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Studies on the Synthesis of Akuammiline Alkaloids. Access to 3,4-Secoakuammilan Derivatives

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Abstract: Cleavage of the C-3/N-4 bond of tetracycles **1** and **6** with chloroformates or acyl chlorides, followed by reduction, led to tetrahydrocarbazoles **4a,b** and **8b-d**, from which dithioacetal **12** and sulfoxides **5a,b**, **11**, and **17** were prepared. Whereas attempts to construct the quaternary C-7 centre of akuammiline alkaloids either by DMTSF-promoted cyclization of **12** or by Pummerer cyclization of sulfoxides **5a,b** and **11** resulted in failure, sulfoxide **17** underwent cyclization on the indole 3-position to give the tetracyclic 3,4-secoakuammilan-type derivative **18**.

One of the few groups of monoterpenoid indole alkaloids that remains synthetically inaccessible to date is the akuammiline group.[1] These alkaloids belong to the Corynanthean biogenetic type,[2] and are characterized by the existence of an additional bond connecting C-7 and C-16,[3] which causes these molecules to adopt a hemispherical shape, with rings C and D in a boat conformation resulting in strong transannular interactions. In fact, not even model structures embodying the characteristic pentacyclic 2,7a-methanoindolo[2,3-*a*]quinolizine skeleton of these alkaloids (*Chemical Abstracts* stereoparent: akuammilan) have been synthesized so far.

An inspection of these rigid and compact structures reveals that the main synthetic difficulty lies in the generation of the highly congested quaternary C-7 centre. Previous attempts to construct this centre either by formation of the C-7/C-16 bond from 3,4-secoindolo[2,3-*a*]quinolizidines (biomimetic approach)[4] or by closure of the C ring by formation of the C-6/C-7 bond from tetracyclic ABED derivatives[5,6] have resulted in failure.[7]

We reasoned that the formation of the quaternary C-7 centre following the latter strategy (formation of the C-6/C-7 bond) would be more easily accomplished if cyclization on the indole 3-position was effected from the more flexible and less crowded tetrahydrocarbazoles resulting from the cleavage of the C-3/N-4 bond of the tetracyclic ABED derivatives we had used in our previous work.[6] This approach would also constitute a synthetic entry to 3,4-secoakuammilan alkaloids, such as those of the echitamine series (2,4-cyclo-3,4-secoakuammilan) or the tetracyclic alkaloid 3,4-seco-3,14-dehydrocabucraline.[8]

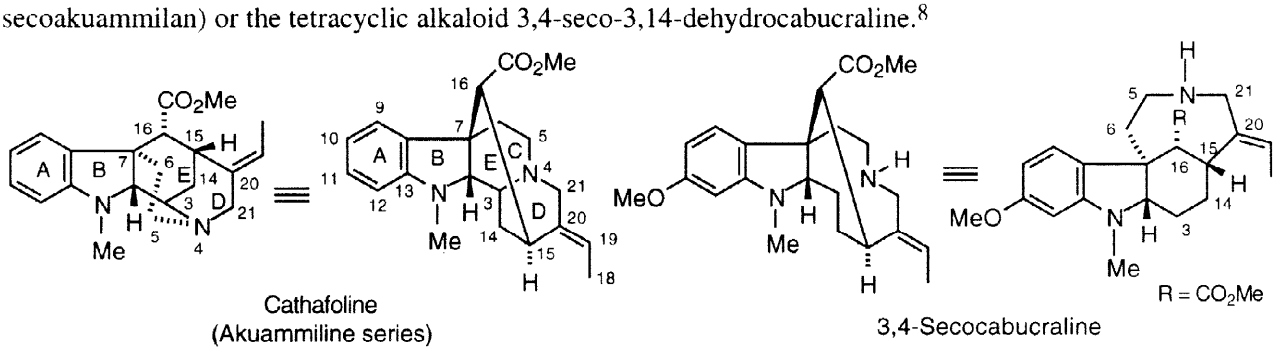

Figure 1

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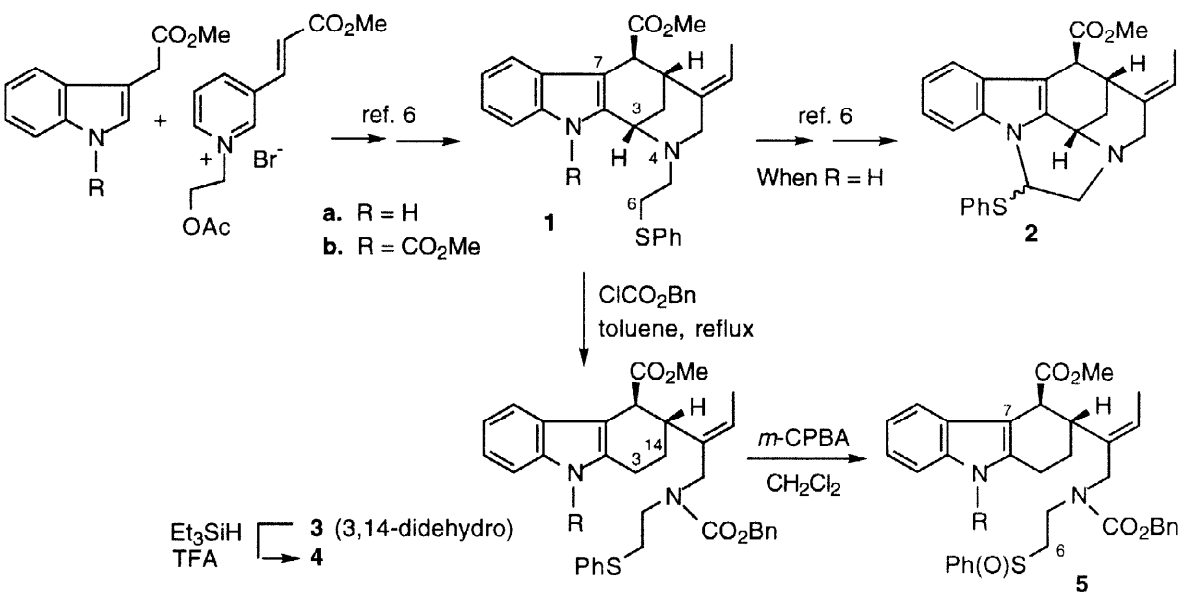
With this aim, we first decided to study the electrophilic cyclization of a thionium ion generated by Pummerer rearrangement[9] of tricyclic amino sulfoxides **5**, which bear an easily removable *N*-benzyloxycarbonyl group. These sulfoxides can be envisaged as 3,4-secoanalogues of the sulfoxides derived from the known tetracyclic sulfides **1**[6](Scheme 1), which had failed to afford pentacyclic akuammiline-type systems by Pummerer reaction: in the N-H indole series cyclization occurred on the indole nitrogen instead of the indole 3-position to give the unnatural pentacycle **2**. Sulfoxides **5** were prepared from sulfides **1**, taking advantage of the easy cleavage of the C-3/N-4 bond in isogramine systems.[10] Thus, treatment of **1a** or **1b** with benzyl chloroformate promoted an elimination reaction via the corresponding *N*-acylammonium salts to give dihydrocarbazoles **3a** or **3b**, respectively, which were chemoselectively reduced with triethylsilane in the presence of trifluoroacetic acid to tetrahydrocarbazoles **4a** and **4b** in 65% overall yield. Subsequent oxidation at the sulfur atom with *m*-CPBA gave the required sulfoxides **5a** and **5b** in 83% yield.

