Conformational Switching and the Synthesis of Spiro[2*H*-indol]-3(1*H*)-ones by Radical Cyclization

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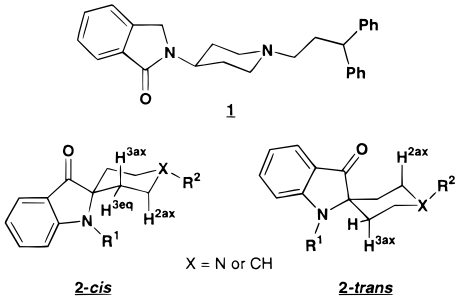
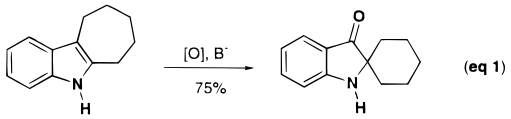
Radical cyclization of 1-(2-bromophenylamino)cyclohexanecarbonitriles (**3**, X = CH) and 4-(2-bromophenylamino)-4-piperidinecarbonitriles (**3**, X = N) provide spiro[2H-indole-2-cyclohexan]-3(1*H*)-imines (**5**, X = CH) and spiro[2H-indole-2,4′-piperidin]-3(1*H*)-imines (**5**, X = N), respectively, in 33−57% yields. This contradicts a recent report that 1-(2-bromophenylamino)cyclohexanecarbonitrile (**3**, X−R^2 = CH_2), treated under apparently identical conditions, led only to nitrile transfer product **6** (X−R^2 = CH_2). Acidic hydrolyses of the imines provide the corresponding ketones **2** in quantitative yields. Single-crystal X-ray analyses of ketone **2e** and nitrile **3e** indicate that the relative configuration of the aromatic nitrogen has been inverted during the cyclization. In addition, NOE NMR analyses of spiroindolepiperidine **2c** and its aniline-nitrogen-methylated analogue **10a** show that the relative conformation of the piperidine ring has inverted. Thus, methylation of **2c** acts as a conformational "switch" for the spiroindolepiperidine ring system.

Introduction

Isoindolylpiperidine (**1**) was identified by high-throughput screening in our laboratories as an inhibitor of microsomal triglyceride-transfer protein (MTP) function.[1] As part of a structure−activity-based study of **1**, we desired to prepare spiro[*2H*-indole-2,4′-piperidin]-3(1*H*)-ones (spiroindoxyls) of general structures **2-cis/2-trans** as conformationally restricted analogues.[2] The spiroindoxyls offer more structural rigidity than the lead compound and would therefore act as probes of the spatial requirements of the biological target. By altering the steric bulk of R^1, we hoped to orient the ring system in one of the two possible chair conformations, **2-cis** or **2-trans** (X = N). Thus, we envisioned the substituent R^1 as a conformational "switch"[3] for the spiroindoxyl ring system. We also anticipated that the *o*-amino ketone functionality of **2** would behave as an arylogous amide and thus mimic the isoindolone electron density.



Spiroindoxyls have been prepared previously by base-catalyzed rearrangements of oxidized indoles (eq 1).[4,5] For our purposes, this was judged not to be an attractive route. Preparation of the necessary indoles would be



difficult and the presence of a basic nitrogen in the saturated ring was anticipated to lead to complications in the oxidative rearrangement step.

We set out to design a mild synthetic route to spiroindoxyls that would accommodate a variety of functionality in the precursors. Anilinonitrile **3** (Scheme 1) appeared to be an attractive intermediate for such a synthetic sequence. Aryl radical **4**α was proposed to undergo 5-exo-dig cyclization to **5**α followed by reduction to form imine **5**. Subsequent hydrolysis of **5** would provide the desired spiroindoxyl **2**.

The feasibility of this reaction sequence was open to question. Potential competing side reactions include the direct reduction of radical **4**α to form **4,** and the cleavage of bond **b** of intermediate **5**α to form **6**α followed by reduction to the nitrile transfer product **6.** In fact, Beckwith[6,7] had shown that a related radical precursor

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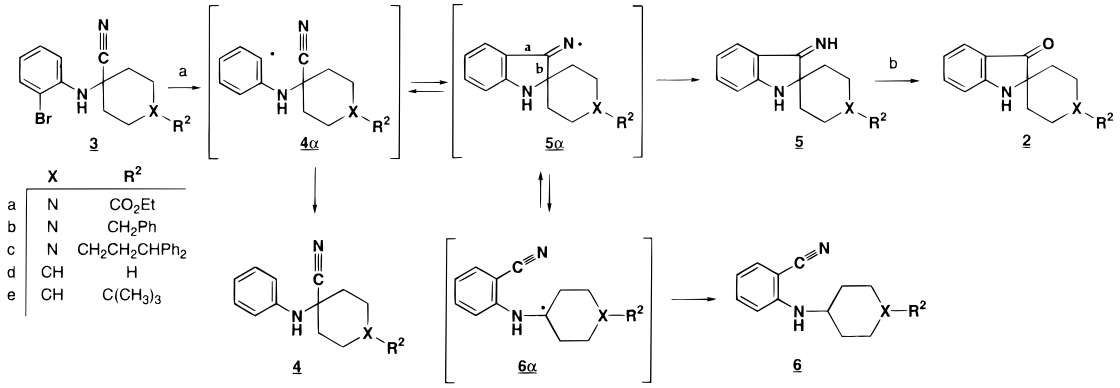
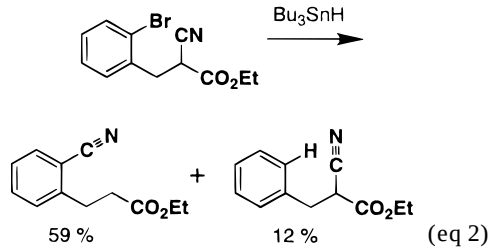
Scheme 1[a]



[a] Key: (a) i. Bu_3SnH, AIBN/toluene, reflux; ii. satd aq KF. (b) 1 M HCl/H_2O or H_2O−MeOH, reflux.

underwent an analogous nitrile transfer as the major pathway (eq 2).

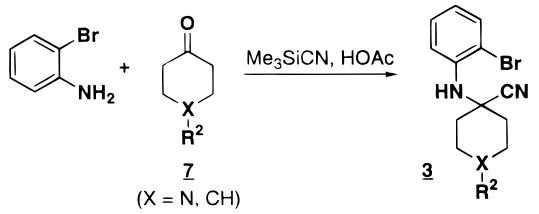


(eq 2)

After the completion of our studies, a report[8] appeared claiming that for the type of radical cyclization under study here (for example, substrate **3d**, Scheme 1), nitrile **6** was the sole reaction product. In contrast, we demonstrate that radical cyclization does provide the desired spiroindoxyl imines in moderate yields. In addition, we demonstrate that the nature of the R^1 substituent can have a dramatic effect on the conformational preference of the spiro ring system, providing either conformer **2-cis** or **2-trans** as desired.

Results and Discussion

Preparation of the substituted aniline **3** was achieved by a modified Strecker reaction.[9] Treatment of a mixture of 2-bromoaniline and cyclic ketones **7a**−**e** in acetic acid with cyanotrimethylsilane at room temperature for prolonged reaction times led to high yields of **3a**−**e** (eq 3, Table 1). This remarkable reaction provided the desired



(eq 3)

products despite a high degree of steric crowding, and occurred even though the substrate was a relatively nonbasic amine. Reaction under standard Strecker conditions (HOAc/KCN) led only to the undesired cyanohydrin.[10] Piperidone **7c** was prepared by alkylation of 1,4-dioxa-8-azaspiro[4.5]decane with 3,3-diphenylpropyl-1-tosylate[11] and subsequent hydrolysis of the ketal.

