was continued at 300 nm. The solution was analyzed by VPC and it was found that concentration of triene **10** decreased and the concentration of diene **5** increased. The diene **5**-triene **10** ratio stabilized at 5:1 after 30 min and remained unchanged after a further 30 min of irradiation. The amounts of several trace-level products, which appeared during the initial 254-nm irradiation, did not appear to change during the 300-nm irradiation.

Irradiation of Argon Matrix Isolated *trans*-Bicyclo[4.4.0]deca-2,4-diene (5). A mixture of *trans*-bicyclo[4.4.0]deca-2,4-diene (**5**) (VPC purified and freeze-thaw degassed) and argon was prepared (diene pressure 1.4 torr, argon pressure 420 torr, diene **5**:Ar = 1:300) and deposited on a sodium chloride plate cooled to 15–18 K by a CTI "Cryodyne" Model 20 refrigerator. A total of 6.42 mmol of the mixture was deposited at a rate of 1.7 to 2.5 mmol/h. The IR spectrum of the sample was recorded on a Perkin-Elmer PE-137 spectrometer, and the sample was irradiated via a Suprasil window, with a modified Mineralight UVS-1 254-nm lamp (the visible-light blocking filter had been removed), placed 8 cm from the sample. After irradiation, several new bands were observed in the IR spectrum at 1437 (weak sh), 990 (w), 954 (m), 862 (w), 841 (m, sh), and 758 (m) cm^{-1}. A decrease in the intensity of starting material bands at 883 cm^{-1} and 1470 cm^{-1} implied that 25 ± 10% of starting material had been consumed. The spectrum changed only slightly during further irradiation for a total of 18.75 h at 254 min.

The 254-nm lamp was replaced with a 300-nm lamp, and irradiation was continued for 4.5 h. The intensity of the new bands decreased relative to those of starting material, but the deterioration of the quality of the matrix due to a slow air leak prevented the quantification of the changes.

Room-Temperature Irradiation of *trans*-Bicyclo[5.4.0]undeca-8,10-diene (6). A 4-mL Vycor tube containing 2 mL of a pentane solution of *trans*-bicyclo[5.4.0]undeca-8,10-diene (**6**) (4.8×10^{-2} M) and dodecane (6.7 mg) as an internal standard was purged with nitrogen, sealed, and irradiated in the Rayonet reactor at 254 nm and room temperature, over a period of 8.5 h. The course of the reaction was followed by VPC and the analysis indicated a rapid disappearance of starting material and the formation of two new products. After prolonged irradiation a third product was seen to develop. Material balance was very poor; starting material was consumed much faster than products were formed.

Low-Temperature Irradiation of *trans*-Bicyclo[5.4.0]undeca-8,10-diene (6). A Vycor tube containing 50 mL of a 4.5 × 10^{-2} M solution of diene **6** in pentane was placed in a quartz Dewar flask, cooled to −55 °C with a stream of cold nitrogen gas, and irradiated at 254 nm for 4 h. The reaction mixture was analyzed by VPC and showed only a single major peak, with the retention time of the starting material, and one trace peak. However, analysis of the mixture by NMR and IR revealed the presence of *cis*-bicyclo[5.4.0]undeca-8,10-diene (IR absorbances at 730 and 674 cm^{-1}; NMR δ 2.50, bridgehead protons) as well. After a further 2 h of irradiation, analysis by UV gave a spectrum similar to that of starting material. Irradiation was continued for a total of 12.5 h, during which time VPC analysis showed only one major peak, corresponding to the cis and trans dienes **12** and **6**, and one minor peak of shorter retention time than that of the dienes. The minor peak reached 5% of the reaction mixture after 12.5 h. The cold reaction mixture was concentrated under vacuum (−78 °C) and reduced with diimide (prepared[10] from 24.1 g (0.12 mol) of potassium diazodecarboxylate. The UV spectrum of the diimide reduction product mixture contained a broad, flat absorbance from 220 to 265 nm, indicating residual unsaturation. Therefore, the mixture was further reduced with H_2 over 10% Pd/carbon. The hydrogenated product mixture exhibited only end absorption above 200 nm. The two major components of the product mixture were isolated by preparative VPC. The component of shorter retention time was identified as bicyclo[5.4.0]undecane on the basis of the following spectral data: IR (neat) 2880 (s), 2830 (s), 1453 (m), 1439 (m), 954 (w) cm^{-1}; NMR δ 0.7–1.9 (br m, maxima at 1.0 and 1.5); low-resolution mass spectrum (70 eV), *m/e* 153 (4.7), 152 (38), 67 (100); high-resolution mass spectrum, parent ion 152.1573, calcd for $C_{11}H_{20}$ 152.1565.

The component of longer retention time was identified as cycloundecane on the basis of the following spectral data: IR (neat) 2865 (s), 2801 (s), 1460 (m), 1431 (m), 746 (w) cm^{-1}; NMR δ 1.42 (s, $W_{1/2}$ = 2 Hz); low-resolution mass spectrum, *m/e* 155 (1.0%), 153 (9), 41 (100); high-resolution mass spectrum, parent ion 154.1714, calcd for $C_{11}H_{22}$ 154.1721.

Registry No. **4**, 2144-23-2; **5**, 7360-96-5; **6**, 40095-24-7; **7**, 1689-67-4; **8**, 13304-05-7; **9**, 40815-18-7; **10**, 74063-32-4; **12**, 40146-40-5; *cis*-bicyclo[4.3.0]nona-2,4-diene, 3054-91-9; 2,3-dibromo-*trans*-decalin, 16781-96-7; cycloheptanone, 502-42-1; butadiene, 106-99-0; bicyclo[5.4.0]undec-9-en-2-one, 74063-33-5; *cis*-bicyclo[5.4.0]undec-9-ene, 16613-71-1; *trans*-bicyclo[5.4.0]undec-9-ene, 21394-36-5; 9,10-dibromo-*trans*-bicyclo[5.4.0]undecane, 74063-34-6; bicyclo[5.4.0]undecane, 4443-69-0; cycloundecane, 294-41-7.

