.1470.

Diethyl 2-(1-(2-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)ethylamino)-3-methylbutylidene)malonate (37). To a solution of **35** (1.00 g, 3.90 mmol) and **12** (1.00 g, 3.55 mmol) in EtOH (4.0 mL) was added K_2CO_3 (638 mg, 4.62 mmol). The reaction vessel was sealed, and the mixture was stirred at rt for 48 h. The resulting yellow solution which contained a white precipitate was poured into H_2O (50 mL) and was extracted with CH_2Cl_2 (3×50 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo to afford crude **37** as a yellow oil. The crude product was purified by chromatography on silica gel (hexanes/EtOAc 4:1) to give **37** (1.37 g, 65%): IR (neat) 3276, 3192, 3112, 3057, 2979, 2935, 2901, 1734, 1653, 1616, 1456, 1375, 1258, 1217, 1154, 1088, 1033, 802, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 0.94 (m, 6H), 1.29 (m, 6H), 1.69 (s, 9H), 1.84 (m, 1H), 2.42 (d, $J = 7.4$ Hz, 2H), 2.98 (t, $J = 7.3$ Hz, 2H), 3.60 (q, $J = 5.9$ Hz, 2H), 4.21 (m, 4H), 7.24 (m, 1H), 7.41 (s, 1H), 7.47 (m, 1H), 8.14 (d, $J = 7.7$ Hz, 1H), 9.85 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.3, 26.7, 28.1, 49.3, 59.5, 59.7, 83.6, 89.7, 115.4, 116.1, 118.4, 122.5, 123.6, 124.6, 129.8, 135.5, 149.5, 159.8, 165.9, 169.2; HRMS calcd for $C_{27}H_{38}N_2O_6$ m/z 487.2781, found 487.2788.

Diethyl 2-((2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-2′-isobutyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-2-yl)malonate (38). A degassed solution of **37** (400 mg, 0.82 mmol) in EtOH (100 mL) was irradiated with a Hanovia 450 W medium-pressure mercury lamp through a Corex filter for 12 h. The solution was concentrated in

vacuo, and the resulting yellow oil was purified by chromatography on silica gel (hexanes/EtOAc 5:1) to afford **38** as a pale yellow oil (248 mg, 62%): IR (neat) 2980, 1727, 1700, 1478, 1376, 1305, 1162, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 6.4 Hz, 6H), 1.25 (tt, J = 7.4, 7.1 Hz, 6H), 1.55 (s, 9H), 1.87 (m, 2H), 2.05 (m, 2H), 2.23 (m, 1H), 2.41 (m, 1H), 3.60 (d, J = 9.3 Hz, 1H), 3.85 (m, 1H), 4.11 (m, 4H), 5.18 (d, J = 9.0 Hz, 1H), 6.98 (dt, J = 7.4, 0.8 Hz, 1H), 7.18 (dt, J = 7.4, 1.0 Hz, 1H), 7.28 (m, 1H), 7.56 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 21.0, 22.7, 23.3, 28.2, 40.9, 44.4, 53.2, 57.6, 60.4, 61.7, 65.3, 66.2, 82.1, 116.5, 123.5, 123.9, 128.3, 134.9, 141.9, 152.3, 166.5, 166.9, 175.5; HRMS calcd for $C_{27}H_{38}N_2O_6$ m/z 486.2730, found 486.2722.

