Synthesis of (±)-10,22-Dioxokopsane and (±)-Kopsanone, Heptacyclic Indole Alkaloids. Synthetic and Mechanistic Studies

Philip Magnus,*† Timothy Gallagher,† Peter Brown,† and John C. Huffman‡

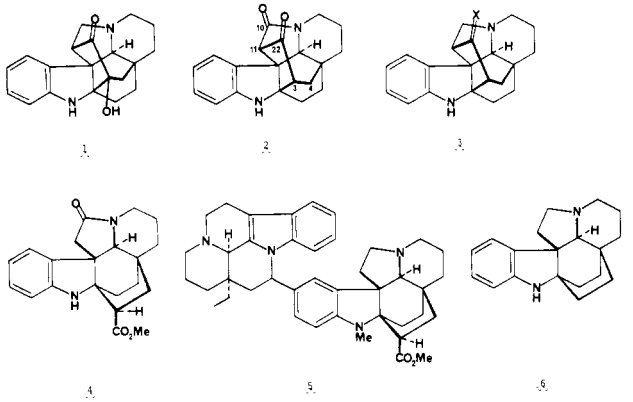
Contribution from the Department of Chemistry, and the Molecular Structure Center, Indiana University, Bloomington, Indiana 47405. *Received September 12, 1983*

Abstract: The total synthesis of the heptacyclic indole alkaloids (±)-10,22-dioxokopsane (**2**) and (±)-kopsanone (**3**, X = O) is described. The imine **20** was condensed with β,β,β-trichloroethyl chloroformate to give the tetracyclic carbamate **21**. Removal of the carbamate protecting group with zinc in acetic acid provided the secondary amine **22**. The amine was converted into the sulfoxide **24**, by treatment with (phenylthio)acetyl chloride followed by oxidation. The sulfoxide **24** was converted directly into the homoannular diene **7** by treatment with trifluoroacetic anhydride in chlorobenzene at 135 °C. The crucial allylation of the C-11 carbanion **31**, derived from **7** by treatment with lithium hexamethyldisilazide, gave exclusively the desired endo-allyl product **28**. In the chiral series we show that the allylation at C-11 takes place with retention of configuration. Heating **28** at 100 °C gave the basic kopsane skeleton **30**. The oxidation level at C-11 was transferred to C-22 by elimination of the sulfoxide **46**, via the anti-Bredt compound **48**, to give **49**. Treatment of **49** with trifluoroacetic anhydride gave *N*-[(*p*-methoxyphenyl)sulfonyl]-10,22-dioxokopsane (**52**). Conversion of **52** into **2** and **3** (X = O) was achieved by reduction with Li/NH_3 and oxidation to give **2** and reduction of **52** with $LiAlH_4$ and oxidation to give **3** (X = O). The synthesis proceeds through 14 steps in an overall yield of 5.8%.

The kopsane alkaloids have enjoyed a long and somewhat exclusive history. Kopsine **1** was first isolated in 1890.[1] Many reports of the isolation of kopsane alkaloids up until the early 1960's exist,[2] but their structures remained unknown. Indeed at one time the kopsanes were thought to belong to the Strychnos family because of their comparative biology. Kopsine possesses cholinergic effects, and its site of action is peripheral, while that of strychnine is at the cerebrospinal axis.[3]

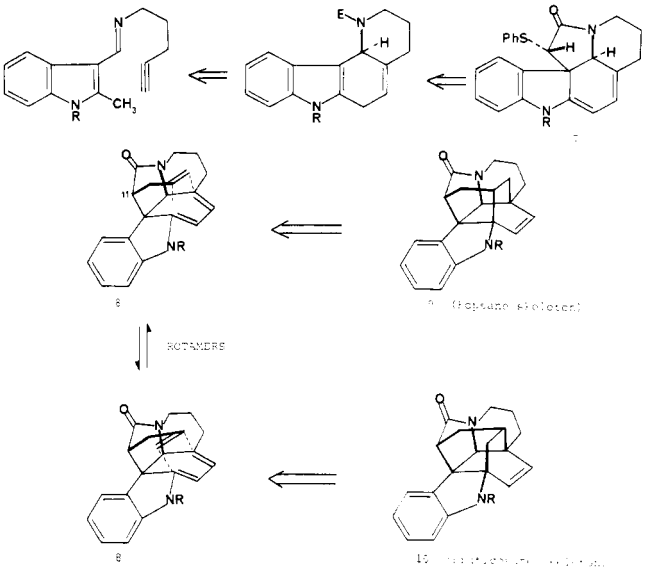
While the chemical degradation studies conducted in the early 1960's uncovered many remarkable transformations,[4] it was not until these data were combined with high-resolution mass spectrometry that the correct structures of the kopsanes finally became known.[5] The correctness of these deductions was subsequently confirmed by a single-crystal X-ray crystallographic structural determination of (±)-kopsanone methiodide.[6]

A central member of the kopsia group of indole alkaloids is 10,22-dioxokopsane (**2**). We chose this as our synthetic objective



because it can readily be converted into the kopsanols **3** (X = H, OH and C-22 epimer), by reduction ($LiAlH_4$), and subsequent oxidation (Me_2SO/DCC) gives kopsanone **3** (X = O).[5] Furthermore, treatment of the nonenolizable β-keto amide system in **2** with NaOMe/MeOH results in cleavage of the 11–22 bond to give nor-N_a-methylpleiocarpinilam (**4**), a member of the aspidofractinine group of indole alkaolids and one-half of the bis alkaloid pleiomutine (**5**).[7] While the hexacyclic alkaloid aspidofractinine (**6**) has been synthesized,[8] there is no literature that

Scheme I



describes any synthetic approaches to the more condensed kopsane alkaloids. Here is described the total synthesis of (±)-10,22-

† Department of Chemistry.
‡ Molecular Structure Center.

(1) Greshoff, M. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3537.
(2) Bhattacharya, A.; Chatterjee, A.; Rose, P. K. *J. Am. Chem. Soc.* **1949**, *71*, 3370. Bhattacharya, A. *Ibid.* **1953**, *75*, 381. Crow, W. D.; Michael, M. *Aust. J. Chem.* **1955**, *8*, 129. Bisset, N. G.; Crow, W. D.; Greet, Y. *Ibid.* **1958**, *11*, 388. Crow, W. D.; Michael, M. *Ibid.* **1962**, *15*, 130.
(3) Mukherjee, S. R.; Maiti, A.; Dey, P. K. *Nature (London)* **1957**, *180*, 916. Dey, P. K.; Chatterjee, M.; Chatterjee, A. *Indian J. Physiol. Allied Sci.* **1962**, *16* (3), 99; *Chem. Abstr.* **1962**, *60*, 8515. Bhattacharya, A. *Sci. Cult.* **1956**, *22*, 120.
(4) Kump, C.; Dugan, J. J.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 1237. Govindachari, T. R.; Nagarajan, K.; Schmid, H. *Ibid.* **1963**, *46*, 433. Kump, C.; Schmid, H. *Ibid.* **1962**, *45*, 1090. Structure of kopsine: Govindachari, T. R.; Pai, B. R.; Rajappa, S.; Viswanathan, N.; Kump, W. G.; Nagarajan, K.; Schmid, H. *Ibid.* **1962**, *45*, 1146; **1963**, *46*, 572.
(5) Achenbach, H.; Biemann, K. *J. Am. Chem. Soc.* **1965**, *87*, 4944. Djerassi, C.; Budzikiewicz, H.; Owellen, R. J.; Wilson, J. M.; Kump, W. G.; LeCount, D. J.; Battersby, A. R.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 742. Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Ibid.* **1964**, *47*, 1147. Schumann, D.; Bycroft, B. W. Schmid, H. *Experientia* **1964**, *20*, 202. Battersby, A. R.; Gregory, H. *J. Chem. Soc.* **1963**, *22*. Ferreira, J. M.; Gilbert, B.; Kitagawa, M.; Paes Leme, L. A.; Durham, L. J. *J. Chem. Soc. C* **1966**, 1260.

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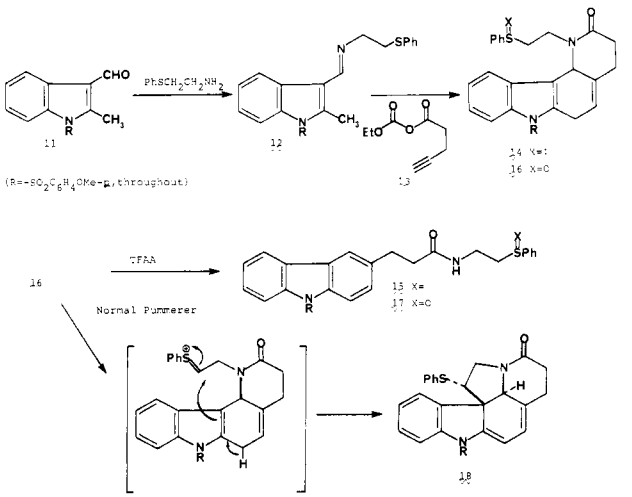
dioxokopsane (**2**) and (±)-kopsanone (**3**, X = O).[9]

Retrosynthetic Analysis. The key compound in the retrosynthetic analysis is the homoannular diene **7**, which should be readily synthesized by using the indole-2,3-quinodimethane strategy via the so-called exocyclic carbamate route[10] (Scheme I). Obviously allylation at C-11 is a very plausible way to introduce the necessary three-carbon bridge (carbons 22, 3, and 4). This leads to the retrosynthetic analysis requiring allylation at C-11 on the concave face of the homoannular diene **7** to give **8**. In principle **8** can undergo intramolecular [2 + 4] cycloaddition in two possible orientations. One leads to the kopsane ring structure **9** and makes a 5, 6-, and 7-membered ring, while the other makes three 6-membered rings, namely the fruticosane structure.[11] The former cyclization to give **9** is far more likely.