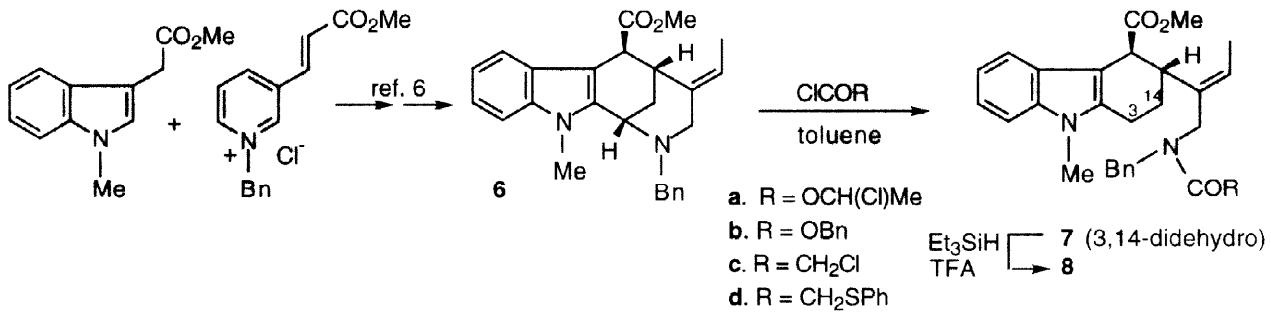
Pummerer rearrangement of sulfoxides **5a** and **5b** was carried out under the usual conditions (TFAA in dichloromethane at 0 °C for 15 min). However, when the presumed acyloxysulfide intermediates were refluxed in dichloromethane for 3 h and the crude reaction mixtures were treated with sodium cyanoborohydride, only the corresponding sulfides **4a** or **4b**, resulting from reduction of the intermediate thionium ions, were isolated in variable yields.



Scheme 1

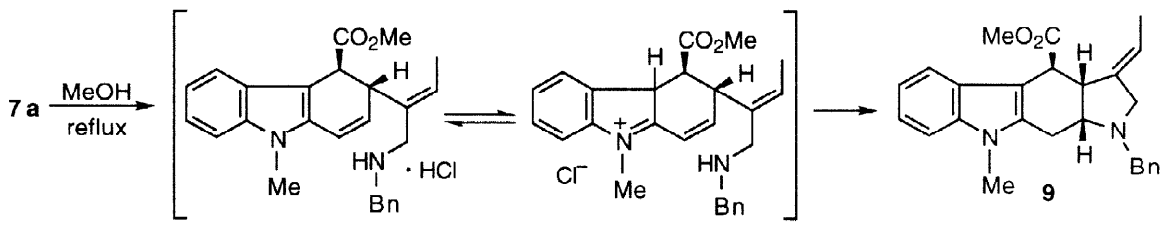
In order to study the key cyclization from different tricyclic substrates, we decided to extend the above elimination-reduction sequence starting from tetracycle **6**,[6] using acylating agents that would either introduce an easily removable group (1-chloroethoxycarbonyl or benzyloxycarbonyl) on the nitrogen atom or incorporate a functionalized two-carbon chain to be used later for the cyclization on the indole 3-position (Scheme 2).

Tetrahydrocarbazoles **8b**, **8c**,[11] and **8d** were easily prepared in 80%, 70%, and 62% overall yield, respectively, by treatment of tetracycle **6** with the appropriate chloroformate or acyl chloride, followed by reduction of the corresponding dihydrocarbazoles **7b-d** with triethylsilane. In the **a** series, although dihydrocarbazole **7a** could be prepared in 57% yield by treatment of **6** with 1-chloroethyl chloroformate, all attempts to reduce the vinyl double bond resulted in decomposition of the product.



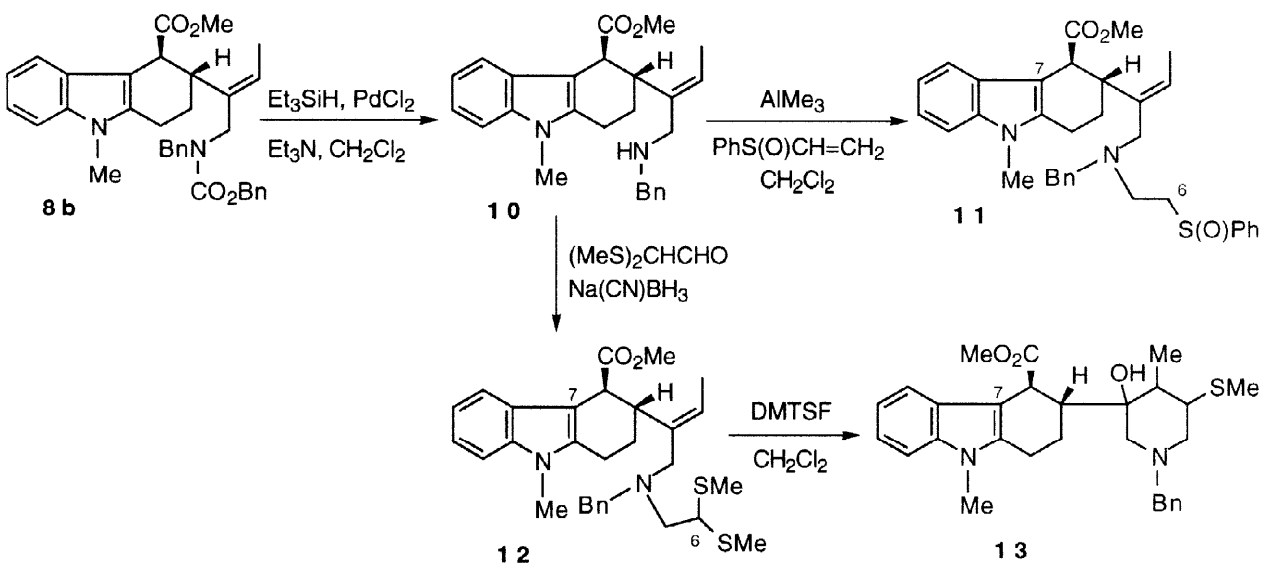
Scheme 2

On the other hand, when **7a** was treated with methanol at reflux temperature in order to remove the carbamate function,[12] the unexpected pyrrolidine **9** was obtained in 62% yield. Its formation can be rationalized by considering that the initially formed secondary amine undergoes an intramolecular conjugate addition upon the vinylindole system, as depicted in Scheme 3.



Scheme 3

In contrast, treatment of tetrahydrocarbazole **8b** with triethylsilane in the presence of palladium chloride and triethylamine[13] promoted effective removal of the *N*-benzyloxycarbonyl protecting group to afford the corresponding secondary amine **10** (80%), from which amino sulfoxide **11** (mixture of stereoisomers) and dithioacetal **12** were prepared in 57% and 72% yield, respectively, by treatment with phenyl vinyl sulfoxide and by reductive alkylation with bis(methylsulfanyl)acetaldehyde (Scheme 4).

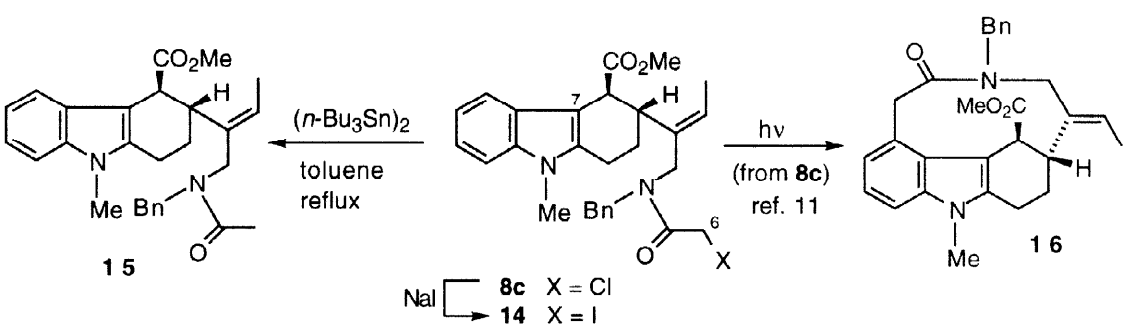


Scheme 4

Pummerer rearrangement of sulfoxide **11** was tried without success under the experimental conditions previously used with other amino sulfoxides. Treatment of **11** with trimethylsilyl triflate and diisopropylethylamine[14] afforded complex reaction mixtures, whereas when the rearrangement was carried out under the usual conditions (TFAA in dichloromethane), and the cyclization was promoted by heating in the presence of boron trifluoride-etherate,[15] formation of small amounts of dealkylation products (**10** or the corresponding *N*-trifluoroacetyl derivative) was observed.[16] On the other hand, DMTSF-induced cyclization[17] of dithioacetal **12** unexpectedly led to (piperidyl)tetrahydrocarbazole **13** as the only isolable product (23%): this compound results from the cyclization of the initially formed thionium ion upon the ethylidene double bond, with final trapping with water.