Diethyl 2-((2*S*,2′*S*,3*R*)-1-(*tert*-Butoxycarbonyl)-2′-isobutylspiro[indoline-3,3′-pyrrolidine]-2-yl)malonate (39). To a solution of **38** (300 mg, 0.62 mmol) in a mixture of MeOH and AcOH (3:1, 12 mL) was added $NaBH_3CN$ (85.0 mg, 1.35 mmol) in one portion. The mixture was stirred at rt for 1 h, after which satd aq $NaHCO_3$ was added slowly. The mixture was concentrated by removing volatiles in vacuo, and the residual oil was extracted with EtOAc (3×). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexanes/EtOAc 1:1 and 10% Et_3N) gave **39** as a colorless oil (271 mg, 90%): IR (neat) 2956, 1731, 1700, 1490, 1377, 1163, 1049, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J = 6.4 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H),1.21 (m, 6H), 1.24 (m, 1H), 1.55 (s, 9H), 1.75 (m, 2 H), 1.89 (m, 2 H), 2.25 (dt, J = 12.5, 7.3, 1H), 3.06 (m, 2 H), 3.29 (d, J = 9.8, 1H), 3.9 (d, J = 7.0 Hz, 1H), 4.11 (m, 4 H), 5.10 (d, J = 7.0 Hz, 1H), 7.00 (t, J = 7.7, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.1, 24.2, 26.4, 28.3, 42.3, 43.6, 44.4, 52.5, 57.7, 58.9, 61.6, 67.4, 81.7, 116.2, 122.7, 125.2, 127.4, 136.1, 141.6, 152.2, 167,1, 168.1; HRMS calcd for $C_{27}H_{41}N_2O_6$ m/z [M + 1] 489.2965, found 489.2936.

1-Isobutyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (7). To a solution of **39** (150 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) was added TFA (200 μL), and the solution was stirred for 24 h. Aqueous Na_2CO_3 was added, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2/MeOH 50: 1) afforded **7** as a colorless oil (45 mg, 40%): IR (neat) 3462, 2943, 2929, 1483, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, J = 6.6 Hz, 3 H), 1.05, (d, J = 6.6 Hz, 3H), 1.63 (m, 3 H), 2.00 (m, 1 H), 2.75 (m, 2H), 3.04 (ddd, J = 13.3, 7.5, 5.8 Hz, 1 H), 3.36 (dt, J = 12.8, 4.8 Hz, 1 H), 4.12 (ddt, J = 8.3, 6.2, 1.8 Hz, 1 H), 7.11 (ddd, J = 7.3, 6.9, 1.2 Hz, 1H), 7.16 (ddd, J = 7.3, 6.9, 1.2 Hz, 1H), 7.33 (dd, J = 7.3, 1.4 Hz, 1H), 7.50 (dd, J = 7.2, 1.5 Hz, 1 H), 7.79 (bs, s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.8, 23.9, 24.6, 42.5, 44.5, 50.5, 108.8, 110.7, 118.0, 119.4, 121.5, 127.6, 135.6, 136.8; HRMS calcd for $C_{15}H_{20}N_2$ m/z 228.1627, found 228.1623.

Benzyl 1-Isobutyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (41). To a solution of **7** (60 mg, 0.26 mmol) and Et_3N (0.1 mL) in CH_2Cl_2 (3 mL) at −10 °C was added benzyl chloroformate (0.06 mL, 0.37 mmol). The mixture was stirred for 75 min at rt and was poured into H_2O. The mixture was extracted with CH_2Cl_2, and the combined extracts were washed with aq $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo, and the residual oil was purified by chromatography on silica gel (hexanes/EtOAc 5:1) to afford **41** as a colorless oil (86 mg, 91%): IR (neat) 3324, 2954, 1671, 1423, 1441, 1222, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) showed severe line broadening with doubling of certain signals due to the presence of rotational conformers; HRMS calcd for $C_{23}H_{26}N_2O_2$ m/z 363.2073, found 363.2069.