Chloroacetamide Photocyclization. Synthesis of 20-Deethylcatharanthine[1]

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Received April 11, 1980

20-Deethylcatharanthine, a potential precursor of vinblastine-type dimeric indole alkaloids, has been synthesized in ten steps from 1-benzenesulfonylindole. The synthesis features a Diels-Alder reaction between 1-carbethoxy-1,2-dihydropyridine and ethyl 2-(1-benzenesulfonylindol-2-yl)acrylate to construct the 7-carbethoxy-7-(2-indolyl)isoquinuclidine skeleton and photocyclization of an *N*-chloroacetyl derivative to introduce the C(5)–C(6) (tryptamine) bridge. Reduction of the lactam is achieved via the thiolactam. With the isolation of six intermediates, the overall yield is 5% from 1-benzenesulfonylindole.

The discovery[2] of the fragmentative coupling of catharanthine *N*-oxide with vindoline has opened for the first time a viable route to derivatives of the vinblastine series of diindole alkaloids. Earlier routes[3,4] had made available only systems of unnatural stereochemistry at C-16′. Much subsequent activity has centered on applying this method

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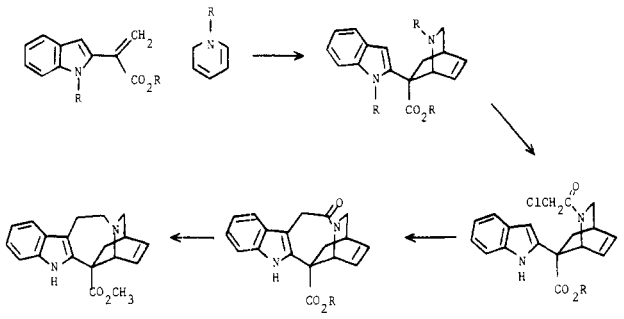
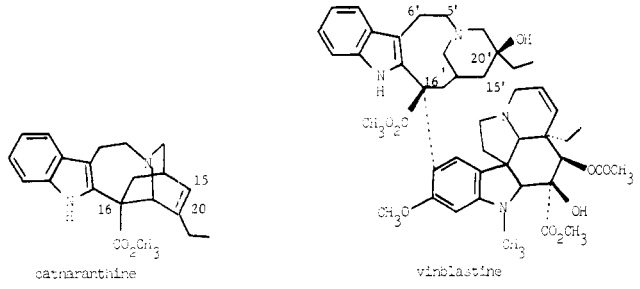
0022-3263/80/1945-3382$01.00/0

Scheme I



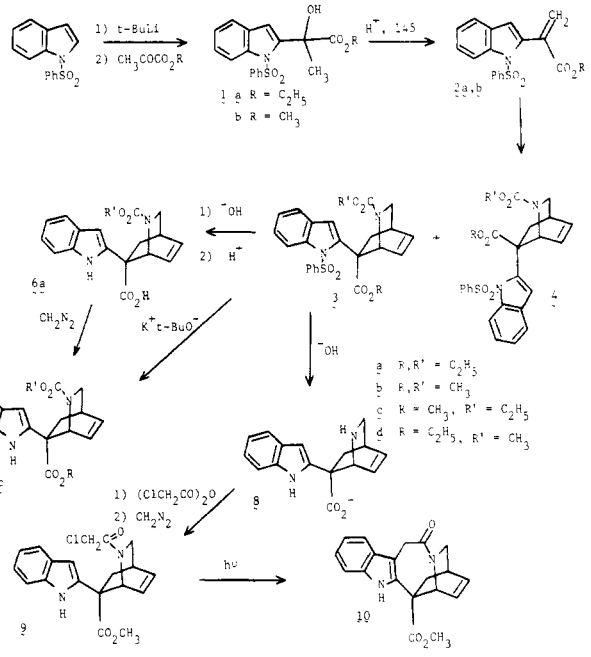
to catharanthine and its derivatives,[5] culminating recently in the synthesis of vinblastine itself.[6] We decided to undertake the synthesis of 20-deethylcatharanthine to provide a starting material for compounds having modified structure in the C(15′)–C(20′) region of the vinblastine molecule.



catharanthine vinblastine

The synthesis of (±)-catharanthine itself was accomplished some years ago. One route[7] involves an oxidative transannular cyclization. This route is not a practical one for application to substances having a modified skeleton, since it gave the desired product only in 5% yield in the final step of a multistage sequence. A second route[8] was developed in the course of a general synthetic effort in the area of the iboga alkaloids. This route consists of about 17 steps, but the yields are good except for a final three-step sequence which introduced the carbomethoxy group at C-16 via reaction of cyanide with a 3-chloroindolenine intermediate. More recently this step was improved in the course of the development of a third approach to the iboga system.[9] We felt that a synthesis which introduced the carbomethoxy group earlier would have advantages. We devised a plan (Scheme I) which incorporated as its key features the use of a Diels–Alder reaction between an indole-2-acrylate and a dihydropyridine to construct all but the C(5)–C(6) bridge, followed by chloroacetamide photocyclization[10] to afford the desired skeleton. We report herein the details of the accomplishment of this plan.

