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A synthetic approach to (±)-aristomakine

Robert B. Perni and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA
Email: ggribble@dartmouth.edu

This paper is dedicated to the memory of Jana M. Dostal

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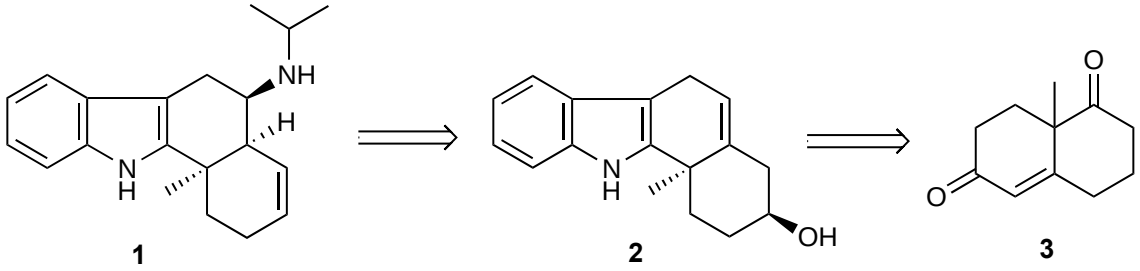
Abstract

We describe the synthesis of *trans*-11b-methyl-2,3,4,6,11,11b-hexahydro-1*H*-benzo[*a*]carbazol-3-ol (**2**) in five steps from the Wieland-Miescher ketone **3** in 17% overall yield. The *N*-benzyl analogue (*trans*-11-Benzyl-11b-methyl-2,3,4,6,11,11b-hexahydro-1*H*-benzo[*a*]carbazol-3-ol) **15** was likewise prepared. Attempts thus far to fashion (±)-aristomakine (**1**) from **2**, **15**, or derivatives have not been successful.



1 **2** **3**

Keywords: *Aristotelia* alkaloids, aristomakine, Wieland-Miescher ketone, Fischer indolization

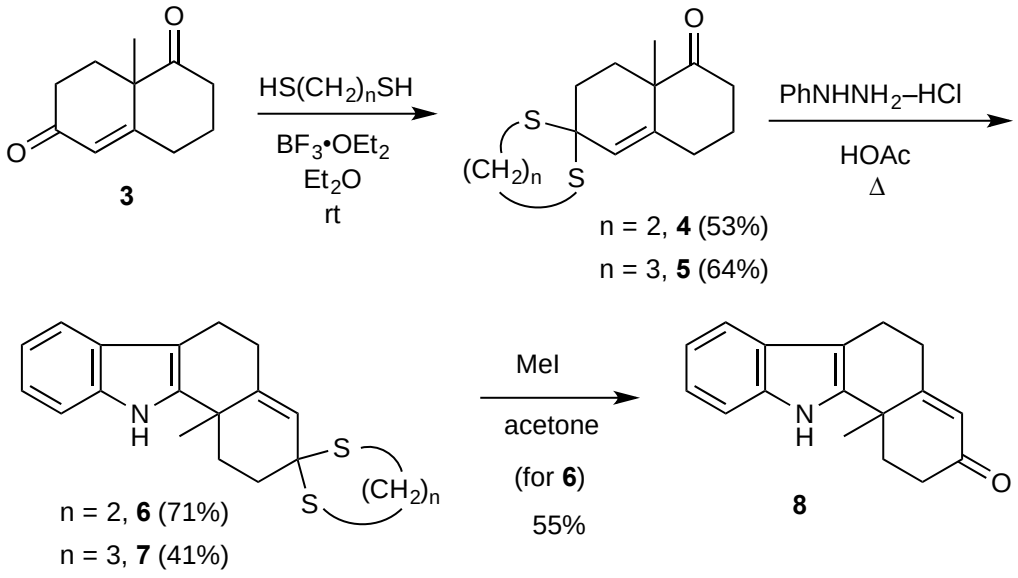
Introduction

In view of our interest in the synthesis of alkaloids of the plant genus *Aristotelia*, namely (–)-hobartine and (+)-aristoteline,[1] we wished to pursue a synthesis of (±)-aristomakine (**1**), an unusual alkaloid from *Aristotelia serrata* containing an *N*-isopropyl group.[2] A biomimetic synthesis of this alkaloid was described by Burkard and Borschberg in 1990,[3] the only synthesis of this rare alkaloid reported to date.

We envisioned a route to **1** that involved the elaboration of *trans*-11b-methyl-2,3,4,6,11,11b-hexahydro-1*H*-benzo[*a*]carbazol-3-ol (**2**), which could be prepared from the venerable Wieland–Miescher ketone (**3**) via Fischer indolization of **3** or a suitable derivative. The obvious challenges lay in the regioselective dehydration of the axial hydroxyl group and the regio- and stereoselective amination of the olefin in **2**. We now describe our progress to this end. All compounds are obtained as racemates.

