Methods for Indole Alkaloid Synthesis. A Specific Procedure for Introducing the 6,7 Double Bond into *Aspidosperma*-Type Alkaloids via Thiolactam Dehydrogenation

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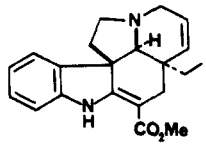
Abstract: Tetracyclic amides **6**, **14**, and **19** were converted into their corresponding thiolactam derivatives **7**, **15**, and **20**, respectively, by treatment with Lawesson's reagent. When these thiolactams were treated with *p*-toluenesulfinyl chloride/*i*-Pr_2NEt/(0 °C) followed by aqueous workup, the α,β-unsaturated thiolactams **8**, **16**, and **21** were isolated in good to excellent yields. S-Alkylation of the α,β-unsaturated thiolactams followed by reduction with $NaBH_4$ gave the tetracyclic allylic tertiary amines **10**, **17**, and **22**. Dealkylation could only be accomplished for the *N*-methyl system **22**, and only in modest yield. The pentacyclic amide **28** was converted into the thiolactam **29** by treatment with Lawesson's reagent, followed by *p*-toluenesulfinyl chloride/*i*-Pr_2NEt/65 °C to give the α,β-unsaturated thiolactam 30 (92%). Extension of this exceptionally mild dehydrogenation procedure to simple monocyclic thiolactams was not successful. A mechanistic rationale for this new procedure is described with an explanation for its unusual selectivity.

During the past few years we have examined a new and highly convergent strategy for the synthesis of indole alkaloids of the *Aspidosperma* type that uses as its central component the so-called indole-2,3-quinodimethane intermediates, Scheme I.[1] If this strategy is to be successful for the synthesis of the more highly functionalized indole alkaloids such as tabersonine **1**[2] and vindoline **2**,[3] a method for introducing the 6,7 double bond is a prerequisite. While in recent years many new and mild methods have been developed to introduce a double bond in conjugation with a carbonyl group,[4] only the phenylselenylation methodology has been applied to the problem of establishing the 6,7 double bond in *Aspidosperma*-type alkaloids,[5] but this procedure did not work for the systems described here. The imine **4**, prepared from



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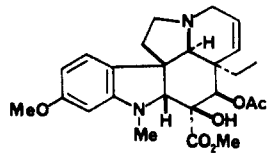

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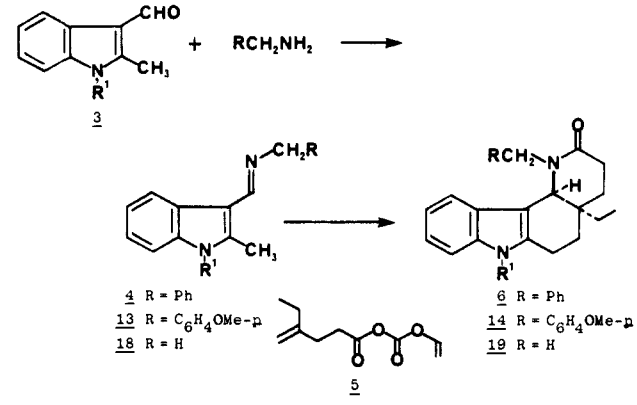
N-[(4-methoxyphenyl)sulfonyl]-2-methylindole-3-carboxaldehyde (**3**) and benzylamine, was treated with the mixed anhydride **5** in chlorobenzene at 140 °C to give the tetracyclic lactam **6** in 40% yield (the problems of low yields are addressed in the accompanying paper).[6] Treatment of **6** with LDA/PhSeBr/−70 to 25 °C, LDA/$PhSO_2SPh$, $LiN(SiMe_3)_2/PhSO_2SPh$ only gave the starting lactam **6** and intractable decomposition products. It appeared that the use of strong bases caused the destruction of **6**. The protons adjacent to a thiolactam (ca. pK_a = 12–16) are



considerably more acidic than those adjacent to a lactam (*ca.* pK_a = 32–36), and as a result the thiolactam derivative of **6** should be capable of dehydrogenation under mildly basic conditions.[7] The lactam **6** was treated with the Lawesson reagent[8] in HMPA to provide the thiolactam **7** (61%). When the thiolactam **7** was exposed to *p*-toluenesulfinyl chloride/CH_2Cl_2/*i*-Pr_2NEt/0 °C, followed by aqueous workup, the α,β-unsaturated thiolactam **8** was isolated in 75% yield. The AB system at 6.14 and 6.55 ppm (J = 10 Hz) clearly indicated the presence of the desired 6,7 double bond. The only other product isolated in this reaction was tolyltoluenethiosulfinate (**9**), presumably formed by disproportionation of *p*-toluenesulfenic acid.[9] To complete the sequence

(1) For a preliminary description of this work see: Magnus, P.; Pappalardo, P. *J. Am. Chem. Soc.* **1983**, *105*, 6525. For references describing the background to this work see: Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739. Gallagher, T.; Magnus, P. *Ibid.* **1983**, *105*, 4750. Magnus, P.; Gallagher, T.; Brown, P. *Ibid.* **1984**, *106*, 2105. Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

(2) For the synthesis of tabersonine see: Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458. Ziegler, F. E.; Bennett, G. B. *Ibid.* **1971**, *93*, 5930. Imanishi, T.; Shin, H.; Yagi, N.; Hanoake, M. *Tetrahedron Lett.* **1980**, *21*, 3285. Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 3022; **1979**, *101*, 6414. Takano, S.; Murakata, C.; Ogarawara, K. *Heterocycles* **1981**, *16*, 247. Lēvy, J.; Laronze, Y. J.; Laronze, J.; Le Men, J. *Tetrahedron Lett.* **1978**, 1579. Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002.

(3) For the synthesis of vindoline see: Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299. Ando, M.; Büchi, G.; Ohnuma, T. *Ibid.* **1975**, *97*, 6880. Kutney, J. P.; Bunzli-Trepp, U.; Chan, K. K.; Souza, de, J. P.; Fujise, Y.; Honda, T.; Katsube, J.; Klein, F. K.; Leutwiler, A.; Morehead, S.; Rohr, M.; Worth, B. R. *Ibid.* **1978**, *100*, 4220.

(4) The most widely used method for converting ketone into the corresponding enone is the selenoxide syn elimination. For leading references see: Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. Reich, H. J.; Reich, I. L.; Renga, J. M. *Ibid.* **1973**, *95*, 5813; **1975**, *97*, 5434. Clive, D. L. J.; Denyer, C. V. *Chem. Commun.* **1973**, 253.

(5) Lēvy, J.; Laronze, J.-Y.; Laronze, J.; Le Men, J. *Tetrahedron Lett.* **1978**, 1579.

(6) Magnus, P.; Cairns, P. M. *J. Am. Chem. Soc.*, following paper in this issue.

(7) The C(SR)=N^+Me_2 group activates the α-hydrogen atom toward proton transfer about 2×10^4 better than the COSR group: Lienhard, G. E.; Wang, T.-Ch. *J. Am. Chem. Soc.* **1968**, *90*, 3781. Thioacetamides readily undergo the aldol-Knoevenagel condensation with benzaldehyde, under conditions comparable to those for the malonic acid condensation: Pappalardo, G.; Tornetta, B.; Scapini, G. *Farmaco*, Ed. Sci. **1966**, *21*, 740; *Chem. Abstr.*, **1967**, *66*, 46363. In view of the fact that thioamides have considerably higher dipole moments than the corresponding amides, a marked increase in the acidity of the α-hydrogen is to be expected. We have estimated this to bring the acidity into the malonate range (pK_a 12-16), since thioamides exhibit similar condensation chemistry (see above).