Scheme II



It was evident at the outset that an N-protected indole-2-acrylate ester would be required since unsubstituted indole-2-acrylate esters are prone to the same types of dimerization reactions[11] which characterize 2-vinylindoles in general.[12] Furthermore, it was expected that an electron-attracting substituent would have a beneficial effect on the reactivity of the acrylate as a dienophile.[13] We chose the benzenesulfonyl group since it would serve the desired functions and also permit introduction of a 2-substitutent via the 2-lithio derivative.[14] Reaction of 2-lithio-1-benzenesulfonylindole with a threefold excess of ethyl pyruvate gave the desired adduct **1a** in 64% yield. The methyl ester **1b** can be prepared analogously.

Our initial efforts to effect dehydration of **1a** to the acrylate **2a** were via the tertiary chloride which was readily obtained from **1a** on reaction with thionyl chloride. This halide proved to be surprisingly inert to a variety of bases. Acid-catalyzed dehydration of **1a** eventually proved to be straightforward and was conveniently carried out by simply melting **1a** with 4 mol % *p*-toluenesulfonic acid (84% yield).

The Diels–Alder reactions of **2** with the readily available 1-carbethoxy-1,2-dihydropyridine[15] were examined. A reaction temperature of 100 °C and a reaction time of 48 h in the absence of solvent were eventually chosen. It was found that a fivefold excess of the dihydropyridine was necessary to effect nearly complete reaction of the acrylate under these conditions. The reaction mixture was separated by chromatography. In addition to some recovered **2a**, there was obtained a major product having the expected composition for the adduct **3a** (62%), a lesser amount (6%) of an isomeric adduct **4a**, and ethyl 2-(1-

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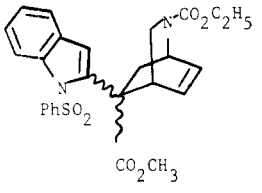
benzenesulfonyl-2-indolyl)propionate (**5a**)[16] (Scheme II). The latter compound is evidently formed as a result of the dihydropyridine acting as a reducing agent. The acrylate **2a** gave this product rapidly and quantitatively on reduction with sodium borohydride.

The NMR spectra of the two adducts confirmed that both were the results of (4 + 2) cycloaddition with the expected regiochemistry.[17] The isomeric structure **A** was



A

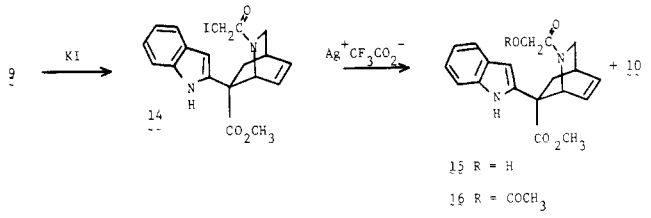
excluded by the fact that the C-1-bridgehead proton revealed no coupling to an adjacent methylene group. Like the spectra of earlier examples of carbamates of isoquinuclidines,[18] the spectra are complicated at room temperature by slow rotation of the carbamate group, but at 80 °C the spectrum is simplified. Spectral data did not provide any conclusive indication of the stereochemistry of the two adducts. Chemical efforts to establish stereochemistry by using iodolactonization of the carboxylic acid **6a** were uniformative, as iodination of the aromatic ring, accompanied by decarboxylation, was the dominant reaction.[19]

Since the projected photocyclization, if successful, also would provide an unambiguous basis for assigning the stereochemistry of the adducts **3a** and **4a**, it was decided to pursue the overall plan by using the major adduct **3a**. Three centers in the adduct **3a** are susceptible to hydrolysis and alcoholysis, and the experiments which were conducted revealed the reactivity to be in the order $PhSO_2N > CC(O)OC_2H_5 \gg NC(O)OC_2H_5$. Thus reaction of **3a** with potassium *tert*-butoxide gave **7a**. Partial hydrolysis to **6a** could be accomplished in 54% yield, and the acid could be converted to the ester **7c** with diazomethane. Finally, vigorous hydrolysis in aqueous ethanol gave a solution presumably containing the amino carboxylate **8**. As is the case with 16-carboxyiboga alkaloids in general,[20] **8** is prone to decarboxylation below pH ~3.

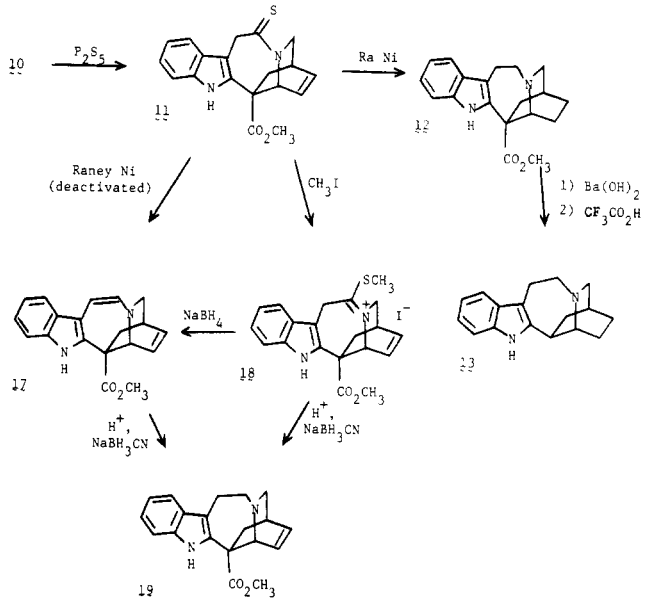
Introduction of the chloroacetyl group was examined under a variety of conditions. The ultimately successful method involved use of chloroacetic anhydride in the presence of excess tris(hydroxymethyl)aminomethane buffer which maintained the solution near pH 9. The *N*-hydroxysuccinimide coupling method[21] also gave the desired product, but the yield was lower. Esterification of the resulting acid by diazomethane led to the desired crystalline photocyclization substrate **9** in 71% yield from **3a**.

