**p-Tolyl 2-(N-Methyl-2-pyrrolidine)thiosulfinate (33).** To a solution of the thiolactam **32** (230 mg) in dichloromethane (8 mL) was added p-toluenesulfinyl chloride (720 mg) and i-$Pr_2NEt$ (517 mg) at -20 °C. Workup in the manner described for the other α,β-unsaturated thiolatams gave **33** (254 mg 50%). NMR (90 MHz) δ 2.30 (2 H, m), 2.40 (3 H, s), 3.28 (3 H, s), 3.80 (2 H, m), 4.70 (1 H, dd, J's = 3 and 9 Hz), 7.2-7.7 (4 H, m). GCMS m/e 113.10 (20%) corresponding to **34**.

**p-Tolyl 2-(N-Methyl-1,4,5,6-tetrahydropyridine)thiosulfinate (36).** Treatment of **35** (140 mg) as above gave **36** (65.4 mg, 23%). NMR (90 MHz) δ 2.37 (4 H, m), 2.40 (3 H, s), 3.55 (2 H, m), 3.57 (3 H, s), 5.46 (1 H, t, J = 6 Hz), 7.1-7.5 (4 H, m).

**Acknowledgment.** The National Institutes of Health (GM 29802) are thanked for their financial support. The National Science Foundation (CHE 81-05004) is thanked for funds to purchase a 360-MHz NMR spectrometer. J. D. Hsi is thanked for conducting experiments on **32** and **35**.

# Methods for Indole Alkaloid Synthesis. Enantiospecific Synthesis of Pentacyclic Desethylaspidosperma-Type Alkaloids Using an Exceptionally Mild Retro-Diels-Alder Reaction

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**Abstract:** Using an enantiomerically pure [2.2.1] system in the indole-2,3-quinodimethane cyclization, the construction of either enantiomer of desethylaspidospermidine-type alkaloids is described. The adduct **10** from the imine **9** and the [2.2.1] acid chloride **7** (X = Cl) was thermolyzed at 180-190 °C to give the retro-Diels-Alder product **11**, thereby introducing the 6,7 double bond. The adducts **10** and **11** were separately converted into the pentacyclic adduct **12** and its enantiomeric purity established as ≥95% by the chiral solvating agent (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

If a practical synthesis of the complex dimeric indole alkaloid vinblastine **1**[1] is to evolve from the indole-2,-quinodimethane strategy,[2] a paramount problem, which must be solved, is the construction of *Aspidosperma*-type systems in an enantiomerically pure form. While we have solved this problem for the synthesis of kopsanes and pleiomutine,[3] using the so-called exocyclic-carbamate route (Scheme I), this methodology is not readily applicable to the more highly functionalized alkaloids needed for the total synthesis of vinblastine.

Here we report a particularly short and convenient route to both enantiomers of desethylaspidosperma-type alkaloids, employing the indole-2,3-quinodimethane strategy operating in the endocyclic amide mode (Scheme II). The placement of chiral auxiliaries in a number of obvious positions did not provide a practical way of obtaining enantiomerically pure alkaloid precursors.[4]

At this point it should be noted that all of the work we have reported using the indole-2,3-quinodimethane strategy has the indole $N^1$ atom inductively deactivated by the (*p*-methoxyphenyl)sulfonyl group. The genesis of this protection has been described in detail[5] and has been adequate, although the key cyclizations have frequently only proceeded in modest yields (33-50%).[6] In the overall view of this strategy as an eventual route to vinblastine **1** it is imperative that the indole-2,3-quinodimethane cyclization step work in high yield. Furthermore, the functionality on the $N^1$-indole nitrogen atom should enable the introduction of functional groups into the C ring. The (*p*-methoxyphenyl)sulfonyl group does not allow this possibility in a convenient manner.[7] It is also essential to introduce the 6,7-unsaturation, and, in principle, this can be combined with enantiospecificity and high yields in the central cyclization step. We decided to deactivate the $N^1$-indole nitrogen as the *O*-methyl carbamate derivative and to mask the 6,7 double bond with an appropriate chiral auxiliary. This strategy is summarized in Scheme III.

If R* is to significantly increase the yield in the key cyclization it should be a rigid group that will hold the appended alkene in a restricted conformation. Also R* must be readily removed to expose the 6,7 double bond, without undue destruction of the relatively complicated product. A clear choice is to use a retro-Diels-Alder reaction that extrudes cyclopentadiene.[8]

## Results

Photooxygenation of 2-furoic acid (**2**) gave 5-hydroxybutenolide (**3**) (~90%),[9] which on treatment with cyclopentadiene at 20 °C cleanly gave the known endo adduct **4** (73%).[10] Resolution of **4** was achieved by treatment with (-)-menthol/TsOH and separation of the resulting diastereomeric lactol ethers **5** and **6**. The pure diastereomers **5** and **6** were hydrolyzed with $TsOH/H_2O$/

(1) For a recent review see "The Synthesis of Bis-Indole Alkaloids and Their Derivatives" Lounasmaa, M.; Nemes, A. *Tetrahedron*, **1982**, *38*, 233. The following references describe the partial synthesis of anhydrovinblastine and vinblastine analogues: Langlois, N.; Guēritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. Langlois, N.; Potier, P. *Tetrahedron Lett.* **1976**, 1099. Kutney, J. P. *Lloydia* **1977**, *40*, 107. Harley-Mason, J.; Rahman, A-ur *Tetrahedron* **1980**, *36*, 1057.

(2) For an account of the indole-2,3-quinodimethane strategy see: Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

(3) Magnus, P.; Gallagher, T.; Brown, P. *J. Am. Chem. Soc.* **1984**, *106*, 2105. Magnus, P.; Brown, P. *J. Am. Chem. Soc., Chem. Commun.* **1985**, 184.

(4) Chiral auxiliaries at the $N^1$ position, and at the imine *N* did not provide a practical method for producing tetracyclic systems in an enantiomerically enriched form. Magnus, P., Exon, C., unpublished work from this laboratory.