(8) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

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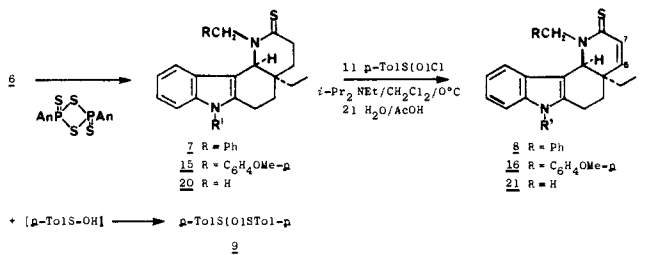
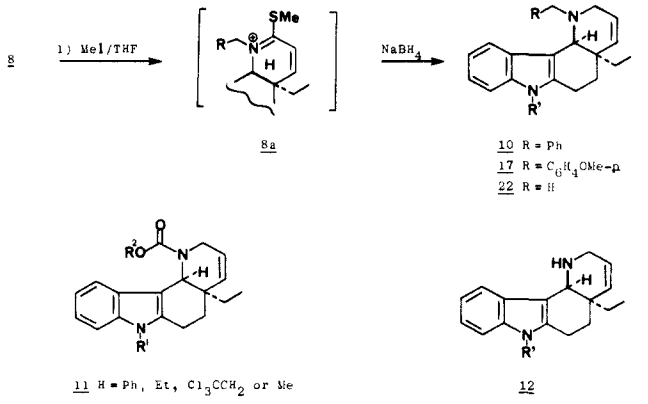


the α,β-unsaturated thiolactam **8** was desulfurized by S-alkylation with MeI/THF, followed by treatment of the resulting *S*-methylthioimminium salt **8a** with $NaBH_4$/MeOH to give the allylic amine **10** (52%).[10] Attempted debenzylation of **10** with phenyl chloroformate, ethyl chloroformate, and β,β,β-trichloroethyl chloroformate[11] did not produce any of the required chloroformate derivative **11**. Likewise, catalytic hydrogenolysis methods did not convert **10** into the *sec*-allylic amine **12**. (See structures below.)

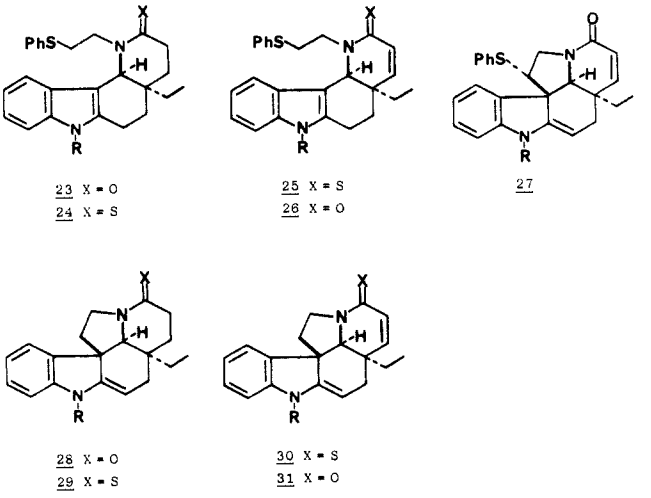
Recently, Martin[12] has used the *p*-methoxybenzyl group for secondary amine protection and commented upon its ready cleavage with methyl chloroformate. Consequently, we synthesized the *p*-methoxybenzyl analogue of **10**. Treatment of the imine **13** with the mixed carbonic anhydride **5**, using the usual conditions



(see **6**), gave the tetracyclic lactam **14** (39%). Exposure of the lactam **14** to the Lawesson reagent in toluene at 90 °C gave the required thiolactam **15** (95%). When **15** was treated with *p*-toluenesulfinyl chloride/CH_2Cl_2/*i*-Pr_2NEt/0 °C, followed by aqueous workup, the α,β-unsaturated thiolactam **16** (62%) resulted. Desulfurization of **16**, MeI/THF, followed by $NaBH_4$/MeOH, gave the allylic amine **17** (57%). Unfortunately, we could not remove the *N*-$CH_2C_6H_4OMe$-*p* group without extensive decomposition. It was concluded that a small group on the piperidine N atom is required since it is most probable that acylation by the chloroformate on the piperidine N atom is the rate-determining step and that this N atom is sterically hindered, Scheme II. Furthermore, the second-step, pathway b, an S_N2 process, is also sterically hindered. Consequently, we turned to *N*-methyl imine **18**, prepared from the aldehyde **3** and methylamine gas. Treatment of the *N*-methyl imine **18** with the mixed anhydride **5**, in chlorobenzene, using the usual conditions, gave the tetracycle **19** (56%), which was transformed into the thiolactam **20** (76%), using Lawesson's reagent. Dehydrogenation of the thiolactam **20** was carried out by treatment with *p*-toluenesulfinyl chloride/*i*-Pr_2NEt/CH_2Cl_2/0 °C to give the α,β-unsaturated thiolactam **21** (99%). Reductive removal of the thiocarbonyl group in **21**, using the usual procedure, MeI/THF, followed by $NaBH_4$, gave the required tertiary amine **22**, but in only 22% yield. Whereas, treatment of **21** with $Et_3O^+BF_4^-$/CH_2Cl_2, followed by LiAl(OBu-*t*)$_3$ gave **22** in 72% yield. The *N*-methyl amine **22** could be demethylated by heating in benzene/MeO_2CCl/$NaHCO_3$ to give the carbamate **11** (R = Me) (46%). Removal of the carbamate protection by treatment of **11** (R = Me) with MeOH/KOH/glyme gave the diamine **12** (R^1 = H) (21%).

While the transformations from the tetracyclic lactams **6**, **14**, and **19** to the tetracyclic allylamines **10**, **17**, and **22**, respectively, proceed in good overall yields (24.7, 33.6, and 54.2%, respectively) through three steps, subsequent dealkylation of **22** and conversion to the diamine **12** (R^1 = H) was less than satisfactory. Consequently, we turned our attention to tetracyclic lactams capable of eventual conversion into pentacyclic α,β-unsaturated lactams similar to **1**.