Results and Discussion

The Wieland-Miescher ketone (**3**) was prepared in 48% yield from the condensation of 2-methyl-1,3-cyclohexanedione with methyl vinyl ketone,[4] but attempts to effect direct indolization of **3** invariably led to intractable tars. Complications in this reaction may arise upon attack of the phenylhydrazine on the more reactive unconjugated carbonyl of **3**, followed by ring fragmentation. However, as shown in Scheme 1, protection of the conjugated ketone and subsequent Fischer indolization smoothly led to the desired indole ring system (**6** and **7**). Thus, thioketals **4** and **5** were easily prepared by treating **3** with 1,2-ethane dithiol or 1,3-propane dithiol and boron trifluoride etherate in dry ether via the method of Smith.[5] Under the relatively mild conditions developed by Dave[6] (glacial acetic acid at 100 °C) **4** cyclized smoothly to give indole **6** in 71% yield after purification. Ketal **5** also reacted with phenylhydrazine to give indole **7** but the yield was only 41%.



Scheme 1. Synthesis of racemic tetracyclic ketone **8.**

Removal of the protecting group to give **8** was attempted under a variety of conditions. Only the treatment of **6** with methyl iodide[7] or silver nitrate[8] afforded **8** in 55% yield (Scheme 1). The results are summarized in Table 1. Origin material refers to material that did not move on TLC.

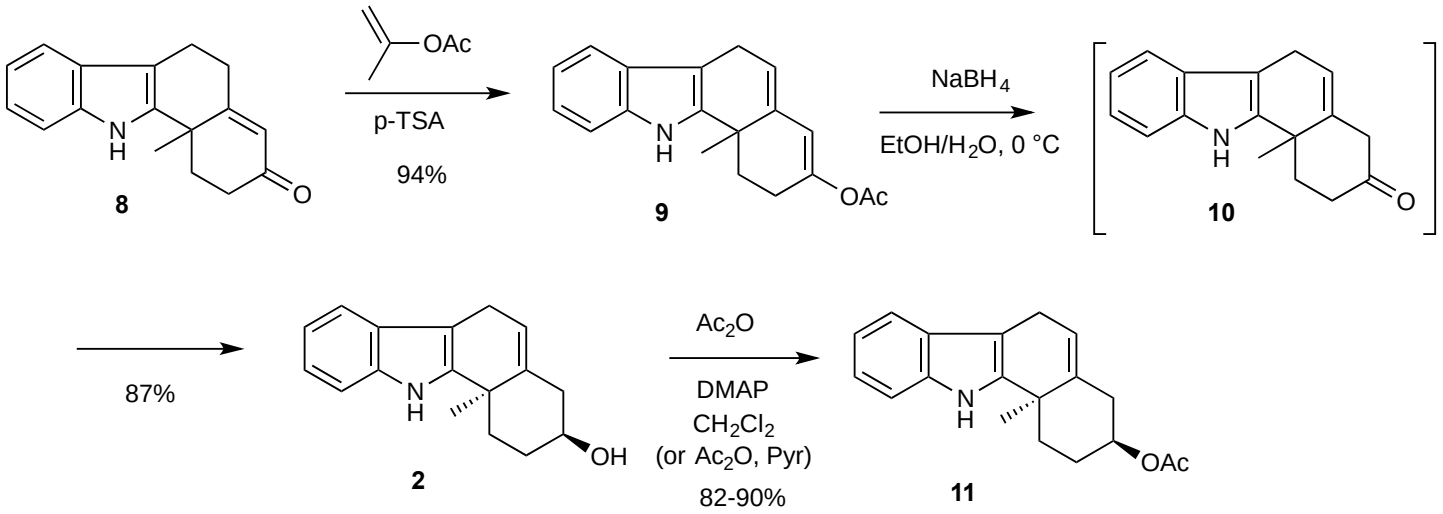
Table 1. Attempts to convert thioketal **6** to ketone **8**

Conditions	Results (by TLC)	Yield
1 MeI/Acetone[7]	**8** + origin material only	55%
2 $AgNO_3$[8]	**8** + origin material only	51%
3 NBS[9]	**8** + 3 unidentified products	undetermined
4 $Tl(NO_3)_3$[10]	**8** + 3 unidentified products	undetermined
5 $(NH_4)_2Ce(SO_4)_3$[11]	Starting material and origin material	---
6 $(NH_4)_2Ce(NO_3)_6$[12]	Tar	---
7 PbO_2[13]	Starting material plus four products	---
8 $CuO/CuCl_2$[14]	Starting material and origin material	---
9 HCl/DMSO[15]	Tar	---

While the deprotection of **6** with silver nitrate was comparable in yield to the reaction with methyl iodide, the former reaction required 1–2 hours while the latter required 24–30 hours for completion. Another advantage of silver ion deprotection is that the ethane dithiol bis-silver salt precipitates during the course of the reaction and is simply removed by filtration. Methyl iodide, on the other hand, generates the dimethyl thioether of ethane dithiol, which must be removed by column chromatography. Similarly, thioketal **7** could be deprotected with silver nitrate in 48% yield, but since **7** was obtained in only 41% yield, we did not study this deprotection step in depth.