(5) Gallagher, T.; Magnus, P. *Tetrahedron* **1981**, *3889*.

(6) Gallagher, T.; Magnus, P.; Huffman, J. *J. Am. Chem. Soc.* **1982**, *104*, 1140. Exon, C.; Gallagher, T.; Magnus, P. *Ibid.* **1983**, *105*, 4739. Gallagher, T.; Magnus, P. *Ibid.* **1983**, *105*, 4750.

(7) Attempts to introduce oxygen or carbon functionality into the C-ring when the $N^1$-atom masked as a sulfonamide have only met with limited success. Southwell, I.; Pappalardo, P., unpublished results from this laboratory.

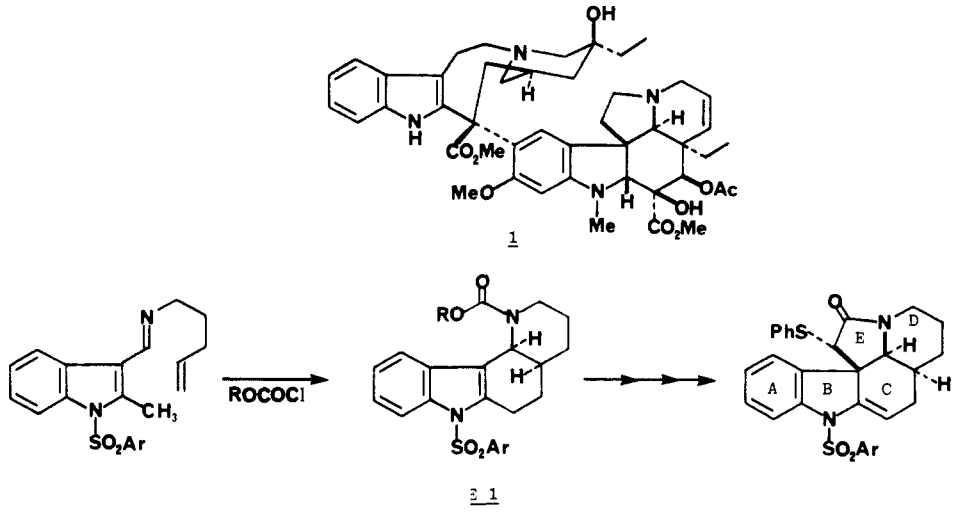
(8) Ripoll, J. L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, 19.

(9) White, J. D.; Carter, J. P.; Kezar, M. S. *J. Org. Chem.* **1982**, *47*, 929.

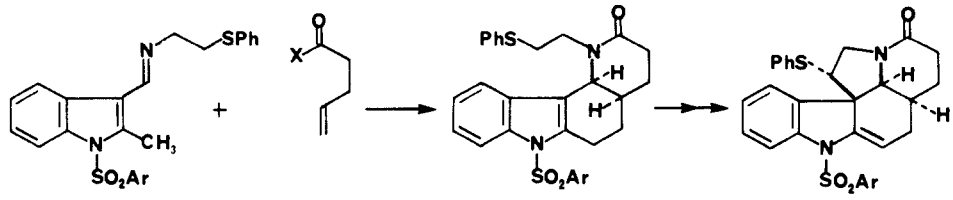
(10) Andreev, V. M.; Usova, A. V. *Izn. Akad. Nauk USSR Ser. Khim.* **1966**, 1404.

0002-7863/86/1508-0217$01.50/0 

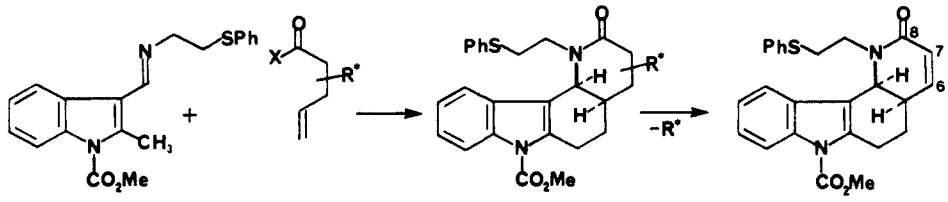
Scheme I



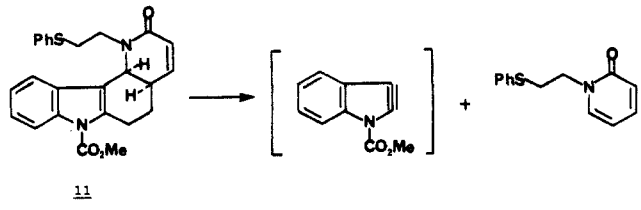
Scheme II



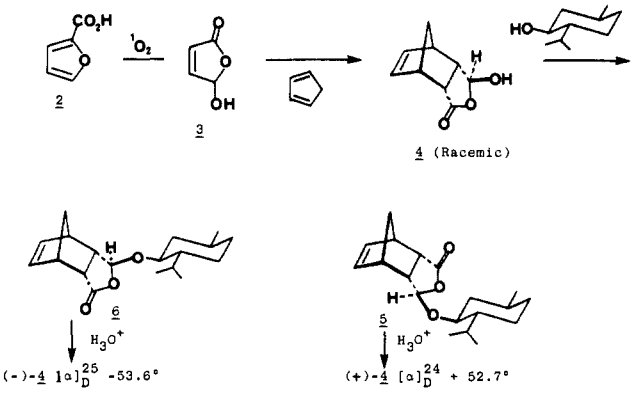
Scheme III



Scheme IV



dioxane to give the enantiomerically pure lactol **4** and its mirror image, respectively. The lactol **4** has previously been resolved via



the diastereomeric ethers formed from **4** and (*S*)-allethrolone.[11] Both **4** and its mirror image were converted into the dienoic acid **7** (X = OH) (76%) by treatment with $Ph_3PCH_2/THF/20$ °C.