The photolysis of **9** was carried out in methanol by following procedures used earlier in our laboratory[10] and gave 45 ± 5% yields of a product having the expected elemental composition. The lack of a proton NMR signal

Scheme III



Scheme IV



near 6.2 ppm was strongly suggestive that the desired photocyclization had occurred. The other available spectral data were consistent with formulating this product as **10**. The structure was unambiguously proven by conversion to 20-deethylibogamine (**13**), a compound which has been previously synthesized by three alternative methods.[22] The lactam **10** was converted to the thiolactam **11** and desulfurized with Raney nickel to give **12**, 20-deethylcoronaridine. Saponification and decarboxylation[23] gave **13**, which was directly compared, by means of NMR and infrared spectra, with previously prepared samples of deethylibogamine.[24] This result secured the structure of the photocyclization product and established that the major adduct **3a** had the correct stereochemistry. The minor adduct can then be assigned structure **4a**.

The possibility that chloroacetamide **9** could be cyclized to **10** under the influence of Friedel–Crafts catalysts was explored. Neither $SnCl_4$ nor $AlCl_3$ gave any indication of promoting cyclization. There was a slow tranformation to an isomeric substance (TLC and mass spectrometric evidence only) which may simply be isomerization of the isoquinuclidine substituent to C-3 of the indole ring. Compound **9** was inert to silver trifluoroacetate. Reaction with potassium iodide in acetone converted **9** to the iodide **14**. This compound reacted rapidly with silver trifluoroacetate in nitromethane to give **10** in 31% yield accom-

(16) Because of a typographical error this is referred to as 2-(1-benzenesulfonylindole-3-yl)propionate in the preliminary communication.

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(24) We thank Professor P. Rosemund for a reference sample of deethylibogamine and Dr. W. Nagata and Professor J. W. Huffman for copies of spectra.

panied by **15** (27%) which was characterized as the acetate **16** (Scheme III). These experiments indicate that photocyclization may be preferable to Friedel–Crafts cyclization, though all the possible Friedel–Crafts catalysts have certainly not been exhausted. The photocyclization has proven to be capable of overcoming unfavorable geometric constraints.[10] Since the preferred geometry at the isoquinuclidine nitrogen is planar, the CH_2Cl is rather distant from the indole ring and, even though the ring being formed is only a seven-membered one, the alignment may be poor for direct cyclization.

The final step for conversion of **10** to deethylcatharanthine required reduction of the amide group in **10** without reduction of the ester function or the 15,20 double bond. We initially examined Raney nickel desulfurization of **11** (Scheme IV). Even after deactivation of the Raney nickel with acetone we observed accompanying reduction at the carbon–carbon double bond. Deactivation of the Raney nickel with dimethyl fumarate resulted in isolation of **17** in which the amide had been reduced to the enamine level. Partial reductions in the iboga series have been noted before[25] and presumably reflect some restriction on the participation of the bridgehead iminium species. Since the enamine **17** could be reduced in acidic solution with $NaBH_3CN$ to the desired deethylcatharanthine, we considered conditions which might permit the reduction to proceed directly without isolation of the enamine. By use of the analogy of the Borch method[26] for reduction of amides via salts of imino ethers, the thiolactam was converted to a salt, presumably **18**, with methyl iodide. Reduction of this salt with $NaBH_3CN$ in aqueous methanol containing acetic acid gave 20-deethylcatharanthine (**19**) in 71% yield.[27] Under basic conditions ($NaBH_4$ in methanol) the enamine **17** is obtained.

The complete route to deethylcatharanthine involves ten chemical steps with isolation of six intermediates from benzenesulfonylindole. The maximum overall yield under the conditions we have developed is on the order of 5%.

Experimental Section

1-Benzenesulfonylindole. Indole (15 g, 0.13 mol) and 17.7 g of 50% aqueous potassium hydroxide (0.31 mol) were added to 150 mL of dimethyl sulfoxide, and the mixture, initially heterogeneous, was stirred *vigorously* for about 2 h, at which point it was almost homogenous. Benzenesulfonyl chloride (23.8 g, 0.13 mol) was added dropwise over a period of 1.0 h. The solution was poured into aqueous ammonium chloride and extracted several times with ether. The ether was washed repeatedly with water, dried, and evaporated, and the resulting oil was crystallized from chloroform–ether, giving 25.1 g (76%) of nicely crystalline material, mp 78–79 °C.

Ethyl 2-(1-Benzenesulfonylindol-2-yl)-2-hydroxypropionate (1a). Recrystallized and vacuum-dried 1-benzenesulfonylindole (24.3 g, 0.095 mol) was dissolved in 400 mL of THF (freshly distilled from benzophenone ketyl/sodium) in a flame-dried flask under a nitrogen atmosphere. The solution was cooled to −11 °C, and 53 mL of *tert*-butyllithium in pentane solution (2.3 M, 0.12 mol of *t*-BuLi) was added slowly by syringe, resulting in a deep red solution. This solution was stirred for 20 min and then transferred under nitrogen to a second flame-dried flask containing 35 g (0.30 mol) of distilled ethyl pyruvate in 400 mL of dry THF cooled to −78 °C. After being stirred for 30 min at −78 °C, the solution was allowed to come to room temperature, poured into aqueous ammonium chloride, and extracted twice with ether. The ether layers were washed with water, dried, and evaporated, and the resulting orange oil was crystallized from chloroform–ether to give 22.7 g (64%) of **1a** as yellow crystals. The analytical sample was recrystallized from the same solvents, yielding white crystals, mp 111–113 °C. Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75. Found: C 61.14; H, 5.16; N, 3.74.