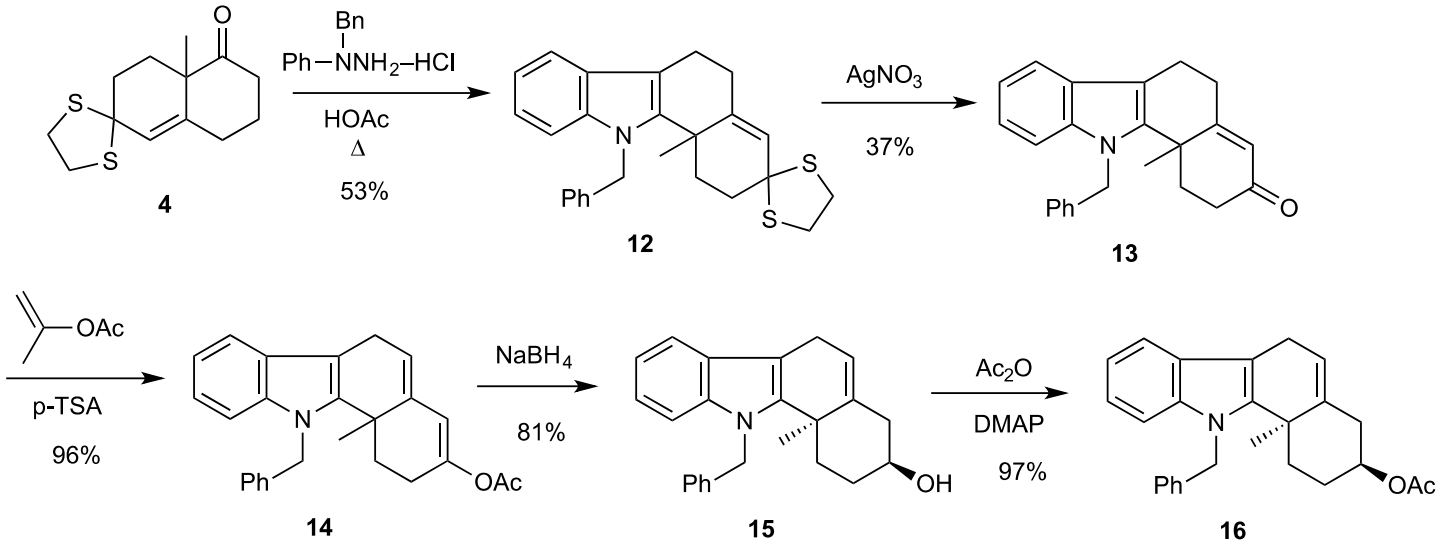
Standard methodology[16–19] was then employed for the two-step conversion of enone **8** to the target alcohol **2** (Scheme 2). The unstable enol acetate **9** was prepared in almost quantitative yield by refluxing **8** in isopropenyl acetate in the presence of a catalytic amount of p-toluenesulfonic acid. Subsequent hydrolysis/reduction of **9/10** with sodium borohydride in aqueous ethanol afforded **2** in 82% yield from **8**. Although systems similar to **9** are known to be stable[16,17] the instability of **9** may be attributed to a double bond migration into conjugation with the indole nucleus. The UV spectrum of **2** (and that of **11**) is that of an indole and not a 3-vinylindole.

It was important to determine the stereochemistry of the hydroxyl group of **2**, although in principle either isomer could be utilized in subsequent reactions. Precedents from terpene chemistry[16,17,20–22] indicated that for most cyclohexanone reductions the predominant product is the equatorial alcohol because of minimization of torsional strain in the transition state.[23,24] For example, Spencer observed the axial methine proton of 10-β-methyl-$\Delta^{5(10)}$-8,9-octal-2β-ol to resonate at δ 3.50, with a small signal due to the equatorial methine proton resonating at δ 4.05.[21] The high field (300 MHz) NMR spectrum of **2** shows the corresponding methine proton at δ 4.25 indicative of an equatorial proton and hence an axial hydroxyl group. To confirm this unexpected stereochemistry, we synthesized acetate **11**. Treatment of **2** with acetic anhydride and 4-dimethylaminopyridine (DMAP) in dichloromethane cleanly gave acetate **11**. Alternatively, **11** was prepared by allowing **2** to react with acetic anhydride in dry pyridine, but this method produced several side products. The proton NMR of **11** shows the (equatorial) methine proton shifted downfield as expected to δ 5.25. The two vinyl protons at δ 5.42 (major) and 5.71 integrate for a factor of 6:1 in favor of the axial acetate **11**. On the basis of these NMR data we conclude that the axial alcohol **2** is the major reduction product from ketone **10**.



Scheme 2. Synthesis of racemic tetracyclic alcohol **2** and acetate **11**.