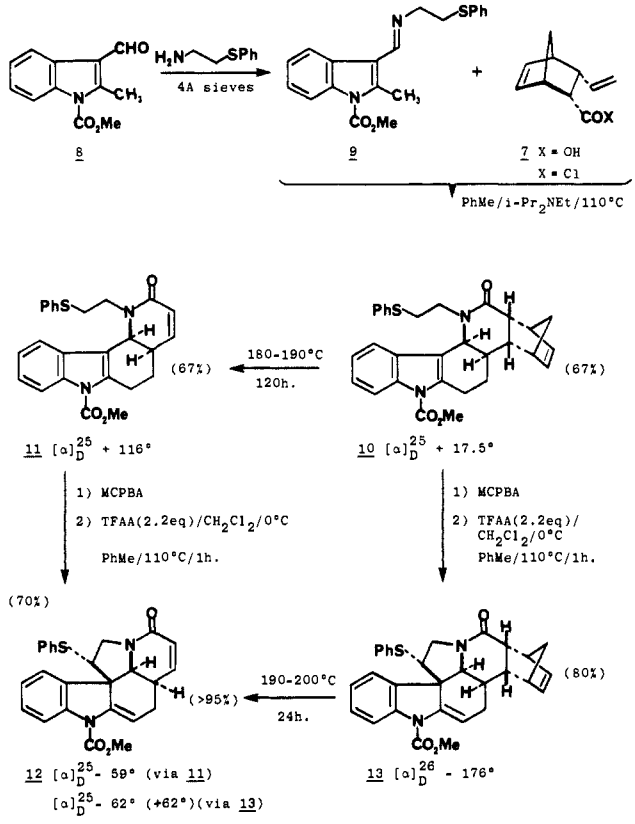
(11) Martel, J. J.; Demoute, J. P.; Leche, A. P.; Tessier, J. R. *Pestic. Sci.* **1980**, *11*, 188.

2-Methyl-3-formylindole was converted into its $N^1$-$CO_2Me$ derivative **8** (76%), using phase-transfer conditions $BnEt_3N^+Cl^-/NaOH/ClCO_2Me/CH_2Cl_2$. It should be noted that comparable conditions for the synthesis of $N^1$-$SO_2Ar$ derivatives did not proceed in greater than 50% yield.

Treatment of the imine **9**, made from **8** and 2-(phenylthio)-ethylamine, with the acid chloride **7** (X = Cl) (1.1 equiv) in toluene containing N-*i*-$Pr_2Et$ (1.2 equiv) at 110 °C, cleaning gave the desired cis-adduct **10** (crude yield 90%) (67% after recrystallization). This represents an increase in yield of some 20% over comparable systems, Scheme II. In the racemic series (using unresolved **4**) the single-crystal X-ray determination of the structure of racemic **13** allowed the relative configuration of the new formed ring-fusion with respect to the [2.2.1] system fused at the 6,7 position to be assigned, Figure 1.[12] Since the absolute configuration of (−)-**4** is known, we can assign **10** the absolute configuration shown, and this corresponds to that needed for the synthesis of vinblastine **1**, or the lower half, namely vindoline.

At this stage the crucial point of the synthetic analysis can be addressed, Scheme III. Can the adduct **10** be induced to undergo extrusion of cyclopentadiene to give **11** without excessive destruction? The literature prognosis of this matter is far from optimistic, since in general temperatures in excess of 300 °C

(12) X-ray data for **13**: A colorless prismatic crystal of **13** was selected and cooled on the goniostat to −158 °C for characterization and data collection. The diffractometer used is a modified Picker four-circle instrument, and it and the low-temperature system have been described previously (Chisholm, M. H.; Folting, K; Huffman, J. C. *Inorg. Chem.* **1984**, *23*, 1021.) The crystal was triclinic, space group $P\bar{1}$ with $a$ = 12.166 (4), Å, $b$ = 11.317 (3) Å, $c$ = 9.280 (3) Å, 96.48 (2)°, $\beta$ = 88.67 (2)°, $X$ = 104.89 (2), and $D_{calcd}$ = 1.344 for $Z$ = 2. The final residuals for the 3444 data (out of 4336 unique) with $F > 3\sigma(F)$ are $R(F)$ = 0.0389 and $Rw(F)$ = 0.0425. Fractional coordinates, thermal parameters, bonded distances and angles, and observed and calculated structure amplitudes are available as supplementary data.

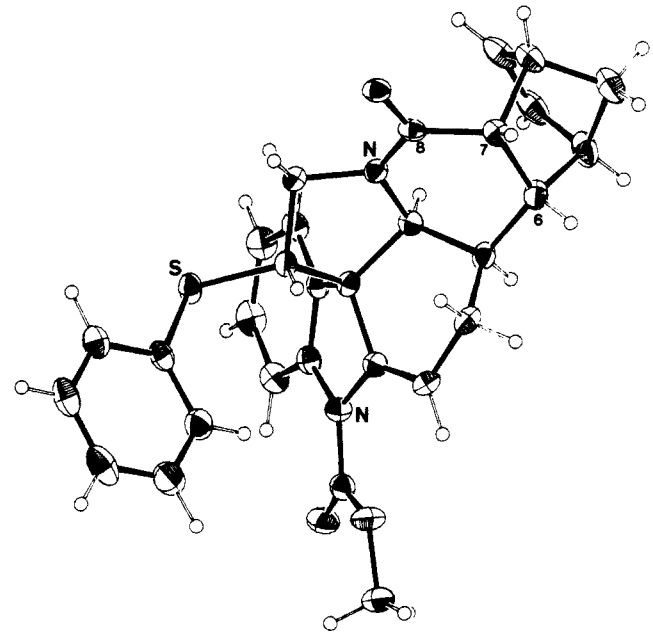



the cis stereochemistry for 11 is based on $^1$H NMR (δ 4.94 (1 H, d, $J$ = 3.9 Hz)), see ref 6; the stereochemistry of the SPh group in **12** is based upon the chemical shift of the C-11 methine proton being similar to that in 13 (X-ray); compounds epimeric at the SPh group show vastly different chemical shifts (unpublished results)