Table 1. Synthesis of Nitriles 3a−e, Spiroindoleimines 5a−e, and Spiroindolones 2a−e from Cyclic Ketones 7a−e

			yield (%)		
7	X	R^2	**3**[a]	**5**[b]	**2**[c]
a	N	CO_2Et	94	33	100
b	N	CH_2Ph	69	57	100
c	N	$CH_2CH_2CHPh_2$	60	57	83
d	CH	H	97	58	100
e	CH	$C(CH_3)_3$	76	45	100

[a] Condensation of 2-bromoaniline and cyclic ketones **7a**−**e** (eq 3). [b] Radical cyclization of **3a**−**e** to **5a**−**e** (Scheme 1). [c] Hydrolysis of **5a**−**e** to **2a**−**e** (Scheme 1).

Refluxing nitrile **3b** in a dilute solution of toluene (0.065 *M*) with 1.1 equiv of tributyltin hydride for 16 h (catalytic AIBN as initiator) and then quenching with half-saturated ammonium hydroxide solution gave two minor and two major products (Scheme 1). The direct reduction product **4b** and the nitrile transfer product **6b** were isolated in 3 and 5% yields, respectively. The two major products, however, were imine **5b**, (31% yield) and the corresponding ketone **2b** (26% yield). Further experimentation showed that reaction times as short as 1 h were sufficient for complete reaction. Quenching the reaction with aqueous potassium fluoride afforded imine **5b** in 57% yield (Table 1) without formation of the ketone **2b**. Changing reactant addition order or rate did not alter product distributions or yields, nor did increasing the relative amount of tributyltin hydride up to three equivalents. The highly fluorescent polar imine, a stable compound in neutral or basic solution, was readily isolated by normal phase silica gel chromatography. For substrates **3a** and **3c**, the yield of the cyclization products **5a** and **5c** were 33 and 57%, respectively, while the yields of the reduction and transfer products **4a,c** and **6a,c** remained low, and little of the reactant **3a** or **3c** was recovered from the reaction mixture. Cyclohexanes **3d** and **3e** also gave moderate yields of cyclized products **5d** and **5e** (Table 1). Hydrolyses of imines **5a**−**e** to ketones **2a**−**e** were effected quantitatively upon brief reflux with dilute hydrochloric acid.

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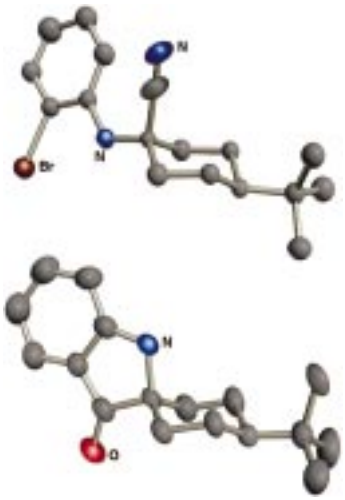


Figure 1. (top) The solid state conformation of **3e**. The apparent thermal ellipsoids of the axial cyano group reflect some angular disorder which persists in the crystal structure at −63 °C. (bottom) The solid state conformation of ketone **2e**.

A recent report[8] on related radical reactions described a very different outcome from that reported here. For example, reaction of **3d** with Bu_3SnH in toluene was reported to provide only **6d** in 45% yield with no cyclization products isolated. Under our reaction conditions, **3d** provided a 35% yield of a 1:24 mixture of **4d** and **6d** and a 58% yield of the spiroimine **5d**. We speculate that the highly polar imine could not have been isolated under the chromatography conditions described by the authors and may well have been present in the unpurified reaction mixture.

The stereochemical assignments for structure **3e** and **2e**, obtained by single-crystal X-ray analysis, provided useful insight with respect to the mechanism of cyclization.[12] The X-ray structure of **3e** (Figure 1), despite a small amount of disorder in the crystal lattice, clearly showed that the anilino nitrogen is equatorial and trans to the *tert*-butyl group. The X-ray structure of ketone **2e** (Figure 1b) indicated that the anilino nitrogen is now in the axial position. This suggests that initially formed radical **3e**α (Figure 2) closes to cyclic imine radical **5e**α, which rapidly undergoes bond scission to nitrile radical **6e**α, inversion to **6e***β*, reclosure to **5e***β*, and finally hydrogen abstraction to form **5e**. No product identifiable as **5f** (the result of **5e**α hydrogen abstraction) was discovered in the reaction mixture. These results suggest that the radical cyclization and ring opening reactions leading from **5e**α to **5e***β* must be rapid and reversible relative to the quenching of intermediates with Bu_3SnH. The barrier to inversion of pyramidal radicals similar to **6e**α and **6e***β* has been estimated at 3−6 kcal/mol[13] and thus low enough to allow a sufficient population of **5e***β* to form and quench to **5e**. Molecular models suggest that the selective trapping of **5e***β* relative to **5e**α is due to a more favorable approach of Bu_3SnH to the equatorial imine radical of **5e***β* where steric interference would be minimized, rather than to the axial imine radical of **5e**α. Alternatively, the reaction outcome may be determined by the stability of the radical intermediates, where the equatorial imine radical **5e***β* is the thermodynamically favored structure.

The indoxyl nitrogen of **2** could be alkylated or acylated (Scheme 2). For example, alkylation of **2a** with iodomethane using sodium bis(trimethylsilyl)amide in THF at 60 °C provided **8a** in 86% yield. Similar treatment of **2a** with benzyl bromide provided **8b** in 70% yield. When the sodium anion of **2b** was treated with stoichiometric allyl bromide for 48 h, compound **9** was produced in 62% yield without any sign of quaternization of the piperidine nitrogen. Removal of the piperidine nitrogen protecting group of **8a**, **8b**, and **9** and alkylation of the resulting piperidines with 3,3-diphenylpropyl tosylate provided compounds **10a**−**c**. In addition, **2c** was reacted with acetyl chloride, giving acetylated spiroindoxyl **10d**.

We examined the conformational preferences of **2c** and its *N*-methylated analogue **10a** by NMR spectroscopy. Assignments of the chemical shifts and *J* values of the ^{1}H NMR spectra for **2c** and **10a** indicate that they each exist in single and distinct conformation.[14] The positions of H^2 in **2c** and **10a** were suggestive of predominant cis and trans conformations, respectively, as shown in Figure 3. Methylated **10a** shows a 0.7-ppm downfield shift of H^{2ax} and a 0.2-ppm downfield shift of H^{2eq} compared to **2c**, indicative of a conformational switch. In addition, large $J_{3ax/2ax}$ coupling constants are seen for both **2c** (J = 9.7 Hz) and **10a** (J = 12.7 Hz), indicating that each compound exists in a distinct chair conformation.

The predominant conformations of **2c** and **10a** shown in Figure 3 were confirmed on the basis of 1D NOE data. A compound in the cis conformation should exhibit 1D nuclear Overhauser enhancements between the N−H (or N−CH_3) proton(s) and both the H^{3eq} and H^{2ax} protons, whereas in the trans conformation, enhancements between the N−H (or N−CH_3) proton(s) and the H^{3ax} proton should be observed. Irradiation of the N−H proton of **2c** led to enhancements of H^{3eq} (2%) and H^{2ax} (4%), consistent with the cis conformer. In contrast, irradiation of the N−CH_3 protons of **10a** led to enhancement of H^{3ax} (7%). No NOE effects were observed for protons H^{2ax} or H^{2eq}, consistent with compound **10a** adopting the trans conformation.