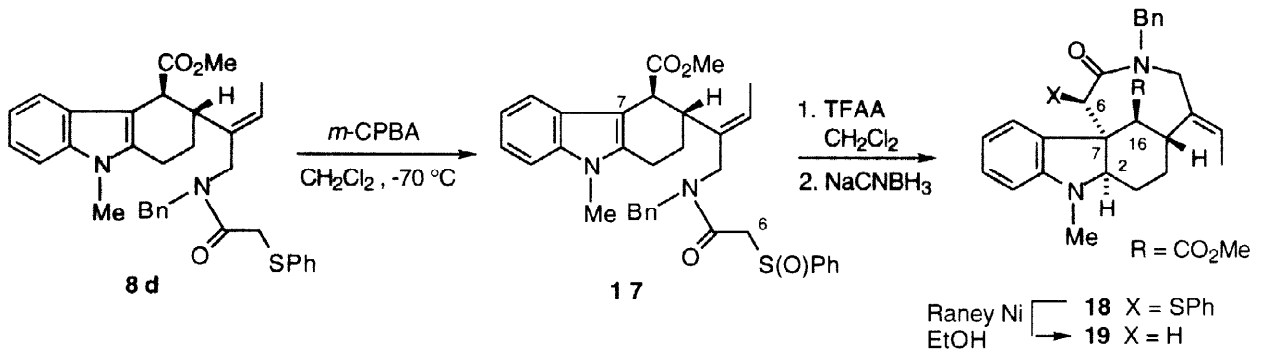
The reluctance of the above tricyclic intermediates to undergo cyclization upon the indole 3-position to give an eight-membered ring was attributed to the high conformational flexibility of β-amino sulfoxides **5** or **11** and dithioacetal **12**. For this reason, we decided to study the key cyclization using tricyclic substrates **8c** or **8d**, in which the reactive carbon atom (C-6) is included in a less flexible chain due to the presence of the amide bond.

In this context, although a previous attempt to induce the closure of the C-6/C-7 bond by cyclization of tetracyclic chloroacetamide **8c** had resulted in failure[11] because cyclization took place upon the indole 4-position to give the ten-membered lactam **16** (Scheme 5), we explored an alternative route for the construction of the 3,4-secoakuammilan skeleton from **8c**, based on a radical cyclization upon the indole nucleus. Treatment of **8c** with sodium iodide in acetone smoothly gave iodoacetamide **14**, which was subjected to different radical cyclization conditions. However, treatment of **14** with *n*-Bu_3SnH or tris(trimethylsilyl)silane in the presence of AIBN gave complex reaction mixtures, whereas treatment with (*n*-$Bu_3Sn)_2$-AIBN afforded acetamide **15** in variable yields depending on the reaction conditions.



Scheme 5

In contrast with the above discouraging results, a Pummerer cyclization from sulfoxide **17**, derived from sulfanylacetamide **8d**, made possible the first synthesis of 3,4-secoakuammilan derivatives (Scheme 6).[18] Thus, **8d** was chemoselectively oxidized at the sulfur atom to give sulfoxide **17** (mixture of stereoisomers) in 72% yield. Pummerer rearrangement of **17** was carried out with TFAA in dichloromethane at 0 °C for 15 min, and the cyclization was promoted by refluxing in dichloromethane for 6 h. After treatment of the crude mixture with sodium cyanoborohydride in order to reduce the α-methyleneindoline double bond, the desired tetracyclic lactam **18** was isolated in 23% yield as a single diastereomer. In all experiments variable amounts of sulfide **8d**, formed by reduction of the intermediate thionium ion, were also obtained. Finally, desulfurization of **18** with Raney nickel (W-2) gave the 3,4-secoakuammilan tetracycle **19** in 80% yield.



Scheme 6

A careful inspection of the NMR spectra of lactam **18** allowed the unambiguous elucidation of its structure with the aid of 2D-NMR techniques (^{1}H-^{1}H COSY, HMQC, HMBC, and NOESY). The observation of a quaternary carbon at δ52.5 in the ^{13}C-NMR spectrum and some HMBC correlations (6-H with C-2 and C-7, and 16-H with C-2, C-6 and C-7) clearly established that cyclization had occurred on the indole 3-position. Furthermore, the UV spectrum shows a characteristic indoline pattern.

On the other hand, the relative configuration at C-2 was deduced from the chemical shift of this carbon (δ 69.2)[19] and from the observation of a NOESY cross peak between 2-H and 6-H that would not exist in the opposite configuration. A similar spectroscopic analysis from **19** was in complete agreement with the above structural assignment. Furthermore, the observation of NOESY correlations between the protons inside the eight-membered ring (6-H, 16-H, and 21-H) and between 9-H and 16-H or 6-H established that the lactam ring is in a boat-chair conformation and that the cyclohexane ring is in a chair conformation, as depicted in Figure 2. In agreement with this conformation, the multiplicity of 2-H in the ^{1}H-NMR spectrum (t, J = 7.5 Hz) indicates that this proton is in the bisecting plane of the angle formed by the vicinal 3-CH_2 protons.

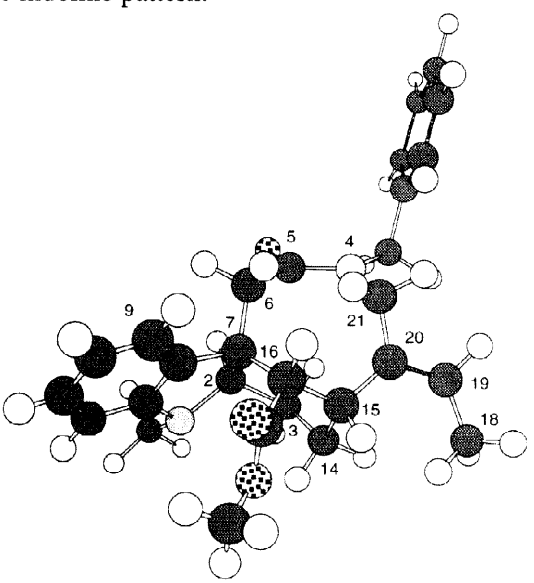


Figure 2. Chem3D Representation of Lactam **19**

The different outcome of the Pummerer reaction from sulfoxide **17** as compared with sulfoxides **5** and **11**, which only differ from **17** in the N-4 substituents, deserves attention as it clearly indicates that the success of the cyclization largely depends on conformational factors associated with the geometry of the starting sulfoxide. The successful cyclization of sulfoxide **17** provides a solution for the construction of the crucial quaternary C-7 centre of akuammiline alkaloids and might open synthetic routes towards the alkaloids of this group, which remain an unattained goal for synthetic organic chemists.