(usually averaging about 350 °C)[8,13] are required to accomplish the retro-Diels–Alder extrusion of cyclopentadiene. We felt that the inherent strain present in **10** would assist the formation of **11** and that thermolysis could be conducted at reasonable temperatures. In the event, heating **10** at 180–190 °C for 120 h gave **11** (67% after chromatography), NMR δ 6.00 (1 H, d, $J$ = 9.8 Hz, 6.68 (1 H, dd, $J$ = 9.8 and 5.6 Hz), and 16% recovered starting material. It is interesting to note that **11** has yet another retro-Diels–Alder reaction available to it and, unfortunately, a completely destructive mode, Scheme IV.[14] Furthermore, it might be expected that at 180–190 °C the elimination of SPh might become competitive with the required extrusion of cyclopentadiene. Both of these pathways might be responsible for the diminished yield of **11** from **10** compared with **12** from **13**.

Oxidation of **11** with MCPBA/$CH_2Cl_2$/0 °C gave a diastereomeric mixture of sulfoxides, which were directly subjected to the standard Pummerer reaction conditions TFAA/$CH_2Cl_2$/0 °C followed by PhMe/110 °C to give **12** (70%). The sequence from the imine **9** and the [2.2.1] chiral auxiliary **7** (X = Cl) via **10**, **11**, and **12** proceeds in four steps in an overall yield of 31.4%.

The initial cyclization product **10** need not necessarily be immediately subjected to the retro-Diels–Alder reaction conditions; the Pummerer cyclization of the E-ring can be carried out first. Treatment of **10** with MCPBA/$CH_2Cl_2$/0 °C followed by TFAA/$CH_2Cl_2$/0 °C and heating in PhMe to 110 °C cleanly gave the required **13** (80%): NMR δ 4.11 (1 H, d, $J$ = 5.0 Hz), 4.62 (1 H, dd, $J$ = 10.9 and 5.8 Hz), 6.32 (1 H, br, s). Thermolysis of **13** at 190–200 °,C over a period of 25 h gave **12** in greater than 95% yield. The rotations of **12** in both enantiomeric series through this complimentary route are equal and opposite within experimental error and differ from the first series by only 3°, which again is within the limits of experimental observation. The final product **12** is capable of a further retro-Diels–Adler pathway that destroys the absolute stereochemistry at the ring fusion between the rings, but preserves the stereocenter at C-11 (adjacent to the SPh group), Scheme V.[15] This possible sequence of events can, in principle, through the intermediate **12a**, result in **12b** (reversal of absolute configuration at the C/D ring fusion, which is tantamount to eperimization at the SPh group in the other enantiomeric series) and/or results in entry into the *iboga*-type alkaloids **12c** where the roles of diene and dienophile have been reversed from that of **12a** ⇌ **12b**. Fortunately, none of these stereochemical or structural discrepancies were detected. The complimentary sequence from the imine **9**, via **10**, **13**, and **12**, proceeds in four steps in an overall yield of 50.9%.




ORTEP DRAWING OF 13

**Figure 1.** ORTEP drawing of **13**.

In summary, the indole-2,3-quinodimethane strategy provides a high-yielding enantiospecific synthesis of pentacyclic *Aspidosperma*-type alkaloids with the necessary 6,7 double bond essential for the construction of precursors for the total synthesis of the important anticancer agent vinblastine **1**.

## Experimental Section

**3-Hydroxy-3a,4,7,7a-tetrahydro-4,5-methano-(3*H*)-isobenzofuran-1-one (4).** Freshly distilled cyclopentadiene (3.3 mL, 40 mmol) was added dropwise to a stirred solution of 5-hydroxy-2(5*H*)-furanone (3.58 g, 35.8 mmol) in dry dichloromethane (25 mL) at 0 °C. After the mixture was warmed to room temperature over 15 h the solvent was evaporated to leave a pale yellow oil. Crystallization from ethyl acetate–hexane gave the lactol **4** as white crystals (4.36 g, 73%), mp 98–100 °C (lit.[10] mp 97–99.5 °C). IR ($CHCl_3$) 3580, 3100–3450, 1765, 1740, 1170 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.44 (1 H, d, $J$ = 8.6 Hz), 1.62 (1 H, dt, $J$ = 8.6, 1.5 Hz), 2.94 (1 H, ddd, $J$ = 8.8, 4.3, 1.4 Hz), 3.21 (1 H, m), 3.31 (1 H, m), 3.39 (1 H, dd, $J$ = 8.8, 4.7 Hz), 4.46 (1 H, br s), 5.23 (1 H, br s), 6.19 (1 H, dd, $J$ = 5.6, 3.0 Hz), 6.23 (1 H, dd, $J$ = 5.6, 3.0 Hz); $^{13}$C NMR ($CDCl_3$) δ 44.74 , 45.63, 48.37, 49.22, 51.82, 100.84, 134.53, 136.10, 178.67; MS 166 ($M^+$, 1), 148 (7), 138 (7), 121 (10), 91 (43), 66 (100, $C_5H_6$).