The tetracyclic lactam **23** (previously described in the synthesis of aspidospermidine)[1] was converted into the thiolactam **24** (62%) by treatment with Lawessons reagent in toluene. Dehydrogenation of **24** was carried out by treatment with *p*-toluenesulfinyl chloride/CH_2Cl_2/*i*-Pr_2NEt/O–20 °C, followed by workup with aqueous AcOH which gave the α,β-unsaturated lactam **25** (82%): ^1H NMR δ 6.08 (1 H, d, J = 9.6 Hz) and 6.44 (1 H, d, J = 9.6 Hz). Non-oxidative conversion of the thioamide **25** into the amide **26** was accomplished by treatment with Meerwein's reagent, followed by KOH/H_2O/THF: 57% yield; ^1H NMR δ 5.91 (1 H, d, J = 9.9 Hz) and 6.46 (1 H, d, J = 9.9 Hz). Oxidation of **26** with MCPBA/CH_2Cl_2/$NaHCO_3$ gave the derived diastereomeric sulfoxides, which were directly subjected to Pummerer-type reaction conditions TFAA/CH_2Cl_2/0 °C followed by heating to



135 °C in chlorobenzene to give the pentacyclic sulfide **27** (65%). To complete the sequence, the pentacyclic aspidospermidine-type precursor **28** (made during the course of a total synthesis of aspidospermidine)[1] was converted into the thiolactam **29** (73%) with Lawesson's reagent. While **29** was inert to the ususal thiolactam dehydrogenation conditions, it was cleanly transformed into the α,β-unsaturated thiolactam **30** (92%) when the dehydrogenation (*p*-toluenesulfinyl chloride/*i*-Pr_2NEt/CH_2Cl_2) was conducted at 65 °C. The thiolactam **30** was transformed into the lactam **31** (80%) by treatment with $Et_3O^+BF_4^-$/CH_2Cl_2, followed by 0.1 N KOH. The sequence from the saturated amide **28** to the α,β-unsaturated amide **31** proceeds in three steps in an overall yield of 54%.

While this mild dehydrogenation procedure works well from the specific and somewhat complicated systems described above, its extension to simple monocyclic and acyclic thioamides is not satisfactory at this stage. For example, treatment of *N*-methyl thiopyrrolidone **32** with *p*-toluenesulfinyl chloride/CH_2Cl_2/*i*-Pr_2NEt gave the *N*-methylpyrrolidone and the adduct **33**. Only when subjected to the severe conditions GCMS/260 °C did **33** decompose to give the α,β-unsaturated thiolactam **34**, as judged by MS. Whereas, similar treatment of *N*-methylthiopiperidone **35** gave the *S*-sulfinylated adduct **36** and the α,β-unsaturated thiolactam **37** (52%). The adduct **36** could *not* be converted into **37** either by thermal or base treatment, thus excluding the proposed 1,4-elimination mechanism, Scheme III.[1]

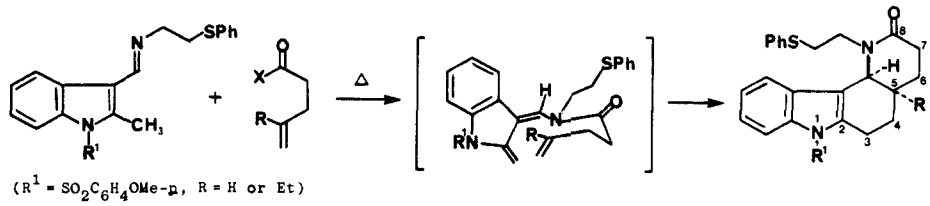
(9) Sulfenic acids readily dimerize with the loss of water to form thiosulfinates: Hogg, D. R.; Stewart, J. *J. Chem. Soc., Perkin Trans. 2* **1974**, *43*.

(10) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, 4061. Sundberg, R.; Walters, C. P.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 3730.

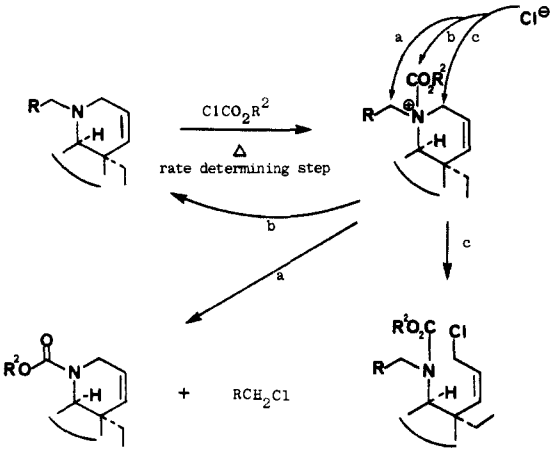
(11) Just, G.; Grozinger, K. *Synthesis* **1976**, 457. Windholz, T. B.; Johnson, D. B. R. *Tetrahedron Lett.* **1967**, 2555.

(12) Martin, S. F.; Tu, C.-Y.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *42*, 3634.

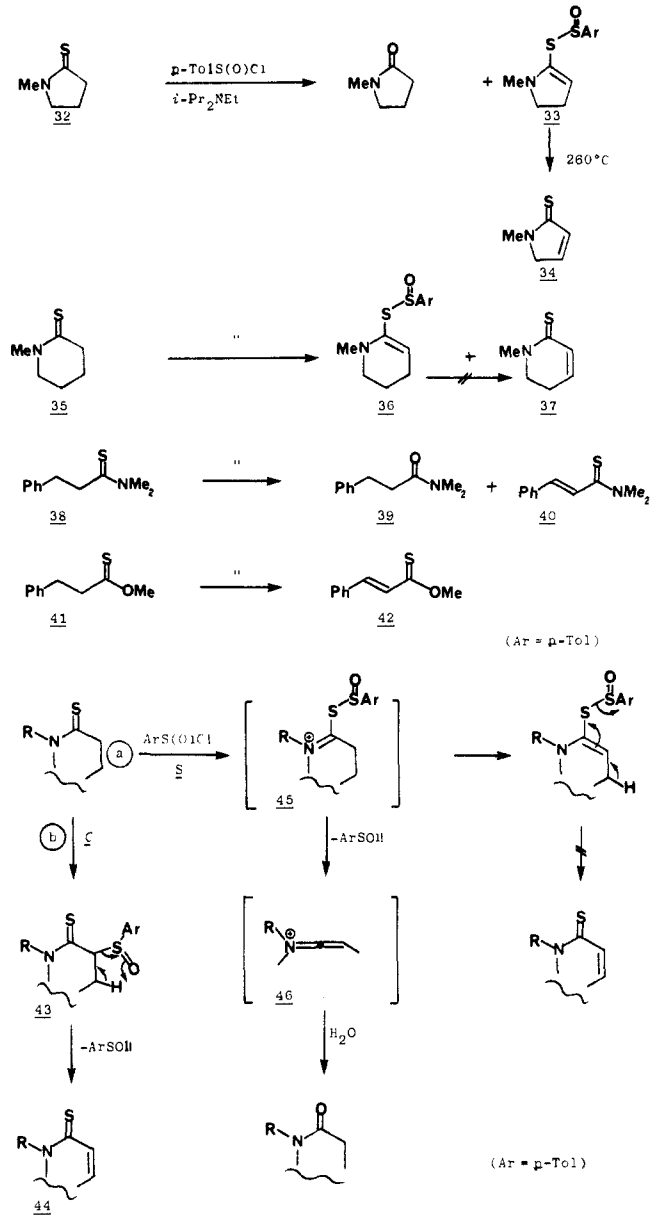
Scheme I



Scheme II



Scheme III



Treatment of the acyclic thioamide **38** with *p*-toluenesulfinyl chloride/CH_2Cl_2/*i*-Pr_2NEt cleanly resulted in conversion to the amide **39**, with a trace (<1%, comparison with an authentic sample) of the α,β-unsaturated thioamide **40**. Whereas, the corresponding thionoester **41**, when exposed to the above conditions, gave the α,β-unsaturated thionoester **42** (60%).