To preclude possible side reactions in the remaining reactions leading to aristomakine (due to the acidic indole NH), we protected the aforementioned compounds as *N*-benzyl analogues. Unfortunately, direct benzylation of indole thioketal **6** with benzyl bromide (KOH/DMSO, butyllithium, or tetra-n-butyl-ammonium hydrogen sulfate/KOH) failed in each case. However, the desired *N*-benzylindole thioketal **12** was synthesized in 53% yield using 1-benzyl-1-phenylhydrazine[25] in a Fischer indolization with ketone **4** (Scheme 3). Ketone deprotection, enol acetate formation, and reduction as previously described afforded alcohol **15**. As before, the acetate of **15** was synthesized (acetic anhydride/DMAP/CH_2Cl_2) to confirm the stereochemistry. The NMR spectra of **15** and **16** show the methine protons at δ 4.20 and 5.30, respectively, indicating an equatorial orientation for the protons, consistent with the results for **2** and **11**. For **15** there is a small resonance at δ 3.45 which may be the axial proton of the epimer of **15**. However, no such resonance appears in the spectrum for acetate **16**. Moreover, no second vinyl proton resonances are observed for either **15** or **16** leading us to believe that the reduction goes highly, if not exclusively, equatorially to afford the axial hydroxyl group (**15**).



Scheme 3. Synthesis of racemic tetracyclic alcohol **15** and acetate **16**.

Our synthesis of aristomakine (**1**) was predicated on the regio- and stereoselective amination of the double bond of **2** or **15**, followed by dehydration of the axial hydroxyl group. Our initial approach was to add an *iso*-propylamino group to the beta face of the double bond of **2** via an intermolecular nitrene insertion,[26] followed by dehydration. However, our attempts to oxidize isopropyl amine with *N*-chlorosuccinimide (NCS) or lead tetraacetate in the presence of **2** led only to starting material. Control experiments with the more reactive 2-norbornene failed to give the expected aziridine, suggesting that intramolecular formation of acetone imine by a 1,2-H shift may supersede an intermolecular nitrene addition. This pathway is known for the pyrolysis of *n*-alkyl azides. For instance, *n*-butyl azide affords an 89% yield of its imine.[27] We then employed Brown's hydroboration-amination method with **2**.[28,29] Thus, Brown showed that 1-methylcyclohexene gives *trans*-2-methylcyclohexylamine upon hydroboration and treatment of the resulting borane with hydroxylamine-*O*-sulfonic acid.[29] Unfortunately, these conditions with **2** yielded a complex mixture.

In conclusion, we have developed an efficient syntheses of key intermediates (**2/15**) in our efforts toward the total synthesis of aristomakine and other *Aristotelia* alkaloids. Intermediates **2** and/or **15** could potentially be used to prepare several members of the *Aristotelia* family.

Experimental Section

General. Infrared spectra were obtained with a Perkin-Elmer 599 infrared spectrophotometer. Ultraviolet spectra were obtained on a Unicam SP 800 or Cary 15 UV-visible spectrophotometer in 10 mm quartz cells. All routine proton NMR spectra (60 MHz) were run on a Hitachi-Perkin-Elmer R-24 spectrometer and carbon NMR (15 MHz) were run on a JEOL FX60Q multinuclear Fourier transform spectrometer. High field proton NMR (300 MHz) and carbon spectra (75 MHz) for compounds **2** and **11** were run on a Varian XL300 superconducting FT spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Low-resolution mass spectra were determined on a Finnigan 4023 GC/MS system. High-resolution mass spectra were determined by Dr. Catherine E. Costello at the Massachusetts Institute of Technology, the National Institutes of Health Regional Facility. Thin layer chromatography (TLC) was performed either on Merck precoated (0.2 mm) silica gel 60 F_{254} plastic sheets or Eastman 13179 silica gel Chromagram sheets. Chromatograms were visualized under 254 nm ultraviolet light or sprayed with a solution of 3% ceric ammonium sulfate in 10% sulfuric acid followed by brief heating. Flash chromatography was performed on silica gel (230–400 mesh). Melting points were determined on a Laboratory Devices Mel-Temp in open-ended capillaries and are uncorrected. Glassware was either oven dried at 110 °C overnight or flame dried immediately prior to use. Organic solvents were removed in vacuo with a Büchi Rotoevaporator device. All reactions were run under a nitrogen atmosphere. Microanalyses were performed by Atlantic Microlabs, Atlanta, Georgia.