(2′*S*,3*R*)-Benzyl 2′-Isobutyl-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (42). To a solution of **41** (47.0 mg, 0.13 mmol) in THF/AcOH/H_2O (3 mL, 1:1:1) was added NBS (25 mg). After vigorous stirring in the dark for 2 h at rt, the mixture was poured slowly into aq $NaHCO_3$ and was extracted with a mixture of EtOAc and Et_3N (6:1, 3 × 5 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes/EtOAc 2:1) gave **42** as a colorless oil (28 mg, 57%) and **43** (15 mg, 30%). Data for **42**: IR (neat) 3420, 2945, 1715, 1613, 1462, 1445, 1407, 1352, 1328, 1109 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 0.72 (m, 3 H), 0.78 (m, 3 H), 1.31 (m, 1H), 1.71 (m, 2 H), 2.06 (m, 1 H), 2.31 (m, 1H), 3.78 (m, 2 H), 4.00 (m, 1H), 5.02 (m, 2H), 6.90 (m, 1H), 6.98 (m, 1H), 7.21 (m, 2 H), 7.30 (m, 5H), 9.20 (bs, d, 1H); ^{13}C NMR (100 MHz, DMSO) δ 22.3, 22.9, 25.2, 34.7, 39.9, 44.6, 55.8, 63.7, 67.1, 109.6, 122.5, 123.1, 128.0, 128.3, 134.2, 136.9, 140.0, 155.0, 178.7; HRMS calcd for $C_{23}H_{27}N_2O_3$ m/z [M + 1] 379.2022, found 379.2031.

6-Deoxyelacomine (36). To a solution of **42** (40.0 mg, 0.11 mmol) in MeOH (4 mL) was added 10% Pd/C (4 mg). The mixture was stirred vigorously under an atmosphere of H_2 at 1 bar for 3 h and then filtered through Celite. The filtrate was evaporated, and the residue was chromatographed on silica gel (EtOAc/MeOH 5:1) to afford **36** as a colorless oil (24 mg, 93%): IR (neat) 3420, 2957, 1705, 1620, 1471, 1346, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H), 0.95 (ddd, J = 12.2, 8.8, 3.7 Hz, 1 H), 1.47 (ddd, J = 14.0, 9.0, 5.0 Hz, 1H), 1.63 (m, 1 H), 2.31 (ddd, J = 13.4, 8.8, 6.8 Hz, 1 H), 2.34 (ddd, J = 13.4, 8.8, 6.8 Hz, 1H), 3.37 (ddd, J = 12.0, 9.6, 5.7 Hz, 1H), 3.45 (dd, J = 10.2, 3.6 Hz, 1H), 3.54 (m, 1H), 6.96 (dd, J = 7.8, 1.0 Hz, 1H), 7.07 (td, J = 8.0, 1.0 Hz, 1 H), 7.24 (m, 2 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.5, 25.8, 37.7, 38.0, 46.2, 58.1, 68.8, 109.6, 122.5, 122.8, 128.0, 131.2, 140.9, 181.4; HRMS calcd for $C_{15}H_{20}N_2O$ m/z 244.1576, found 244.1585.

Diethyl 2-(1-(2-(1-(*tert*-Butoxycarbonyl)-6-methoxy-1*H*-indol-3-yl)ethylamino)-3-methylbutylidene)malonate (45). To a solution of **44** (160 mg, 0.62 mmol) and **35** (160 mg, 0.51 mmol) in EtOH (1.0 mL) was added K_2CO_3 (92 mg, 0.70 mmol). The reaction vessel was sealed, and the mixture was stirred at rt for 48 h. The resulting yellow solution which contained residual K_2CO_3 was poured into H_2O (50 mL) and was extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo to afford crude **53** as a yellow oil. The crude product was purified by chromatography on silica gel (hexanes/EtOAc 4:1) to give pure **45** (1.37 g, 65%) as a pale yellow oil: IR (neat) 2977, 1730, 1648, 1597, 1488, 1444, 1383, 1256, 1159, 1110, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (m, 6 H), 1.23 (m, 6 H), 1.68 (s, 9H), 1.86 (m, 1 H), 2.44 (d, J = 7.4 Hz, 2 H), 2.95 (t, J = 7.0 Hz, 2H), 3.58 (tt, J = 5.8, 6.9 Hz, 2H), 3.89 (s, 9H), 4.21 (m, 5 H), 6.90 (m, 1H), 7.28 (m, 1H), 7.36 (m, 2H), 7.76 (s, 1H), 9.85 (bs, s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.4, 22.4, 26.3, 27.6, 28.2, 37.1, 43.3, 55.6, 59.3, 60.4, 92.7, 116.7, 118.9, 122.1, 158.0, 166.4, 168.0, 169.2; HRMS calcd for $C_{28}H_{40}N_2O_7$ m/z 516.2836, found 516.2851.