The synthesis of **8** presents two substantial problems. First, the construction of the homoannular diene portion and, second, the allylation at C-11 from what appears to be the more sterically encumbered face. A carbonyl group at C-10 (amide) could, in principle, enable epimerization at C-11 and under conditions of kinetic protonation force the C-11 allyl group into the concave face of the diene. A detailed analysis of the allylation at C-11 is described later.

Results

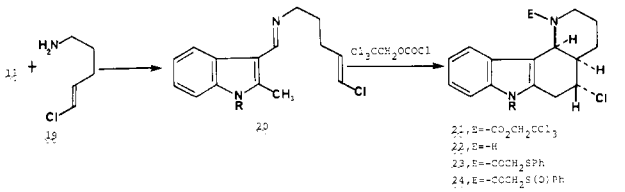
Indole-2,3-quinodimethane Portion. Synthesis of the Homoannular Diene 7. *N*-[(4-Methoxyphenyl)sulfonyl]-2-methylindole-3-carboxaldehyde (**11**)[13,10] was condensed with 2-(phenylthio)ethylamine and the resulting imine **12** treated with the mixed anhydride **13** (made from ethylchloroformate and 4-pentynoic acid) at 120 °C in chlorobenzene to give the 1,4-dihydrocarbazole **14** (37%). Higher temperatures resulted in large



amounts of 1,4-elimination to give **15**. Oxidation of **14** (MCPBA/CH_2Cl_2/0 °C) gave the diastereomeric sulfoxides **16** (>95%). Exposure of **16** to the conditions that have been very successfully used to make the C-11, C-12 bond,[10] namely, TFAA/CH_2Cl_2/0 °C (usually followed by heating to 130 °C in PhCl), immediately, even at −70 °C, resulted in acid-catalyzed 1,4-elimination to give **17**.[12] No trace of the homoannular diene **18** could be detected.

These results demonstrate that the order of events would benefit from being reversed. The C-11, C-12 bond must be made before the formation of the homoannular diene component. In this way the 1,4-elimination–aromatization would be blocked. A straightforward way of doing this is to conduct the indole-2,3-quinodimethane cyclization with a masked acetylene as the intramolecular cycloaddition trap.

(*E*)-1,3-Dichloropropene[14] was homologated to the amine **19** by standard methods and condensed with **11** to give the imine **20** (>98%), ν_{max} 1635 cm^{-1}. The imine **20** was treated with Cl_3CCH_2OCOCl (2.0 equiv/N-*i*-Pr_2Et/PhCl/120 °C to give the tetracyclic carbamate **21** (50%) after purification. The secondary

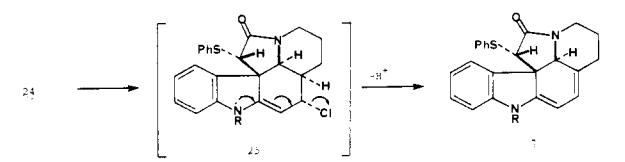


chlorine substituent is equatorial and cis to the adjacent methine proton. By way of contrast the (*Z*)-vinylchloroisomer gave the corresponding axial chloro isomer of **21** in very low yield (<5%). Removal of the 2,2,2-trichloroethyl group and concomitant decarboxylation by treatment of **21** with Zn/AcOH/THF/H_2O/20 °C gave the secondary amine **22** (90%). The secondary equatorial chlorine atom remains intact during the carbamate deprotection step. Acylation of the secondary amine **22** with (phenylthio)acetyl chloride gave the amide **23**, which was directly oxidized by using *m*-chloroperbenzoic acid to give the sulfoxides **24** (91%, from **22**) as a mixture of diastereomers.

When the sulfoxides **24** were treated with trifluoroacetic anhydride (2 equiv)/CH_2Cl_2/0 °C and the resulting solution was added to chlorobenzene at 135 °C, the homoannular diene **7** crystallized upon treatment with MeOH in 78% yield. The formation of the C-11, C-12 bond (**24** → **25**) must precede the elimination of HCl (**25** → **7**), since we know that the 1,4-dihydrocarbazole would result from prior elimination of HCl aromatizes (**16** → **17**, and also in the exocyclic carbamate series).[12]

It should be noted that the N_a atom is still able to use its lone pair of electrons. The indolic nitrogen is inductively deactivated, but not resonance wise. This statement is qualified by a number of single-crystal X-ray crystallographic studies,[10] which demonstrate that the $SO_2C_6H_4OMe$-*p* is not in the same plane as either of the adjacent π-system(s) (see also Figure 1) (11.14° out of plane).

The configuration at C-11 is based upon our previous experiences[10] with this reaction (confirmed by X-ray) and further evidence presented here. The diagnostic ^1H NMR spectrum with signals at δ 4.12 (1 H, s, C-11), 4.37 (1 H, s, C-19), 5.76 (1 H, d, *J* = 6 Hz), and 6.19 (1 H, d, *J* = 6 Hz) confirm the structural assignment for **7**. The diene system in **7** is severely skewed out



(6) Craven, B. M.; Gilbert, B.; Paes Leme, L. A. *Chem. Commun.* **1968**, 955. See also: Craven, B. M. *Acta Crystallogr., Sect. B* **1969**, *B25* (10), 2131.

(7) Thomas, D. W.; Achenbach, H.; Biemann, K. *J. Am. Chem. Soc.* **1966**, *88*, 1537. Kump, W. G.; Schmid, H. *Helv. Chim. Acta* **1961**, *44*, 1503. Hesse, M.; Bodmer, F.; Schmid, H. *Ibid.* **1966**, *49*, 964.

(8) Ban, Y.; Honma, Y.; Oishi, T. *Tetrahedron Lett.* **1976**, 1111. A biosynthetic route to the aspidofractinine alkaloids has been proposed: Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98. Experimental evidence for this proposal was provided: Schnoes, H. K.; Biemann, K. *Ibid.* **1964**, *86*, 5693. For a synthesis of 19-hydroxyaspidofractinine, see: Cartier, D.; Patigny, D.; Lévy, J. *Tetrahedron Lett.* **1982**, *23*, 1897.

(9) A preliminary communication describing part of this work has been published: Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086.

(10) For a complete account of the development of the indole-2,3-quinodimethane strategy and its application to the synthesis of aspidospermidine, see: Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739; Gallagher, T.; Magnus, P.; Huffman, J. C. *Ibid.* **1983**, *105*, 4750.

(11) The fruticosanes are heptacyclic indole alkaloids, isomeric with certain kopsanes: Battersby, A. R.; Byrne, J. C.; Gregory, H.; Popli, S. F. *Chem. Commun.* **1966**, 786. Guggisberg, A.; Hesse, M.; von Philipsborn, W.; Nagarajan, K.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 2321.

(12) Exon, C.; Gallagher, T.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1982**, 613.

(13) Gallagher, T.; Magnus, P. *Tetrahedron* **1981**, *37*, 3889.

(14) A mixture of (*E*)-/(*Z*)-1,3-dichloropropene is commercially available from Fluka and readily separated by fractional distillation. (*E*)-5-Chloro-4-entenoic acid: Dangyan, M. T.; Shakhnazaryan, G. M. *Izv. Akad. Nauk Arm. SSR* **1960**, *13*, 259; *Chem. Abstr.* **1961**, *55*, 20950*h*.

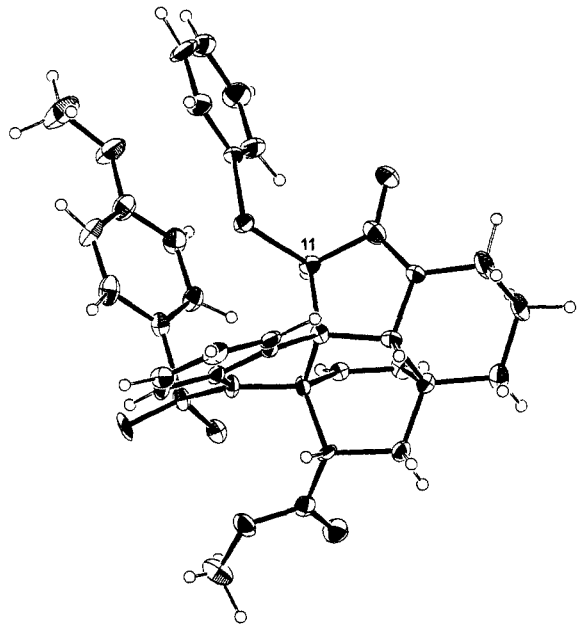


Figure 1. ORTEP plot of **27**.