EXPERIMENTAL SECTION

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 300 (300 and 74.5 MHz, respectively) or, when indicated, on a Varian VXR-500 (500 MHz) instrument. Chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer or on a Autospec-VG (HRMS). EI and CI mean electron-impact and chemical ionisation, respectively. Flash chromatography were carried out on SiO_2 (silica gel 60, SDS, 0.04-0.06 mm). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

Methyl *trans*-3-{1-[*N*-Benzyloxycarbonyl-*N*-(2-phenylsulfanylethyl)aminomethyl]-1(*E*)-propenyl}-1,2,3,4-tetrahydrocarbazole-4-carboxylate (4a). Benzyl chloroformate (0.18 ml, 1.2 mmol) was slowly added to a solution of sulfide **1a**[6] (150 mg, 0.25 mmol) in anhydrous toluene (10 ml), and the mixture was refluxed for 15 min. The reaction mixture was partitioned between 10% aqueous Na_2CO_3 solution and Et_2O, and extracted with Et_2O. The organic extracts were dried and concentrated to give a residue (crude dihydrocarbazole **3a**), which was dissolved in CH_2Cl_2 (10 ml). Et_3SiH (0.12 ml, 0.78 mmol) and TFA (0.10 ml, 1.3 mmol) were added to the resulting solution, and the mixture was refluxed for 2 h. The reaction mixture was poured into 10% aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (7:3 hexanes-AcOEt) to give tetrahydrocarbazole **4a**: 92 mg (mixture of rotamers, 65%); IR (NaCl) 3460 (NH), 1727, 1681 (CO); ^{1}H-NMR 1.59 (m, 3H, 18-H), 1.81 (m, 2H, 14-H), 2.50-2.68 (m, 2 H), 3.00-3.55 (m, 5H), 3.59 and 3.63 (2s, 3H, OMe), 3.86 (m, 2H), 4.16 (m, 1H, 16-H), 5.13 (m, 2H, OCH_2), 5.25 (m, 1H, 19-H), 7.00-7.45 (m, 14H, Ar), 7.98 (s, 1H, NH); ^{13}C-NMR 13.0 (C-18), 23.2 (C-3), 26.8 (C-14), 30.8 (C-6), 39.0 (C-15), 43.6 (C-16), 45.2, 49.4 (C-5, C-21), 51.6 (OMe), 67.3 (CH_2O), 107.1 (C-7), 110.6 (C-12), 117.6 (C-9), 119.5 (C-10), 121.3, 123.4 (C-11, C-19), 127.2-128.5 (complex signal, Ph, C-8), 134.2 (C-2), 136.5, 136.8 (C-13, C-20), 155.9, 174.9 (CO); MS, *m/z* (EI) 568 (M^+, 1), 536 (2), 445 (43); HRMS calcd for $C_{34}H_{36}N_2O_4S$ 568.2383, found 568.2396.

Methyl *trans*-3-{1-[*N*-Benzyloxycarbonyl-*N*-(2-phenylsulfanylethyl)aminomethyl]-1(*E*)-propenyl}-9-(methoxycarbonyl)-1,2,3,4-tetrahydrocarbazole-4-carboxylate (4b). Operating as above, from sulfide **1b**[6] (100 mg, 0.2 mmol) and benzyl chloroformate (0.15 mL, 1 mmol) was obtained crude dihydrocarbazole **3b**, which was allowed to react with Et_3SiH (0.09 ml, 0.62 mmol) and TFA (0.078 ml, 1 mmol) to give tetrahydrocarbazole **4b** after flash chromatography (hexanes-Et_2O): 81 mg (mixture of rotamers, 65%); IR (NaCl) 1735, 1702, 1698 (CO); ^{1}H-NMR (major rotamer) 1.57 (m, 3H, 18-H), 2.08 (m, 2H, 14-H), 2.50-2.80 (m, 2H), 2.90-3.50 (m, 5H), 3.59 (s, 3H, OMe), 3.65-3.90 (m, 2H), 3.97 (s, 3H, OMe), 4.15 (m, 1H, 16-H), 5.11 (m, 2H, OCH_2), 5.25 (m, 1H, 19-H), 7.00-7.40 (m, 13H, Ar), 8.12 (d, *J*=8 Hz, 1H, 12-H); ^{13}C-NMR (major rotamer) 12.7 (C-18), 22.4 (C-14), 25.5 (C-3), 31.0 (C-6), 39.9 (C-15), 43.9 (C-16), 46.1, 48.3 (C-5, C-21), 51.8, 53.2 (OMe), 67.1 (CH_2O), 114.2 (C-7), 115.4 (C-12), 117.6 (C-9), 122.9 (C-10), 123.7, 126.1 (C-11, C-19), 127.5, 128.5 (complex signal, Ph, C-8), 134.1, 134.3, 136.5 (C-2, C-13, C-20); 152.1, 156.0, 174.8 (CO); MS, *m/z* (EI) 626 (M^+, 28), 596 (20), 503 (22); HRMS calcd for $C_{36}H_{38}N_2O_6S$ 626.2441, found 626.2450.

Methyl *trans*-3-{1-[*N*-Benzyloxycarbonyl-*N*-(2-phenylsulfinylethyl)aminomethyl]-1(*E*)-propenyl}-1,2,3,4-tetrahydrocarbazole-4-carboxylate (5a). *m*-CPBA (36 mg, 0.21 mmol) in CH_2Cl_2 (4 ml) was slowly added to a solution of sulfide **4a** (100 mg, 0.17 mmol) in CH_2Cl_2 (10 ml) at -70 °C, and the resulting mixture was stirred at -70 °C for 15 min. The reaction was quenched with solid K_2CO_3 (excess) and the mixture was stirred at room temperature for 2 h and filtered. The filtrate was washed with H_2O, dried, and concentrated. The resulting residue was chromatographed (hexane-AcOEt, increasing polarity) to give sulfoxide **5a**: 85 mg (83%); IR (NaCl) 3330 (NH), 1730, 1696 (CO); ^{1}H-NMR 1.62 (m, 3H, 18-H), 1.75 (m, 2H, 14-H), 2.50-2.81 (m, 2H), 2.85-3.51 (m, 5H), 3.63 (s, 3H, OMe), 3.82-4.03 (m, 2 H), 4.20 (m, 1H, 16-H), 5.11 (m, 2H, OCH_2), 5.35 (m, 1H, 19-H), 7.00-7.55 (m, 14H, Ar), 7.98 (s, 1H, NH); ^{13}C-NMR 13.0 (C-18), 23.2 (C-3), 26.9 (C-14), 39.0 (C-15), 43.5 (C-16), 49.8, 54.8 (C-5, C-6, C-21), 51.6 (OMe), 67.3 (CH_2O), 107.0 (C-7), 110.6 (C-12), 117.6 (C-9), 119.4 (C-10), 121.2, 123.7 (C-11, C-19), 126.3 (C-8), 127.0-128.5 (complex signal, Ph), 134.4, 134.7, 135.8 (C-2, C-13, C-20), 155.9, 174.9 (CO); MS, *m/z* (EI) 484 (M^+, 18), 568 (6), 445 (8); HRMS calcd for $C_{34}H_{36}N_2O_5S$ 584.2321, found 584.2345. Anal. Calcd for $C_{34}H_{36}N_2O_5 \cdot 1/2CH_2Cl_2$: C, 66.06; H, 5.94; N, 4.46. Found: C, 65.77; H, 6.00; N, 4.35.