Diethyl 2-((2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-2′-isobutyl-6-methoxy-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-2-yl)malonate (46). A degassed solution of **45** (200 mg, 0.41 mmol) in EtOH (100 mL) was irradiated with a Hanovia 450 W medium-pressure mercury lamp through a Corex filter for 12 h. The solution was concentrated in vacuo, and the resulting yellow oil was purified by chromatography on silica gel (hexanes/EtOAc 5:1) to afford **46** as a pale yellow oil (116 mg, 58%): IR (neat) 2957, 1733, 1706, 1616, 1597, 1500, 1453, 1369, 1306, 1256, 1226, 1161, 1035, 860, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (dd, J = 6.5, 1.8 Hz, 6 H), 1.26 (dd, J = 7.1, 6.8 z, 6H), 1.55 (s, 9H), 1.87 (m, 1 H), 2.38 (m, 2H), 3.02 (m, 2H), 3.58 (d, J = 9.2 Hz, 2 H), 3.82 (s, 3 H), 4.15 (m, 4H), 6.83 (d, J = 8.4 Hz, 1H), 7.22 (s, 1 H), 7.35 (m, 1H), 7.76 (s, 1H), 9.85 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 22.7, 23.3, 26.3, 28.2, 40.9, 44.3, 53.2, 55.5, 57.5, 61.7, 65.6, 66.0, 82.1, 102.6, 109.6, 124.3, 126.8, 143.2, 152.2, 160.2, 166.5, 166.9, 175.8; HRMS calcd for $C_{28}H_{40}N_2O_7$ m/z 516.2836, found 516.2841.

Diethyl 2-((2*S*,2′*S*,3*R*)-1-(*tert*-Butoxycarbonyl)-2′-isobutyl-6-methoxyspiro[indoline-3,3′-pyrrolidine]-2-yl)malonate (47). To a solution of **46** (170 mg, 0.33 mmol) in MeOH and AcOH (3:1, 4 mL) was added $NaBH_3CN$ (45 mg, 0.66 mmol) in one portion. The mixture was stirred at rt for 1 h, after which satd aq $NaHCO_3$ was added slowly. The mixture was concentrated by removing volatiles in vacuo, and the residue was extracted with EtOAc (3×). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexanes/EtOAc 1:1 and 10% Et_3N) gave **47** as a colorless oil (155 mg, 90%): IR (neat) 2956, 1707, 1498, 1369, 1163, 1036, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (dd, J = 21.5, 6.1 Hz, 6 H), 1.24 (tt, J = 7.9, 7.2 Hz, 6 H), 1.56 (s, 9H), 1.72 (m, 2 H), 1.91 (m, 2 H), 2.23 (m, 1H), 3.03 (m, 2 H), 3.26 (dd, J = 10.8, 1.6 Hz, 1H), 3.80 (t, 1H), 3.81 (s, 3H), 4.15 (m, 4 H), 5.10 (d, J = 7.0 Hz, 1H), 6.54 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.0, 24.2, 26.3, 28.3, 42.5, 43.5, 44.2, 52.5, 55.4, 58.7, 61.6, 67.9, 81.7, 102.4, 108.2, 120.5, 124.3, 125.5, 127.9, 144.1, 153.1 159.4, 167.1, 168.1; HRMS calcd for $C_{28}H_{42}N_2O_7$ m/z 518.2992, found 518.2982.