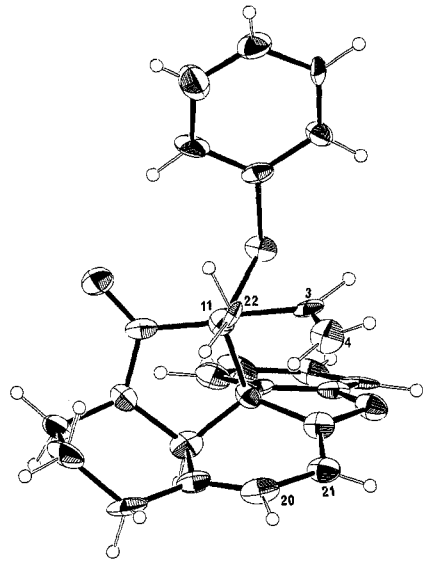


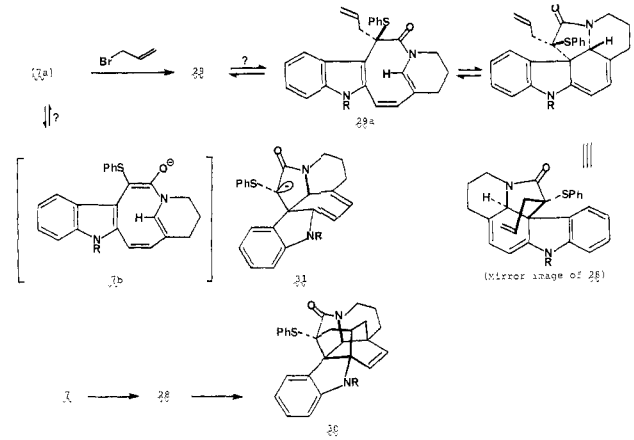
Figure 2. ORTEP plot of **28** with the *p*-$MeOC_6H_4SO_2$ group removed for clarity.

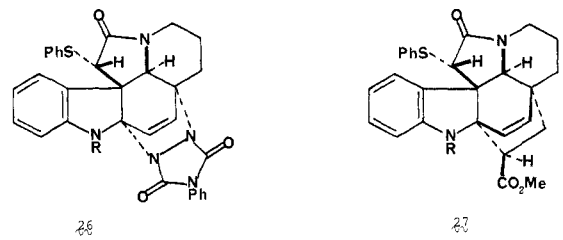
of plane with a dihedral angle between $C_{20}H$ and $C_{21}H$ of approximately 14°42′ (see Figure 2). With a short, straightforward route to **7** available (29.5% from **20**), we first examined its intermolecular [2 + 4] cycloaddition chemistry.

Ban[8] synthesized a similar homoannular diene during his important studies on the synthesis of aspidofractinine (**6**) and constructed the [2.2.2] system by reaction with nitroethylene followed by conversion to aspidofractinine itself. There is no definite evidence that the cycloaddition of nitroethylene had taken place from the exo face of the diene, since the subsequent degradation sequence to aspidofractinine (**6**) destroys any memory of the original exo/endo stereoselectivity. It is by no means a forgone conclusion that, for example, an acrylate derivative will add to **7** from the exo face. If the addition were from the endo face, then entry into the pleiocarpinilam series **4** would be direct.

The skewed homoannular diene **7** was rather unreactive toward dienophiles. We could not add dimethyl acetylenedicarboxylate or acrylate esters, although *N*-phenyltriazolinedione[15] gave the adduct **26** at 20 °C. Acryloyl chloride in toluene at 100 °C reacted cleanly with **7** to give the adduct **27** (workup with MeOH).

Scheme II

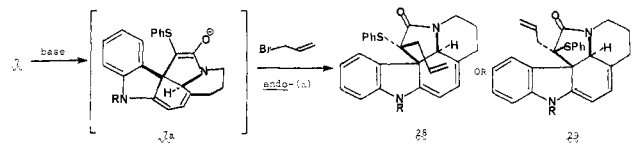




Its structure and relative stereochemistry was determined by single-crystal X-ray crystallography (Figure 1)[16] and shows that the [2 + 4] cycloaddition of acryloyl chloride takes place from the exo face. The relative configuration of the SPh group at C-11 is also unambiguously defined as β or exo.

Alkylation at C-11, Stereochemistry. The above results make it mandatory that the three carbons C-22, C-3, and C-4 are introduced in an intramolecular fashion as described in the retrosynthetic Scheme I. It is, of course, essential that the allyl group is on the concave face of the homoannular diene (**8** → **9**/**10**).

If treatment of **7** with an appropriate base results in a planar enolate species **7a**, it is not absolutely clear which face at C-11 is more accessible toward an allylating agent. Consequently, it was predicted that an epimeric mixture at C-11 would result, and both the required **28** and its C-11 epimer **29** would be formed.



There exists the intriguing possibility that **29** can be converted into the mirror image of **28** by sequence of cycloreversion–recyclization transformations. This sequence (Scheme II) inverts the configuration at both C-12 and C-19, which has the overall effect of turning the C-11 allyl group from the exo (β) face of the diene to the endo (α) face. The configuration at C-11 is not perturbed, provided an intermediate such as **7b** is not involved. Consequently this analysis might provide a pathway from **29** to **28** if the stereochemical outcome of the allylation at C-11 is

(15) Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *J. Chem. Soc. C* **1967**, 1905.

(16) Compound **27** crystallizes in space group *PT* with cell dimensions (at −164 °C) a = 18.835 (7) Å, b = 11.486 (3) Å, c = 9.273 (2) Å, α = 82.51 (2)°, β = 62.51 (1)°, γ = 62.49 (2)°, D_{calcd} = 1.413 for Z = 2. The θ–2θ scan technique, diffractometer, and data handling techniques have been described in detail elsewhere (Huffman, J. C.; Lewis, L. N.; Caulton, K. G. *Inorg. Chem.* **1980**, *19*, 2755–2762). The structure was solved by direct methods and Fourier techniques, and all atoms (including hydrogens) were refined by full-matrix least squares using 4558 observed (out of 5540 unique) data to final residuals of R_F = 0.068 and R_{wF} = 0.072. Complete crystallographic data are available as MSC Report 82047.[19]

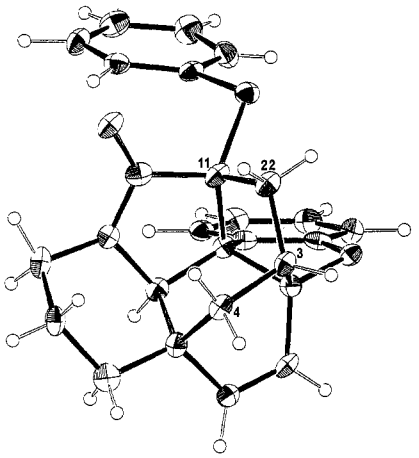


Figure 3. ORTEP plot of **30** with the *p*-$MeOC_6H_4SO_2$ group removed for clairty.

incorrect.[17] More important, this hypothesis can be readily tested in the chiral series, since the overall sequence results in inversion of absolute configuration of the skewed diene.

Treatment of **7** with $KN(SiMe_3)_2$/THF/0 °C followed by allyl bromide gave **28** in 89% yield after chromatography: ^1H NMR δ 4.70 (1 H, d, J = 17 Hz), 4.91 (1 H, d, J = 10 Hz), 5.73 (1 H, br d, J = 6 Hz), 7.25 (1 H, d, J = 6 Hz). The melting point of **28** is 158–160 °C followed by conversion to **30**, mp 234–235 °C: ^1H NMR δ 3.36 (1 H, s), 6.05 (1 H, d, J = 8 Hz), 6.11 (1 H, d, J = 8 Hz). Obviously ^1H NMR is not diagnostic, being subject to interpretation, and for the structures **28** and **30** only indicated the appropriate changes but not definitive structures. Consequently the structures of both **28** and **30** were elucidated by single-crystal X-ray crystallography, (Figures 2 and 3).[18,19]

The most practical way to make **30** is to heat a solution of **28** in benzene at 100 °C. In this way **30** was isolated in 81% yield.

The exclusive formation of the endo (α) C-11 allyl isomer requires explanation and/or rationalization. It could well be that the carbanion at C-11 is not a delocalized species such as **7a**, since delocalization of negative charge into the amide carbonyl group destroys the amide resonance (ca. 12–15 kcal mol^{-1}), whereas the gain from delocalization is about the same. Therefore the inductive effects of both the SPh and $CONR_2$ groups could be sufficient to stabilize the C-11 carbanion as a pyramidal species, **31**. The only way to discriminate between these various possibilities is to carry out the above transformations with chiral **7** and its C-11 phenylthio epimer.

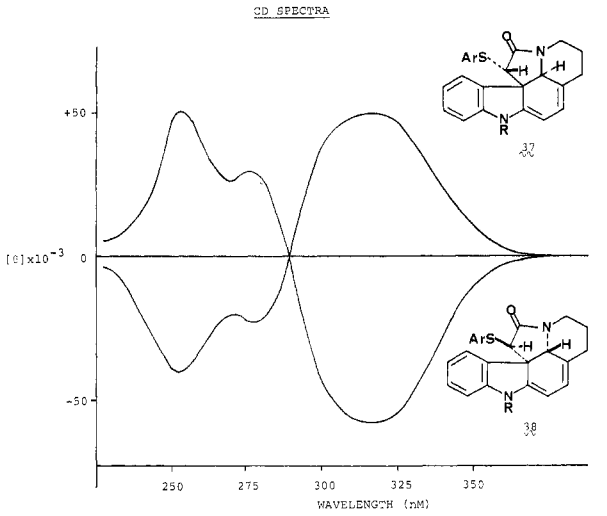


Figure 4.