**Resolution of the Hydroxy Lactone 4.** A solution of the racemic tricyclic lactol **4** (1.46 g, 8.79 mmol), (−)-menthol (1.37 g, 8.77 mmol), and *p*-toluenesulfonic acid·$H_2O$ (15 mg) in benzene was heated at reflux for 3 h with the azeotropic removal of water (Dean-Stark trap). Evap-

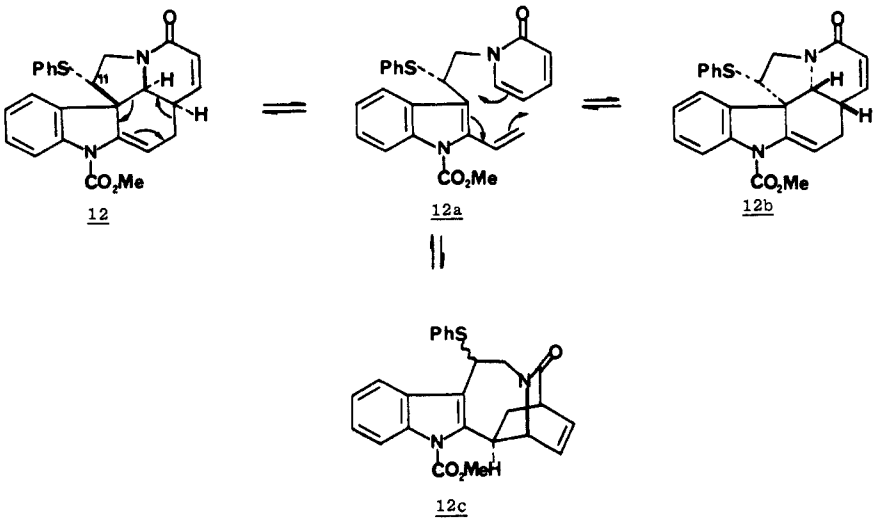
(13) Heating tabersonine at 205 °C gives rise to 3-ethylpyridine and 2-methyl-3-hydroxycarbazole. Scott, A. I.; Wei, C. C. *Tetrahedron* **1974**, *30*, 3003.

(14) Ring opening of $N^1$-(phenylsulfonyl)-2,3-diiodoindole takes place on treatment with butyllithium. Gribble, G. W.; Saulnier, M. G. *J. Org. Chem.* **1983**, *48*, 607.

(15) For the transformations shown in Scheme V embody the so-called tryptoamine-derived biosynthetic proposals: Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98. Thomas, R. *Tetrahedron Lett.* **1961**, 544. Qureshi, A. A.; Scott, A. I. *Chem. Commun.* **1968**, 945, 947, 948. Scott, A. I. *Acc. Chem. Res.* **1970**, *3*, 151. For references describing attempts to carry out both *inter-* and *intramolecular* versions of the secodine and dihydrosecodine chemistry, see the citations in ref 6.

(16) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263.

Scheme V




oration of solvent followed by chromatography on silica gel gave, on elution with ethyl acetate–petroleum (1:19) the ethers **5** and **6** as a colorless glass (2.51 g, 98%). Separation of the diastereoisomer was achieved by preparative HPLC with ethyl acetate–hexane (3:97). A mixture of the lower $R_f$ lactone ether **6** (1.196 g, 4.12 mmol) and *p*-toluenesulfonic acid·$H_2O$ (120 mg, 0.63 mmol) in dioxane (18 mL) and water (18 mL) was heated at reflux for 3 h. The mixture became homogeneous after ca. 20 min. After neutralization with triethylamine (88 μL, 0.63 mmol), the solvents were evaporated, and the residue was chromatographed on silica gel. Elution with ethyl acetate–petroleum (1:9) gave recovered (−)-menthol. Further elution with ethyl acetate–petroleum (1:1) gave the (3*S*,3a*S*,4*S*,7*s*,7a*R*)-hydroxy lactone (−)-**4** (0.56 g, 82%) as white crystals. Recrystalization from ethyl acetate–hexanes gave colorless needles (330 mg, 48%), mp 134–135 °C (lit.[11] mp 133 °C) $[\alpha]^{25}_D$ −53.6° ($CHCl_3$, *c* 0.50) (lit. $[\alpha]^{20}_D$ −47.5° ($CHCl_3$, *c* 1.0)). In the same way, hydrolysis of lactone ether **5** gave the (3*R*,3a*R*,4*S*,7*R*,7a*S*)-hydroxy lactone (+)-**4** mp 134–135 °C (lit. mp 132–133 °C). $[\alpha]^{24}_D$ +52.7° ($CHCl_3$, *c* 0.55) (lit.[11] $[\alpha]^{20}_D$ +49.5° ($CHCl_3$, *c* 1.0)).

**(±)-(2,3-*endo*)-3-Ethenylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (7, X = OH).** A solution of the lactol **4** (444 mg, 2.67 mmol) in dry THF (7 mL) was added dropwise over 5 min to a stirred solution of methylenetriphenylphosphorane at 0 °C, prepared from *n*-butyllithium in hexane (5.2 mL, 1.55 M, 8.0 mmol) and methyltriphenylphosphonium iodide (3.23 g, 8.0 mmol) in dry THF (35 mL); 0 °C to room temperature, 30 min. The reaction mixture was stirred at room temperature for 13 h. Excess ylide was destroyed by the dropwise addition of saturated aqueous sodium bicarbonate (10 mL) and the bulk of the solvent removed by evaporation. The residue was partitioned between ethyl acetate (30 mL) and water (50 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL, discarded), acidified with 2 M hydrochloric acid, and extracted with ether (3 × 40 mL). The combined ether extracts were washed with water and brine, dried, and evaporated to leave a yellow crystalline solid. Chromatography gave on elution with ether–petroleum (1:4) bicyclic acid **7** (X = OH) (335 mg, 76%) as a white crystalline solid, mp 72.5–74 °C (EtOAc–hexane). IR ($CHCl_3$) 2400–3300, 1705 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) δ 1.36 (1 H, d, *J* = 8.5 Hz), 1.48 (1 H, dt, *J* = 8.5, 1.6 Hz), 2.85 (1 H, br s), 3.09 (1 H, br s), 3.11–3.19 (2 H, m), 4.95 (1 H, dd, *J* = 9.9, 2.0 Hz), 5.12 (1 H, dd, *J* = 16.9, 2.0 Hz), 5.33–5.43 (1 H, m), 6.14 (1 H, dd, *J* = 5.6, 3.0 Hz), 6.34 (1 H, dd, *J* = 5.6, 2.9 Hz), 11.1 (1 H, br s $CO_2H$); $^{13}C$ NMR (75.43 MHz) δ 45.8, 49.1, 49.2, 49.3, 49.4, 116.0, 134.3, 136.5, 139.3, 179.3; MS 164 ($M^+$, 12), 119 (15), 99 (21), 91 (20), 67 (24), 66 (100, $C_5H_6$). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.86; H, 7.48. $^1H$ and $^{13}C$ NMR analysis indicated less than 5% of the (2,3 endo, exo) isomer. Similar yields of acid **7** could be obtained by using the ylide generated with dimsyl sodium in $Me_2SO$: (−)-lactol **4** into (−)-acid **7** $[\alpha]^{25}_D$ − 44.6° ($CHCl_3$, *c* 0.81); (+)-lactol **4** into (+)-acid **7** $[\alpha]^{25}_D$ +48.2° ($CHCl_3$, *c* 1.23).