Methyl *trans*-3-{1-[*N*-Benzyloxycarbonyl-*N*-(2-phenylsulfinylethyl)aminomethyl]-1(*E*)-propenyl}-9-(methoxycarbonyl)-1,2,3,4-tetrahydrocarbazole-4-carboxylate (5b). Operating as above, from sulfide **4b** (100 mg, 0.16 mmol) was obtained sulfoxide **5b** after flash chromatography (9:1 Et_2O-DEA): 86 mg (83%, mixture of stereoisomers at sulfur); IR (NaCl) 1732, 1701 (CO); ^{1}H-NMR 1.62 (m, 3H, 18-H), 2.01 (m, 2H, 14-H), 2.80 (m, 2H), 3.00-3.40 (m, 5H), 3.65 (s, 3H, OMe), 3.65-3.90 (m, 2 H), 4.01 (s, 3H, OMe), 4.30 (m, 1H, 16-H), 5.07 (m, 2H, OCH_2), 5.40 (m, 1H, 19-H), 7.00-7.65 (m, 13H, Ar), 8.14 (m, 1H, 12-H); ^{13}C-NMR (major stereoisomer) 12.7 (C-18), 22.4 (C-3), 25.6 (C-14), 39.9 (C-15), 43.8 (C-16), 49.8, 49.0, 54.7 (C-5, C-6, C-21), 51.7, 52.0 (OMe), 67.2 (OCH_2), 114.3 (C-7), 115.4 (C-12), 117.5 (C-9), 122.9 (C-10), 125.4 (C-8), 125.7, 128.1 (C-11, C-19), 128.5 (complex signal, Ph), 134.3, 135.6 (C-2, C-13, C-20), 152.1, 156.5, 174.5 (CO).

Methyl *trans*-3-{1-[*N*-Benzyl-*N*-(1-chloroethoxycarbonyl)aminomethyl]-1(*E*)-propenyl}-9-methyl-3,4-dihydrocarbazole-4-carboxylate (7a). A mixture of tetracycle **6**[6] (150 mg, 0.37 mmol) and 1-(chloroethyl)chloroformate (0.45 ml, 4.1 mmol) in toluene (10 ml) was refluxed for 3 h. The reaction mixture was poured into 10% aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (8:2 hexanes-Et_2O) to give dihydrocarbazole **7a**: 110 mg (mixture of stereoisomers, 57%); IR (NaCl) 1724 (CO); ^{1}H-NMR (major stereoisomer) 1.65-1.90 (m, 6H, 18-H and OCHCl*Me*), 3.63 (s, 3H, OMe), 3.72 (s, 3H, NMe), 3.75-4.60 (m, 6H), 5.40 (m, 1H, 19-H), 5.72 (m, 1H, 14-H), 6.57 (m, 2H, 3-H and OC*H*ClMe), 7.00-7.30 (m, 8H, Ar), 7.40 (m, 1H, 9-H); MS, *m/z* (CI, CH_4) 507 (M+1, 54); HRMS calcd for $C_{29}H_{31}N_2O_4Cl$ 506.1977, found 506.1972.

Methyl *trans*-3-{1-[*N*-Benzyl-*N*-(benzyloxycarbonyl)aminomethyl]-1(*E*)-propenyl}-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (8b). Tetracycle **6**[6] (150 mg, 0.37 mmol) was allowed to react with benzyl chloroformate (0.53 ml, 3.7 mmol) in boiling toluene (10 ml) for 2.5 h. After workup, the resulting residue (crude **7b**) was treated with Et_3SiH (0.18 ml, 1.1 mmol) and TFA (0.14 ml, 1.8 mmol) as described for the preparation of **4a**. After flash chromatography (7:3 hexanes-Et_2O), **8b** was obtained: 160 mg (mixture of rotamers, 80%); mp 90-92 °C (Et_2O-hexane); IR (NaCl) 1732, 1698 (CO); ^{1}H-NMR 1.70 (m, 3H, 18-H), 1.90 (m, 2H, 14-H), 2.80 (m, 2H, 3-H), 3.32 (m, 1H, 15-H); 3.59 (s, 3H, OMe), 3.70 (s, 3H, NMe), 3.95 (m, 1H,

16-H), 4.12 (m, 2H, CH_2Ph), 4.30 (m, 1H, 21-H), 4.70 (m, 1H, 21-H), 5.17 (m, 2H, OCH_2), 5.41 (m, 1H, 19-H), 7.00-7.40 (m, 14 H, Ar); ^{13}C-NMR 13.0 (C-18), 22.2 (C-3), 26.7 (C-14), 29.0 (NMe), 39.0 (C-15), 43.8 (C-16), 48.4, 49.0 (C-21, CH_2Ph), 51.6 (OMe), 67.3 (OCH_2), 106.4 (C-7), 108.7 (C-12), 117.6 (C-9), 119.2 (C-10), 120.9, 121.2 (C-11, C-19), 125.7 (C-8), 128.0-128.9 (complex signal, Ph), 134.3, 136.6, 136.9 (C-2, C-13, C-20), 156.6, 174.9 (CO); MS, *m/z* (CI, CH_4) 537 (M+1, 100). Anal. Calcd for $C_{34}H_{36}N_2O_4$: C, 76.10; H, 6.76; N, 5.22. Found: C, 75.97; H, 6.77; N, 5.14.

Methyl *trans*-3-{1-[*N*-Benzyl-*N*-(2-phenylsulfanylacetyl)aminomethyl]-1(*E*)-propenyl}-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (8d). Operating as above, from tetracycle **6**[6] (150 mg, 0.37 mmol), $PhSCH_2COCl$ (470 mg, 4.1 mmol), Et_3SiH (0.18 ml, 1.1 mmol), and TFA (0.14 ml, 1.8 mmol), tetrahydrocarbazole **8d** was obtained as an oil after flash chromatography (hexanes-Et_2O, increasing polarity): 127 mg (mixture of rotamers, 62%); IR (NaCl) 1728, 1648 (CO); ^{1}H-NMR 1.65 (d, *J*=6.8 Hz, 3H, 18-H), 1.86 (m, 2H, 14-H), 2.84 (m, 2H, 3-H), 3.33 (m, 1H, 15-H), 3.61 (s, 3H, OMe), 3.68 (s, 5H, NMe, 6-H), 3.90 (m, 2H, 16-H, 21-H), 4.60 (m, 2H, CH_2Ph), 5.45 (q, *J*=6.8 Hz, 1H, 19-H), 7.05-7.60 (m, 14 H, Ar); ^{13}C-NMR 12.8 (C-18), 22.1 (C-3), 26.8 (C-14), 29.1 (NMe), 36.4 (C-6), 38.8 (C-15), 43.8 (C-16), 47.4 (C-21), 48.8 (CH_2Ph), 51.8 (OMe), 105.9 (C-7), 108.7 (C-12), 117.4 (C-9), 119.3 (C-10), 120.3, 121.0 (C-11, C-19), 125.5 (C-8), 133.5 (C-20), 135.4 (C-2), 136.9 (C-13), 169.7, 174.7 (CO); MS, *m/z* (CI, CH_4) 553 (M+1, 3). Anal. Calcd for $C_{34}H_{36}N_2O_3S{\cdot}H_2O$: C, 71.55; H, 6.70; N, 4.90. Found: C, 71.72; H, 6.58; N, 4.83.