We propose that **2c** exists in the cis conformer so that the carbonyl avoids the H^2 axial protons to minimize 1,3-diaxial interactions found in the trans-conformation. In the case of **10a**, the methyl group is more sterically demanding than the carbonyl, and thus the carbonyl group now prefers to be in proximity to the H^2 axial protons in the trans-conformation. Thus, alkylation of the indoxyl nitrogen results in an inversion of the piperidine chair conformation.

Summary

We have demonstrated that, despite a conflicting report,[8] aryl radical cyclizations of nitriles **3a**−**e** do lead to cyclized products in moderate yields. The discrepancy between our observations and those previously reported[8] may be due to the high polarity and masking fluorescence

(12) Coordinates for the X-ray determinations have been deposited in the Cambridge Crystallographic Database and can be obtained upon request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(13) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1981; pp 677−681.

(14) Coupling constants (free base in DMSO-d_6). **2c**: J_{2gem} = 11.7 Hz, $J_{3eq/2ax}$ < 2 Hz, J_{3gem} = 12.2 Hz, $J_{3ax/2ax}$ = 9.7 Hz. **10a**: J_{2gem} = 11.0 Hz, $J_{3ax/2ax}$ = 12.7 Hz, $J_{3ax/2eq}$ = 4.6 Hz, J_{3gem} = 11.6 Hz.

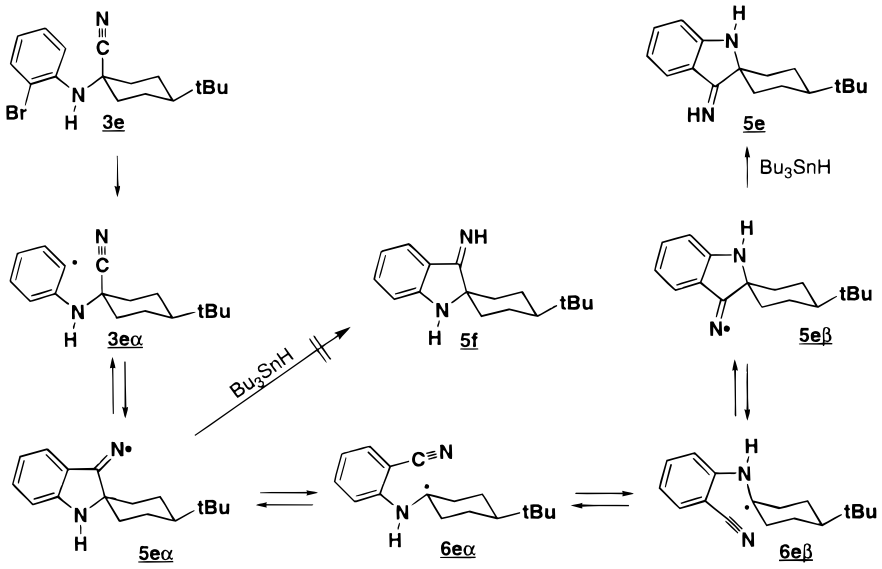


Figure 2. Postulated reaction scheme for the formation of spiroindoxylimine **2e** from nitrile **1e**.

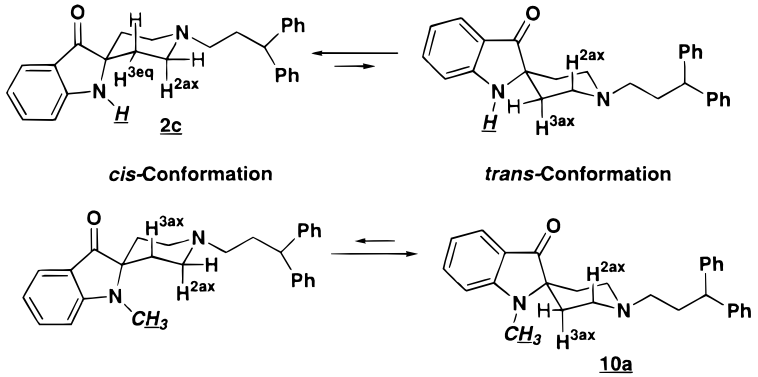
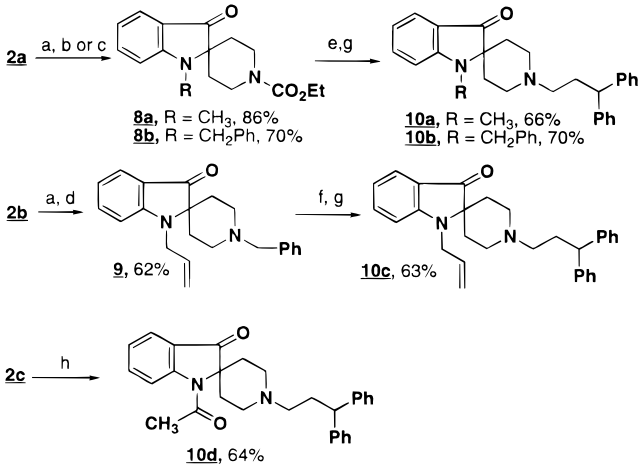


Figure 3. Nuclear Overhauser enhancement experiment on compounds **2c** and **10a**. Italicized and underlined protons were irradiated; bold-faced protons indicate NOE enhancement.

Scheme 2[a]



[a] Key: (a) $NaN(TMS)_2$/THF; (b) CH_3I; (c) $PhCH_2Br$; (d) 1.1 equiv $CH_2{=}CHCH_2Br$; (e) TMSI/CH_3CN; (f) CH_3CHClO_2CCl/CH_2Cl_2; (e) K_2CO_3/^{i}PrOH, $Ph_2CHCH_2CH_2OTs$; (n) CH_3COCl/CH_2Cl_2.

of imines **5a**−**e**,[15] making identification and isolation unobvious. The spiroindoxyl imines **5a**−**e** are thermally and chemically stable compounds, and are the first indol-3-imines to be reported. In addition, both the imines **5a**−**c** and the corresponding ketones **2a**−**c** are the first examples of a previously unreported spiro system.

Furthermore, unalkylated spiroketone **2a** and its *N*-methylated counterpart **10a** have been shown to exist in different and distinct ring conformations. The presence or absence of substituent R^1 serves as a "conformational switch", a phenomenon which may have broader applicability in molecular design.

(15) The 254-nm fluorescence of commonly used TLC plates makes the fluorescent imine difficult to see against the background.

Experimental Section

General Experimental Details. Melting points are uncorrected. 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR spectra were recorded using $CDCl_3$ as the solvent unless otherwise indicated, and signal positions (δ values) were measured relative to the signals for TMS (δ 0.00) and $CDCl_3$ (δ 77.0), respectively. Nuclear Overhauser enhancement experiments were performed at 500 MHz field strength. TLC was carried out using commercial glass-backed silica gel 60 plates. Flash chromatography was performed on 230−400 mesh silica gel (E. Merck).

All reactions were carried out under an atmosphere of dry argon using flame-dried or oven-dried glassware.

General Procedure for the Preparation of 4-(2-Bromophenylamino)-4-piperidinecarbonitrile or Cyclohexanecarbonitriles (3). To a stirred mixture of the 4-piperidone or cyclohexanone (30.0 mmol) and 2-bromoaniline (5.16 g, 30.0 mmol) in HOAc (25 mL) at room temperature was added

TMSCN (4.20 mL, 31.5 mmol). After 24−112 h, the reaction was poured into ice-cold 7 N NH_4OH (100 mL). The resulting solids were collected, washed with water, and dried in vacuo at 40 °C. Purified products were obtained either by recrystallization or flash column chromatography on silica gel.