8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (3).[4] A magnetically stirred mixture of 2-methyl-1,3-cyclohexanedione (50.0 g, 0.40 mol), methyl vinyl ketone (44.0 mL, 0.54 mol), and potassium hydroxide (0.25 g) in methanol (250 mL) was refluxed for 3 h. The solvent and excess methyl vinyl ketone were removed *in vacuo* and the residue was dissolved in benzene (250 mL). Pyrrolidine (3 mL) was added and the solution was refluxed with a Dean-Stark trap until the theoretical amount of water was collected. The reaction mixture was allowed to cool to room temperature and diluted with ether (250 mL), washed with 5% aqueous hydrochloric acid (100 mL), and water (100 mL). The combined washes were extracted with ether (1 x 50 mL). The combined organic portions were washed with water (1 x 100 mL) and brine (1 x 100 mL), dried over sodium sulfate and concentrated *in vacuo* to afford a brown oil. This oil was chromatographed on Florisil

(ether/benzene, 1:1), stored at 0 °C overnight, and the resulting crystals were collected. This cooling procedure was repeated twice to give 33.9 g (48%) of **3**, which was usually used without further purification. The product was recrystallized from ether to give **3**, mp 47–51 °C (lit.[4] mp 47–50 °C); IR ($CHCl_3$) 1720 (s), 1670 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 3H), 1.70–3.00 (m, 10H), 5.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 22.9, 29.4, 31.4, 33.3, 37.3, 50.3, 125.4, 165.4, 197.6, 210.4.

4a-Methyl-4,4a,7,8-tetrahydro-3*H*-spiro[naphthalene-2,2'-[1,3]dithiolan]-5(6*H*)-one (4).[5] To a magnetically stirred solution of **3** (20.0 g, 0.11 mol) and 1,2-ethanedithiol (9.40 mL, 0.11 mol) in dry ether (150 mL) was added boron trifluoride etherate (1.0 mL). Stirring was continued overnight at room temperature. The reaction mixture was poured into water (200 mL) and the layers were separated. The aqueous portion was extracted with ether (2 x 50 mL) and the combined organic portions were washed with saturated sodium bicarbonate solution (1 x 100 mL), water (1 x 100 mL), and dried over sodium sulfate. Concentration *in vacuo* afforded 23.3 g (82%) of crude product as yellow crystals. Recrystallization from ether afforded 15.2 g (53%) of **4**, mp 116–118 °C (lit.[5] mp 123–124 °C); IR (KBr) 2920 (m), 1694 (s), 1416 (m), 1230 (m), 1014 (m), 820 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.40–2.80 (m, 10H), 3.31 (s, 4H), 5.68 (br s, 1H).

4a-Methyl-4,4a,7,8-tetrahydro-3*H*-spiro[naphthalene-2,2'-[1,3]dithian]-5(6*H*)-one (5). The same procedure as for the preparation of **4** afforded **5** (64%) as a colorless oil following chromatography on Florisil (Et_2O). This oil crystallized on standing at 0 °C overnight. Recrystallization from ether (2X) gave analytically pure material, mp 98–99.5 °C; IR ($CHCl_3$) 2950 (s), 1708 (s), 1665 (m), 1420 (m), 1200 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.40–3.20 (m, 16H), 5.57 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 24.6, 24.8, 25.0, 26.4, 26.8, 27.8, 31.0, 32.5, 37.8, 48.2, 50.6, 125.2, 143.4, 212.2 ppm. *Anal.* Calcd for $C_{14}H_{20}OS_2$: C, 62.64; H, 7.51; S, 23.89. Found: C, 62.35; H, 7.58; S, 23.95.

11b-Methyl-1,2,5,6,11,11b-hexahydrospiro[benzo[*a*]carbazole-3,2'-[1,3]dithiolane] (6). To glacial acetic acid (100 mL) at room temperature was added **4** (5.00 g, 19.6 mmol) and commercial (Pfaltz & Bauer) phenylhydrazine hydrochloride (2.84 g, 19.6 mmol). The mixture was magnetically stirred and the temperature was brought to 100 °C and maintained for 2 h. As the temperature was raised the solids gradually went into solution. The solution was allowed to cool to room temperature, poured into distilled water (100 mL), and placed in the refrigerator for 30 min. The resultant precipitate was suction filtered, dried *in vacuo*, and chromatographed on a Florisil column with benzene. Only one 250 mL fraction was collected. The benzene solution was concentrated to one-half its volume *in vacuo*, hexane (125 mL) was added, and the mixture was placed in the refrigerator for several hours. The product was then collected by suction filtration to afford 4.57 g (71%) of **6** as a fluffy white powder, mp 216–217 °C; IR ($CHCl_3$) 3500 (s), 3020 (m), 2945 (s), 2770 (m), 1478 (s), 1310 (m), 1303 (m), 1246 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.75–3.05 (m, 8H), 3.10–3.50 (m, 4H), 5.71 (s, 1H), 7.00–7.80 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.5, 26.7, 29.9, 34.9, 35.5, 38.1, 39.5, 40.3, 65.0, 108.5, 110.5, 118.1, 119.3, 121.3, 126.3, 127.1, 136.1, 140.6, 142.3 ppm; UV λ_{max}^{EtOH} 227, 278, 292 nm; MS (70 eV) m/e 327 (34% M^+), 312 (28%), 252 (24%), 219 (100%), 109 (39%). *Anal.* Calcd for $C_{19}H_{21}NS_2$: C, 69.68; H, 6.46; N, 4.28; S, 19.58. Found: C, 69.78; H, 6.51; N, 4.28; S, 19.53.