All of the thiolactams that were successfully converted into their corresponding α,β-unsaturated derivatives, with no complications arising from S-sulfinylation, are substrates where iminium ion participation (pathway a, Scheme III) is minimized because of strain (substrates **7**, **15**, **20**, **23**, and **29**). These substrates presumably undergo C-sulfinylation to give **43**, which, because of the highly polarized nature of the thiocarbonyl double bond (C=S ↔ C^+—S^-), readily *syn*-eliminates *p*-toluenesulfenic acid to give the unsaturated thiolactam **44**. Thiolactams that undergo S-sulfinylation (**32**, **35**, and **38**), in the presence of a tert-amine base, undergo proton loss to give the stable enamines **33** and **36**. For the acyclic system **38** the intermediate **45** can eliminate *p*-toluenesulfenic acid to give a ketiminum salt **46** that hydrates upon workup to give the observed amide **39**. The thionoester does not suffer from any of the complications of iminium ion participation and therefore proceeds via pathway b, C-sulfinylation, to give **42**. (See Scheme III.)

In summary, C-sulfinylation (pathway b) leads to the α,β-unsaturated thioamides, whereas S-sulfinylation (pathway a) is a dead end.

For the time being, we have not explored the full scope of this new procedure, since our interests have been in specific problems associated with indole alkaloid synthesis. Clearly, this mild dehydrogenation reaction provides a useful method for introducing the 6,7 double bond into *Aspidosperma*-type alkaloids, with the general restrictions referred to above. The investigation of modifications of this procedure, in order to extend its usefulness and generality, will be the subject of future research.

Experimental Section

(*E*)-1-[(*p*-Methoxyphenyl)sulfonyl]-2-methyl-3-(*N*-benzylformimidoyl)indole (4). The 3-formylindole **3** (0.5 g 1.5 mmol) and benzylamine (160 mg) in dry benzene (15 mL) containing molecular sieves (4A) were stirred at 25 °C for 18 h and filtered and the filtrate was evaporated in vacuo to give **4** (474 mg 76%) as a foam. IR ($CHCl_3$) 1630, 1590, 1260, 1180, 745 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.63 (3 H, s), 3.63 (3 H, s), 4.63 (2 H, s), 6.72 (2 H, d, J = 9 Hz), 7.20 (7 H, m), 7.61 (2 H, d, J = 9 Hz), 8.10 (1 H, t, J = 4.5 Hz), 8.33 (1 H, t, J = 4.5 Hz), and 8.51 (1 H, s). This material was used directly in the next stage.

(*E*)-1-[(*p*-Methoxyphenyl)sulfonyl]-2-methyl-3-[*N*-(4-methoxybenzyl)formimidoyl]indole (13). Prepared as above in 95% yield. IR ($CHCl_3$) 1630 cm^{-1}; NMR (90 MHz $CDCl_3$) δ 2.70 (3 H, s), 3.54 (3 H, s), 3.67 (3 H, s), 4.70 (2 H, br s), 6.68 (2 H, d, J = 12 Hz), 6.79 (2 H, d, J = 12 Hz), 7.23 (4 H, m), 7.67 (2 H, d, J = 9 Hz), 8.24 (1 H, t, J = 4.5 Hz).

(*E*)-1-[(*p*-Methoxyphenyl)sulfonyl]-2-methyl-3-(*N*-methylformimidoyl)indole (18). A solution of the 3-formylindole **3** (1.0 g, 3.3 mmol) in EtOH (30 mL) at 25 °C was treated with $MeNH_2$ gas (bubbled through the solution) for 20 min. After 18 h at 25 °C the mixture was cooled to 0 °C and filtered to give **18** (962 mg, 83%), mp 133–135 °C ($CHCl_3$–hexane). IR ($CHCl_3$) 1635 cm^{-1}; NMR (630 MHz $CDCl_3$) δ 2.74 (3 H, s), 3.51 (3 H, s), 3.75 (3 H, s), 6.83 (2 H, d, J = 9 Hz), 7.29 (2 H, quintet), 7.71 (2 H, d, J = 9 Hz), 8.20 (1 H, d, J = 8 Hz), 8.29

(1 H, d, J = 8 Hz), 8.49 (1 H, d, J = 1.4 Hz). Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.84; H, 5.33; N, 7.98.

Vinyl(4-ethyl-4-pentenoyl)carbonate (5). 4-Ethyl-4-pentenoic acid (2.30 g, 18 mmol) and triethylamine (1.82 g, 18 mmol) in dichloromethane (55 mL) at −20 °C were treated with vinyl chloroformate (1.94 g, 18 mmol) dropwise over 10 min. After 0.5 h at 0 °C the slurry was concentrated in vacuo and chlorobenzene (18 mL) added. The suspension was filtered, and the filtrate containing the mixed anhydride **5** (ca. 1 M) was stored at 0 °C for direct use in the subsequent cyclization reactions.

***cis*-4a-Ethyl-1,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-benzyl-2*H*-pyrido[3,2-*c*]carbazol-2-one (6).** To a solution of the *N*-benzyl imine **4** (474 mg 1.13 mmol) in chlorobenzene (5 mL) at 60 °C was added a solution of the mixed anhydride **5** (3 mL of a 1 M solution in PhCl, 3 mmol), and the mixture was heated at 140 °C for 5 h. After being cooled, the mixture was concentrated in vacuo and the residue chromatographed over silica, eluting with $CHCl_3$–hexane (35/36) to give **6** (224 mg 40%), mp 203–205 °C (from $CHCl_3$–hexane). IR ($CHCl_3$) 1660 cm^{-1}; NMR (220 MHz $CDCl_3$) δ 0.73 (2 H, t, J = 7.5 Hz), 1.04 (2 H, q, J = 7.5 Hz), 1.59 (3 H, m), 1.8 7 (1 H, quintet, J = 6 Hz), 2.49 (2 H, q, J = 6 Hz), 2.83 (2 H, t, J = 6 Hz), 3.79 (3 H, s), 4.42 (1 H, s), 4.47 (1 H, d, J = 15 Hz), 4.66 (1 H, d, J = 15 Hz), 6.71 (2 H, d, J = 7.5 Hz), 6.91 (2 H, d, J = 10 Hz), 7.07 (3 H, m), 7.32 (3 H, m), 7.76 (2 H, d, J = 7.5 Hz), 8.24 (1 H, d, J = 9 Hz). Anal. Calcd for $C_{31}H_{32}N_2O_4S$: C, 70.45; H, 6.06; N, 5.30. Found: C, 70.20; H, 6.07; N, 5.22.

***cis*-4a-Ethyl-1,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)-sulfonyl]1-(*p*-methoxybenzyl)-2*H*-pyrido-[3,2-*c*]carbazol-2-one (14).** To a solution of the imine **13** (2.66 g, 5.94 mmol) in chlorobenzene (60 mL) at reflux was added the mixed anhydride **5** (18 mL, 1 M solution in PhCl). Workup as for **6** gave **14** (1.296 g, 39%), mp 180.5–181.5 °C (from $CHCl_3$–hexane). IR ($CHCl_3$) 1640 and 1630 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.74 (3 H, t, J = 7.4 Hz), 1.03 (2 H, q, J = 7.4 Hz), 1.43 (1 H, m), 1.55 (2 H, t, J = 6.6 Hz), 1.84 (1 H, m), 2.44 (2 H, m), 2.81 (2 H, t, J = 6.4 Hz), 3.74 (3 H, s), 3.82 (3 H, s), 4.31 (1 H, d, J = 15 Hz), 4.36 (1 H, s), 4.59 (1 H, d, J = 15 Hz), 6.60 (4 H, ABq, J = 9 Hz), 6.90 (2 H, d, J = 9 Hz), 7.25 (3 H, m), 7.72 (2 H, d, J = 9 Hz), 8.21 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{32}H_{34}N_2O_5S$: C, 68.82; H, 6.09; N, 5.02. Found: C, 68.54; H, 5.98; N, 4.90.