Ethyl 4-(2-Bromophenylamino)-4-cyano-1-piperidinecarboxylate (3a): Reaction of ethyl 4-oxo-1-piperidinecarboxylate (5.00 g, 27.3 mmol, reaction time 112 h) as described in the general procedure gave, after purification by silica gel chromatography (1:49 Et_2O/CH_2Cl_2), **3a** (9.64 g, 94%) as a colorless oil: ^{1}H NMR δ 7.49 (dd, 1 H, J = 1.4, 8.0 Hz), 7.25 (dt, 1 H, J = 1.4, 8.2 Hz), 7.18 (dd, 1 H, J = 1.6, 8.0 Hz), 6.77 (dt, 1 H, J = 1.6, 7.5 Hz), 4.30 (s, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 3.96 (br d, 2 H, J = 13.7 Hz), 3.42 (dt, 2 H, J = 3.8, 10.0 Hz), 2.37 (br dd, 2 H, J = 3.2, 13.5 Hz), 1.90 (dt, 2 H, J = 4.0, 10.0 Hz), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 155.0, 140.2, 133.0, 128.4, 121.1, 119.5, 115.7, 112.5, 61.7, 52.3, 39.7, 35.3, 14.6; IR (thin film) 2230, 1700 cm^{-1}; MS (CI) m/z 369/371 (M + NH_3), 351/353 (M + H), 325/327 (M − CN).

4-(2-Bromophenylamino)-1-(phenylmethyl)-4-piperidinecarbonitrile (3b). Reaction of 1-(phenylmethyl)-4-piperidone (1.00 g, 5.28 mmol, reaction time 65 h) as described in the general procedure gave, after purification by silica gel chromatography (3:17 EtOAc/hexane), **3b** (1.35 g, 69%) as a white solid: mp 91−93 °C; ^{1}H NMR δ 7.46 (dd, 1 H, J = 1.3, 8.0 Hz), 7.3−7.1 (m, 5 H), 6.71 (dt, 1 H, J = 1.8, 7.4 Hz), 4.40 (s, 1 H), 3.54 (s, 2 H), 2.73 (br d, 2 H, J = 11.4 Hz), 2.50 (dt, 2 H, J = 2.6, 9.7 Hz), 2.37 (dd, 2 H, J = 3.0, 13.7 Hz), 1.99 (br t, 2 H, J = 11.8 Hz); ^{13}C NMR δ 140.6, 137.8, 132.8, 128.9, 128.3, 127.2, 120.5, 120.3, 115.4, 112.1, 62.5, 52.0, 48.9, 35.6; IR (thin film) 2228 cm^{-1}; MS (CI) m/z 370/372 (M + H).

4-(2-Bromophenylamino)-1-(3,3-diphenylpropyl)-4-piperidinecarbonitrile (3c). Reaction of 1-(3,3-diphenylpropyl)-4-piperidone (2.93 g, 9.23 mmol, reaction time 24 h) as described in the general procedure gave, after purification by silica gel chromatography (1:4 EtOAc/hexane), **3c** (2.85 g, 60%) as a colorless oil: ^{1}H NMR δ 7.41 (dd, 1 H, J = 1.0, 8.5 Hz), 7.22 (m, 8 H), 7.14 (m, 4 H), 6.64 (dt, 1 H, J = 2.9, 5.6 Hz), 4.37 (s, 1 H), 3.97 (t, 1 H, J = 7.5), 2.62 (br d, 2 H, J = 9.5 Hz), 2.4−2.1 (m, 8 H), 1.92 (br t, 2 H, J = 15 Hz); ^{13}C NMR δ 144.5, 140.4, 132.7, 128.2, 128.1, 127.6, 126.0, 120.4, 120.0, 115.3, 112.0, 55.9, 51.8, 48.8, 48.6, 35.5, 32.6; IR (thin film) 2230 cm^{-1}; MS (CI) m/z 474/476 (M + H), 447/449 (M − CN). Anal. Calcd for $C_{27}H_{28}N_3Br$: C, 68.35; H, 5.95; N, 8.86; Br, 16.84. Found: C, 68.13; H, 5.87; N, 9.02; Br, 16.64.

1-(2-Bromophenylamino)-1-cyclohexanecarbonitrile (3d). Reaction of cyclohexanone (2.95 g, 30.0 mmol, reaction time 48 h) as described in the general procedure gave, after purification by silica gel chromatography (1:4 EtOAc/hexane) and recrystallization, **3d** (8.13 g, 97%) as a white solid: mp 98−99 °C (hexane); ^{1}H NMR δ 7.46 (dd, 1 H, J = 1.3, 8.0 Hz), 7.19 (m, 2 H), 6.70 (dt, 1 H, J = 2.0, 6.9 Hz), 4.40 (s, 1 H), 2.35 (m, 2 H), 1.73 (m, 6 H), 1.38 (dt, 2 H, J = 5.2, 9.0 Hz); ^{13}C NMR δ 140.7, 132.7, 128.2, 120.6, 115.2, 111.8, 53.3, 36.1, 24.7, 21.8; MS (CI) m/z 278/280 (M + H). Anal. Calcd for $C_{13}H_{15}N_2$-Br: C, 55.93; H, 5.42; N, 10.03; Br, 28.62. Found: C, 55.95; H, 5.43; N, 10.03; Br, 28.45.

***trans*-1-(2-Bromophenylamino)-4-(1,1-dimethylethyl)-cyclohexanecarbonitrile (3e).** Reaction of 4-(1,1-dimethylethyl)cyclohexanone (4.63 g, 30.0 mmol, reaction time 48 h) as described in the general procedure gave, after recrystallization, **3e** as white needles: mp 149−150 °C (EtOAc); ^{1}H NMR δ 7.47 (dd, 1 H, J = 1.4, 8.0 Hz), 7.19 (m, 2 H), 6.70 (ddd, 1 H, J = 0.8, 1.8, 7.1 Hz), 4.40 (s, 1 H), 2.59 (dd, 2 H, J = 2.0, 17.8 Hz), 1.88 (m, 2 H), 1.53 (m, 2 H), 1.11 (m, 1 H), 0.91 (s, 9 H); ^{13}C NMR δ 144.0, 132.8, 128.3, 120.3, 120.1, 115.3, 111.9, 54.4, 47.0, 37.2, 32.3, 27.4, 23.7; MS (CI) m/z 334/336 (M + H). Anal. Calcd for $C_{17}H_{23}N_2Br$: C, 60.90; H, 6.91; N, 8.36; Br, 23.83. Found: C, 60.92; H, 6.88; N, 8.35; Br, 23.83.

1-(3,3-Diphenylpropyl)-4-piperidone (7c). To a stirred solution of 1,4-dioxa-8-azaspiro[4.5]decane (2.15 g, 15.0 mmol) and 3,3-diphenylpropyl-1-tosylate (5.49 g, 15.0 mmol) in ^{i}PrOH (30 mL) under argon at room temperature was added anhydrous K_2CO_3 (3.1 g, 22.5 mmol). The mixture was refluxed for 4 h, cooled, and filtered (washing with CH_2Cl_2), and the filtrate was evaporated. Purification by silica gel chromatography (3:1 EtOAc/hexanes) gave 8-(3,3-diphenylpropyl)-1,4-dioxa-8-azaspiro[4.5]decane as a light yellow oil: 4.30 g, 85% yield; ^{1}H NMR δ 7.23 (m, 8 H), 7.14 (m, 2 H), 3.97 (t, 1 H, J = 7.4 Hz), 3.89 (s, 4H), 2.47 (br s, 4 H), 2.25 (m, 4 H), 1.73 (t, 4 H, J = 5.5 Hz); ^{13}C NMR δ 144.7, 128.3, 127.7, 126.0, 107.2, 64.0, 56.3, 51.3, 49.0, 34.8, 33.0; MS (CI) m/z 338 (M + H).