Methyl 2-(1-Benzenesulfonylindol-2-yl)-2-hydroxypropionate (1b). Crystalline **1b** was prepared in the same manner as **1a** in 49% yield; mp 136–137 °C. Anal. Calcd for $C_{18}H_{17}NO_5S$: C, 60.16; H, 4.78. Found: C, 60.01; H, 4.82.

Ethyl 2-(1-Benzenesulfonylindol-2-yl)-2-chloropropionate. Alcohol **1a** (4.18 g, 0.011 mol) was dissolved in 8.0 mL of thionyl chloride and stirred under N_2 at room temperature for 3 h. The brown solution was evaporated to dryness and the residue crystallized from chloroform–ether–hexane, giving 2.45 g (56%) of the chloride as a yellow solid. Recrystallization from chloroform–hexane yielded a white analytical sample, mp 127–129 °C. Anal. Calcd for $C_{19}N_{18}ClNO_4S$: C, 58.25; H, 4.60; N, 3.58. Found: C, 58.07; H, 4.69; N, 3.52.

Ethyl 2-(1-Benzenesulfonylindol-2-yl)acrylate (2a). Alcohol **1a** (50.6 g, 0.136 mol) was powdered with *p*-toluenesulfonic acid (0.94 g, 0.0054 mol) and placed in a 500-mL, round-bottomed flask. The flask was evacuated and heated in an oil bath at 145 °C while the vacuum was maintained. Vigorous evolution of water was observed. When TLC (1:1:1 ether–chloroform–hexane, silica plate) showed the absence of starting material, the heat was removed and the black hard glass allowed to cool under vacuum. The glass was dissolved in chloroform, and the solution was washed with aqueous sodium bicarbonate, dried, and reduced to a small volume. Passing the chloroform solution through a silica gel column (eluant 1:1:1 ether–chloroform–hexane) removed all the black color. Evaporation of the solvents followed by addition of ether gave immediate crystallization. Olefin **2a** (40.3 g, 84%) was obtained as off-white, well-formed crystals. Recrystallization from chloroform–ether afforded the analytical sample, mp 107–108 °C. Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.23; H, 4.79; N, 3.94. Found: C, 64.14; H, 4.81; N, 3.91.

Methyl 2-(1-Benzenesulfonylindol-2-yl)acrylate (2b). Olefin **2b** (20.2 g, 80%) was prepared from alcohol **1b** (26.4 g, 0.074 mol) and *p*-toluenesulfonic acid (0.50 g, 0.0030 mol) in the same manner as that described for **2a**. It was found that 1:1:1 ether–chloroform–hexane was an unsatisfactory eluant for the quick chromatographic purification as it caused **2b** to crystallize on the column. Pure chloroform or 1:1 chloroform–ether was found to be superior. The resulting pale yellow crystals had a melting point of 157–158 °C. Anal. Calcd for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.44; N, 4.10. Found: C, 63.38; H, 4.50; N, 4.10.

Diel–Alder Reactions. (a) 1-Carbethoxy-1,2-dihydropyridine with 2a. Freshly prepared *N*-carbethoxy-1,2-dihydropyridine[15] (5.96 g, 0.039 mol) and olefin **2a** (2.77 g, 0.0078 mol) were placed together in a 100-mL, round-bottomed flask and flushed with nitrogen. The mixture was heated at 100 °C for 2 days at which point most of the **2a** had reacted. The mixture was cooled and dissolved in chloroform and this mixture was washed several times with 2% hydrochloric acid to remove basic byproducts and then with water, dried, and evaporated. The resulting orange oil was dissolved in a small volume of ether and chilled overnight, affording major adduct **3a** in addition to some sticky polar material, possibly a pyridinium salt. Washing the collected material on the filter paper with cold ethanol left behind fairly pure **3a**. Chromatography of the mother liquor (1:1:1 ether–chloroform–hexane, neutral silica) afforded four compounds listed in order of increasing polarity: (a) reduction product **5a** in variable yields, usually about 5–10%, contaminated with large amounts of unidentified materials from the decomposition of the dihydropyridine (pure **5a** was crystallized from ether); (b) recovered **2a**; (c) major adduct **3a**; (d) minor adduct **4a** in about 5% yield after crystallization from ethanol. The total yield of crystalline **3a** was 2.45 g (62%). The analytical sample of **3a** was prepared by recrystallization from chloroform–ether; mp 145–146 °C. Anal. Calcd for $C_{27}H_{24}N_2O_6S$ (**3a** and **4a**): C, 63.78; H, 5.51; N, 5.51. Found (for **3a**): C, 63.61; H, 5.59; N, 5.49.

Adduct **4a** was recrystallized from absolute ethanol; 191–196 °C dec. Found (for **4a**): C, 63.58; H, 5.56; N, 5.46. The analytical sample of **5a** was obtained from chloroform–ether; mp 109–110 °C. Anal. Calcd for $C_{19}H_{19}NO_4S$ (**5a**): C, 63.84; H, 5.37; N, 3.92.

(25) Nagata, W.; Hirai, S.; K. Kawata, K.; Okumuara, T. *J. Am. Chem. Soc.* **1967**, *89*, 5046. Nagata, W.; Hirai, S.; Okumura, T.; Kawata, K. **1968**, *90*, 1650.

(26) Borch, R. F. *Tetrahedron Lett.* **1968**, 61.

(27) The generality of this very mild amide to amine reduction sequence is being explored.

Found: C, 63.81; H, 5.39; N, 3.91.