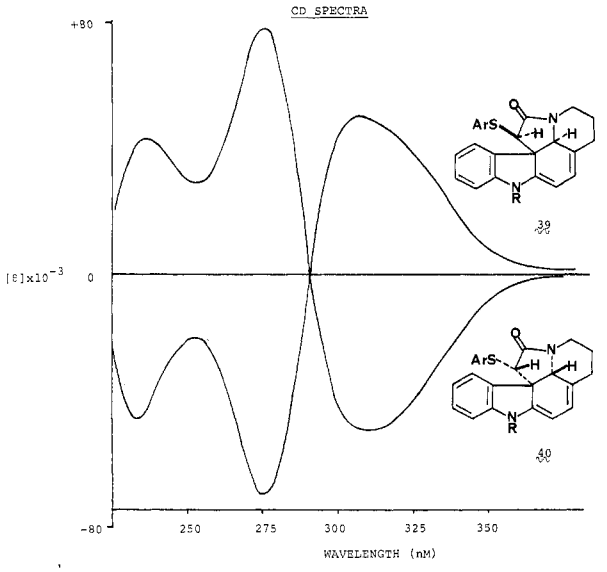


Figure 5.

Mechanistic Studies. The secondary amine **22** lends itself to optical resolution more conveniently than any other substrate in this series. Classical methods of diastereomeric salt formation (dibenzoyltartaric acid) failed. In principle the most efficient way to resolve **22** would be to use a chiral sulfoxide derivative of **24** that contains the C-10 and C-11 carbon atoms of the tryptamine bridge. In this way the resolving agent would be incorporated into the subsequent derivatives and not inefficiently discarded.

(*S*)-(−)-Menthol *p*-toluenesulfinate[20] (**32**) of optical purity 100%, $[\alpha]^{25}_{436}$ −433.5° (*c* 11.2, Me_2CO), was treated with methylmagnesium iodide to give (*R*)-(+)-*p*-tolyl methyl sulfoxide (**33**), with inversion of configuration at sulfur. Treatment of **33** with LDA/THF/0 °C followed by quenching of the resulting carbanion with carbon dioxide gave the required (*R*)-(+)-(*p*-tolylsulfinyl)acetic acid (**34**), $[\alpha]^{25}_D$ + 143.5° (*c* 33.0, Me_2CO).[21] The secondary amine **22** was coupled to **34** by using the modified carbodiimide reagent 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[22] to give a mixture of diastereomers **34** (47%), $[\alpha]^{25}_D$ +80.8° (*c* 11.2, $CHCl_3$), and **36** (47%), $[\alpha]^{25}_D$ +94.0° (*c* 11.6, $CHCl_3$). As expected the rotation of both

(17) While the diene/triene (**7**/**7b** and /or **29**/**29a**) interconversion exists as a formal possibility, with many literature analogies (see: Marvell, E. N. "Thermal Electrocyclic Reactions"; Academic Press: New York, 1980; pp 260–305), the energetics of such a process, by comparison with literature data, would suggest that at 25 °C the equilibrium would be overwhelmingly on the side of the diene and that cycloreversion would not occur. For example, cyclononatriene at room temperature (all-cis form) gave *cis*-bicyclo[4.3.0]-nonadiene: Vogel, E.; Grimme, W.; Dinne, E. *Tetrahedron Lett.* **1965**, 391. Glass, D. S.; Watthey, J. W. H.; Winstein, S. *Ibid.* **1965**, 377. Heating the homoannular diene **43** to 220 °C caused extensive decomposition with no evidence for cycloreversion, that is, epimerization at C-11. We are currently examining the photochemical cycloreversion possibility.

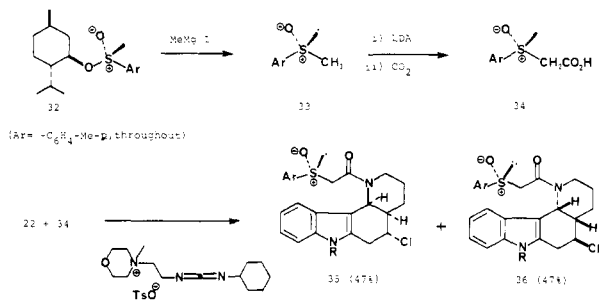
(18) Compound **28** crystallizes in space group $P2_1/n$ (alternate setting of $P2/c$) with cell dimensions (at −163 °C) of a = 15.064 (3) Å, b = 18.701 (4) Å, c = 9.851 (2) Å, β = 98.49 (1)°, D_{calcd} = 1.410 gm/cm^3 for Z = 4. Experimental details are as referenced in ref 16 for the θ–2θ scan technique. The structure was solved by direct methods and Fourier techniques, and all atoms, including hydrogens, were located and refined. Final residuals for the 2336 observed (out of 3602 unique) data are R_F = 0.091 and R_{wF} = 0.072. Complete crystallographic details are available[19] in MSC Report 82052.

(19) Compound **30** crystallizes in space group $P2_1/a$ with cell dimensions (at −163 °C) of a = 17.386 (10) Å, b = 12.079 (6) Å, c = 12.754 (6) Å, β = 95.21 (2)°, and D_{calcd} = 1.451 gm/cm^3 for Z = 4. The structure was solved by direct methods and Fourier techniques, and all atoms (including hydrogens) were refined. Final residuals are R_F = 0.053 and R_{wF} = 0.051 for the 2186 observed (out of 3501 unique) data. Complete crystallographic details are available in microfilm form only from the Indiana University Chemistry Library, Bloomington, IN 47405. Request MSC Report 82053.

(20) Phillips, H. *J. Chem. Soc.* **1925**, 2552.

(21) While esters of **34** have been used in asymmetric synthesis (see: Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H., *J. Am. Chem. Soc.* **1980**, *102*, 6613. Mioskowski, C.; Solladie, G., *Tetrahedron* **1980**, *36*, 227, the acid **34** has not been reported.

(22) Lin, L. J.; Foster, J. F., *Anal. Biochem.* **1975**, *63*, 485.



diastereomers was dominated by the chiral sulfoxide group attached to the C-10/C-11 tryptamine bridge.[23] The diastereomers **35** and **36** were readily separated by high-pressure liquid chromatography on silica gel. When the individual, separated, chiral diastereomers **35** and **36** were exposed to the usual Pummerer conditions, namely, TFAA/CH_2Cl_2/0 °C, then heated to 130 °C in chlorobenzene, the enantiomers **37** and **38** were formed in good yield (Figure 4). The circular dichroism curves confirm the conversion of diastereomers into enantiomers; the CD curves are mirror images. The Weiss[25] homoannular diene rule allows us to assign the absolute configuration of **37** as *S*, at C-19, drawn in its correct configuration. Interestingly, in both the above Pummerer reactions, we were able to isolate approximately 5% of the *p*-tolylthio epimers at C-11, namely, **39** and **40**. These epimers at C-11 were formed by acid-catalyzed epimerization at C-11% the kinetic product from the Pummerer reaction is the C-11, β epimer, prolonged (6 h) exposure of **37**/**38** to the TFAA/PhCl/120 °C resulted in the thermodynamic equilibration to give **39** and **40** (Figure 5).

There is apparently no steric problem with the epimerization of the SAr group to the endo face of the homoannular diene. We have in another context observed 11-epithioaryl compounds and confirmed the stereochemistry at C-11 by X-ray crystallography. For the C-11 epimers **37** and **39** the C-11 proton appears at δ 4.04 and 3.13, respectively.

Treatment of the chiral homoannular diene **37** with either $KN(SiMe_3)_2$/THF/0 °C/allyl bromide or LDA/THF/−70 °C/allyl bromide gave a single endo allyl isomer **41**, in the same enantiomeric series as the starting material **37** (CD curve is virtually identical). Furthermore the C-11 epimer **39** when exposed to the above allylation conditions gave exclusively the endo isomer **41**. Complete inversion at C-11 has taken place. These results exclude the cycloreversion–recyclization possibility (Scheme II) and a pyramidally stable carbanion. For amide enolates there is also the possibility of O-allylation followed by [3.3]-sigmatropic rearrangement (Scheme III). There seems to be no compelling reason why this process should be completely stereoselective. Likewise, there is the somewhat remote possibility of S-allylation followed by [2.3]-sigmatropic rearrangment (Scheme III). Treatment of **7** with LDA/THF/−70 °C/MeI gave a single C-11 methyl compound **43** assigned the endo methyl configuration at C-11 by analogy with the allylation stereochemistry. No C-11 methyl exo epimer could be detected (HPLC). This result excludes both the O- and S-allylation processes. Treatment of **7** with KO-*t*-Bu/HO-*t*-Bu/20 °C, with the intention of epimerizing at C-11, or LDA/THF followed by HOAc only gave the starting material **7**, with no indication of the C-11 epimer. This should be contrasted with the acid-catalyzed epimerization.