A stirred mixture of 8-(3,3-diphenylpropyl)-1,4-dioxa-8-azaspiro[4.5]decane (4.30 g, 14.2 mmol) in 6 M HCl (48 mL) was set to reflux for 40 min. The resulting solution was cooled, brought to pH 10 with 1 M NaOH solution, and extracted twice with CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4), and evaporated to give **7c** (3.40 g, 91% yield) as a yellow solid: mp 88−90 °C; ^{1}H NMR δ 7.28 (m, 8 H), 7.18 (m, 2 H), 4.05 (t, 1 H, J = 7.6 Hz), 2.68 (t, 2 H, J = 6.0 Hz), 2.42 (t, 4 H, J = 6.0 Hz), 2.28 (t, 2 H, J = 7.3 Hz); ^{13}C NMR δ 209.1, 144.6, 128.4, 127.7, 126.1, 48.8, 41.1, 33.2; MS (CI) m/z 294 (M + H).

1′-(Phenylmethyl)-spiro[2*H*-indole-2,4′-piperidine]-3(1*H*)-imine (5b), 1-(Phenylmethyl)-4-(2-cyanophenyl)-1-piperidine (6b), and 1′-(Phenylmethyl)-spiro[2*H*-indole-2,4′-piperidin]-3(1*H*)-one (2b). To a refluxing solution of **3b** (605 mg, 1.63 mmol) in toluene (25 mL) was added AIBN (15 mg, 0.1 mmol) and then Bu_3SnH (0.480 mL, 1.79 mmol), dropwise, over 40 min. After 2 h and again after 4 h, an additional portion of AIBN (5 mg) was added. After 16 h of reflux, the reaction was cooled and then vigorously stirred with 7 M NH_4OH (20 mL). After 40 min, the reaction was extracted twice with EtOAc. The organic extracts were combined, dried (Na_2SO_4), and purified by silica gel chromatography. The first fraction, eluted with 9:1 EtOAc/hexane provided **6b** (35 mg, 5% yield) as a colorless oil: ^{1}H NMR δ 7.38 (m, 9 H), 6.61 (m, 2 H), 4.43 (d, 1 H, J = 7.0 Hz), 3.40 (m, 1 H), 2.88 (br d, 2 H, J = 17.0 Hz), 2.13 (m, 2 H), 2.03 (br d, 2 H, J = 17.0 Hz) 1.62 (m, 2 H); ^{13}C NMR δ 149.2, 138.2, 134.1, 132.9, 129.0, 128.2, 127.0, 117.9, 116.2, 111.0, 95.8, 63.0, 51.9, 49.6, 32.0; IR (thin film) 2215 cm^{-1}; MS (CI) m/z 292 (M + H).

Further elution with 1:4 MeOH/EtOAc provided two fractions: less polar **2b** (124 mg, 26% yield) as a yellow solid, mp 142−143 °C (EtOH/H_2O); ^{1}H NMR δ 7.60 (d, 1 H, J = 7.7 Hz), 7.43 (dt, 1 H, J = 1.0, 7.0 Hz), 7.33 (m, 5 H), 6.87 (d, 1 H, J = 8.1 Hz), 6.80 (t, 1 H, J = 7.4 Hz), 5.20 (br s, 1 H), 3.58 (s, 1 H), 2.98 (dt, 2 H, J = 3.5, 11.9 Hz), 2.23 (dt, 2 H, J = 2.2,12.0 Hz), 2.08 (dt, 2 H, J = 3.8, 11.8 Hz), 1.43 (d, 2 H, J = 13.0 Hz); ^{13}C NMR δ 204.1, 159.7, 138.0, 137.0, 128.9, 128.2, 127.0, 124.8, 120.4, 118.8, 112.6, 64.8, 63.0, 49.9, 33.0; IR (thin film) 1670, 1620 cm^{-1}; MS (CI) m/z 293 (M + H). Anal. Calcd for $C_{19}H_{20}N_2O\cdot 0.17H_2O$: C, 77.23; H, 6.94; N, 9.48. Found: C, 77.16; H, 6.72; N, 9.55.

More polar **5b** (148 mg, 31% yield) as an amorphous foam: ^{1}H NMR δ 7.83 (br s, I H), 7.54 (d, 1 H, J = 7.3 Hz), 7.4−7.2 (m, 6 H), 6.80 (d, 1 H, J = 8.3 Hz), 6.79 (t, 1 H, J = 7.2 Hz), 4.95 (br s, 1 H), 3.59 (s, 1 H), 2.98 (br d, 2 H, J = 11.8 Hz), 2.25 (dt, 2 H, J = 1.8,12.2 Hz), 2.01 (dt, 2 H, J = 1.9, 5.9 Hz), 1.54 (dd, 2 H, J = 2.0,13.3 Hz); ^{13}C NMR δ 183.8, 154.7, 138.0, 137.9, 134.2, 128.9, 128.2, 127.1, 122.9, 121.8, 118.7, 111.8, 63.8, 63.0, 50.0, 35.5; IR (thin film) 1740, 1625 cm^{-1}; MS (CI) m/z 292 (M + H).

Alternatively, the crude reaction mixture was treated with saturated KF (see procedure for **5a** below) to provide the imine **5b** in 57% yield.

Ethyl 1,3-Dihydro-3-imino-spiro[2*H*-indole-2,4′-piperidine]-1′-carboxylate (5a). To a stirred, argon-purged solution of **3a** (7.90 g, 22.4 mmol) and AIBN (450 mg) in toluene (350 mL) was added Bu_3SnH (6.7 mL, 24.6 mmol) at room temperature. The solution was evacuated and purged three times with argon and then set to reflux for 1 h. The resulting bright yellow solution was cooled to room temperature, and the reaction was quenched with saturated KF solution (100 mL). After 30 min of vigorous stirring, the reaction was diluted with EtOAc and filtered through Celite. The organic layer was separated, dried (Na_2SO_4), and evaporated. Purification by silica gel chromatography (1:49 MeOH/EtOAc) gave **5a** as an amorphous yellow solid (2.00 g, 33% yield): ^{1}H NMR δ 8.35 (br s, 1 H), 7.48 (d, 1 H, J = 7.5 Hz), 7.31 (dt, 1 H, J = 1.2, 8.1 Hz), 6.79 (d, 1 H,

J = 7.9 Hz), 6.79 (t, 1 H, *J* = 7.1 Hz), 5.39 (br s, 1 H), 4.25 (br d, 2 H, *J* = 9.5 Hz), 4.15 (q, 2 H, *J* = 7.1 Hz), 3.12 (br t, 2 H, *J* = 11.9 Hz), 1.90 (dt, 2 H, *J* = 4.7, 12.3 Hz), 1.55 (d, 2 H, *J* = 12.6 Hz), 1.27 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 183.1, 155.2, 154.4, 134.0, 122.5, 121.0, 118.5, 111.7, 63.5, 61.2, 40.1, 34.9, 14.4; IR (KBr pellet) 3360, 1616 cm^{-1}; MS (CI) *m*/*z* 274 (M + H). Anal. Calcd for $C_{15}H_{19}N_3O_2 \cdot 0.4EtOAc$: C, 64.61; H, 7.25; N, 13.62. Found: C, 64.59; H, 7.20; N, 13.95.