1-Isobutyl-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (49). To a solution of **47** (80 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) was added TFA (100 μL), and the solution was stirred for 24 h. Aqueous Na_2CO_3 was added, and the mixture was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (CH_2Cl_2/MeOH 50: 1) gave **49** as a colorless solid (24 mg, 38%): mp 146 − 149 °C; IR (neat) 3462, 2954, 1699, 1628, 1465, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 6.5 Hz, 3H), 1.05, (d, J = 6.5 Hz, 3H), 1.61 (m, 1 H), 1.66 (m, 1H), 1.94 (m, 1 H), 2.71 (m, 2H), 3.04 (ddd, J = 12.7, 8.0, 5.5 Hz, 1H), 3.36 (dt, J = 12.7, 4.7 Hz, 1 H), 3.85 (s, 3H), 4.11 (ddt, J = 8.7, 5.5, 2.1 Hz, 1H), 6.75 (dd, J = 8.6, 2.2 Hz, 1H), 6.84 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.61 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.7, 23.9, 24.6, 42.4, 44.5, 50.5, 55.8, 95.0, 108.6, 108.7, 118.5, 122.1, 134.8, 136.6, 156.1; HRMS calcd for $C_{16}H_{22}N_2O$ m/z 258.1732, found 258.1732.

7-Hydroxy-1-isobutyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (50). To a solution of **49** (170 mg) in CH_2Cl_2 (3 mL) was added dropwise BBr_3 (1.7 mL, 1 M in CH_2Cl_2) at rt under argon. The solution was stirred for 12 h, MeOH was added, and the mixture was poured into H_2O (10 mL). The mixture was extracted with CH_2Cl_2 and Et_3N (3×20 mL, 2 mL), and the combined extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 50:1) to provide **50** as an unstable solid (125 mg, 78%): IR (neat) 3462, 2954, 1629, 1456, 1152, 1124 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 10.8 Hz, 3 H), 1.02, (d, J = 10.8 Hz, 3H), 1.62 (m, 2 H), 1.97 (m, 1 H), 2.71 (m, 2H), 3.04 (m, 2 H), 3.36 (dt, J = 12.7, 4.7 Hz, 2 H), 4.07 (m, 1 H), 6.67 (dd, J = 8.4, 2.1 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 7.31 (OH, 1H), 7.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.7, 23.9, 24.6, 42.4, 44.3, 50.5, 97.0, 108.5, 109.3, 118.5, 121.8, 135.1, 136.6, 152.3; HRMS calcd for $C_{15}H_{20}N_2O$ m/z 244.1576, found 244.1571.

Benzyl 7-(Benzyloxycarbonyloxy)-1-isobutyl-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-2(9*H*)-carboxylate (51). To a solution of **50** (180 mg, 0.74 mmol) and Et_3N (0.5 mL) in CH_2Cl_2 (25 mL) at −10 °C was added benzyl chloroformate (1.5 mL, 2.4 mmol). The mixture was stirred for 75 min at rt and was poured into H_2O. The mixture was extracted with CH_2Cl_2 (3×), and the combined extracts were washed with aq $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel (hexanes/EtOAc 5:1) to give **51** as a colorless oil (260 mg, 65%): IR (neat) 3351, 2954, 1695, 1456, 1423, 1227, 1095 cm^{-1}; ^1H NMR (400 MHz, DMSO, severe line broadening and doubling of certain signals), δ 0.92 (d, J = 6.0 Hz, 2 H), 0.99 (d, J = 6.0 Hz, 2H), 1.1 (d, J = 6.0 Hz, 2H), 1.52 (m, 2 H), 1.77 (m, 2 H), 2.73 (m, 2H), 3.19 (m, 1 H), 4.44 (d, J = 7.9 Hz, 1 H), 5.28 (m, 5H), 6.91 (m, 1H), 7.10 (m, 1H), 7.46 (m, 10 H), 7.80 (m, 1H); ^{13}C NMR (100 MHz, DMSO, severe line broadening and doubling of certain signals), δ 20.9, 21.5, 22.4, 23.4, 24.9, 25.1, 37.9, 38.2, 43.9, 44.3, 49.8, 49.9, 67.3, 67.6, 70.3, 103.6, 108.0, 108.6, 113.0, 118.3, 118.5, 125.1, 127.8, 128.0, 128.2, 128.7, 134.9, 135.5, 135.9, 146.8, 154.6, 155.9; HRMS calcd for $C_{31}H_{32}N_2O_5$ m/z 512.2311, found 512.2322.