All of the above results are compatible with the carbanion at C-11 having a large orbital coefficient in the endo direction. The

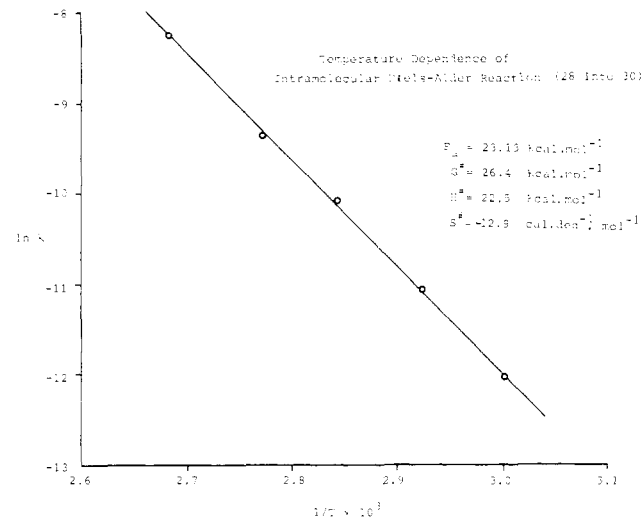
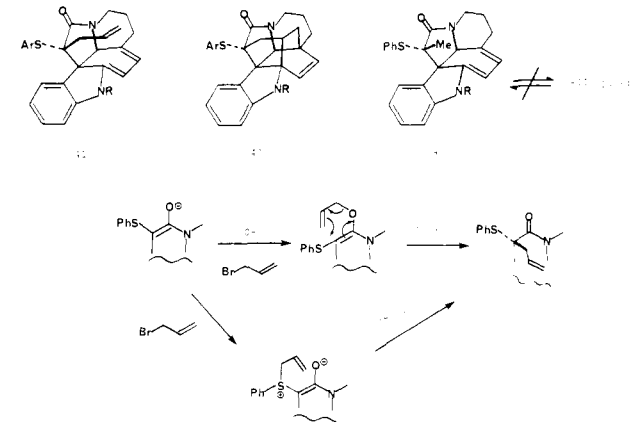
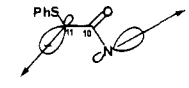


Figure 6.

Scheme III



most probable reason for this preference for charge polarization in the endo direction is that the dipole along the C-10, C-11 bond is minimized. The amide nitrogen lone pair is trans copolanar to the endo carbanion **44**. There are indications, particularly in



the β-lactam area, that alkylation of conformationally rigid amide enolates takes place from the face opposite the nitrogen lone pair.[24]

Another intriguing feature of this part of the synthesis is the [2 + 4] intramolecular cycloaddition of the endo allyl homoannular diene **28** into the basic kopsane structure **30**. None of the isomeric fruticosane (**10**) structure was detected. The activation energy and change in entropy associated with the conversion of **28** into **30** were measured. It requires very small amounts of molecular movement to convert **28** into **30**. In fact **28** is almost sitting in a transition-state conformation (see Figures 2 and 3).[26] The plot $1/T$ vs. ln K (Figure 6) through the temperature range 60–100 °C gave the data $\Delta S^{\ddagger}$ −12.93 cal mol^{-1} deg^{-1}, $\Delta G^{\ddagger}$ 26.37 kcal mol^{-1}, and $\Delta H^{\ddagger}$ 22.54 kcal mol^{-1}. The negative entropy change is smaller than that usually associated with an intramolecular [4 + 2] cycloaddition (ca. −15 to −18 cal mol^{-1} deg^{-1})[27] and must reflect the extremely small amount of reorganization that **28** needs

(23) Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 1958. Axelrod, M.; Bickart, P.; Jacobus, J.; Green, M. M.; Mislow, K. *Ibid.* **1968**, *90* 4835. Harpp, D. N.; Vines, S. M.; Montillier, J. P.; Chan, T. H. *J. Org. Chem.* **1976**, *41*, 3987.

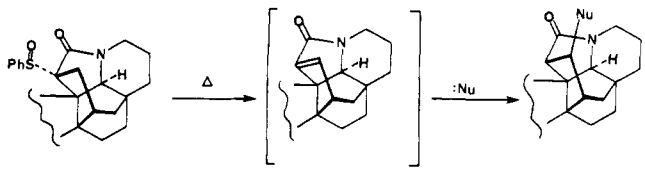
(24) This could be a manifestation of an antiperiplanar effect; see: Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: Oxford, 1983. Professor W. D. Ollis is acknowledged for suggesting that the amide nitrogen lone pair may be involved.

(25) Moscowitz, A.; Charney, E.; Weiss, U.; Ziffer, H. *J. Am. Chem. Soc.* **1961**, *83*, 4661.

(26) Murray-Rust, P.; Bürgi, H. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 921. Dunitz, J. D. "X-ray Analysis and the Structure or Organic Molecules"; Cornell University Press: Ithaca, NY, 1979; Chapter 7.

(27) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

Scheme IV

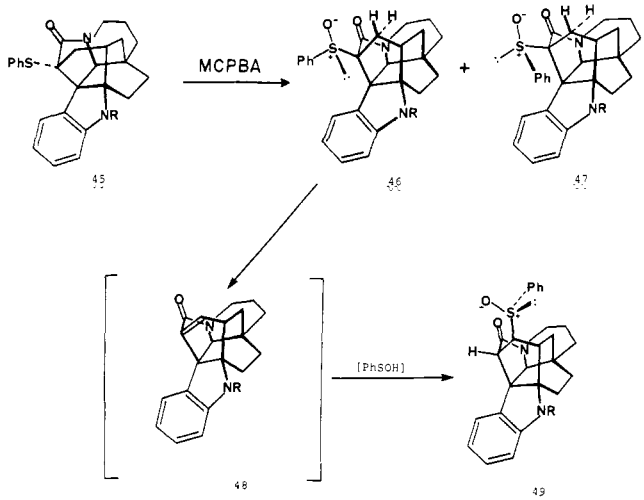


to arrive at the transition state for conversion into **30**. The activation energy is about average, as are $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$, reflecting the changes in hybridization late in the reaction profile.[28]

Anti-Bredt Strategy. The heptacyclic indole alkaloids 10,22-dioxokopsane (**2**) and kopsanone (**3**, X = O) have a carbonyl group at C-22. Attempts to incorporate an oxygen functionality at C-22 by treatment of **7** with LDA/THF/0 °C or −78 °C followed by quenching with either acrolein, acrylic anhydride, or acryloyl chloride gave **7** or a complex mixture. Thus all efforts to introduce the 22-oxygen substituent by acylation at C-11 failed. A solution to this problem is to transfer the oxidation level at C-11, namely, the phenylthio group, to C-22. In principle this can be achieved by an oxidation–elimination–addition (Scheme IV). To accomplish such a process would require the intervention of an anti-Bredt compound.

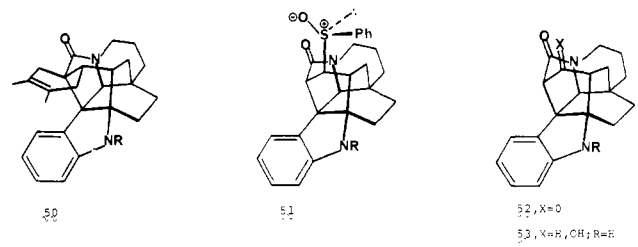
Reduction of the isolated double bond in **30** with diimide, generated in situ by treatment of $TsNHNH_2$ with NaOAc/EtOH[29] heated at reflux, gave **45** (95%). Oxidation of **45** using *m*-CPBA at −70 °C/CH_2Cl_2 gave a mixture of two diastereomeric sulfoxides **46** (68%) and **47** (19%). These assignments are based on the subsequent thermolysis reaction. Only one of the sulfoxides **46**/**47** can orientate the sulfur–oxygen bond in a syn-coplanar fashion to the β-hydrogen atom to undergo syn elimination.[30] The wrong enantiomer has to force the *S*-phenyl group into the indoline ring to achieve the correct conformation for the syn elimination of benzenesulfenic acid. A priori we had no way of unambiguously knowing whether the major or minor sulfoxide would lead to the torsionally strained α,β-unsaturated amide **48** or, if indeed, the syn elimination would take place at all.

The mixture of the sulfoxides **46**/**47** was heated in toluene, in a sealed tube, at 215 °C. The major sulfoxide, **46** (68%), disappeared and was replaced by a single new sulfoxide **49** (>95%,



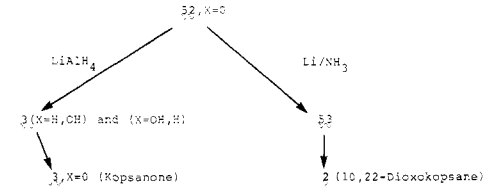
based on recovered **46**). The minor sulfoxide **47** (19%) (now assignable) was thermally stable to these severe thermolysis conditions and was recovered intact. Fortunately the minor sulfoxide was recyclable by reduction (TFAA/NaI)/acetone to **45** and reoxidation to **46** and **47**. The assignment of configuration for **49** is based on the cis addition of benzenesulfenic acid to the torsionally strained α,β-unsaturated amide **48**.[31] Conducting the sulfoxide elimination in the presence of thiophiles such as $P(OEt)_3$ or PhSH did not intercept the benzenesulfenic acid, and **49** was formed. Whereas thermolysis of **46** in 2,3-dimethylbutadiene at 230 °C gave none of the sulfoxide **49**, only the compound **50** formed by trapping the anti-Bredt compound **48**. Overall this unusual sequence transfers the PhS(O) group from C-11 to C-22, in the correct position to be converted into a carbonyl group. The extremely high temperature (215 °C) required for the syn elimination of benzenesulfenic acid sould be contrasted with the usual conditions (ca. 110–120 °C) and reflects the extremely torsionally strained nature of the unsaturated amide **48**.