1′-(3,3-Diphenylpropyl)-spiro[2*H*-indole-2,4′-piperidine]-3(1*H*)-imine (5c). Cyclization of **3c** (2.73 g, 5.75 mmol) as for **3a** above, provided, after purification by silica gel chromatography (EtOAc, followed by 3:17 MeOH/EtOAc), **5c** as an amorphous yellow solid (1.30 g, 57% yield): ^{1}H NMR δ 8.55 (br s, 1 H), 7.25 (m, 9 H), 7.16 (m, 2 H), 6.76 (m, 2 H), 4.91 (br s, 1 H), 4.06 (t, 1 H, *J* = 7.2 Hz), 2.92 (d, 2 H, *J* = 11.1 Hz), 2.11 (t, 2 H, *J* = 11.7 Hz), 2.01 (t, 2 H, *J* = 11.1 Hz), 1.50 (d, 2 H, *J* = 12.5 Hz); ^{13}C NMR δ 183.6, 154.5, 144.6, 133.9, 128.2, 127.7, 125.9, 122.8, 121.8, 118.6, 111.6, 63.8, 56.5, 50.0, 48.5, 35.5, 32.6; IR (KBr pellet) 3414, 1620 cm^{-1}; MS (CI) *m*/*z* 396 (M + H). Anal. Calcd for $C_{27}H_{29}N_3O_2 \cdot 1.5H_2O$: C, 76.74; H, 7.63; N, 9.94. Found: C, 76.66; H, 7.84; N, 9.90.

1-(Phenylamino)cyclohexanecarbonitrile (4d), Spiro-[2*H*-indole-2-cyclohexane]-3(1*H*)-imine (5d), and *N*-Cyclohexyl-2-aminobenzonitrile (6d). To a stirred, argon-purged solution of **3d** (1.40 g, 5.01 mmol) and AIBN (50 mg, 0.3 mmol) in toluene (80 mL) was added Bu_3SnH (1.50 mL, 5.5 mmol) in one portion at room temperature. The solution was evacuated and purged three times with argon and then set to reflux. After 1 h, reverse-phase HPLC analysis indicated that no **3d** remained and two products had formed. After 16 h of reflux, HPLC showed no change in the ratio of products. The resulting bright yellow solution was cooled to room temperature, saturated KF solution (20 mL) was added, and the reaction was stirred rapidly for 30 min. The mixture was diluted with EtOAc and filtered through Celite. The organic phase was separated, dried (Na_2SO_4), and evaporated to give a yellow syrup (1.32 g). Purification by silica gel chromatography (2:3 CH_2Cl_2/hexanes) provided a white solid (381 mg). NMR analysis showed this to be an inseparable 1:24 mixture of **4d** and **6d** (35%). Data for **4d**: ^{1}H NMR δ 7.45 (d, 2 H), 4.40 (br s, 1 H), 2.70 (q, 1 H), 2.35 (m, 4 H); ^{13}C NMR δ 141, 127.9, 119.9, 114.9, 53.0, 35.8, 21.6. Data for **6d**: ^{1}H NMR δ 7.32 (m, 2 H), 6.60 (m, 2 H), 4.45 (br d, 1 H, *J* = 7.4 Hz), 3.31 (dt, 1 H, *J* = 4.0, 9.9 Hz), 2.00 (br d, 2 H, *J* = 11.0 Hz), 1.62 (m, 4 H), 1.23 (m, 6 H); ^{13}C NMR δ 149.1, 133.8, 132.4, 117.7, 115.6, 110.7, 95.0, 50.9, 32.6, 25.3, 24.4; MS (FAB) *m*/*z* 201 (M + H). Further elution with 7:43 MeOH/EtOAc followed by trituration with CH_2Cl_2/hexane provided **5d** (575 mg, 58%) as a yellow solid: mp 40−41 °C; ^{1}H NMR δ 8.70 (br s, 1 H), 7.51 (d, 1 H, *J* = 7.6 Hz), 7.28 (dt, 1 H, *J* = 1.9, 8.2 Hz), 6.77 (d, 1 H, *J* = 8.2 Hz), 6.76 (dd, 1 H, *J* = 7.6, 8.2 Hz), 5.09 (br s, 1 H), 1.8−1.3 (m, 10 H); ^{13}C NMR δ 184.6, 154.7, 133.8, 122.7, 121.3, 118.1, 111.5, 65.6, 35.3, 24.7, 22.4; MS (CI) *m*/*z* 201 (M + H). Anal. Calcd for $C_{13}H_{16}N_2 \cdot 0.12CH_2Cl_2$: C, 75.13; H, 7.62; N, 13.23. Found: C, 75.12; H, 7.70; N, 13.36.

General Procedure for the Preparation of Spiro[2*H*-indole-2,4′-piperidin]-3(1*H*)-ones and Cyclohexan-3(1*H*)-ones (2). A mixture of **5** (5.0 mmol) and 1 M HCl (10 mL) was heated at 100 °C under argon for 1 h. The resulting solution was cooled and adjusted to pH 8 with saturated $NaHCO_3$ solution followed by extraction with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated. Trituration with Et_2O provided **2** as a bright yellow fluorescent solid sufficiently pure for elemental analysis.

Ethyl 1,3-Dihydro-3-oxo-spiro[2*H*-indole-2,4′-piperidine]-1′-carboxylate (2a). Hydrolysis of **5a** (1.18 g, 4.32 mmol) as described in the general procedure gave **2a** (1.18 g, 100%) as a yellow solid: mp 133−135 °C; ^{1}H NMR δ 7.60 (dd, 1 H, *J* = 0.6, 7.5 Hz), 7.46 (dt, 1 H, *J* = 1.3, 7.0 Hz), 6.90 (dd, 1 H, *J* = 0.6, 7.7 Hz), 6.83 (dt, 1 H, *J* = 0.6, 7.4 Hz), 5.55 (br s, 1 H), 4.16 (m, 4 H), 3.23 (br t, 2 H, *J* = 11.6 Hz), 1.94 (ddd, 2 H, *J* = 4.5, 6.8, 12.4 Hz), 1.48 (d, 2 H, *J* = 13.4 Hz), 1.28 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 203.4, 159.9, 155.4, 137.3, 124.8, 119.9, 119.0, 112.6, 64.4, 61.4, 40.1, 32.5, 14.6; IR (KBr pellet) 3304, 1694, 1678 cm^{-1}; MS (CI) *m*/*z* 275 (M + H). Anal. Calcd for $C_{15}H_{18}N_3O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.78; H, 6.51; N, 10.08.

1′-(Phenylmethyl)-spiro[2*H*-indole-2,4′-piperidin]-3(1*H*)-one (2b). Hydrolysis of **5b** (1.31 g, 4.49 mmol) as described in the general procedure gave **2b** (1.31 g, 100%) as a yellow solid, mp 142−144 °C, which was identical to that which was obtained directly from **3b** as described above.

1′-(3,3-Diphenylpropyl)-spiro[2*H*-indole-2,4′-piperidin]-3(1*H*)-one (2c). Hydrolysis of **5c** (485 mg, 1.23 mmol) as described in the general procedure gave **2c** (440 mg, 83%) as a yellow solid (the monohydrochloride salt): mp >240 °C; ^{1}H NMR (free base in DMSO-d_6) δ 7.70 (s, 1 H), 7.37 (m, 2 H), 7.31 (m, 8 H), 7.16 (m, 1 H), 6.85 (d, 1 H, *J* = 8.2 Hz), 6.66 (t, 1 H, *J* = 7.6 Hz), 4.03 (t, 1 H, *J* = 6.5 Hz), 2.80 (d, 2 H, *J* = 11.7 Hz), 2.23 (m, 6 H), 1.75 (dt, 2 H, *J* = 9.7, 12.2 Hz), 1.21 (d, 2 H, *J* = 12.2 Hz); ^{13}C NMR (in $CDCl_3$) δ 204.0, 159.7, 144.7, 137.0, 128.4, 127.8, 124.8, 124.8, 120.4, 118.9, 112.6, 64.9, 56.6, 50.0, 48.6, 33.0, 32.6; IR (KBr pellet) 3202, 2496, 1697 cm^{-1}; MS (CI) *m*/*z* 397 (M + H). Anal. Calcd for $C_{27}H_{28}N_2O \cdot HCl$: C, 74.90; H, 6.75; N, 6.47; Cl, 8.19. Found: C, 74.68; H, 6.79; N, 6.57; Cl, 8.36.