Methyl (3a*RS*, 4*SR*, 10a*RS*)-1-Benzyl-3(*E*)-ethylidene-9-methyl-2,3,3a,4,10,10a-hexahydro-1*H*-pyrrolo-[2,3-*b*]carbazole-4-carboxylate (9). A solution of dihydrocarbazole **7a** (140 mg, 0.28 mmol) in MeOH (10 ml) was refluxed for 3 h. The solvent was removed, and the residue was diluted with H_2O and extracted with Et_2O. The organic extracts were dried and concentrated. Flash chromatography (1:1 hexanes-Et_2O) of the residue gave pyrrolidine **9**: 68 mg (62%); mp 104-105 °C (Et_2O-cyclohexane); IR (KBr) 1732 (CO); ^{1}H-NMR 1.62 (dd, *J*=6.8, 2.7 Hz, 3H, 18-H), 2.96 (m, 2H, 3-H), 3.16 (dd, *J*=8.5, 5 Hz, 1H, 15-H), 3.34 (d, *J*=13.6 Hz, 1H, CH_2Ph), 3.38 (masked, 1H), 3.47 (s, 3H, OMe), 3.73 (br s, 1H), 3.78 (s, 3H, NMe), 3.80 (masked, 1H), 3.94 (d, *J*=8.5 Hz, 1H, 16-H), 4.02 (d, *J*=13.6 Hz, 1H, CH_2Ph), 5.30 (qd, *J*=6.8, 2.7 Hz, 1H, 19-H), 7.00-7.40 (m, 9H, Ar); ^{13}C-NMR 14.4 (C-18), 28.8 (NMe), 42.6 (C-15), 43.0 (C-16), 52.2 (OMe), 57.8 (C-21), 58.2 (CH_2Ph), 62.7 (C-14), 104.5 (C-7), 108.7 (C-12), 115.9 (C-9), 117.8 (C-10), 119.0, 120.6 (C-11, C-19), 125.7 (C-8), 126.7, 128.0 (Ph), 133.3, 137.2 (C-2, C-20), 139.4 (C-13), 140.1 (Ph), 176.3 (CO); MS, *m/z* (EI) 400 (M^+, 8), 341 (3). Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.98; H, 7.04; N, 6.99. Found: C, 78.03; H, 7.07; N, 6.98.

Methyl *trans*-3-[1-(*N*-Benzylaminomethyl)-1(*E*)-propenyl]-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (10). Et_3N (0.05 ml, 0.4 mmol), $PdCl_2$ (20 mg), and Et_3SiH (0.31 ml, 1.9 mmol) were successively added to a solution of **8b** (200 mg, 0.37 mmol) in CH_2Cl_2 (6 mL) , and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with 10% aqueous Na_2CO_3 solution, dried, and concentrated. The resulting residue was chromatographed (1:1 hexanes-Et_2O) to give amine **10**: 120 mg (80%); mp 104-106 °C (Et_2O-hexane); IR (NaCl) 1732 (CO); ^{1}H-NMR 1.66 (d, *J*=6.8 Hz, 3H, 18-H), 2.01 (m, 2H, 14-H), 2.84 (m, 2H, 3-H), 3.31 (m, 3H, 15-H, 21-H), 3.61 (s, 3H, OMe), 3.67 (s, 3H, NMe), 3.80 (s, 2H, CH_2Ph), 4.17 (d, *J*=10.5 Hz, 1H, 16-H), 5.65 (q, *J*=6.8 Hz, 1H, 19-H), 7.04-7.36 (m, 9H, Ar); ^{13}C-NMR 13.0 (C-18), 22.3 (C-3), 27.5 (C-14), 29.1 (NMe), 39.4 (C-15), 44.3 (C-16), 51.7 (OMe), 51.8 (C-21), 59.3 (CH_2Ph), 106.7 (C-7), 108.7 (C-12), 117.7 (C-9), 119.2 (C-10), 120.8, 123.0 (C-11, C-19), 125.8

(C-8), 126.7, 128.0 (Ph), 135.9 (C-2, C-20), 138.5 (C-13), 140.1 (Ph); MS *m/z* (EI) 402 (M^+, 16), 343 (41). Anal. Calcd for $C_{26}H_{30}N_2O_2$: C, 77.59; H, 7.50; N, 6.96. Found: C, 77.57; H, 7.60; N, 6.96.

Methyl *trans*-3-{1-[*N*-Benzyl-*N*-(2-phenylsulfinylethyl)aminomethyl]-1(*E*)-propenyl}-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (11). $AlMe_3$ (2M in toluene, 0.64 ml, 0.32 mmol) was slowly added under N_2 to a solution of amine **10** (100 mg, 0.25 mmol) in CH_2Cl_2 (4 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. Phenyl vinyl sulfoxide was then added, and stirring was continued at room temperature for 4 days. The reaction mixture was poured into 10% aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. The organic extracts were washed with brine and concentrated. Flash chromatography (hexanes-Et_2O, increasing polarity) of the residue gave sulfoxide **11**: 78 mg (mixture of stereoisomers at sulfur, 57%): mp 60-62 °C (Et_2O); IR (NaCl) 1731 (CO); ^{1}H-NMR 1.68 (m, 3H, 18-H), 1.90 (m, 2H, 14-H), 2.50-3.01 (m, 6H), 3.05 (dd, 1H, *J*=14.5, 5 Hz, 1H, 21-H), 3.27 (m, 1H, 15-H), 3.31 (dm, *J*=14.5, 1H, 21-H), 3.58 (dm *J*=14.5 Hz, 1H, CH_2Ph), 3.62 (s, 3H, OMe), 3.64 (s, 3H, NMe), 3.72 (d, *J*=14.5 Hz, 1H, CH_2Ph), 4.14 (d, *J*=8 Hz, 1H, 16-H), 5.75 (q, *J*=6.8 Hz, 1H, 19-H), 7.00-7.52 (m, 14H, Ar); ^{13}C-NMR (major stereoisomer) 13.3 (C-18), 22.3 (C-3), 27.2 (C-14), 29.1 (NMe), 39.4 (C-15), 43.9 (C-16), 46.7 (C-7), 51.6 (OMe), 55.4 (C-21), 58.5, 58.9 (C-5, CH_2Ph), 106.4 (C-7), 108.7 (C-12), 117.6 (C-9), 119.1 (C-10), 120.8, 123.8 (C-11, C-19), 125.8 (C-8), 127.5-128.7 (complex signal, Ar), 136.0, 136.8 (C-2, C-20), 138.6 (C-13), 175.4 (CO); MS, m/z (EI) 554 (M^+, 7), 428 (21).

Methyl *trans*-3-{1-[*N*-Benzyl-*N*-(2,2-bis(methylsulfanyl)ethyl)aminomethyl]-1(*E*)-propenyl}-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (12). Bis(methylsulfanyl)acetaldehyde[20] (0.085 ml, 0.6 mmol) and $NaCNBH_3$ (70 mg, 1.12 mmol) were added to a solution of the hydrochloride of amine **10** (150 mg, 0.37 mmol) in dry MeOH (7 ml), and the resulting mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with 10% aqueous Na_2CO_3 solution. Concentration of the organic extracts, followed by flash chromatography of the residue (7:3 hexanes-Et_2O) gave dithioacetal **12**: 140 mg (72%); IR (KBr) 1731 (CO); ^{1}H-NMR 1.68 (d, *J*=6.8 Hz, 3H, 18-H), 1.97 and 1.99 (2s, 6H, SMe), 2.15 (m, 2H, 14-H), 2.66 (dd, *J*=12.6, 6.5 Hz, 1H, 5-H), 2.81 (m, 3H, 3-H, 5-H), 3.00 (d, *J*=14.3 Hz, 1H, 21-H), 3.31 (m, 2H, 15-H, 21-H), 3.48 (d, *J*=13.8 Hz, 1H, CH_2Ph), 3.62 (s, 3H, OMe), 3.63 (s, 3H, NMe), 3.79 (d, *J*=13.8 Hz, 1H, CH_2Ph), 3.91 (dd, *J*=8, 6.5 Hz, 1H, 6-H), 4.20 (d, *J*=10.7 Hz, 1H, 16-H), 5.89 (q, *J*=6.8 Hz, 1H, 19-H), 7.03 (t, *J*=8 Hz, 1H, 10-H), 7.12 (t, *J*=8 Hz, 1H, 11-H), 7.20-7.32 (m, 6H, Ar), 7.40 (d, *J*=8 Hz, 1H, 9-H); ^{13}C-NMR 12.4 and 12.7 (SMe), 13.2 (C-18), 22.4 (C-3), 27.4 (C-14), 29.1 (NMe), 39.5 (C-15), 43.6 (C-16), 51.7 (OMe), 52.9 (C-6), 57.8, 58.6, 59.3 (C-5, C-21, CH_2Ph), 106.6 (C-7), 108.7 (C-12), 117.7 (C-9), 119.1 (C-10), 120.7, 124.8 (C-11, C-19), 125.9 (C-8), 126.7, 128.0 (Ph), 136.0, 136.9 (C-2, C-13, C-20), 140.1 (Ph), 174.9 (CO); MS, *m/z* (EI) 552 (M^+, 2), 416 (32), 415 (100); HRMS calcd for $C_{30}H_{38}N_2O_2S_2$ 522.2393, found 522.2375.