When the sulfoxide **49** was treated with TFAA/CH_2Cl_2/20 °C, it was equilibriated to the epimeric sulfoxide **51** (**49** and **51** were reduced to the same sulfide), but on warming (PhCl) to 130 °C *N*-[(*p*-methoxyphenyl)sulfonyl]-10,22-dioxokopsane **52** was



isolated in 70% yield: IR ($CHCl_3$) 1758, 1685 cm^{-1}, confirming the presence of a cyclopentanone and amide, respectively.

Treatment of **52** with $LiAlH_4$/THF/67 °C gave epikopsanol (**3**, X = H, OH) and kopsanol (**3**, X = OH, X),[5] which were oxidized by using Me_2SO/1-cyclohexyl-3-(2-morphinoethyl)-carbodiimide metho-*p*-toluenesulfonate to give (±)-kopsanone (**3**, X = O) (66%). Similarly, treatment of **52** with Li/NH_3 gave epikopsanol 10-lactam **53** (X = H, OH) and kopsanol 10-lactam **53** (X = OH, H),[5] which were oxidized as above to (±)-10,22-dioxokopsane (**2**) (66%). Both **2** and **3** (X = O) were compared



with authentic samples (IR, ^1H NMR, MS, and TLC) kindly supplied by Professor Manfred Hesse from the collection of the late Professor Hans Schmid (Zurich). We have not yet converted the chiral heptacyclic kopsane system **42** into the optically active kopsanes themselves, but intend to do so in the course of the total synthesis of the dimeric indole alkaloid, pleiomutine (**5**).[32]

Summary

The synthesis of the kopsane alkaloids uses, in the early steps, the indole-2,3-quinodimethane strategy to construct the homoannular diene **7**. It is a measure of the efficiency of this strategy that, in six steps, a complicated, highly functionalized heterocyclic system can be assembled from simple indole precursors. Allylation of **7** at C-11 leading exclusively to the endo allyl compound **28** may provide a general stereoelectronic phenomenon. Namely,

(28) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.
(29) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555.
(30) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887 and references therein.
(31) For the syn addition of sulfenic acids to double bonds, see: Block, E. *J. Am. Chem. Soc.* **1972**, *94*, 642. Jones, D. N.; Lewton, D. A. *J. Chem. Soc., Chem. Commun.* **1974**, 457. The torsionally strained α,β-unsaturated amide **48** (anti-Bredt) would be expected to be extremely susceptible to nucleophilic addition. For a review of bridgehead olefins, see: Keese, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 528. House, H. O.; Outcalt, R. J.; Cliffton, M. D. *J. Org. Chem.* **1982**, *47*, 2413.
(32) We have currently converted optically active **37** into chiral **49** (as the *p*-tolyl sulfoxide) as part of the total synthesis of pleiomutine (**5**). This will be reported in the near future.

that in rigid cyclic amides alkylation of the derived enolate under kinetic conditions takes place from the face opposite the amide nitrogen lone pair of electrons. We are examining this possible phenomenon in simple amides, with and without the adjacent phenylthio group.

The unusual anti-Bredt strategy provides a unique sample in natural product chemistry to transfer the oxidation state from one carbon atom (C-11) to the adjacent carbon atom, through the intermediacy of the torsional strained α,β-unsaturated amide **48**. This type of strategy should, in a more general sense, provide a way to functionalize otherwise inaccessible sites.

The synthesis of (±)-10,22-dioxokopsane (**2**) starting from *N*-[(*p*-methoxyphenyl)sulfonyl)]-2-methyl-3-formylindole (**11**) takes 14 steps, proceeding in an overall yield of 5.8%.

Experimental Section

For general experimental protocol, see ref 10.

1,3,4,6,7,11c-Hexahydro-7-[(*p*-methoxyphenyl)sulfonyl]-1-[2-(phenylthio)ethyl]-2*H*-pyrido[3,2-*c*]carbazol-2-one (14) and Derived Sulfoxide 16. To a hot (135 °C) solution of imine **12** [prepared from aldehyde **11** (330 mg, 1 mmol)][10] in chlorobenzene (10 mL) was added over 2 h a solution of mixed anhydride **13** [prepared in the usual way from 4-pentynoic acid (196 mg, 2 mmol), triethylamine (200 mg, 2 mmol), and ethyl chloroformate (220 mg, 2 mmol)] in chlorobenzene (10 mL).[10] After an additional 30 min the solution was concetrated in vacuo, and hot methanol (ca. 10 mL) was added and the mixture rapidly heated to boiling. The product began to crystallize almost immediately to give **14** (220 mg, 37%) as colorless crystals: mp 164–165 °C; IR ($CHCl_3$) 1645, 1595, 1168 cm^{-1}; NMR ($CDCl_3$) δ 8.29 (1 H, J = 7 Hz), 7.75 (2 H, d, J = 10 Hz), 7.45–7.25 (3 H, m), 7.14–7.00 (3 H, m), 6.93–6.77 (4 H, m), 5.77 (1 H, br s), 5.32 (1 H, t, J = 8 Hz); 3.91 (2 H, m), 3.73 (4 H, br s), 3.00–2.57 (6 H, m), 2.32 (1 H, m). MS, *m/e* calcd for $C_{30}H_{28}N_2O_4S_2$ 544.150, found 544.149.

A rapidly stirred mixture of **14** (110 mg, 0.20 mmol) in CH_2Cl_2 (7 mL) and 10% aqueous $NaHCO_3$ (5 mL) was cooled to 0 °C, and a solution of *m*-chloroperoxybenzoic acid (55 mg 80–90% pure) in CH_2Cl_2 (4 mL) was added over 1 h. The reaction mixture was quenched by addition of 10% aqueous sodium bisulfite (5 mL). The organic layer was separated and dried ($MgSO_4$) to give after removal of solvent a quantitative yield of **16** as a colorless solid. The product was a 1:1 mixture of diastereoisomers as judged by TLC and NMR.

3-[*N*-((*p*-Methoxyphenyl)sulfonyl)carbazol-4-yl]-*N*-[2-(phenylthio)-1-ethyl]propionamide (15) and Derived Sulfoxide 17. A solution of **16** (110 mg, 0.196 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C under argon, and a saturated solution of HBr in CH_2Cl_2 was added in small portions, the reaction being followed by TLC. A rapid reaction took place to give two products by TLC. The mixture was quenched with 10% aqueous $NaHCO_3$ and the organic solution separated and dried (Na_2SO_4). Removal of solvent and purification of the residue by flash chromatography gave (i), on elution with 1:1 $CHCl_3$–petroleum ether, **15** (22 mg, 20%) as colorless crystals from $CHCl_3$–hexane (mp 109–111 °C; IR ($CHCl_3$) 3415, 1660, 1590, 1160 cm^{-1}; NMR ($CDCl_3$) δ 8.39–8.20 (2 H, m), 7.87 (1 H, d, J = 7 Hz), 7.79–7.70 (3 H, m), 7.52 (1 H, t, J = 7 Hz), 7.41–7.16 (7 H, m), 6.75 (2 H, d, J = 10 Hz), 5.79 (1 H, br), 3.68 (3 H, s), 3.43 (2 H, q, J = 9 Hz), 3.09 (2 H, t, J = 9 Hz), 2.95 (2 H, t, J = 9 Hz), 2.50 (2 H, t, J = 9 Hz); MS (no M^+ observed), *m/e* 235 (11%), 136 (100%)) and (ii), on elution with 9:1 EtOAc–MeOH **17** (66 mg, 60%) as colorless crystals from $CHCl_3$–hexane (mp 157–158 °C; IR ($CHCl_3$) 3410 (br, NH), 1660, 1595, 1160 cm^{-1}; NMR ($CDCl_3$) δ 8.39–8.23 (2 H, m), 7.87 (1 H, d, J = 7 Hz), 7.79–7.70 (3 H, m), 7.57–7.29 (7 H, m), 6.93 (1 H, br t, J = 9 Hz), 6.70 (2 H, d, J = 10 Hz), 3.77 (1 H, m), 3.64 (3 H, s), 3.50 (1 H, m), 3.14–3.00 (3 H, m), 2.70 (1 H, m), 2.55 (2 H, t, J = 9 Hz); MS (no M^+ ion observed), *m/e* 463 (10%), 434 (69%), 350 (30%)).

Sulfoxide **17** was the only observed product (TLC) when **14** was treated with (i) trifluoroacetic anhydride/CH_2Cl_2, (ii) $^+CPh_3BF_4^-$ and (iii) $CH_3OCO{\cdot}Cl$.