**1-Carbomethoxy-2-methyl-3-formylindole (8).** Methyl chloroformate (7.3 mL, 94.5 mmol) was added dropwise over 15 min to a rapidly stirred mixture of 2-methyl-3-formylindole (10.0 g, 62.8 mmol) and benzyltriethylammonium chloride (0.72 g, 3.2 mmol) in dichloromethane (100 mL) and 30% (w/v) aqueous sodium hydroxide (100 mL) at 0 °C. After a additional 1 h at 0 °C the two phases were separated and the aqueous phase extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with water (150 mL) and brine (150 mL) dried ($Na_2SO_4$), and evaporated to leave a pale yellow crystalline solid. Recrystallization from ethyl acetate–hexanes gave colorless prisms (10.33 g, 76%), mp 132–133 °C. IR ($CHCl_3$) 1740, 1660, 1440, 1345, 1325 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.92 (3 H, s), 4.11 (3 H, s), 7.32–7.36 (2 H, m), 8.01–8.06 (1 H, m), 8.28–8.33 (1 H, m), 10.32 (1 H, s); $^{13}C$ NMR ($CDCl_3$) δ 13.37 (q), 54.11 (q), 114.98 (4), 118.60 (s), 120.86 (d), 124.49 (d), 125.01 (d), 125.95 (s), 135.17 (s), 148.65 (s), 151.77 (s), 185.69 (d); MS 217 ($M^+$, 100), 216 (30), 172 (61), 158 (20), 144 (28), 130 (49), 103 (22), 59 (27). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.11; N, 6.45. Found: C, 66.23; H, 5.18; N, 6.66.

**(*E*)-1-Carboxymethoxy-2-methyl-3-[*N*-(2-(phenylthio)ethyl)formimidoyl]indole (9).** A solution of the indole (869 mg, 4.0 mmol) and 2-(phenylthio)ethylamine (620 mg, 4.05 mmol) in dry dichloromethane (40 mL) containing powdered 4 Å molecular sieves (4 g) was stirred for 16 h. The mixture was filtered through Celite and the filtrate evaporated to give the imine **9** as a colorless glass. the crude imine was used directly in the cyclization step. IR ($CHCl_3$) 1735, 1635, 1440, 1345, 1325 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.73 (3 H, s), 3.32 (2 H, t, *J* = 6.9 Hz), 3.87 (2 H, t, *J* = 6.9 Hz), 4.05 (3 H, s), 7.16 (1 H, t, *J* = 7.3 Hz), 7.24–7.32 (4 H, m), 7.39–7.42 (2 H, m), 8.04–8.06 (1 H, m), 8.38–8.41 (1 H, m), 8.53 (1 H, s).

**Hexacyclic Adduct 10.** Freshly distilled oxalyl chloride (0.7 mL, 8.0 mmol) was added dropwise to a stirred solutions of the acid **7**, X = OH (722 mg, 4.4 mmol), in dry benzene (12 mL) containing 1 drop (3 μL) of pyridine at 10 °C. The solution was allowed to warm to room temperature over 15 h. The solvent was evaporated and the residue azeotroped with dry benzene (2 × 2 mL) to leave the acid chloride **7** (X = Cl), IR ($CHCl_3$) 1795 $cm^{-1}$, as a straw-colored oil. The acid chloride **7** (X = Cl) was taken up in dry toluene (6 mL) and added dropwise to a stirred solution of the imine **9** (4 mmol) and diisopropylethylamine (10.85 mL, 4.88 mmol) in dry toluene (30 ml) at 0 °C. The mixture was allowed to warm to room temperature over 0.5 h and then slowly heated to reflux over 2 h. TLC indicated that the cyclization began at ca. 80 °C. After being heated at reflux for an additional 1 h, the mixture was washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), and evaporated to leave a pale yellow crystalline solid. Recrystallization from methanol gave the hexacyclic adduct **10** (1.33 g, 67%) as fine white needles, mp 173–175 °C. IR ($CHCl_3$) 1735, 1635, 1455, 1440, 1330 $cm^{-1}$; $^1H$ NMR (360 MHz) ($CDCl_3$) δ 1.23 (1 H, br d, *J* = 8.4 Hz), 1.49 (1 H, dt, *J* = 8.4, 1.8 Hz), 1.93–2.02 (2 H, m), 2.21–2.34 (1 H, m), 2.25–2.46 (2 H, m), 2.94 (1 H, br s), 3.06–3.16 (4 H, m), 3.31 (2 H, br s), 4.04 (3 H, s), 4.47 (1 H, br s), 4.70–4.80 (1 H, br s), 6.13 (1 H, br s), 6.32 (1 H, dd, *J* = 5.6, 2.9 Hz, 7.15–7.35 (8 H, m), 8.11 (1 H, d, *J* = 8.3 Hz) many signals broadened by amide resonance; MS 498 ($M^+$, 8), 432 (M − $C_5H_6$, 8), 296 (25), 295 (34), 217 (33), 149 (37), 137 (45), 136 (33), 124 (100). Anal. Calcd for $C_{30}H_{30}N_2O_3S$: C, 72.76; H, 6.06; N, 5.62. Found: C, 72.77; H, 6.21; N, 5.67. (−)-(1*S*,2*R*,3*S*,4*R*)acid **7** (X = OH) gave (+)-hexacyclic adduct **10** as fine colorless needles, mp 196–197 °C; $[\alpha]^{25}_D$ +17.5° ($CHCl_3$, *c* 1.10). Similarly, (+)-acid **7** (X = OH) gave the (−)-hexacycle **10**, mp 194–195°C; $[\alpha]^{25}_D$ −17.2° ($CHCl_3$, *c* 1.10).