***cis*-4a-Ethyl-1,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-methyl-2*H*-pyrido[3,2-*c*]carbazol-2-one (19).** To a solution of the imine **18** (4.10 g, 12 mmol) in chlorobenzene (120 mL) at reflux was added the mixed anhydride **5** (42 mmol, 3.5 equiv as a 1 M solution in PhCl). After 7 h at reflux, the solution was concentrated in vacuo and the residue chromatographed over silica gel, eluting with chloroform–hexane (1:1) to give **19** (3.04 g, 56%), mp 174–176 °C (from chloroform–hexane). IR ($CHCl_3$) 1645, 1635, 1625 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.85 (3 H, t, J = 7.4 Hz), 1.22 (2 H, q, J = 7.6 Hz), 1.62 (1 H, m), 1.70 (1 H, m), 1.82 (1 H, m), 1.96 (1 H, m), 2.35 (2 H, m), 2.79 (3 H, s), 2.96 (1 H, m), 3.15 (1 H, m), 4.26 (1 H, s), 6.85 (2 H, d, J = 9 Hz), 7.28 (2 H, q, J = 8.5 Hz), 7.41 (1 H, d, J = 7.5 Hz), 7.67 (2 H, d, J = 9 Hz), 8.19 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{25}H_{28}N_2SO_4$: C, 66.35; H, 6.24; N, 6.19. Found: C, 66.29; H, 6.24; N, 6.20.

***cis*-4a-Ethyl-1,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-benzyl-2*H*-pyrido[3,2-*c*]carbazol-2-thione (7).** The lactam **6** (250 mg, 0.47 mmol) and the Lawesson reagent (215 mg 0.53 mmol) in HMPA (5 mL) were heated at 85 °C for 18 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with water (3 × 30 mL), and dried (Na_2SO_4). The residue was purified by chromatography over silica gel, eluting with $CHCl_3$–hexane (1:9) to give the thiolactam **7** (156 mg, 61%), mp 201–202 °C (for $CHCl_3$–hexane). IR ($CHCl_3$) 1590, 1570 cm^{-1}; NMR (220 MHz $CDCl_3$) δ 0.72 (3 H, t, J = 7.5 Hz), 1.28 (3 H, m), 1.54 (2 H, m), 1.88 (1 H, m), 2.65 (2 H, m), 2.93 (1 H, m), 3.18 (1 H, m), 3.82 (3 H, s), 4.50 (1 H, s), 4.83 (1 H, br d, J = 15 Hz), 5.74 (1 H, br d, J = 15 Hz), 6.77 (2 H, d, J = 7.5 Hz), 7.02 (5 H,m), 7.31 (3 H, m), 7.79 (2 H, d, J = 7.5 Hz), 8.30 (1 H, d, J = 7.5 Hz). Anal. Calcd for $C_{31}H_{32}N_2O_3S_2$: C, 68.35; H, 5.92; N, 5.14. Found: C, 67.92; H, 5.87; N, 4.96.

***cis*-4a-Ethyl-1,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-(*p*-methoxybenzyl)-2*H*-pyrido[3,2-*c*]carbazol-2-thione (15).** The lactam **14** (0.5 g, 0.896 mmol) and the Lawesson reagent (0.5 g) in dry toluene (30 mL) were heated at 90 °C for 23 h. Workup as for **7** gave **15** (484 mg, 95%), mp 182–184 °C (from $CHCl_3$–hexane). NMR (220 MHz $CDCl_3$) δ 0.72 (3 H, t, J = 7 Hz), 1.07 (2 H, q, J = 7 Hz), 1.26 (2 H, m), 1.55 (1 H, m), 1.86 (1 H, m), 2.67 (2 H, m), 2.88 (1 H, dd, J = 5 and 10 Hz), 3.15 (1 H, m), 3.72 (3 H, s), 3.81 (3 H, s), 4.46 (1 H, s), 4.75 (1 H, m), 5.71 (1 H, br d, J = 12.5 Hz), 6.53 (2 H, d, J = 10 Hz), 6.74 (2 H, d, J = 8 Hz), 6.96 (2 H, d, J = 10 Hz), 7.35 (3 H, m), 7.79 (2 H, d, J = 10 Hz), 8.31 (1 H, d, J = 10 Hz). Anal. Calcd for $C_{32}H_{34}N_2O_4S_2$: C, 66.90; H, 5.92; N, 4.88. Found: C, 66.74; H, 5.84; N, 4.70.

***cis*-4a-Ethyl-1,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-methyl-2*H*-pyrido[3,2-*c*]carbazol-2-thione (20).** The lactam **19** (3.04 g, 6.72 mmol) and the Lawesson reagent (2.9 g) in toluene (80 mL) were heated at 90 °C for 12 h. Workup gave **20** (2.39 g, 76%), mp 177–179 °C (from EtOAc–hexane). IR ($CHCl_3$) 1590, 1340 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.88 (3 H, t, J = 7.3 Hz), 1.25 (2 H, m), 1.37 (1 H, m), 1.74 (1 H, m), 1.81 (2 H, m), 2.83 (2 H, m), 2.94 (1 H, m), 3.13 (1 H, m), 3.29 (3 H, s), 3.78 (3 H, s), 4.38 (1 H, s), 6.86 (2 H, d, J = 9 Hz), 7.30 (3 H, m), 7.68 (2 H, d, J = 9 Hz), 8.19 (1 H, d, J = 5.5 Hz). Anal. Calcd for $C_{25}H_{28}N_2S_2O_3$: C, 64.07; H, 6.02; N, 5.98. Found: C, 64.09; H, 6.13; N, 5.95.

***cis*-4a-Ethyl-1,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-benzyl-2*H*-pyrido[3,2-*c*]carbazol-2-thione (8).** To a solution of the thiolactam **7** (150 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) containing *i*-Pr_2NEt (0.25 mL) was added *p*-toluenesulfinyl cnloride (120 mg, 0.69 mmol) in CH_2Cl_2 (1 mL) dropwise over 10 min. The solution was stirred at 0 °C for 30 min, layered with 0.1 M AcOH (10 mL), and warmed to 25 °C. After 12 h the mixture was diluted with $CHCl_3$ (10 mL), and the organic phase filtered in vacuo and crystallization of the residue from $CHCl_3$ (2 mL)–hexane gave the α,β-unsaturated thiolactam **8** (111.5 mg, 75%), mp 221–225 °C. IR ($CHCl_3$) 1590, 1570 cm^{-1}; NMR (220 MHz $CDCl_3$) δ 0.59 (3 H, t, J = 10 Hz), 1.07 (2 H, q, J = 10 Hz), 1.71 (1 H, m), 2.01 (1 H, m), 2.76 (1 H, m), 2.91 (1 H, m), 3.79 (3 H, s), 4.74 (1 H, s), 5.27 (1 H, br s), 5.66 (1 H, br s), 6.14 (1 H, d, J = 10 Hz), 6.55 (1 H, d, J = 10 Hz), 6.89 (1 H, d, J = 7.5 Hz), 6.99 (2 H, m), 7.15 (3 H, m), 7.35 (4 H, m), 7.69 (2 H, d, J = 7.5 Hz), 8.22 (1 H, d, J = 7.5 Hz). Anal. Calcd for $C_{31}H_{30}N_2O_3S_2$: C, 68.61; H, 5.57; N, 5.16. Found: C, 68.25; H, 5.32; N, 4.99.