(*E*)-5-Chloro-4-pentenylamine (19). (*E*)-5-Chloro-4-pentenoic acid (mp 52–56 °C, bp 82–85 °C/(0.4 mmHg)) was prepared from (*E*)-1,3-dichloropropene and diethyl malonate by analogy to a literature procedure.[14]

(*E*)-5-Chloro-4-pentenoic acid (16 g, 0.12 mol) in CH_2Cl_2 (300 mL) was cooled to 0 °C and treated with triethylamine (12 g, 0.12 mol) followed, after 10 min, by freshly distilled ethyl chloroformate (13.1 g, 0.12 mol). The mixture was stirred at 0 °C for 1 h; then ice cold 0.88 ammonia solution (400 mL) was added. The mixture was stirred for 15 h. The dichloromethane layer was separated and dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue from $CHCl_3$–petroleum ether gave (*E*)-5-chloro-4-pentenamide (8.0 g, 63% based on recovered acid, unreacted carboxylic acid was recovered from the mother liquors by base extraction/acidification): mp 98–99 °C; IR (Nujol) 3350, 3180, 1660, 1630 cm^{-1}; NMR ($CDCl_3$) δ 6.25–5.64 (4 H, m), 2.48–2.27 (4 H, m). Anal. Calcd for C_5H_8ClNO: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.08; H, 6.25; N, 10.58. To a stirred slurry of lithium aluminum hydride (4.2 g, 0.11 mol) in dry ether (50 mL) was added a solution of (*E*)-5-chloro-4-pentenamide (9.3 g, 0.07 mol) in ether (500 mL). The mixture was stirred for 15 h at 20 °C and cooled to 0 °C, and water (15.5 mL) was cautiously added. The mixture was filtered, the solids washed with ether, and the filtrate washed with brine and dried (Na_2SO_4). The solvent was carefully distilled at atmospheric pressure. When the volume was approximately 20 mL the residue was distilled through a short-path apparatus to give (*E*)-5-chloro-4-pentenylamine (5.6 g, 67%): bp 162–165 °C; IR (thin film) 3460, 3390, 1625, 930 cm^{-1}; NMR ($CDCl_3$) δ 6.05–2.86 (2 H, m), 2.74 (2 H, t, J = 7 Hz), 2.13 (2 H, m), 1.61 (2 H, q, J = 7 H), 1.07 (2 H, s, NH_2).

(*E*)-1-[(*p*-Methoxyphenyl)sulfonyl]-2-methyl-3-[*N*-((*E*)-5-chloro-4-penten-1-yl)formimidoyl]indole (20). A solution of **11** (6.6 g, 20 mmol) in CH_2Cl_2 (150 mL) was treated with **19** (2.6 g, 22 mmol). After 30 min freshly activated 4-Å molecular sieves (ca. 20 g) were added, and the mixture was stirred for 15 h. The mixture was filtered and the filtrate concentrated in vacuo to give imine **20** (8.5 g, 98%) as a colorless oil:[10] IR ($CHCl_3$) 1635, 1168 cm^{-1}; NMR ($CDCl_3$) δ 8.53 (1 H, s), 8.43–8.12 (2 H, m), 7.75 (2 H, d, J = 10 Hz), 7.42–7.20 (2 H, m), 6.81 (2 H, d, J = 10 Hz), 6.00–5.85 (2 H, m), 3.70 (3 H, s), 3.60 (2 H, t, J = 7 Hz), 2.74 (3 H, s), 2.40–1.60 (4 H, m). Used directly in the next step.

2,2,2-Trichloroethyl *cis*-2,3,4,4a,5,6,7,11c-Octahydro-5α-chloro-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole-1-carboxylate (21, E = $-CO_2CH_2CCl_3$). A solution of imine **20** [prepared from aldehyde **11** (825 mg, 2.5 mmol)] in chlorobenzene (25 mL) was cooled to 0 °C and treated with diisopropylethylamine (650 mg, 876 μL, 5 mmol) followed by freshly distilled 2,2,2-trichloroethyl chloroformate (1.06 g, 725 μL, 5 mmol).

The mixture was allowed to warm to room temperature and then heated to 120–122 °C (bath temperature) over the course of 40 min.

After 3 h at this temperature 2,2,2-trichloroethyl chloroformate (365 μL, 2.5 mmol) was added, after a total of 7 h at 120–122 °C the mixture was cooled to room temperature, and diisopropylamine (438 μL, 2.5 mmol) and 2,2,2-trichloroethyl chloroformate (363 μL, 2.5 mmol) were added. The mixture was then heated at 120–122 °C for an additional 1 h (total heating time 8 h). The mixture was concentrated in vacuo, and purification by flash chromatography gave, on elution with chloroform–petroleum ether (1:4) **21** (750 mg, 50%) as a pale yellow foam.

In another experiment (same scale) **21** was obtained in 42% yield by direct crystallization. After removal of the solvent in vacuo the resulting dark oil was taken up in hot methanol (ca. 40 mL) and heated to boiling. The product began to crystallize almost immediately to give **21** as colorless crystals: mp 191–193 °C; IR ($CHCl_3$) 1710, 1595, 1165 cm^{-1}; NMR ($CDCl_3$) δ 8.16 (1 H, d, J = 9 Hz), 7.77–7.66 (2 H, m), 7.45–7.11 (3 H, m), 6.95–6.84 (2 H, m), 6.07 and 6.00 (1 H, two broad singlets due to amide resonance), 5.14, 4.73 and 5.00, 4.87 (two AB quartets, J = 12 Hz Cl_3CCH_2, amide resonance resulting in two sets of signals), 4.48 (1 H, br s), 4.16 (1 H, m), 3.77 (3 H, s), 3.64–3.55 (2 H, m), 2.59–2.29 (2 H, m), 1.79–1.50 (3 H, m), 1.34 (1 H, m). Anal. Calcd for $C_{25}H_{24}Cl_4N_2O_5S$: C, 49.47; H, 3.99; N, 4.62. Found: C, 49.23; H, 4.07; N, 4.51.

***cis*-2,3,4,4a,5,6,7,11c-Octahydro-5α-chloro-7-[(*p*-methoxyphenyl)-sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole (22, E = H).** A solution of carbamate **21** (850 mg, 1.4 mmol) in THF (40 mL), water (8 mL), and glacial acetic acid (8 mL) was treated with zinc dust (325 mg, 5 mmol) over 1 h. The mixture was stirred for an additional 2 h, then concentrated in vacuo to ca. 10 mL, and diluted with water (120 mL) and 1 N NaOH (90 mL), and the product was extracted with dichloromethane (3 × 25 mL). The extracts were washed with brine and dried (An_2SO_4). Removal of the solvent gave a pale yellow solid. Methanol (20 mL) was added, and, after boiling, the mixture was allowed to cool in a refrigerator overnight to give **22** as colorless crystals (545 mg, 90%).

An analytical sample was recrystallized from ethyl acetate–petroleum ether: mp 207–209 °C; IR ($CHCl_3$) 1592, 1162 cm^{-1}; NMR ($CDCl_3$) δ 8.18 (1 H, d, J = 9 Hz), 7.77 (2 H, d, J = 10 Hz), 7.61 (1 H, br s), 7.36–7.18 (2 H, m), 6.91 (2 H, d, J = 10 Hz), 4.73 (1 H, m), 4.25 (1 H, br s), 3.86 (1 H, m), 3.79 (3 H, s), 3.32 (1 H, m), 2.95–2.77 (2 H, m), 2.23 (1 H, br), 2.07 (1 H, m), 1.77–1.43 (4 H, m). Anal. Calcd for $C_{22}H_{23}ClN_2O_3S$: C, 61.31; H, 5.38; N, 6.50. Found: C, 60.97; H, 5.37; N, 6.46.

***cis*-1-[(Thiophenyl)acetyl]-2,3,4,4a,5,6,7,11c-octahydro-5α-chloro-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole (23, E = $-COCH_2SPh$) and the Derived Sulfoxide 24 [E = $-COCH_2S(O)Ph$].** A solution of amine **22** (782 mg, 1.82 mmol) in CH_2Cl_2 (50 mL) and 1 N NaOH (50 mL) was cooled to 0 °C, and a solution of (phenylthio)acetyl

chloride (384 mg, 2.18 mmol) in CH_2Cl_2 (10 mL) was slowly added with rapid stirring.

After 15 min the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 25 mL). The combined extracts were dried (Na_2SO_4), and evaporation of the solvent gave a quantitative yield of **23** as a colorless foam: IR ($CHCl_3$) 1636, 1595, 1164 cm^{-1}; NMR ($CDCl_3$) 8.14 (1 H, m), 7.79–7.64 (2 H, m), 7.57–7.43 (2 H, m), 7.39–6.98 (6 H, m), 6.93–6.77 (2 H, m), 6.39 and 5.59 (1 H, comprising two broad singlets), 4.59–4.41 (2 H, m), 4.11–3.86 (2 H, m), 3.75 (3 H, s), 3.64–3.50 (2 H, m), 2.79–2.11 (2 H, m), 1.77–1.16 (4 H, m); MS, *m/e* calcd for $C_{30}H_{29}ClN_2O_4S_2$ 580.125, found 580.127.

A solution of amide **23** (1.86 g, 3.2 mmol) in CH_2Cl_2 (100 mL) and 10% aqueous sodium bicarbonate (75 mL) was cooled to 0 °C, and a solution of 3-chloroperoxybenzoic acid (722 mg, 80–90% pure) in CH_2Cl_2 (10 mL) was added over 2 h.