(b) 1-(Carbomethoxy)-1,2-dihydropyridine with 2b. By use of the same procedure as for **3a**, adducts **4a** (36%, mp 193.5–194.5 °C) and **4b** (6%, mp 201–202 °C) were obtained as white crystals from ethanol–ether and ether, respectively. Anal. Calcd for $C_{25}H_{24}N_4O_6S$ (**3b** and **4b**): C, 62.49; H, 5.04. Found (for **3b**): C, 62.54; H, 5.09. Found (for **4b**): C, 62.55; H, 5.06.

A third component of the reaction mixture was identified as the reduction product methyl 2-(1-benzenesulfonyl-2-indolyl)-propionate (**5b**), mp 105–107 °C. Anal. Calcd for $C_{18}H_{17}NO_4S$ (**5b**): C, 62.96; H, 5.00. Found: C, 63.06; H, 5.07.

(c) 1-(Carbomethoxy)-1,2-dihydropyridine with 2a. By use of the same procedure as for **3a**, adduct **3d** was obtained as a white solid in 48% yield (mp 212–213.5 °C) upon crystallization from ether–hexane. Anal. Calcd for $C_{26}H_{26}N_2O_6S$: C, 63.13; H, 5.31; N, 5.67. Found: C, 63.16; H, 5.32; N, 5.67. The reaction mixture contained a small amount of a product assumed to be the minor adduct **4d**, but this compound was not isolated. Reduction product **5a** was also present in the mixture.

Methyl 2-Carbethoxy-7-*exo*-(indol-2-yl)-2-azabicyclo-[2.2.2]oct-5-ene-7-*endo*-carboxylate (7c). Adduct **3a** (105 mg, 0.21 mmol) was refluxed for 2.25 h in a solution of 1.0 g of potassium hydroxide in 2.5 mL of water and 7.5 mL of ethanol. The mixture was cooled and poured into water, and unreacted **3a** was extracted with ether. The aqueous fraction was chilled in ice, acidified with cold dilute hydrochloric acid and immediately extracted into ether. Treatment of the ether solution with diazomethane gave **7c** in yields up to 54%. Recrystallization from ether gave the analytical sample, mp 148–150 °C. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.80; H,6.21; N, 7.91. Found: C, 67.80; H, 6.26; N, 7.88.

Ethyl 2-(Carbethoxy-7-*exo*-(indol-2-yl)-2-azabicyclo-[2.2.2]oct-5-ene-7-*endo*-carboxylate (7a). Adduct **3a** (256 mg, 0.504 mmol) was added to a solution of 275 mg of potassium *tert*-butoxide in 15 mL of freshly distilled, dry THF. The mixture was stirred at room temperature for 2.5 h, at which point TLC showed that all the **3a** had been consumed. The cloudy mixture was poured into aqueous ammonium chloride and the mixture extracted twice with ether. The ether fraction was washed with water, dried over potassium carbonate, and evaporated to give a white hard foam (170 mg, 92%, a single spot by TLC). The foam was crystallized from ether–hexane to give well-formed white crystals of **7a** (157 mg, 85%). Recrystallization from chloroform–hexane afforded the analytical sample, mp 138.5–140 °C. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.45; H, 6.58. Found: C, 68.38; H, 6.62.

Methyl 2-(Chloroacetyl)-7-*exo*-(indol-2-yl)-2-azabicyclo-[2.2.2]oct-5-ene-7-*endo*-carboxylate (9). (a) Chloroacetic Anhydride Method. Adduct **3a** (2.04 g, 4.0 mmol) was refluxed under nitrogen for 48 h in a mixture of 30 mL of 20% potassium hydroxide and 60 mL of ethanol. It was cooled, transferred to a 2-L flask, and diluted with 100 mL of water. The mixture was cooled to 0 °C and stirred rapidly while 130 mL of 2% hydrochloric acid was added in small portions, bringing the pH to 9. A pH 9 buffer solution consisting of 2.04 g of Trizma hydrochloride and 21.92 g of Trizma base [tris(hydroxymethyl)aminomethane, Sigma] dissolved in 400 mL of water was added at once. With the rapidly stirring mixture kept at about 10 °C, a solution of 12.5 g of chloroacetic anhydride in 100 mL of THF was added over a period of 0.5 h. The pH dropped from 9 to about 8 during the addition. After the mixture was stirred for 2.0 h, the cloudy mixture was filtered through Celite and transferred to a large flask equipped for rapid stirring, and 300 mL of chloroform was added. The mixture was cooled to 0 °C, and 2% hydrochloric acid was added while the mixture was stirred rapidly until pH 5 was reached in the aqueous layer. The mixture was immediately separated and the aqueous layer extracted twice with chloroform. The combined chloroform layers were washed twice with water, dried over sodium sulfate, and immediately treated with diazomethane in ether. The excess diazomethane was quenched with acetic acid, and the pale yellow chloroform solution was washed with bicarbonate, dried, and evaporated. Compound **9** (1.01 g, 71%) was crystallized from chloroform–hexane. Chromatography of the mother liquor afforded small amounts of **9** in addition to a white crystalline solid identified as **7c**, due to incomplete hydrolysis. The analytical sample of **9** was prepared by recrystallization from chloroform–hexane, mp 210–211 °C. Anal. Calcd for $C_{19}H_{19}N_2O_3Cl$: C, 63.62; H, 5.30; N, 7.81. Found: C, 63.44; H, 5.38; N, 7.78.