11b-Methyl-1,2,5,6,11,11b-hexahydrospiro[benzo[*a*]carbazole-3,2'-[1,3]dithiane (7). The same procedure as for the preparation of **6** afforded 41% of **7** as a yellow solid following chromatography on Florisil (benzene). Recrystallization from benzene (2X) gave analytically pure material, mp 235–237 °C; IR (KBr) 3330 (s), 2910 (s), 1461 (s), 1440 (s), 860 (s), 725 (s) cm^{-1}; ^1H NMR ($CDCl_3$/$DMSO_{d6}$) δ 1.49 (s, 3H), 1.65–3.40 (m, 14H), 5.62 (s, 1H), 6.90–7.45 (m, 5H) ppm; ^{13}C NMR ($DMSO_{d6}$) δ 22.4, 24.5, 25.5, 26.2, 26.4, 29.5, 31.9, 32.6, 35.8, 48.2, 106.1, 110.7, 117.5, 118.1, 120.3, 123.3, 126.3, 136.2, 141.2, 144.7 ppm; UV λ_{max}^{EtOH} 228, 281 nm; MS (70 eV) m/e 342 (6% M^+), 220 (18%), 145 (100%), 78 (48%). *Anal.* Calcd for $C_{20}H_{23}NS_2$: C, 70.33; H, 6.79; N, 4.10; S, 18.78. Found: C, 70.29; H, 6.83; N, 4.06; S, 18.71.

11-Benzyl-11b-methyl-1,2,5,6,11,11b-hexahydrospiro[benzo[*a*]carbazole-3,2'-[1,3]dithiolane] (12). The same procedure as for the preparation of **6** except 1-benzyl-1-phenylhydrazine hydrochloride (Pfaltz & Bauer) was used instead of phenylhydrazine, afforded **12** in 53% yield following crystallization from dichloromethane/ethanol. Recrystallization (2X) from dichloromethane/ethanol gave analytically pure material, mp 124–126 °C; IR ($CHCl_3$) 3005 (m), 2935 (m), 1467 (s), 1345 (s), 905 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H), 1.60–3.00 (m, 8H), 3.10–3.35 (m, 4H), 5.47 (br s, sh), 5.74 (br s, 1H), 6.75–7.60 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 23.1, 25.4, 30.6, 35.2, 36.5, 37.9, 39.5, 40.2, 48.5, 64.6, 109.8, 118.0, 119.2, 121.4, 125.5, 125.9, 126.6, 126.9, 128.5, 137.7, 137.8, 141.0, 144.1 ppm; UV λ_{max}^{EtOH} 239, 290, 334 nm; MS (70 eV) m/e 417 (2% M^+), 195 (18%), 118 (68%), 91 (100%). *Anal.* Calcd for $C_{26}H_{27}NS_2$: C, 74.77; H, 6.52; N, 3.35; S, 15.36. Found: C, 74.70; H, 6.55; N, 3.31; S, 15.38.

11b-Methyl-1,2,5,6,11,11b-hexahydro-3*H*-benzo[*a*]carbazol-3-one (8). Procedure A. To a magnetically stirred solution of **6** (0.50 g, 1.5 mmol) in 96% aqueous acetone (25 mL) was added methyl iodide (1 mL). The mixture was brought to reflux and the reaction was monitored by TLC (ethyl acetate). Additional methyl iodide was added periodically after several hours until the disappearance of starting material was noted. When the solution had cooled to room temperature, it was diluted with methylene chloride (25 mL), washed with saturated sodium bicarbonate (1 x 25 mL), water (1 x 25 mL), dried over sodium sulfate and concentrated *in vacuo*. The oily residue was chromatographed on Florisil (hexanes, then ether) to give 0.21 g (55%) of **8** as a white amorphous foam; IR ($CDCl_3$) 3490 (m), 3020 (m), 2980 (m), 2940 (m), 1675 (s), 915 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3H), 1.80–3.30 (m, 8H), 5.94 (s, 1H), 7.00–7.61 (m, 4H), 8.52 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 21.7, 25.2, 31.0, 34.0, 35.1, 37.8, 108.5, 110.7, 118.2, 119.6, 121.8, 125.4, 126.6, 136.4, 138.9, 168.1, 197.8 ppm; UV λ_{max}^{EtOH} 228 (log ? = 4.28), 270 (log ? = 4.23) nm; HRMS MS *m/z* calcd for $C_{17}H_{17}NO$: 251.1310 (M^+). Found: 251.1319.

Procedure B. To a magnetically stirred solution of **6** (3.00 g, 9.2 mmol) in acetone (85 mL) was added dropwise over 10 min a solution of silver nitrate (3.34 g, 19.7 mmol) in water (5 mL). The reaction was monitored by TLC as in Procedure A, but was usually complete within 2 h. The suspension was collected by suction on a sintered glass funnel and the silver salt was washed with dichloromethane (3 x 25 mL). The combined solutions were concentrated *in vacuo* and chromatographed on Florisil (ether) to afford 1.15 g (50%) of **8** as an amorphous white solid, identical by TLC, IR, and NMR with that obtained from Procedure A.