Spiro[2*H*-indole-2,4′-cyclohexan]-3(1*H*)-one (2d). Hydrolysis of **5d** (260 mg, 1.29 mmol) was accomplished in refluxing MeOH (5 mL) and 1 M HCl (5 mL) for 1 h under argon. The reaction mixture was brought to pH 8 with 1 M KOH and extracted twice with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Recrystallization from CH_2Cl_2/hexane gave **2d** (260 mg, 100%) as yellow platelets: mp 133−135 °C; ^{1}H NMR δ 7.59 (d, 1 H, *J* = 7.7 Hz), 7.42 (dt, 1 H, *J* = 1.4, 7.3 Hz), 6.89 (d, 1 H, *J* = 8.6 Hz), 6.77 (dt, 1 H, *J* = 2.1, 7.7 Hz), 5.53 (br s, 1 H), 1.85 (d, 2 H, *J* = 7.7 Hz), 1.77 (d, 2 H, *J* = 8.1), 1.46 (m, 6 H); ^{13}C NMR δ 205.0, 160.0, 136.9, 124.7, 120.0, 118.3, 112.5, 32.7, 24.7, 22.4; IR (KBr pellet) 3333, 1680 cm^{-1}; MS (CI) *m*/*z* 202 (M + H). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.39; H, 7.54; N, 6.91.

***trans*-4′-(1,1-Dimethylethyl)-spiro[2*H*-indole-2-cyclohexane]-3(1*H*)-imine (5e) and *trans*-4′-(1,1-Dimethylethyl)-spiro[2*H*-indole-2-cyclohexane]-3(1*H*)-one (2e).** Cyclization of **2e** (1.07 g, 3.19 mmol) as described for the synthesis of **5a** gave **5e** (365 mg, 45%) as a bright yellow glass: MS (CI) *m*/*z* 257 (M+H). Hydrolysis of 150 mg (0.59 mmol) of **5e** was accomplished in refluxing MeOH (2 mL) and 3 M HCl (2 mL) for 1 h under argon. The reaction mixture was brought to pH 8 with 1 M KOH and extracted twice with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Recrystallization gave **2e** (149 mg, 100% yield) as fine yellow needles: mp 215−216 °C (CH_2Cl_2/hexane); ^{1}H NMR δ 7.61 (d, 1 H, *J* = 7.7 Hz), 7.44 (dt, 1 H, *J* = 1.0, 7.1 Hz), 6.89 (d, 1 H, *J* = 8.5 Hz), 6.81 (t, 1 H, *J* = 7.7 Hz), 5.11 (br s, 1 H), 4.06 (t, 1 H, *J* = 7.0 Hz), 1.92 (d, 2 H, *J* = 3.8 Hz), 1.78 (dt, 2 H, *J* = 4.5, 16.6 Hz), 1.51 (d, 2 H, *J* = 12.1 Hz), 1.18 (m, 4 H), 0.91 (s, 9 H); ^{13}C NMR δ 205.0, 159.9, 136.9, 124.9, 120.6, 118.7, 112.6, 66.9, 46.6, 33.4, 32.4, 27.4, 23.7; IR (KBr pellet) 3290, 1674 cm^{-1}; MS (CI) *m*/*z* 258 (M + H). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.35; H, 9.03; N, 5.33.

Ethyl 1,3-Dihydro-3-oxo-spiro[2*H*-indole-2,4′-piperidine]-1′-carboxylate (8a). To a stirred solution of **2a** (532 mg,1.94 mmol) in THF (10 mL) at room temperature under argon was added $NaN(TMS)_2$ solution (2.0 mL, 2.0 mmol, 1 M in THF) over 5 min. A deep red, nearly unstirrable slurry formed. After 1 h, CH_3I (0.15 mL, 2.4 mmol) was added in one portion. After an additional 3 h, the resulting light yellow solution was quenched with brine and extracted twice with EtOAc. The organic extracts were combined, dried ($MgSO_4$), and evaporated. Purification by silica gel chromatography (1:24 Et_2O/CH_2Cl_2) provided **8a** (477 mg, 86%) as a light yellow amorphous solid: ^{1}H NMR δ 7.55 (dd, 1 H, *J* = 0.6, 7.7 Hz), 7.46 (dt, 1 H, *J* = 1.3, 7.2 Hz), 6.74 (d, 1 H, *J* = 8.3 Hz), 6.71 (t, 1 H, *J* = 7.4 Hz), 4.15 (q, 2 H, *J* = 7.0 Hz), 4.12 (br s, 2 H), 3.72 (br s, 2 H), 2.88 (s, 3 H), 1.89 (dt, 2 H, *J* = 4.7, 12.7 Hz), 1.47 (d, 2 H, *J* = 11.7 Hz), 1.29 (t, 2 H, *J* = 7.1 Hz); ^{13}C NMR δ 203.6, 159.4, 155.5, 137.5, 124.6, 118.3, 117.0, 108.4, 64.9, 61.2, 38.1, 28.3, 26.7, 14.6; IR (KBr pellet) 1688 cm^{-1}; MS (CI)

m/*z* 306 (M + NH_4), 289 (M + H). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.57; H, 6.79; N, 7.13.

1-Methyl-1′-(3,3-diphenylpropyl)-spiro[2*H*-indole-2,4′-piperidin]-3(1*H*)-one (10a). To a stirred solution of **8a** (359 mg, 1.25 mmol) in rigorously dried CH_3CN (4 mL) at room temperature under argon was added TMSI (190 μL, 1.33 mmol). The reaction was heated to reflux for 16 h and then quenched with MeOH. The reaction mixture was evaporated twice from MeOH and then twice from CH_2Cl_2 to provide a yellow foam. At rt under argon, this foam was dissolved in ^{i}PrOH (10 mL) and, with stirring, 3,3-diphenylpropyl tosylate (460 mg, 1.26 mmol) followed by K_2CO_3 (430 mg, 3.1 mmol). After 16 h of reflux, the reaction mixture was cooled and filtered, and the filtrate was evaporated. Purification by silica gel chromatography of the residue (3:17 ^{i}PrOH/hexane) provided **10a** (338 mg, 66%) as a yellow fluorescent solid after trituration in Et_2O: mp 114−116 °C; ^{1}H NMR (DMSO-d_6) δ 7.46 (dd, 1 H, J = 6.9, 8.3 Hz), 7.37 (d, 1 H, J = 7.8 Hz), 7.3−7.2 (m, 8 H), 7.15 (dd, 1 H, J = 6.8, 7.8 Hz), 6.89 (d, 1 H, J = 8.3 Hz), 6.65 (dd, 1 H, J = 6.9, 7.8 Hz), 4.02 (t, 2 H, J = 7.8 Hz), 2.88 (s, 3 H), 2.80 (dd, 2 H, J = 11.0, 12.7 Hz), 2.65 (ddd, 2 H, J = 4.6, 11.0, 11.6 Hz), 2.30 (m, 2 H), 2.22 (m, 2 H), 1.93 (dt, 2 H, J = 4.6, 11.6 Hz), 1.33 (d, 2 H, J = 11.6 Hz); ^{13}C NMR ($CDCl_3$) δ 204.0, 159.5, 144.7, 137.2, 128. 4, 127.8, 126.1, 124.7, 118.7, 116.8, 108.3, 65.2, 56.7, 49.3, 57.5, 32.8, 28.6, 26.9; IR (KBr pellet) 1692 cm^{-1}; MS (CI) *m*/*z* 411 (M + H). Anal. Calcd for $C_{28}H_{30}N_2O\cdot 0.18Et_2O$: C, 81.38; H, 7.56; N, 6.61. Found: C, 81.37; H, 7.32; N, 6.78.