(2′*S*,3*R*)-Benzyl 6-(Benzyloxycarbonyloxy)-2′-isobutyl-2-oxospiro[indolin-3,3′-pyrrolidine]-1′-carboxylate (52). To a solution of **51** (150 mg) in THF/AcOH/H_2O (18 mL, 1:1:1) was added NBS (58 mg, 0.33 mmol). After being stirred vigorously in the dark for 2 h at rt, the mixture was poured slowly into aq $NaHCO_3$ and was extracted with a mixture of EtOAc and Et_3N (6:1, 3×15 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. Purification of the residue by chromatography on silica gel (hexanes/EtOAc 2:1) afforded **52** as a colorless oil (78 mg, 48%): IR (neat) 3247, 2957, 1712, 1458, 1412, 1230, 1110 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 0.75 (m, 6H), 0.71 (m, 1H), 1.30 (bs, 2H), 1.68 (m, 2H), 2.08 (m, 1H), 2.27 (m, 1H), 3.78 (m, 2H), 3.98 (m, 1H), 5.30 (m, 4H), 6.77 (m, 1H), 7.03 (m, 1H), 7.30 (m, 10 H); ^{13}C NMR (100 MHz, DMSO) δ 22.1, 22.9, 24.7, 24.8, 25.2, 35.2, 40.9, 45.4, 61.4, 67.1, 70.6, 71.0, 104.0, 114.5, 125.8, 127.0, 128.0, 128.4, 128.5, 128.6, 128.7, 128.9, 134.6, 141.8, 151.3, 153.5, 155.7, 180.8; HRMS (FAB) calcd for $C_{31}H_{32}N_2O_6$ m/z [M + Na] 551.2158, found 551.2139.

(±)-Elacomine (8). To a solution of **52** (70 mg, 0.13 mmol) in MeOH (20 mL) was added 10% Pd/C (7 mg), and the suspension was stirred vigorously under an atmosphere of H_2 at 1 bar for 3 h. The suspension was filtered through Celite, the filtrate was concentrated, and the residue was chromatographed on silica gel (EtOAc/MeOH 5:1) to afford **8** as a colorless solid (24 mg, 93%): mp 173−177 °C dec; IR (neat) 3264, 2957, 1699, 1632, 1468, 1346, 1156, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H), 0.95 (ddd, J = 13.8, 9.0, 4.3 Hz, 1 H), 1.36 (ddd, J = 13.8, 9.5, 5.4 Hz, 1H), 1.51 (m, 1 H), 2.21 (ddd, J = 13.3, 9.4, 6.1 Hz, 1 H), 2.25 (ddd, J = 13.3, 8.8, 5.5 Hz, 1H), 3.14 (ddd, J = 11.8, 9.4, 6.0 Hz, 1H), 3.21 (dd, J = 9.2, 4.3 Hz, 1H), 3.37 (ddd, J = 12.0, 8.4, 6.2, 1H), 6.40 (d, J = 2.1 Hz, 1 H), 6.47 (dd, J = 8.0, 2.1 Hz, 1H), 7.05 (d, J = 8.3, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 22.3, 25.2, 37.0, 38.3, 45.1, 57.4, 67.0, 97.8, 108.7, 121.5, 122.7, 142.8, 157.7, 182.9; HRMS calcd for $C_{15}H_{20}N_2O_2$ m/z 260.1525, found 260.1531.

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Supporting Information Available: Experimental procedures and characterization data not included in the Experimental Section; ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.