11-Benzyl-11b-methyl-1,2,5,6,11,11b-hexahydro-3*H*-benzo[*a*]carbazol-3-one (13). Compound 12 was treated as in Procedure B to afford crude **13** as a green oil. Flash chromatography of the crude product gave 37% of **13** as an amorphous yellow foam; IR ($CHCl_3$) 3000 (m), 2960 (m), 2920 (m), 1670 (m), 1465 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (s, 3H), 1.80–3.40 (m, 8H), 5.56 (s, 2H), 5.97 (s, 1H), 6.60–7.85 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.1, 23.9, 31.7, 34.0, 34.6, 38.3, 48.5, 109.9, 110.0, 118.2, 119.6, 122.0, 124.9, 125.4, 126.2, 127.1, 128.6, 137.5, 137.9, 139.2, 169.4, 197.6 ppm; UV λ_{max}^{EtOH} 231, 284 nm; HRMS MS *m/z* calcd for $C_{24}H_{23}NO$: 341.1780 (M^+). Found: 341.1780.

11b-Methyl-2,6,11,11b-tetrahydro-1*H*-benzo[*a*]carbazol-3-yl acetate (9). A solution of enone **8** (0.70 g, 2.8 mmol) in isopropenyl acetate (25 mL) with a catalytic amount of *p*-toluenesulfonic acid monohydrate was refluxed overnight. The reaction mixture was allowed to cool to room temperature and was diluted with dichloromethane (25 mL). This solution was washed with saturated aqueous sodium bicarbonate (1 x 25 mL), water (1 x 25 mL), filtered through a pad of barium oxide and concentrated *in vacuo*. The dark oily residue was chromatographed on Florisil (Et_2O) to afford 0.77 g (94%) of **9**; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 2.16 (s, 3H), 1.75–3.10 (m, 8H), 5.39 (m, 1H), 5.65 (br s, 1H), 6.90–7.80 (m, 4H), 8.02 (br s, 1H) ppm; UV λ_{max}^{EtOH} 227, 260, 290 nm; HRMS MS *m/z* calcd for $C_{19}H_{19}NO_2$: 293.1416 (M^+). Found: 293.1423.

11-Benzyl-11b-methyl-2,6,11,11b-tetrahydro-1*H*-benzo[*a*]carbazol-3-yl acetate (14). The same procedure as for the preparation of **8** afforded **14** as a yellow oil in 96% yield after column chromatography on Florisil (CH_2Cl_2); IR (neat) 2940 (m), 1755 (s), 1468 (s), 1365 (s), 1215 (s), 735 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3H), 2.12 (s, 3H), 1.60–3.35 (m, 6H), 5.26 (m, 1H), 5.47 (s, 2H), 5.63 (s, 1H), 6.73–7.85 (m, 9H) ppm; UV λ_{max}^{EtOH} 228, 275 nm; HRMS MS *m/z* calcd for $C_{26}H_{25}NO_2$: 383.1885 (M^+). Found: 383.1932.

***trans*-11b-Methyl-2,3,4,6,11,11b-hexahydro-1*H*-benzo[*a*]carbazol-3-ol (2)**. To a solution of enol acetate **9** (0.77 g, 2.6 mmol) in ethanol (25 mL) at 0 °C was added a suspension of sodium borohydride (1.32 g) in 20% aqueous ethanol (20 mL). The resulting suspension was capped with a rubber septum and a small bore syringe needle was pushed through the septum to bleed off evolved hydrogen. The reaction flask was placed in the refrigerator at 0 °C for 40 h. The mixture was allowed to come to room temperature and 10% aqueous sodium hydroxide (3 mL) was added. After being stirred at room temperature for 15 min the mixture was diluted with brine (25 mL) and extracted with dichloromethane (2 x 25 mL). The layers were separated and the organic portion was washed with water (2 x 25 mL), dried over sodium sulfate, and concentrated *in vacuo* to afford a yellow oil. This oil was column chromatographed on Florisil (ether) to afford 0.58 g (87%) of **2** as a white amorphous foam; IR ($CDCl_3$) 3605 (m), 1460 (s), 1392 (s), 1008 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3H), 1.86 (s, 1H), 1.65–3.10 (m, 8H), 4.21 (m, 1H), 5.50 (s, 1H), 6.98–7.66 (m, 4H), 7.80 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 22.7, 27.2, 29.0, 30.0, 34.0, 35.6, 67.6, 108.4, 110.5, 118.0, 119.2, 121.2, 125.3, 127.1, 136.2, 141.0; 144.2 ppm; UV λ_{max}^{EtOH} 226, 282, 291 nm; HRMS MS *m/z* calcd for $C_{17}H_{19}NO$: 253.1467 (M^+). Found: 253.1497.