Attempted Cyclization of Dithioacetal 12. A solution of dithioacetal **12** (70 mg, 0.13 mmol) in CH_2Cl_2 (3 ml) was slowly added under N_2 to a solution of DMTSF (32 mg, 0.14 mmol) in CH_2Cl_2 (20 ml) at 0 °C, and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with 10% aqueous Na_2CO_3 solution (10 ml) and stirred at room temperature for 30 min. The organic extracts were dried and concentrated, and the residue was chromatographed (hexanes-Et_2O, increasing polarity) to give piperidine **13**: 15 mg (23%, mixture of stereoisomers); IR (KBr) 3450 (OH), 1736 (CO); ^{1}H-NMR (500 MHz) 1.05 (d, *J*=7.5 Hz, 3H, 18-H), 1.81 (dm, *J*=13 Hz, 1H, 14-H), 1.94 (s, 3H, SMe), 2.09 (dm, *J*=13 Hz, 1H, 14-H), 2.20 (d,

J=12, 1H, 21-H), 2.28 (dm, *J*=7.5 Hz, 1H, 19-H), 2.35 (dm, *J*=10.5 Hz, 1H, 15-H), 2.40-2.70 (m, 6H), 2.46 (masked d, *J*=14 Hz, 1H, CH_2Ph), 2.72 (dm, *J*=7.5 Hz, 1H, 3-H), 3.50 (d, *J*=14 Hz, 1H, CH_2Ph), 3.53 (s, 3H, OMe), 3.60 (s, 3H, NMe), 4.16 (d, *J*=10.5 Hz, 1H, 16-H), 6.92-7.50 (m, 9H, Ar); ^{13}C-NMR 15.8 (SMe), 17.0 (C-18), 21.6 (C-2), 29.1 (NMe), 29.7 (C-14), 38.4 (C-19), 39.9 (C-15), 42.0 (C-16), 49.8 (C-6), 51.1 (C-5), 57.9 (C-21), 62.4 (CH_2Ph), 75.5 (C-20), 105.8 (C-7), 108.6 (C-12), 118.5 (C-9), 118.9 (C-10), 120.6 (C-11), 126.5 (C-8), 127.1, 128.2, 128.6, 136.5 (Ph), 137.1 (C-2), 137.9 (C-13); MS, *m/z* (CI, CH_4) 493 (M+1, 100), 475 (20); HRMS calcd for $C_{29}H_{36}N_2O_3S$ 492.2437, found 492.2447.

Methyl *trans*-3-{1-[*N*-Benzyl-*N*-(2-iodoacetyl)aminomethyl]-1(*E*)-propenyl}-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (14). NaI (100 mg, 0.67 mmol) was added to a solution of chloroacetamide **8c**[11] (250 mg, 0.52 mmol) in anhydrous acetone (8 ml). The flask was protected from light, and the reaction mixture was stirred at room temperature for 4 h. After filtration, the filtrate was concentrated, and the residue was taken up in Et_2O. The solution was washed with H_2O, dried, and concentrated. Flash chromatography (1:1 hexanes-Et_2O) gave iodoacetamide **14**: 265 mg (mixture of rotamers, 89%); mp 148-149 °C (hexane-Et_2O); IR (KBr) 1735, 1649 (CO); ^{1}H-NMR (major rotamer) 1.69 (d, *J*=6.9 Hz, 3H, 18-H), 1.93 (m, 2H, 14-H), 2.86 (m, 2H, 3-H), 3.28 (td, *J*=11.6, 6.2, 2.0 Hz, 1H, 15-H), 3.62 (s, 3H, OMe), 3.67 (masked, 2H, CH_2I), 3.73 (s, 3H, NMe), 3.76-3.92 (m, 3H, 16-H, 21-H), 4.58 (m, 2 H, CH_2Ph), 5.40 (q, *J*=6.8 Hz, 1H, 19-H), 7.00-7.40 (m, 9H, Ar); ^{13}C-NMR (major rotamer) -3.4 (C-6), 12.7 (C-18), 22.0 (C-3), 26.8 (C-14), 29.0 (NMe), 38.8 (C-15), 43.8 (C-16), 48.6, 48.8 (C-21, CH_2Ph), 51.8 (OMe), 105.8 (C-7), 108.8 (C-12), 117.4 (C-9), 119.0 (C-10), 120.7, 121.6 (C-11, C-19), 125.9 (C-8), 127.6, 128.3 (Ph), 133.9, 135.3, 136.9 (C-2, C-13, C-20, Ph), 169.2, 174.6 (CO); MS, *m/z* (CI, CH_4), 571 (M+1, 2). Anal. Calcd for $C_{28}H_{31}N_2O_3I$: C, 58.96; H, 5.47; N, 4.91; I 22.25. Found: C, 58.80; H, 5.58; N, 4.89; I, 22.13.

Attempted Cyclization of Iodoacetamide 14. A solution of iodoacetamide **14** (90 mg, 0.16 mmol), $(n\text{-}Bu_3Sn)_2$ (0.16 ml, 0.32 mmol), and AIBN (3 mg, 0.02 mmol) in toluene (15 ml) was irradiated with a 275-W sunlamp for 10 h at reflux temperature. The solvent was evaporated, and the residue was partitioned between H_2O and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated. Flash chromatography (Et_2O) of the residue gave acetamide **15**: 20 mg (mixture of rotamers, 30%); IR (NaCl) 1729, 1649 (CO); ^{1}H-NMR (major rotamer) 1.70 (dd, *J*=6.8, 1.8 Hz, 3H, 18-H), 1.96 (m, 2H, 14-H), 2.16 (s, 3H, MeCO), 2.85 (m, 2H, 3-H), 3.35 (m, 1H, 15-H), 3.62 (s, 3H, OMe), 3.72 (s, 3H, NMe), 3.80-4.10 (m, 3H, 16-H, 21-H), 4.55 (m, 2H, CH_2Ph), 5.40 (q, *J*=6.8 Hz, 1H, 19-H), 7.00-7.60 (m, 9H, Ar); ^{13}C-NMR (major rotamer) 12.9 (C-18), 21.1 (MeCO), 22.2 (C-3), 27.0 (C-14), 29.1 (NMe), 38.9 (C-15), 43.9 (C-16), 48.1 (C-21), 51.9 (OMe), 58.5 (CH_2Ph), 106.1 (C-7), 108.9 (C-12), 117.5 (C-9), 119.4 (C-10), 121.1 (C-11, C-19), 125.9 (C-8), 127.6, 128.3 (Ph), 133.4, 135.5, 137.0 (C-2, C-13, C-20, Ph), 171.6, 174.8 (CO); MS, *m/z* (CI, CH_4) 445 (M+1, 100); HRMS calcd for $C_{28}H_{32}N_2O_3$ 444.2421, found 444.2413.