**(±)-*cis*-1,4a,5,6,7,11c-Hexahydro-7-carbomethoxy-1-[2-(phenylthio)ethyl]-2*H*-pyrido[3,2-*c*]carbazol-2-one (11).** A solution of the hexacyclic adduct **10** (363 mg, 0.73 mmol) in toluene (8 mL) was degassed (freeze–thaw, 0.1 torr) and heated at 180–190 °C (oil bath) in a re-

sealable Carius tube for 120 h. Evaporation of the solvent followed by chromatography of the residue gave, on elution with ethyl acetate–petroleum (3:2), the tetracycle **11** as a white foam (251 mg, 80%), and on recrystallization from ethyl acetate–petroleum colorless prisms (210 mg, 67%), mp 132–134 °C. IR ($CHCl_3$) 1735, 1660, 1600, 1440, 1355, 1305 $cm^{-1}$; $^1H$ NMR (360 MHz) ($CDCl_3$) $\delta$ 1.93–1.99 (1 H, m), 2.19–2.29 (1 H, m), 2.44–2.49 (1 H, m), 2.84–3.06 (3 H, m), 3.27 (1 H, ddd, $J$ = 19.06, 6.4, 2.4 Hz), 3.40 (1 H, ddd, $J$ = 13.8 8.7, 6.4 Hz), 3.92 (1 H, ddd, $J$ = 13.8, 8.7, 4.9 Hz), 4.06 (3 H, s), 4.94 (1 H, d, $J$ = 3.9 Hz), 6.00 (1 H, d, $J$ = 9.8 Hz), 6.68 (1 H, dd, $J$ = 9.8, 5.6 Hz), 6.83–6.86 (2 H, m), 6.87–7.00 (3 H, m), 7.25 (1 H, td, $J$ = 7.4, 1.3 Hz), 7.30 (1 H, td, $J$ = 7.4, 1.6 Hz), 7.40 (1 H, dd, $J$ = 7.4, 1.6 Hz), 8.09 (1 H, dd, $J$ = 7.4, 1.3 Hz); MS 432 ($M^+$, 54), 323 (12), 309 (33), 296 (100), 280 (87), 279 (48), 268 (77), 109 (52). Anal. Calcd for $C_{25}H_{24}N_2O_3S$: C, 69.42; H, 5.69; N, 6.48. Found: C, 69.66; H, 5.73; N, 6.53. Further elution with ethyl acetate–petroleum (4:1) gave recovered hexacycle **10** (50 mg, 16%). (+)-Hexacyclic adduct **10** gave (+)-tetracycle **11** as a white foam, $[\alpha]^{26}_D$ +116° ($CHCl_3$, $c$ 0.53).

**(±)-Heptacyclic Adduct 13.** A solution of *m*-chloroperoxybenzoic acid (133 mg, 80–90% pure, 0.66 mmol) in dichloromethane (6 mL) was added dropwise over 0.5 h, to a rapidly stirred solution of the hexacyclic sulfide **10** (326 mg, 0.65 mmol) in dichloromethane (10 mL) and 10% aqueous sodium bicarbonate (10 mL) at 0 °C. After an additional 0.5 h at 0 °C the phases were separated, and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic extracts were dried ($Na_2SO_4$) and evaporated to leave a quantitative yield of the derived sulfoxides as a white foam. TLC and $^1H$ NMR analysis indicated that the sulfoxides were present as a 1:1 mixture of diastereoisomers.

Trifluoroacetic anhydride (0.20 mL, 1.44 mmol) was added dropwise to a stirred solution of the above sulfoxides in dry dichloromethane (6.5 mL) at 0 °C. After 1 h at room temperature the dichloromethane was evaporated and replaced with dry toluene (13 mL). The resulting solution was degassed, placed under argon, and heated at reflux for 1 h, whereupon, TLC indicated conversion to essentially one product. The reaction mixture was washed with saturated sodium bicarbonate and brine, dried ($Na_2SO_4$), and evaporated to leave a yellow oil. Crystallization from methyl acetate–hexanes gave the heptacyclic adduct **13** as colorless prisms, mp 229–231 °C (259 mg, 80%). An analytical sample was recrystallized from ethyl acetate–hexanes, mp 231–232 °C. IR ($CHCl_3$) 1710, 1620, 1475, 1440, 1370 $cm^{-1}$; $^1H$ NMR (360 MHz) ($CDCl_3$) $\delta$ 1.38 (1 H, br, d, $J$ = 8.5 Hz), 1.46 (1 H, br d, $J$ = 8.5 Hz), 1.58–1.81 (1 H, m), 2.03–2.08 (2 H, m), 2.48 (1 H, dd, $J$ = 9.1, 3.2 Hz), 2.92 (1 H, dd, $J$ = 9.1, 4.2 Hz), 3.01 (1 H, br s), 3.09 (1 H, t, $J$ = 12.1 Hz), 3.16 (1 H, dd, $J$ = 12.1, 5.8 Hz), 3.37 (1 H, br s), 3.88 (3 H, s), 4.11 (1 H, d, $J$ = 5.0 Hz), 4.62 (1 H, dd, $J$ = 10.9, 5.8 Hz), 6.16 (1 H, dd, $J$ = 5.6, 2.9 Hz), 6.29 (1 H, dd, $J$ = 5.6, 2.9 Hz), 6.32 (1 H, br s), 7.10–7.24 (7 H, m), 7.35–7.40 (1 H, m), 7.84 (1 H, br d, $J$ = 7.7 Hz); MS 496 ($M^+$, 28), 430 ($M - C_5H_6$, 23), 294 (31), 293 (100), 169 (38), 115 (38), 110 (71), 109 (37). Anal. Calcd for $C_{30}H_{28}N_2O_3S$: C, 72.55; H, 5.68; N, 5.64. Found: C, 72.33; H, 5.85; N, 5.56. (+)-Hexacycle **10** gave the (−)-heptacycle **13**, white foam after chromatography, $[\alpha]^{26}_D$ −176° ($CHCl_3$, $c$ 0.53). Similarly, the (−)-hexacycle **10** gave the (+)-heptacycle **13** $[\alpha]^{25}_D$ +172° ($CHCl_3$, $c$ 2.35).