***trans*-11-Benzyl-11b-methyl-2,3,4,6,11,11b-hexahydro-1*H*-benzo[*a*]carbazol-3-ol (15).** Same procedure as for the preparation of **2** afforded **15** as a white glassy material in 81% yield after column chromatography on Florisil (ether); IR ($CHCl_3$) 3612 (m), 3010 (s), 2945 (s), 1464 (s), 1452 (s), 1345 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H), 1.40–3.15 (m, 8H), 4.20 (m, 1H), 5.49 (s, 3H), 6.81–7.65 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 23.4, 26.0, 29.0, 30.7, 34.0, 37.2, 48.5, 67.2, 109.7, 198.8, 118.0, 119.2, 121.5, 125.2, 125.6, 126.9, 128.5, 137.8, 138.0, 141.4, 147.5 ppm; UV λ_{max}^{EtOH} 229, 285, 293 nm; HRMS MS *m/z* calcd for $C_{24}H_{25}NO$: 343.1936 (M^+). Found: 343.1904.

***trans*-11b-Methyl-2,3,4,6,11,11b-hexahydro-1*H*-benzo[*a*]carbazol-3-yl acetate (11). Procedure A.** To a stirred solution of **2** (112 mg, 0.44 mmol) in 2 mL dry pyridine was added acetic anhydride (0.5 mL, 5 mmol). The resulting solution was refluxed for 45 min. The reaction mixture was allowed to cool to room temperature and water (5 mL) was added. After standing at 0 °C for 30 min the supernatant was decanted from an oily yellow residue. The residue was dissolved in dichloromethane (10 mL), dried over sodium sulfate, and passed through a small Florisil column. Concentration *in vacuo* gave 108 mg (82%) of crude **11**. Flash chromatography (ether/hexanes, 1:1) afforded **11**, mp 133–135 °C; IR ($CHCl_3$) 3475 (m), 3005 (m), 2947 (m), 2920 (m), 1755 (s), 1245 (s), 1205 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (s, 3H), 1.70–2.95 (m, 8H), 2.09 (s, 3H), 5.31 (m, 1H), 5.48 (s, 1H), 7.00–7.57 (m, 4H), 7.83 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 21.3, 22.8, 24.9, 27.2, 30.2, 34.0, 35.7, 70.5, 108.8, 110.7, 118.3, 119.5, 121.3, 121.6, 127.4, 136.5, 140.8, 146.5, 170.8 ppm; UV λ_{max}^{EtOH} 222, 279; MS (70 eV) m/e 295 (12%, M^+), 220 (100%), 146 (61%). *Anal.* Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.47; H, 7.26; N, 4.69.

Procedure B. To a stirred solution of alcohol **2** (106 mg, 0.42 mmol) and acetic anhydride (0.20 mL, 2.2 mmol) in dichloromethane (5 mL) was added dimethylamino pyridine (DMAP) (204 mg, 1.7 mmol). The reaction was monitored by TLC (ether). After 45 min at room temperature methanol was added to the reaction mixture and the solvents were removed *in vacuo*. The solid residue was redissolved in dichloromethane (10 mL). This solution was washed with 10% cold aqueous hydrochloric acid (1 x 10 mL), 10% cold aqueous potassium hydroxide (1 x 10 mL) and water (2 x 10 mL). Drying over sodium sulfate and filtration through a short Florisil

column afforded, after concentration *in vacuo*, 111 mg (90%) of **11**. This material exhibited the same spectral properties as the material obtained from Procedure A.

***trans*-11-Benzyl-11b-methyl-2,3,4,6,11,11b-hexahydro-1*H*-benzo[*a*]carbazol-3-yl acetate (16).** The same procedure as for the preparation of **11** afforded **16** as an amorphous yellow solid in 97% yield following chromatography on Florisil (CH_2Cl_2); IR (KBr) 2940 (m), 1731 (s), 1467 (s), 1240 (s), 736 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3H), 2.03 (s, 3H), 1.15–3.17 (m, 8H), 5.07–7.63 (m, 2H), 5.48 (s, 2H), 6.65–7.65 (m, 9H); UV λ_{max}^{EtOH} 228, 280, 294 nm; HRMS MS *m/z* calcd for $C_{26}H_{27}NO_2$: 385.2042 (M^+). Found: 385.2080.

1-Benzyl-1-phenylhydrazine. To a magnetically stirred solution of phenylhydrazine (10.8 g, 0.100 mol) in distilled water (30 mL) were added sodium bicarbonate (20 g) and benzyl bromide (11.9 mL, 0.100 mol). The resultant mixture was refluxed for 3 h and then allowed to cool to 25 °C. The layers were separated and the yellow upper layer was diluted with ether (100 mL), dried over sodium sulfate, and concentrated *in vacuo* to afford 19.6 g (99%) of the product as a yellow oil. This material was identical by NMR with a sample prepared from the commercial hydrochloride salt, and was normally used without further purification. However, on standing for several weeks at 0 °C the oil darkened, requiring distillation; bp 125–130 °C/1.5 Torr (lit.[30] bp 124–127 °C/0.55 Torr); ^1H NMR ($CDCl_3$) δ 3.31 (br s, 2H), 4.49 (s, 2H), 6.57–7.52 (m, 5H), 7.24 (s, 5H).

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