***cis*-4a-Ethyl-1,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-(*p*-methoxybenzyl)-2*H*-pyrido-[3,2-*c*]-carbazol-2-thione (16).** Thiolactam **15** (150 mg, 0.261 mol) was treated as for **8** to give the α,β-unsaturated thiolactam **16** (92 mg, 62%), mp 197–199 °C (from $CHCl_3$–hexane). NMR (220 MHz $CDCl_3$) δ 0.62 (3 H, t, J = 6 Hz), 1.09 (2 H, q, J = 6 Hz), 1.71 (1 H, m), 2.03 (1 H, m), 2.78 (1 H, m), 2.97 (1 H, m), 3.81 (3 H, s), 3.84 (3 H, s), 4.73 (1 H, s), 5.18 (1 H, br s), 5.82 (1 H, br s), 6.09 (1 H, d, J = 10 Hz), 6.53 (1 H, d, J = 10 Hz), 6.75 (2 H, d, J = 10 Hz), 6.94 (2 H, d, J = 10 Hz), 7.05 (2 H, d, J = 9 Hz), 7.40 (3 H, m), 7.70 (2 H, d, J = 10 Hz), 8.24 (1 H, d, J = 9 Hz). Anal. Calcd for $C_{32}H_{32}N_2O_4S_2$: C, 67.13; H, 5.60; N, 4.90. Found: C, 66.90; H, 5.59; N, 4.78.

***cis*-4a-Ethyl-1,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-methyl-2*H*-pyrido[3,2-*c*]carbazol-2-thione (21).** The thiolactam **20** (150 mg, 0.32 mmol) was treated as for **8** to give the α,β-unsaturated thiolactam **21** (148 mg, 99%) as yellow needles, mp 183–185 °C (from $CHCl_3$–hexane). IR ($CHCl_3$) 1590, 1490, 1370, and 1305 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.88 (3 H, t, J = 7.5 Hz), 1.40 (2 H, q, J = 7.5 Hz), 1.77 (1 H, m), 2.07 (1 H, m), 3.07 (2 H, m), 3.46 (3 H, s), 3.80 (3 H, s), 4.57 (1 H, s), 6.07 (1 H, d, J = 9.6 Hz), 6.44 (1 H, d, J = 9.6 Hz), 6.86 (2 H, d, J = 9 Hz), 7.29 (2 H, m), 7.41 (1 H, d, J = 7 Hz), 7.66 (2 H, d, J = 9 Hz), 8.19 (1 H, d, J = 7.7 Hz). Anal. Calcd for $C_{25}H_{26}N_2S_2O_3$: C, 64.35; H, 5.62; N, 6.00. Found: C, 64.14; H, 5.65; N, 5.89.

***cis*-4a-Ethyl-2,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)-sulfonyl]1-1-benzyl-1*H*-pyrido[3,2-*c*]carbazole (10).** The α,β-unsaturated thiolactam **8** (150 mg, 0.276 mmol) in THF (3 mL) was treated with MeI (1.5 mL) at 25 °C. The mixture was heated at 65 °C for 7 h, and evaporated in vacuo, and the residue was dissolved in methanol (5 mL) and treated with $NaBH_4$ (excess). After 1 h at 25 °C the mixture was diluted with chloroform (25 mL), washed with water (2 × 40 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed over silica, eluting with $CHCl_3$–hexane (15:85) to give the allylic amine **10** (73 mg, 52%), mp 72–76 °C (from MeOH). IR ($CHCl_3$) 1590, 1360, 1260 cm^{-1}; NMR (220 MHz $CDCl_3$) δ 0.80 (3 H, t, J = 7.5 Hz), 1.19 (2 H, q, J = 7.5 Hz), 1.73 (2 H, dd, J's = 6 and 12.5 Hz), 2.49 (2 H, m), 2.76–3.40 (4 H, m), 3.61 (3 H, s), 3.65 (1 H, s), 5.68 (2 H, s), 6. 74 (2 H, d, J = 7.5 Hz), 7.21 (7 H, m), 7.67 (3 H, br s, J = 10 Hz). Anal. Calcd for $C_{31}H_{32}N_2O_3S$: C, 73.63; H, 6.29; N, 5.46. Found: C, 72.33; H, 6.51; N, 5.41.

***cis*-4a-Ethyl-2,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-(*p*-methoxybenzyl)-1*H*-pyrido[3,2-*c*]carbazole (17).** The α,β-unsaturated thiolactam **16** (92 mg, 0.161 mmol) in THF (3 mL) was treated as for **10** to give **17** (49.5 mg, 57%) as a foam. NMR (220 MHz $CDCl_3$) δ 0.80 (3 H, t, J = 6 Hz), 1.20 (2 H, q, J = 6 Hz), 1.73 (1 H, dd, J's = 6 and 10 Hz), 2.47 (1 H, m), 2.78–3.36 (4 H, m), 3.60 (1 H, s), 3.63 (3 H, s), 3.74 (3 H, s), 5.68 (2 H, s), 6.76 (3 H, d, J = 7.5 Hz), 7.02 (2 H, d, J = 7.5 Hz), 7.33 (3 H, m), 7.65 (3 H, m), 8.24 (1 H, m).

***cis*-4a-Ethyl-2,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)-sulfonyl]-1-methyl-1*H*-pyrido[3,2-*c*]carbazole (22).** To a solution of the

α,β-unsaturated thiolactam **21** (50 mg, 0.107 mmol) in CH_2Cl_2 (2 mL) at 25 °C was added $Et_3O^+BF_4^-$ (26 mg) in CH_2Cl_2 (1 mL). The solution was cooled to −40 °C and treated with $LiAl(O\text{-}t\text{-}Bu)_3H$ (100 mg). The slurry was warmed to 25 °C and EtOAc (15 mL) added, followed by 2 N NaOH (3 mL). The organic phase was washed with brine (30 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by flash chromtography to give the amine **22** (33.8 mg, 72%). NMR (360 MHz $CDCl_3$) δ 0.75 (3 H, t, J = 7.3 Hz), 1.11 (2 H, q, J = 7.3 Hz), 1.69 (1 H, dd, J's = 6.5 and 13.5 Hz), 2.16 (3 H, s), 2.32 (1 H, m), 2.87 (2 H, ddd, J's = 7, 11.7, and 18.6 Hz), 2.97 (1 H, d, J = 16.7 Hz), 3.22 (1 H, m), 3.24 (1 H, s), 3.79 (3 H, s), 6.84 (2 H, d, J = 9 Hz), 7.26 (2 H, m), 7.50 (1 H, d, J = 7.5 Hz), 7. 79 (2 H, d, J = 9 Hz), 8.17 (1 H, d, J = 9 Hz).