**(±)-2,3,6,7-Tetrahydro-1-carbomethoxy-11β-(phenylthio)-20,21-dinoraspidospermidin-8-one (12). (A) Retro-Diels–Alder Reaction of Heptacyclic Adduct 13.** A degassed (freeze–thaw, 0.1 torr) solution of the heptacycle **13** (110 mg, 0.22 mmol) in toluene (6 mL) contained in a resealable Carius tube was heated in an oil bath at 190–200 °C for 25 h. The progress of the reaction was monitored by analytical HPLC (ethyl acetate; flow 1.5 mL/min). Evaporation of solvent gave the pentacycle **12** in quantitative yield as a white foam. The purity was greater than 95%, as judged by HPLC and $^1H$ NMR analysis. Crystallization from methanol gave **12** as white crystals, (54 mg, 62%), mp 183–185 °C. IR ($CHCl_3$) 1715, 1665, 1605, 1480, 1440, 1380, 1370, 1305 $cm^{-1}$; $^1H$ NMR (360 MHz) ($CDCl_3$) 2.01–2.09 (1 H, m), 2.10–2.14 (1 H, m), 2.23–2.26 (1 H, m), 3.36 (1 H, t, $J$ = 11.8 Hz), 3.44 (1 H, dd, $J$ = 11.8, 5.8 Hz), 3.91 (3 H, s), 4.50 (1 H, dd, $J$ = 10.7, 5.8 Hz), 4.55 (1 H, d, $J$ = 5.4 Hz), 6.00 (1 H, d, $J$ = 9.9 Hz), 6.42 (1 H, br d, $J$ = 7 Hz), 6.61 (1 H, dd, $J$ = 9.9, 5.7 Hz), 7.15–7.33 (7 H, m), 7.40 (1 H, td, $J$ = 8.4, 1.2 Hz), 7.87 (1 H, br, d, $J$ = Hz); MS 430 ($M^+$, 26), 294 (26), 293 (100), 216 (27), 215 (74), 201 (56), 200 (25), 183 (29), 91 (90), 69 (50). Anal. Calcd for $C_{25}H_{22}N_2O_3S$: C, 69.74; H, 5.15; N, 6.51. Found: C, 69.82; H, 5.17; N, 6.47. (−)-Heptacyclic adduct **13** gave the (−)-pentacycle **12** as a colorless glass $[\alpha]^{25}_D$ −62° ($CHCl_3$, $c$ 1.61). Similarly, the (+)-heptacycle **13** gave (+)-pentacycle **12** $[\alpha]^{25}_D$ +62° ($CHCl_3$, $c$ 1.63).

**(B) Pummerer Cyclization of Tetracycle 11.** A solution of *m*-chloroperoxybenzoic acid (63 mg, 0.31 mmol) in dichloromethane (4 mL) was added dropwise over 0.5 h to a stirred solution of the tetracyclic sulfide **11** (133 mg, 0.31 mmol) in dichloromethane (4 mL), and 10% aqueous sodium bicarbonate (4 mL) at 0 °C. After the mixture was stirred for an additional 0.5 h at 0 °C the phases were separated, and the aqueous phase was extracted with dichloromethane (5 mL). The combined organic extracts were dried ($Na_2SO_4$) and evaporated to leave a quantitative yield of the sulfoxides as a 1:1 mixture of diastereoisomers as judged by TLC and $^1H$ NMR analysis.

Trifluoroacetic anhydride (96 μL, 0.68 mmol) was added dropwise to a stirred solution of the above sulfoxides in dry dichloromethane (3 mL) at 0 °C. After the mixture was stirred at room temperature for 1 h the dichloromethane was evaporated and replaced with dry toluene (6 mL). The resulting solution was degassed, placed under argon, and heated at reflux for 1 h. TLC showed conversion to essentially one product. The reaction mixture was washed with saturated sodium bicarbonate and brine, dried ($Na_2SO_4$), and evaporated to leave a pale yellow gum. Crystallization from chloroform–hexanes gave the pentacycle **12** as white crystals (94 mg, 70%), mp 183–185 °C, identical in all respects with the pentacycle obtained from **13**. (+)-Tetracycle **11** gave the (−)-pentacycle **12** as a white foam $[\alpha]^{26}_D$ −59° ($CHCl_3$, $c$ 1.155). The enantiomeric purity of the (+)-pentacycle **12** was found to be ≥95% ee as determined by NMR (360 MHz) with use of the chiral solvating agent (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[16] The enantiomeric purity of the diene acid **7** (X = OH) was determined by NMR (360 MHz) on the derived amides formed from (*S*)-(−)-1-phenylethylamine to be ≥95%.

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**Supplementary Material Available:** Fractional coordinates, thermal parametes, bonded distances and angles, and observed and calculated structure amplitudes (7 pages). Ordering information is given on any current masthead page.