(b) *N*-(α-Chloroacetoxy)succinimide Method. The activated succinimide ester was prepared by standard means.[21] Adduct **3c** (870 mg, 1.76 mmol) was refluxed for 48 h under nitrogen in a solution of 30 mL of 20% potassium hydroxide. It was cooled to 0 °C and the pH brought to 9 by slow addition of 2% hydrochloric acid. *N*-(α-Chloroacetoxy)succinimide (2.02 g, 10.5 mmol) dissolved in THF was added and the pH readjusted to 9 with a few drops of dilute sodium hydroxide. The mixture was stirred for 6 h at room temperature and then cooled to 0 °C and the pH was brought to 5. After immediate extraction with chloroform, the organic fraction was treated with diazomethane as described above. Crystallization from chloroform–hexane followed by chromatography of the mother liquor followed by crystallization gave 260 mg (41%) of compound **9** comparable in purity to the material obtained in part a.

Methyl 2-(Iodoacetyl)-7-*exo*-(indol-2-yl)-2-azabicyclo-[2.2.2]oct-5-ene-7-*endo*-carboxylate (14). Chloroacetamide **9** (200 mg, 0.56 mmol) was dissolved in 40 mL of acetone. Powdered potassium iodide (500 mg) was added and the mixture stirred at room temperature for 8 h. It was poured into water and extracted twice with chloroform. The chloroform fraction was washed with water, dried, and evaporated to give 201 mg (80%) of **14** as a yellow amorphous solid. Crystallization from chloroform–hexane gave compound **14** (159 mg, 63%). The analytical sample, prepared by recrystallization from the same solvent, decomposed when a melting point determination was attempted. Anal. Calcd for $C_{19}H_{19}N_2O_3I$: C, 50.68; H, 4.26; N, 6.18. Found: C, 50.57; H, 4.28; N, 6.18.

Reaction of 14 with Silver Trifluoroacetate. Iodoacetamide **14** (75 mg, 0.17 mmol) was dissolved in 20 mL of dry, distilled nitromethane. To this solution was added 56 mg (0.25 mmol) of silver trifluoroacetate. The mixture was protected from light and stirred at room temperature for 6.5 h. The cloudy green mixture was filtered through Celite and poured into water, giving a yellow silver iodide precipitate. Extraction of the aqueous layer with ether, drying the extracts, and evaporating the ether gave 72 mg of a yellow foam having three components by TLC (1:1:1 ether–chloroform–hexane, trace methanol) which were separated by preparative thin-layer chromatography using the same solvent mixture. In order of increasing polarity they were unreacted **14** (trace), lactam **10** (16.5 mg, 31%), and alcohol **15** (15.5 mg, 27%). The above weights were for noncrystalline material. Lactam **10** was identical with the product obtained by photolysis of chloride **9**. Alcohol **15** was noncrystalline and was converted to its crystalline acetate by treatment with acetic anhydride and pyridine. Acetate **16** crystallized from chloroform–ether to give a white solid, mp 154–155 °C. Anal. Calcd for $C_{21}H_{22}O_5N_2$: C, 65.95; H, 5.81; N, 7.33. Found: C, 65.71; H, 5.82; N, 7.28.

5-Oxo-20-deethylcatharanthine by Photolysis of 9. The chloroacetamide **9** (605 mg, 1.69 mmol) was dissolved in 680 mL of methanol, and about 1 g of sodium bicarbonate was added. The solution was photolyzed under nitrogen for 1.25 h or until TLC showed no remaining **9** by using a 450-W mercury-arc Hanovia lamp in a quartz immersion well equipped with a Vycor filter sleeve. The methanol was evaporated, yielding a brown oil which was partitioned between chloroform and water. The chloroform fraction was washed with water, dried, and evaporated to give a brown oil which contained one mobile TLC spot on silica in addition to a large amount of colored polar material. Purification was effected by rapidly passing the oil through a silica column (eluant 1:1:1 ether–chloroform–hexane). Crystallization of the purified material from chloroform–hexane or ethyl acetate–hexane gave 257 mg (47%) of lactam **10** as an off-white crystalline solid. Recrystallization yielded the analytical sample, mp 292–294 °C. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.64; N, 8.69. Found C, 70.75; H, 5.64; N, 8.65.

5-Thioxo-20-deethylcatharanthine (11). Lactam **10** (47.3 mg, 0.147 mmol), 5 mL of dry benzene, and 49 mg of phosphorus pentasulfide were refluxed together under nitrogen for 5 h at which point TLC indicated that all **10** had been consumed. The mixture was filtered through Celite and rinsed ten times with excess chloroform. The filtrate was washed with aqueous bicarbonate, dried over potassium carbonate, and evaporated to give a yellow

foam. This was purified by passing it quickly through a silica column with 1:1:1 ether–chloroform–hexane as the eluant. A small amount of nonpolar material which eluted very quickly was found to be sulfur. The eluted product was evaporated and crystallized from chloroform–hexane to give 38.2 mg (77%) of yellow crystalline thioamide **11**, mp 112–117 °C dec. The thioamide **11** was reduced directly in all subsequent preparations.

20-Deethylcoronaridine (12). A sample of thioamide **11** (17 mg, 0.05 mmol) was dissolved in 20 mL of ethanol and refluxed for 4 h with ~100 mg of Raney nickel. The mixture was filtered and the nickel washed thoroughly with ethanol. The ethanol was evaporated to dryness and the residue partitioned between ether and 2% hydrochloric acid. The product was isolated from the acid layer by basification and extraction with ether. Compound **12** was crystallized from benzene–hexane: 6.5 mg (42%); mp 176–177 °C. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14. Found: C, 73.26; H, 7.21.