Methyl *cis*-4a-Ethyl-2,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole-1-carboxylate (11, R = Me). To a solution of the *N*-methyl amine **22** (93.4 mg, 0.214 mmol) and $NaHCO_3$ (100 mg) in benzene (4 mL) at 80 °C was added freshly distilled methyl chloroformate (120 mg, 6 equiv). After being heated at reflux for 7 h, the cooled mixture was washed with brine (15 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by preparative layer chromatography to give the methyl carbamate **11** (R = Me) (47 mg, 46%) as a glass. NMR (360 MHz $CDCl_3$) δ 0.79 (3 H, t, J = 7.3 Hz), 1.35 (2 H, q, J = 7 Hz), 2.46 (3 H, dd, J's = 5 and 18 Hz), 2.68 (3 H, br d, J = 18 Hz), 3.62 (3 H, br d), 3.76 (3 H, s), 5.30 (1 H, m), 5.60 (1 H, br d), 5.84 (1 H, m), 6.06 (1 H, t, J = 4.2 Hz), 6.80 (2 H, d, J = 9 Hz), 7.07 (1 H, t, J = 7.5 Hz), 7.29 (2 H, m), 7.63 (2 H, d, J = 9 Hz), 7.88 (1 H, d, J = 8 Hz), MS $C_{26}H_{28}N_2O_5S$, m/e 480.174, requires 480.174.

***cis*-4a-Ethyl-2,4a,5,6,7,11c-hexahydro-1*H*-pyrido[3,2-*c*]carbazole (12, R^1 = H).** To a solution of the methyl carbamate **11** (R = Me) (25 mg, 0.052 mmol) in glyme (2 mL) was added 0.5 mL of 20% methanolic KOH, and the mixture was heated at 110 °C for 5 h. The mixture was diluted with water and extracted with EtOAc (2 × 15 mL). The dried (Na_2SO_4) extract was evaporated in vacuo and the residue purified by preparative layer chromatography to give on elution with MeOH/EtOAc/hexane (5:12:8) the diamine **12** (R^1 = H) (2.7 mg, 21%), mp ca. 230 °C dec. NMR (360 MHz $CDCl_3$) δ 0.79 (3 H, t, J = 7.4 Hz), 1.25 (2 H, m), 1.63 (1 H, dd, J's = 6.2 and 13.5 Hz), 2.45 (1 H, m), 2.69 (2 H, m), 3.02 (1 H, d, J = 16.5 Hz), 3.36 (1 H, s), 3.44 (1 H, dd, J's = 4 and 16.4 Hz), 5.66 (1 H, d, J = 10 Hz), 5.78 (1 H, m), 7.11 (2 H, m), 7.30 (1 H, dd, J's = 1.8 and 6 Hz), 7.56 (1 H, dd, J's = 2.3 and 6.5 Hz), 8.12 (1 H, br s). MS $C_{17}H_{20}N_2$, m/e 252.168, requires 252.167.

***cis*-4a-Ethyl-1,3,4,4a,5,6,7,11c-octahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1-[2-(phenylthio)ethyl]-2*H*-pyrido[3,2-*c*]carbazol-2-thione (24).** A mixture of the tetracyclic lactam **23** (252 mg, 0.44 mmol) and the Lawesson reagent (250 mg, 0.61 mmol) in toluene (20 mL) was heated at 90 °C for 2 h. Workup in the usual manner gave **24** (162 mg, 62%), mp 180–181 °C (from EtOAc–hexane). IR ($CHCl_3$) 1590, 1490, 1410, 1265, 1200–1040 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.86 (3 H, t, J = 7.4 Hz), 1.17 (2 H, m), 1.33 (1 H, m), 1.79 (2 H, m), 1.91 (1 H, m), 2.64 (1 H, m), 2.79–3.20 (6 H, m), 3.71 (3 H, s), 4.27 (1 H, m), 4.40 (1 H, s), 6.80 (2 H, d, J = 9 Hz), 8.27 (1 H, d, J = 8.3 Hz). Anal. Calcd for $C_{32}H_{34}N_2S_3O_3$: C, 65.06; H, 5.80; N, 4.74. Found: C, 65.05; H, 5.83; N, 4.66.

***cis*-4a-Ethyl-1,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1-[2-(phenylthio)ethyl]-2*H*-pyrido-[3,2-*c*]carbazole-2-thione (25).** To a solution of the thiolactam **24** (150 mg, 0.254 mmol) and *i*-Pr_2NEt (0.5 Ml) in CH_2Cl_2 (4 mL) at −20 °C was added *p*-toluenesulfinyl chloride (111 mg, 0.64 mmol) in CH_2Cl_2 (1 mL) dropwise over 5 min. The mixture was warmed to 20 °C over a period of 6 h and layered with 0.1 M AcOH (10 mL), and the two-phase system was rapidly stirred for 4 h. The solution was diluted with chlororm (20 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by flash chromatography, eluting with $CHCl_3$–hexane (1:1) to give **25** (122 mg, 82%), mp 183–185 °C (from EtOAc–hexane). IR ($CHCl_3$) 1590, 1570, 1490, 1470, 1450, 1370, 1305, 1295, 1260, 1170–1090 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.88 (3 H, t, J = 7. 5 Hz), 1.38 (2 H, m), 1.78 (1 H, m), 2.08 (1 H, m), 2.69 (1 H, m), 2.94 (1 H, m), 3.11 (2 H, br t, J = 8 Hz), 3.68 (3 H, s), 4.18 (1 H, m), 4.30 (1 H, m), 4.64 (1 H, s), 6.08 (1 H, d, J = 9.6 Hz), 6.44 (1 H, d, J = 9.6 Hz), 6.76 (2 H, d, J = 9 Hz), 6.85 (2 H, m), 7.02 (2 H, dd, J's = 2 and 5 Hz), 7.29 (2 H, m), 7.37 (2 H, m), 7.68 (2 H, d, J = 9 Hz), 8.25 (1 H, d, J = 8.8 Hz). Anal. Calcd for $C_{32}H_{32}N_2S_3O_3$: C, 65.28; H, 5.48; N, 4.76. Found: C, 65.50; H, 5.57; N, 4.29.

***cis*-4a-Ethyl-1,4a,5,6,7,11c-hexahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1-[2-(phenylthio)ethyl]-2*H*-pyrido[3,2-*c*]carbazol-2-one (26).** To a solution of the thiolactam **25** (243 mg, 0.4 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added $Et_3O^+BF_4^-$ (102 mg) in CH_2Cl_2 (5 mL). The mixture was stirred for 10 min at 0 °C and 1 h at 25 °C and evaporated to dryness. The residue was dissolved in THF (10 mL) and treated with 0.1 N KOH (5 mL). After 3 h at 25 °C the solution was diluted with water (10 mL), extracted with EtOAc (2 × 10 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by flash chromatography, eluting with $CHCl_3$–hexane (9:11) followed by crystallization from EtOAc–hexane to give **26** (136.8 mg 57%), mp 204–206 °C. IR ($CHCl_3$) 1665, 1660, 1645 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.87 (3 H, t, J = 7.4 Hz), 1.36 (2 H, q, J = 7.4 Hz), 1.77 (1 H, m), 2.16 (1 H, m), 2.45 (1 H, m), 2.75 (1 H, m), 3.10 (2 H, m), 3.42 (1 H, m), 3.67 (3 H, s), 3.76 (1 H, m), 4.63 (1 H, s), 5.91 (1 H, d, J = 9.9 Hz), 6.46 (1 H, d, J = 9.9 Hz), 6.76 (2 H, d, J = 9 Hz), 6.89 (2 H, dd, J's = 2 and 7.8 Hz), 7.03 (2 H, m), 7.26 (1 H, m), 7.38 (3 H, m), 7.67 (2 H, d, J = 9 Hz), 8.24 (1 H, d, J = 8.3 Hz). Anal. Calcd for $C_{32}H_{32}N_2S_2O_4$: C, 67.11; H, 5.63; N, 4.89. Found: C, 67.04; H, 5.53; N, 4.61.