Methyl *trans*-3-{1-[*N*-Benzyl-*N*-(2-phenylsulfinylacetyl)aminomethyl]-1(*E*)-propenyl}-9-methyl-1,2,3,4-tetrahydrocarbazole-4-carboxylate (17). Operating as in the preparation of sulfoxide **5a**, from sulfide **8d** (150 mg, 0.27 mmol) and *m*-CPBA (56 mg, 0.32 mmol) was obtained sulfoxide **17** after flash chromatography (8:2 Et_2O-DEA): 112 mg (mixture of stereoisomers at sulfur, 72%); mp 78-80 °C (hexane-Et_2O); IR (KBr) 1735, 1642 (CO); ^{1}H-NMR 1.57 (m, 3H, 18-H), 1.84 (m, 2H, 14-H), 2.82 (m, 2H, 3-H), 3.28 (ddd, *J*=11, 10, 1.9 Hz, 1H, 15-H), 3.60 (s, 3H, OMe), 3.67 (s, 3H, NMe), 3.70-4.20 (m, 5H, 21-H, 16-H, 6-H), 4.50 (m, 2H, CH_2Ph), 5.14 (m, 1H, 19-H), 7.05-7.70 (m, 14H, Ar); ^{13}C-NMR (major stereoisomer) 12.9 (C-18), 22.1 (C-

3), 26.8 (C-14), 29.1 (NMe), 38.8 (C-15), 43.7 (C-16), 47.3 (C-21), 48.8 (CH_2Ph), 51.9 (OMe), 61.2 (C-6), 105.9 (C-7), 108.9 (C-12), 117.5 (C-9), 119.4 (C-10), 121.1, 124.5 (C-11, C-19), 125.5 (C-8), 133.0 (C-20), 135.4 (C-2), 136.6 (C-13), 165.4, 174.6 (CO); MS, *m/z* (CI, CH_4) 569 (M+1, 1). Anal. Calcd for $C_{34}H_{36}N_2O_4S$: C, 71.81; H, 6.37; N, 4.93; S, 5.64. Found: C, 71.51; H, 6.53; N, 4.93; S, 5.40.

Methyl (3*RS*, 4*SR*, 4a*SR*, 9a*RS*, 14*RS*)-12-Benzyl-10(*E*)-ethylidene-9-methyl-13-oxo-14-(phenylsulfanyl)-1,2,3,4,4a,9a-hexahydro-3,4a-(ethanoiminoethano)carbazole-4-carboxylate (18). TFAA (0.025 ml, 0.18 mmol) was added to a solution of sulfoxide **17** (70 mg, 0.12 mmol) in CH_2Cl_2 (12 ml) at 0 °C. After being stirred at 0 °C for 15 min, the reaction mixture was refluxed for 6 h. The solvent was removed, and the resulting residue was dissolved in MeOH (10 ml), treated with $Na(CN)BH_3$ (50 mg, excess) at 0 °C, and stirred at 0 °C for 1 h. Evaporation of the solvent, followed by flash chromatography (8:2 hexanes-Et_2O) of the residue gave **18**: 16 mg (23%); IR (NaCl) 1728, 1648 (CO); ^{1}H-NMR (500 MHz) 1.55 (m, 1H, 14-H), 1.65 (d, *J*=6.5 Hz, 3H, 18-H), 1.80 (m, 1H, 14-H), 2.22 (m, 1H, 3-H), 2.40 (m, 1H, 3-H), 2.84 (s, 3H, NMe), 3.01 (s, 1H, 16-H), 3.13 (s, 3H, OMe), 3.24 (d, *J*=15.5 Hz, 1H, 21-H), 3.49 (dd, *J*=10, 9.5 Hz, 1H, 15-H), 3.79 (d, *J*=15 Hz, 1H, CH_2Ph), 3.91 (dd, *J*=8, 10 Hz, 1H, 2-H), 4.30 (d, *J*=15.5 Hz, 1H, 21-H), 4.34 (s, 1H, 6-H), 5.42 (q, *J*=6.5 Hz, 1H, 19-H), 5.62 (d, *J*=15 Hz, 1H, CH_2Ph), 6.42 (d, *J*=8 Hz, 1H, 12-H), 6.64 (dd, *J*=7, 7.5 Hz, 1H, 10-H), 7.10-7.30 (m, 11H, Ph, 11-H), 7.65 (dd, *J*=7.5, 1 Hz, 1H, 9-H); ^{13}C-NMR 13.2 (C-18), 21.3 (C-14), 24.2 (C-3), 33.1 (C-15), 34.3 (NMe), 48.2 (CH_2Ph), 49.0 (C-16), 51.5 (C-21), 51.6 (OMe), 52.5 (C-7), 62.3 (C-6), 69.2 (C-2), 106.3 (C-12), 117.0 (C-10), 127.3-130.5 (complex signal), 131.5 (C-8), 135.5 (C-20), 153.0 (C-13), 170.4, 174.7 (CO); UV (MeOH, λ_{max}) 259, 208 nm; MS, *m/z* (EI) 552 (M^+, 10), 520 (8), 443 (4), 263 (100); HRMS calcd for $C_{34}H_{36}N_2O_3S$ 552.2460, found 552.2447. On elution with 1:1 hexane-Et_2O, variable amounts of sulfide **8d** (10-15%) were obtained.

Methyl (3*RS*, 4*SR*, 4a*SR*, 9a*RS*)-12-Benzyl-10(*E*)-ethylidene-9-methyl-13-oxo-1,2,3,4,4a,9a-hexahydro-3,4a-(ethanoiminoethano)carbazole-4-carboxylate (19). Raney Ni (W-2, 1 spatula) was added to a solution of indoline **18** (10 mg, 0.02 mmol) in MeOH-THF (1:2, 6 ml). The mixture was refluxed for 1,5 h, cooled, and filtered through a Celite pad. The solids were washed with MeOH (2x10 ml), and the combined organic solutions were concentrated to give tetracycle **19**: 6 mg (80%); IR (NaCl) 1737, 1638 (CO); ^{1}H-NMR (500 MHz) 1.02 (m, 1H, 14-H), 1.65 (d, *J*=7 Hz, 3H, 18-H), 1.77 (m, 1H, 3-H), 2.04 (m, 1H, 14-H), 2.14 (m, 1H, 3-H), 2.72 (s, 3H, NMe), 2.79 (d, *J*=13.5 Hz, 1H, 6-H), 3.02 (s, 1H, 16-H), 3.08 (s, 3H, OMe), 3.20 (t, *J*=8.5 Hz, 1H, 15-H), 3.28 (d, *J*=16 Hz, 1H, 21-H), 3.31 (d, *J*=13.5 Hz, 1H, 6-H), 3.52 (d, *J*=14.5 Hz, 1H, CH_2Ph), 3.73 (t, *J*=7.5 Hz, 1H, 2-H), 4.37 (d, *J*=16 Hz, 1H, 21-H), 5.34 (d, *J*=14.5 Hz, 1H, CH_2Ph), 5.37 (q, *J*=7 Hz, 1H, 19-H), 6.36 (d, *J*=8 Hz, 1H, 12-H), 6.51 (dd, *J*=7, 8 Hz, 1H, 10-H), 6.88 (d, *J*=7 Hz, 1H, 9-H), 7.00 (dd, *J*=7, 8 Hz, 1H, 11-H), 7.20-7.30 (m, 5H, Ph); ^{13}C-NMR 13.5 (C-18), 22.7 (C-14), 22.8 (C-3), 33.2 (C-15), 33.6 (NMe), 46.6 (CH_2Ph), 47.5 (C-7), 50.3 (C-6), 51.3 (C-16), 51.6 (OMe), 52.6 (C-21), 65.4 (C-2), 106.8 (C-12), 116.5 (C-10), 123.1 (C-9), 126.9 (C-19), 127.4 (C-11), 128.4, 128.6 (Ph), 134.7 (C-8), 136.4 (Ph), 137.0 (C-20), 151.4 (C-13), 170.4, 174.9 (CO); MS, *m/z* (EI) 444 (M^+, 22), 412 (30), 323 (10), 263 (100); HRMS calcd for $C_{28}H_{32}N_2O_3$ 444.2424, found 444.2413.

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