20-Deethylibogamine (13). A solution of **12** (25 mg, 0.08 mmol) in 20 mL of 1:1 aqueous dioxane was refluxed with 300 mg of barium hydroxide for 7 h. The solution was cooled and treated with CO_2. The precipitate was removed by centrifugation and washed with ethanol. The wash and supernatant solution were combined and evaporated. The residual gum was dissolved in 6 mL of 1:2 water–dioxane, and 0.5 mL of trifluoroacetic acid was added. The solution was stirred at room temperature for 2 h and then warmed to 80 °C for 1 h. The solution was poured into 5 mL of 10% sodium hydroxide, extracted with ether, dried and evaporated to give an oil having TLC behavior and an NMR spectrum identical with those of authentic deethylibogamine. Crystalline deethylibogamine (5.5 mg, 25%, mp 183–186 °C) was obtained by slow evaporation of an ethanol–hexane solution. The infrared spectrum was identical with that of deethylibogamine.

5,6-Dehydro-20-deethylcatharanthine (17). (a) By Raney Nickel Desulfurization. Raney nickel (about 200 mg) was refluxed overnight under nitrogen with 15 mL of acetone containing 300 mg of dimethyl fumarate. The mixture was cooled, the nickel allowed to settle, and the acetone withdrawn by pipet. The nickel was washed five times with fresh acetone. Thioamide **11** (10 mg) was added and the mixture refluxed overnight under nitrogen. The nickel was removed by Celite filtration and the acetone evaporated. Ether was added, giving a bright green solution which was extracted several times with 2% hydrochloric acid, giving a pink aqueous layer. The aqueous layer was made basic and extracted twice with ether. The ether fraction was washed with water, dried, and evaporated to given an orange oil identified as enamine **17** by its mass spectrum (m/e 306) and comparison with another sample which was converted to **19** by cyanoborohydride reduction.

(b) By $NaBH_4$ Reduction of 18. Salt **18** was prepared as described in the following experiment from 29 mg (0.086 mmol) of thioamide **11**. It was dissolved in 1 mL of absolute methanol, and 6.2 mg of sodium borohydride was added. The immediate discharge of color and evolution of methanethiol were evident. The solution was stirred for 12 h at 25 °C, poured into water, and extracted with ether. The ether layer was extracted with 2% hydrochloric acid. The aqueous layer was made basic and extracted twice with ether. The ether fraction was washed with water, dried over potassium carbonate and evaporated to give enamine **17** as a colorless glass (10 mg, 38%).

20-Deethylcatharanthine (19). (a) From Thioamide 11. Thioamide **11** (216.2 mg, 0.640 mmol) was dissolved in dry, distilled THF, and 2 mL of distilled methyl iodide was added at once. Immediately, a yellow color developed followed by the gradual precipitation of the insoluable white methylthioimmonium iodide salt **18**. This mixture was stirred for 7 h under nitrogen at room temperature, all the solvents were removed, and the yellow solid was dried under vacuum. The yellow salt was dissolved in 10 mL of absolute methanol and 180 mg of sodium cyanoborohydride added, resulting in discharge of the yellow color and obvious evolution of methanethiol. After 5 min, 10 mL of 1:1 water–acetic acid was added, and the clear, colorless solution was stirred for 5 h. Water (100 mL) was added and the pH was brought to 1 by addition of 18% hydrochloric acid. Nonbasic impurities were removed by extraction with ether. The ether fraction contained only a small amount of lactam **10**, formed by hydrolysis of **18**. The aqueous fraction was made basic (pH 10) and extracted three times with ether. The ether layer was washed twice with water, dried over potassium carbonate, and evaporated to give 20-deethylcatharanthine (**19**) as a white amorphous solid (140.4 mg, 71.3%). Recrystallization from acetone–hexane afforded the analytical sample, 155–160 °C dec. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 73.99; N, 6.55; N, 9.09. Found: C, 73.85; H, 6.58; N, 9.05.

(b) From Enamine 17. Enamine **17** (10 mg, 0.033 mmol) was dissolved in 1 mL of 1:1:1 methanol–water–acetic acid and 7.2 mg (0.12 mmol) of sodium cyanoborohydride added. After the mixture was allowed to sit at room temperature for 4 h, 20 mL of water was added and enough 18% hydrochloric acid to bring the pH to 1. The acidic solution was extracted with ether and made basic with 15% sodium hydroxide, and the amine was extracted into ether. The ether fraction was washed with water, dried over potassium carbonate, and evaporated to give 7.2 mg (71%) of amine **19** as a colorless hard glass, identified by its mass spectrum.

Registry No. **1a**, 71294-99-0; **1b**, 74185-40-3; **2a**, 71295-00-6; **2b**, 74185-41-4; **3a**, 71294-94-5; **3b**, 74195-04-3; **3c**, 74185-42-5; **3d**, 74185-43-6; **4a**, 74185-44-7; **4b**, 74185-45-8; **5a**, 74185-46-9; **5b**, 74185-47-0; **7a**, 74185-48-1; **7c**, 74185-49-2; **9**, 71294-95-6; **10**, 71294-93-4; **11**, 74194-97-1; **12**, 26518-00-3; **13**, 19034-53-8; **14**, 74195-05-4; **15**, 74185-50-5; **16**, 74195-06-5; **17**, 74231-06-4; **18**, 74195-07-6; **19**, 74194-98-2; 1-benzenesulfonyl indole, 40899-71-6; indole, 120-72-9; benzenesulfonyl chloride, 98-09-9; ethyl pyruvate, 617-35-6; ethyl 2-(1-benzenesulfonylindol-2-yl)-2-chloropropionate, 74185-51-6; thionyl chloride, 7719-09-7; *N*-(carboethoxy)-1,2-dihydropyridine, 57956-33-9; 1-(carbomethoxy)-1,2-dihydropyridine, 33707-36-7; chloroacetic anhydride, 541-88-8; *N*-(α-chloroacetoxy)succinimide, 27243-15-8.