2,3,6,7-Tetrahydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-aspidospermidin-8-one (27). The α,β-unsaturated lactam **26** (80 mg, 0.14 mmol) was partitioned between CH_2Cl_2 (2 mL) and 10% aqueous $NaHCO_3$ (2 mL) at 0 °C, and 80% MCPBA (36 mg, 0.167 mmol) in CH_2Cl_2 (4 mL) was added over a period of 0.5 h. Workup gave a mixture of diastereomeric sulfoxides (117 mg). To a solution of these sulfoxides (50 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added trifluoroacetic anhydride (0.1 mL). After 1 h at 0 °C the mixture was diluted with dry chlorobenzene (6 mL) and heated to 135 °C. After 1 h the mixture was cooled, diluted with EtOAc (20 mL), washed with 10% aqueous $NaHCO_3$ (30 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by preparative layer chromatography to give **27** (29.7 mg, 65%), mp 203–207 °C (from EtOAc–hexane). IR ($CHCl_3$) 1660, 1650, 1600 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.88 (3 H, t, J = 6.9 Hz), 1.26 (2 H, m), 2.08 (2 H, m), 3.20 (2 H, m), 3.63 (2 H, s), 4.03 (1 H, s), 4.37 (1 H, q, J = 5.5 Hz), 5.90 (1 H, d, J = 10 Hz), 6.13 (1 H, q, J = 4.4 Hz), 6.36 (1 H, d, J = 10 Hz), 6.77 (2 H, d, J = 9 Hz), 7.05 (2 H, m), 7.18 (4 H, m), 7.41 (2 H, m), 7.84 (2 H, d, J = 9 Hz), 7.99 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{32}H_{30}N_2S_2O_4$: C, 67.37; H, 5.26; N, 4.91. Found: C, 66.98; H, 5.20; N, 4.80.

2,3-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]aspidospermidine-8-thione (29). A mixture of the pentacyclic lactam **28** (128 mg, 0.276 mmol) and the Lawesson reagent (100 mg, 0.25 mmol) in toluene (10 mL) was heated at 90 °C for 2.5 h. The cooled mixture was filtered, and the filtrate was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by flash chromatography to give **29** (96.6 mg, 73%), mp 189–190 °C (from EtOAc–hexane). IR ($CHCl_3$) 1590, 1490, 1480, 1360 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.70 (3 H, t, J = 7.3 Hz), 0.97 (2 H, q, J = 7.3 Hz), 1.03 (1 H, t, J = 6 Hz), 1.11 (1 H, m), 1.44 (1 H, m), 1.74 (1 H, dd, J's = 3.5 and 15.7 Hz), 1.94 (1 H, m), 2.24 (1 H, m), 2.49 (1 H, m), 3.07 (1 H, m), 3.23 (1 H, s), 3.45 (1 H, m), 4.32 (1 H, dd, J's = 8 and 13.3 Hz), 6.19 (1 H, dd, J's = 3.5 and 8.4 Hz), 7.67 (2 H, d, J = 9 Hz), 7.08 (2 H, m), 7.33 (1 H, t, J = 7.6 Hz), 7.67 (1 H, d, J = 8.7 Hz), 7.90 (1 H, d, J = 8.3 Hz). Anal. Calcd for $C_{26}H_{28}N_2S_2O_3$: C, 64.97; H, 5.87; N, 5.83. Found: C, 64.75; H, 6.06; N, 5.61.

2,3,6,7-Tetrahydro-1-[(*p*-methoxyphenyl)sulfonyl]aspidospermidine-8-thione (30). To a solution of the thiolactam **29** (10 mg, 0.021 mmol) and *i*-Pr_2NEt (1.0 μL) in CH_2Cl_2 (0.5 mL) at 25 °C was added *p*-toluenesulfinyl chloride (10 mg, 0.06 mL) in CH_2Cl_2 (0.5 mL). After 15 min at 25 °C the solution was heated at 65 °C for 6 h and cooled to 28 °C, and 0.1 M AcOH (2 mL) was added. The mixture was diluted with $CHCl_3$ (10 mL), dried (Na_2SO_4), and evaporated. The residue was purified by preparative layer chromatography to give the α,β-unsaturated thiolactam **30** (9.2 mg, 92%), mp 166–168 °C (from EtOAc–hexane). IR ($CHCl_3$) 1610, 1600, 1590, 1360, 1310, 1260, 1200 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.70 (3 H, t, J = 7.4 Hz), 0.94–1.30 (4 H, m), 1.96 (1 H, dd, J's = 3.5 and 15.8 Hz), 2.10 (1 H, m), 3.45 (1 H, m), 3.79 (1 H, s), 3.81 (3 H, s), 4.46 (1 H, dd, J's = 7.5 and 13 Hz), 6.10 (1 H, d, J = 9.6 Hz), 6.16 (1 H, dd, J's = 3.5 and 8.6 Hz), 6.42 (1 H, d, J = 9.6 Hz), 6.86 (2 H, d, J = 9 Hz), 7.13 (2 H, m), 7.34 (1 H, m), 7.69 (2 H, d, J = 9 Hz), 7.90 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{26}H_{26}N_2S_2O_3$: C, 65.25; H, 5.47; N, 5.85. Found: C, 64.98; H, 5.71; N, 6.06.

2,3,6,7-Tetrahydro-1-[(*p*-methoxyphenyl)sulfonyl]aspidospermidine-8-one (31). The thiolactam **30** (21 mg, 0.044 mmol) in CH_2Cl_2 (1 mL) at 0 °C was treated with $Et_3O^+BF_4^-$ (12 mg, 0.06 mmol) in CH_2Cl_2 (0.5 mL). After 1 h at 25 °C, THF (1 mL) followed by 0.1 N KOH (2 mL) was added, and the mixture was stirred at 25 °C for 2 h. Workup gave **31** (16.2 mg, 80%), mp 168–171 °C (from EtOAc–hexane). IR ($CHCl_3$) 1655, 1590 cm^{-1}; NMR (360 MHz $CDCl_3$) δ 0.69 (3 H, t, J = 7.4 Hz), 0.97 (1 H, m), 1.08 (2 H, q, J= 7.4 Hz), 1.11–1.30 (1 H, m), 1.99 (1 H, dd, J's = 2.7 and 15.6 Hz), 2.07 (1 H, m), 3.08 (1 H, m), 3.81 (3 H, s), 3.83 (1 H, s), 3.99 (1 H, dd, J's = 3.7 and 8.5 Hz), 6.38 (1 H, d, J = 10 Hz), 6.85 (2 H, d, J = 9 Hz), 7.12 (2 H, m), 7.32 (1 H, m), 7.68 (2 H, d, J = 9 Hz), 7.89 (1 H, d, J = 8 Hz). Anal. Calcd for $C_{26}H_{26}N_2SO_4$: C, 67.51; H, 5.67; N, 6.06. Found: C, 66.66; H, 5.86; N, 5.83.

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).

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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 $TsOH/H_2O$/

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