1′-(3,3-Diphenylpropyl)-1-(phenylmethyl)-spiro[2*H*-indole-2,4′-piperidin]-3(1*H*)-one (10b). By the same procedure as **8a**, **2b** (0.500 g, 1.82 mmol) and benzyl bromide (0.25 mL, 2.5 mmol) gave **8b** (465 mg, 70%) as a yellow amorphous solid. The compound was used in the next procedure without characterization.

To a stirred solution of **8b** (445 mg,1.82 mmol) in rigorously dried CH_3CN (4 mL) at room temperature under argon was added TMSI (280 μL, 2.0 mmol). The reaction was heated to reflux for 16 h and then quenched with MeOH. The reaction mixture was evaporated twice from MeOH and then twice from CH_2Cl_2 to provide a yellow foam. At rt under argon, this foam was dissolved in ^{i}PrOH (10 mL) and, with stirring, 3,3-diphenylpropyl tosylate (450 mg,1.22 mmol) was added, followed by K_2CO_3 (420 mg, 3.0 mmol). After 16 h of reflux, the reaction mixture was cooled and filtered, and the filtrate was evaporated. Purification by silica gel chromatography of the residue (3:47 ^{i}PrOH/hexane) provided **10b** (325 mg, 55%) as a yellow fluorescent solid after trituration in Et_2O: mp 156−158 °C; ^{1}H NMR δ 7.59 (d, 1 H, J = 7.6 Hz), 7.32−7.12 (m, 16 H), 6.68 (t, 1 H, J = 7.4 Hz), 6.44 (d, 1 H, J = 8.3 Hz), 4.56 (s, 2 H), 3.98 (t, 2 H, J = 7.6 Hz), 2.92 (dt, 2 H, J = 2.1, 11.8 Hz), 2.71 (d, 2 H, J = 11.1 Hz), 2.42 (m, 2 H), 2.28 (m, 2 H), 2.01 (dt, 2 H, J = 4.4, 12.8 Hz), 1.59 (d, 2 H, J = 13.5 Hz); ^{13}C NMR δ 203.6, 158.9, 144.8, 138.0, 137.1, 128.6, 127.7, 127.0, 126.1, 126.0, 124.7, 118.7, 117.1, 109.2, 65.9, 56.6, 49.2, 47.4, 44.7, 32.9, 29.8; IR (KBr pellet) 1690 cm^{-1}; MS (CI) *m*/*z* 487 (M + H). Anal. Calcd for $C_{34}H_{34}N_2O\cdot 0.15H_2O$: C, 83.09; H, 7.19; N, 5.61. Found: C, 83.09; H, 7.07; N, 5.54.

1′-(3,3-Diphenylpropyl)-1-(2-propenyl)-spiro[2*H*-indole-2,4′-piperidin]-3(1*H*)-one (10c). By the same procedure as **8a**, **2b** (1.012 g, 3.46 mmol) and allyl bromide (0.35 mL, 4.0 mmol) gave **9** (723 mg, 63%) as a yellow oil. The compound was used in the next procedure without characterization.

To a stirred solution of **9** (720 mg, 2.18 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon was added 1-chloroethyl chloroformate (0.2 mL, 2.4 mmol). After 3 h, the reaction mixture was evaporated at <30 °C, and the residue was treated with MeOH (10 mL). After 16 h, the reaction mixture was evaporated, and the residue was triturated with Et_2O. Filtration isolated a bright yellow solid, the piperidinium hydrochloride (592 mg, 98%).

At rt under argon, this solid was dissolved in DMF (5 mL) and, with stirring, 3,3-diphenylpropyl tosylate (770 mg, 2.1 mmol) followed by K_2CO_3 (670 mg, 5.0 mmol) was added. After 16 h of heating at 70 °C, the reaction was cooled, quenched with H_2O, and extracted three times with Et_2O. The extracts were combined, dried (Na_2SO_4), and evaporated. Purification by preparative HPLC (YMC S-100DS column, 50 to 100% gradient of 0.2% H_3PO_4 in MeOH/H_2O) provided **10c** (485 mg, 58% yield) as a yellow oil: ^{1}H NMR δ 7.54 (d, 1 H, J = 7.6 Hz), 7.38 (dd, 1 H, J = 1.2, 7.2 Hz), 7.30−7.13 (m, 10 H), 6.67 (t, 1 H, J = 7.4 Hz), 6.63 (d, 1 H, J = 8.2 Hz), 5.78 (m, 1 H), 5.22 (d, 2 H, J = 14.0 Hz), 5.16 (d, 2 H, J = 13.7 Hz), 3.96 (m, 3 H), 2.91 (dt, 2 H, J = 2.3, 12.0 Hz), 2.80 (d, 2 H, J = 11.1 Hz), 2.42 (m, 2 H), 2.30 (m, 2 H), 1.98 (dt, 2 H, J = 4.6, 12.8 Hz), 1.51 (d, 2 H, J = 12.8 Hz); ^{13}C NMR δ 203.7, 158.5, 144.8, 137.0, 133.8, 128.3, 127.7, 126.1, 124.6, 118.4, 116.7, 108.9, 65.6, 56.7, 49.3, 47.4, 43.2, 32.9, 29.7; IR (thin film) 1690 cm^{-1}; MS (CI) *m*/*z* 437 (M + H). Anal. Calcd for $C_{30}H_{32}N_2O\cdot 0.35H_2O$: C, 81.36; H, 7.44; N, 6.33. Found: C, 81.34; H, 7.40; N, 6.65.

1-Acetyl-1′-(3,3-diphenylpropyl)-spiro[2*H*-indole-2,4′-piperidin]-3(1*H*)-one (10d). To a stirred solution of **2c** (450 mg, 1.13 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon was added freshly distilled acetyl chloride (85 μL, 1.25 mmol) over 5 min. The resulting solution was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was partitioned between saturated $NaHCO_3$ solution and EtOAc. The organic extract was dried (Na_2SO_4) and evaporated. Purification by silica gel chromatography (9:1 EtOAc/hexane) gave **10d** (315 mg, 64%) as a tan solid: mp 127−128 °C; ^{1}H NMR δ 7.87 (br s, 1 H), 7.74 (d, 1 H, J = 7.6 Hz), 7.63 (dd, 1 H, J = 1.2, 7.9 Hz), 7.7−7.1 (m, 11 H), 4.07 (t, 2 H, J = 7.6 Hz), 2.91−2.77 (m, 6 H), 2.54 (s, 3 H), 2.44 (m, 3 H), 2.28 (m, 2 H), 1.53 (d, 2 H, J = 9.4 Hz); ^{13}C NMR δ 201.5, 168.3, 151.1, 144.8, 136.7, 128.2, 127.8, 125.9, 124.5, 123.7, 122.4, 117.0, 67.6, 55.7, 48.8, 47.7, 32.8, 28.3, 27.2; IR (thin film) 1711, 1690 cm^{-1}; MS (CI) *m*/*z* 439 (M + H). Anal. Calcd for $C_{29}H_{30}N_2O_2\cdot 0.14H_2O$: C, 78.97; H, 6.92; N, 6.35. Found: C, 78.97; H, 6.81; N, 6.51.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and details of the X-ray structural analyses of **2e** and **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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