The organic phase was then separated and the aqueous phase extracted with CH_2Cl_2 (20 mL). The combined extracts were dried (Na_2SO_4), and removal of solvent gave a quantitative yield of **24** as a colorless foam. Both TLC and ^1H NMR analysis indicated that **24** was a 1:1 mixture of diastereoisomers. This mixture was used directly in the next step.

2,3,4,5-Tetradehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-20,21-dinoraspidospermidin-10-one (7). An ice-cold solution of sulfoxides **24** (1.91 g, 3.2 mmol) in CH_2Cl_2 (50 mL) was treated with trifluoroacetic anhydride (0.93 mL). After 15 min at 0 °C chlorobenzene (40 mL) was added, and the mixture was heated to 135 °C over 30 min. During this time the dichloromethane was allowed to boil out of the reaction mixture in a stream of dry argon. The mixture was heated at 135 °C for ca. 2.5 h. The solvent was removed in vacuo, and the dark residue was treated with hot methanol (ca. 80 mL). The methanolic solution was rapidly brought to boiling and the product began to crystallize almost immediately to give **7** (1.36 g, 78%) as a colorless solid, mp 225–227 °C dec. An analytical sample was recrystallized from ethyl acetate: mp 227–229 °C dec; IR ($CHCl_3$) 1690, 1595, 1258 cm^{-1}; NMR ($CDCl_3$) 7.85–7.80 (3 H, m), 7.37 (1 H, t, J = 7 Hz), 7.24–7.13 (6 H, m), 7.02 (1 H, t, J = 7 Hz), 6.75 (2 H, d, J = 10 Hz), 6.19 (1 H, d, J = 6 Hz), 5.76 (1 H, d, J = 6 Hz), 4.37 (1 H, s), 4.32 (1 H, dd, J = 13, 5 Hz), 4.12 (1 H, s), 3.68 (3 H, s), 2.95 (1 H, dt, J = 13, 3 Hz), 2.52 (1 H, d, J = 14 Hz), 2.17 (1 H, m), 1.79 (1 H, d, J = 15 Hz), 1.62 (1 H, m); λ_{max} (CH_3CN) 327 (ε 3510), 278 (9840), 247 (19340), 228 (15920). Anal. Calcd for $C_{30}H_{26}N_2O_4S_2$: C, 66.39; H, 4.83; N, 5.16. Found: C, 66.16; H, 4.70; N, 4.88.

***N*-Phenyltriazolinedione Adduct 26 and the Acryloyl Adduct 27.** A solution of **7** (54 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) was treated with acryloyl chloride (300 μL), and the mixture was heated in a resealable tube at 110 °C for 20 h. Methanol (4 mL) was then added and the mixture boiled. After cooling, removal of solvent followed by purification by PLC (3:2 EtOAc–petroleum ether) gave **27** (40 mg, 65%): mp 261–262 °C (EtOAc–petroleum ether); IR ($CHCl_3$, 1730, 1688 cm^{-1}; NMR ($CDCl_3$) δ 7.94 (1 H, d, J = 8 Hz), 7.82 (2 H, d, J = 10 Hz), 7.42 (1 H, t, J = 7 Hz), 7.13–6.98 (5 H, m), 7.08 (1 H, d, J = 9 Hz), 6.72–6.06 (2 H, m), 6.64 (2 H, d, J = 10 Hz), 6.15 (1 H, d, J = 9 Hz), 4.15 (1 H, m), 3.87 (1 H, s), 3.76 (3 H, s), 3.53 (1 H, s), 3.05 (1 H, dd, J = 9, 6 Hz), 2.76 (1 H, dd, J = 12, 4 Hz), 2.14 (1 H, d, J = 12 Hz), 1.81 (1 H, dd, J = 13, 5 Hz), 1.74–1.44 (4 H, m). Anal. Calcd for $C_{34}H_{32}N_2O_6S_2$: C, 64.95; H, 5.13; N, 4.45. Found: C, 64.71; H, 5.37; N, 4.29.

4-Phenyl-Δ^1-1,2,4-triazoline-3,5-dione in CH_2Cl_2 reacted immediately with **7** to give an adduct **26** as colorless crystals, mp 226–228 °C dec (CH_2Cl_2–MeOH).

2,3,4,5-Tetradehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-11α-(prop-2-en-1-yl)-20,21-dinoraspidospermidin-10-one (28). An ice-cold solution of diene **7** (1.49 g, 2.75 mmol) in THF (130 mL) was treated with a solution of potassium hexamethyldisilazide in THF [prepared from KH (1.36 g, 22% slurry in oil), hexamethyldisilazane (6.25 mL) in THF (20 mL)].

The solution was stirred at 0 °C for 20 min, and then allyl bromide (6 mL, freshly distilled from P_2O_5) was added. Rapidly a precipitate (KBr) formed. The mixture was stirred at 0 °C for 10 min after which time saturated aqueous NH_4Cl (50 mL) and water (50 mL) were added.

The product was extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine and dried (Na_2SO_4).

Removal of solvent and purification of the residue by flash chromatography gave, on elution with $CHCl_3$–petroleum ether (1:4), **28** (1.42 g, 89%) as a colorless foam.

An analytical sample was crystallized from methanol: mp 158–160 °C; IR ($CHCl_3$) 1687, 1595, 1160 cm^{-1}; NMR ($CDCl_3$) δ 7.98 (2 H, d, J = 10 Hz), 7.79 (1 H, d, J = 8 Hz), 7.32–6.91 (8 H, m), 7.84 (1 H, d, J = 7 Hz), 7.61 (1 H, t, J = 7 Hz), 7.25 (1 H, d, J = 6 Hz), 5.91 (1 H, m), 5.73 (1 H, br d, J = 6 Hz), 4.91 (1 H, d, J = 10 Hz), 4.70 (1 H, d, J = 17 Hz), 4.64 (1 H, br s), 4.59 (1 H, m), 3.79 (3 H, s), 3.02–2.82 (2 H, m), 2.64–2.41 (2 H, m), 2.14 (1 H, m), 1.82 (1 H, m), 1.52 (1 H, m). Anal. Calcd for $C_{33}H_{30}N_2O_4S_2$: C, 68.01; H, 5.19; N, 4.81. Found: C, 68.30; H, 5.23; N, 4.83.

20,21-Didehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(phenylthio)-kopsan-10-one (30). A solution of allylated diene **28** (470 mg, 0.81 mmol) in benzene (40 mL) was heated in a resealable tube at 95–100 °C for 4 h. This reaction was repeated twice; i.e., total amount of **28** (1.41 g, 2.42 mmol) and the benzene solutions from all three runs were combined. Removal of solvent and purification by flash chromatography gave, on elution with $CHCl_3$–petroleum ether (2:3), **30** (1.14 g, 81%) as a colorless foam. An analytical sample was crystallized from ethyl acetate–hexane: mp 234–235 °C; IR ($CHCl_3$) 1688, 1594 cm^{-1}; NMR ($CDCl_3$) δ 8.02 (2 H, d, J = 10 Hz), 7.55 (1 H, d, J = 8 Hz), 7.34–7.00 (8 H, m), 6.91–6.73 (2 H, m), 6.11 (1 H, d, J = 8 Hz), 6.05 (1 H, d, J = 8 Hz), 4.25 (1 H, m), 3.86 (3 H, s), 3.36 (1 H, s), 3.11 (1 H, m), 2.91 (1 H, m), 2.34–2.16 (2 H, m), 1.98–1.36 (6 H, m); λ_{max} 260 (ε 10460), 234 (16530) 220 (14590) (CH_3CN). Anal. Calcd for $C_{33}H_{30}N_2O_4S_2$: C, 68.01; H, 5.19; N, 4.81. Found: C, 68.26; H, 5.36; N, 4.69.

It was also observed (TLC) that **28** was converted cleanly to **30** simply by melting in a capillary tube.

1-[(*p*-Methoxyphenyl)sulfonyl]-11β-(phenylthio)kopsan-10-one (45). A solution of **30** (1.14 g, 1.96 mmol) in 1:1 THF/H_2O (60 mL) and *p*-toluenesulfonyl hydrazide (4.52 g) was heated to reflux, and over the course of 4 h a solution of sodium acetate (3.3 g) in H_2O (15 mL) was added. Heating was continued for an additional hour.

The mixture was then concentrated to ca. 10 mL, saturated aqueous NH_4Cl (40 mL) and water (20 mL) were added, and the product was extracted with dichloromethane (4 × 30 mL). The combined extracts were washed with 2 N NaOH (2 × 20 mL) and dried (Na_2SO_4). Removal of solvent and purification of the residue by flash chromatography gave, on elution with $CHCl_3$–petroleum ether (2:3), **45** (1.13 g, 99%) as a colorless foam. An analytical sample was crystallized from EtOAc–petroleum ether: mp 213–214.5 °C. IR ($CHCl_3$) 1684, 1593 cm^{-1}; NMR ($CDCl_3$) δ 8.02 (2 H, d, J = 10 Hz), 7.50 (1 H, d, J = 8 Hz), 7.34–6.86 (10 H, m), 4.11 (1 H, dd, J = 14, 5 Hz), 3.86 (3 H, s), 3.57 (1 H, s), 3.36 (1 H, m), 2.87 (1 H, m), 2.61 (1 H, m), 2.34–2.11 (2 H, m), 1.91–1.18 (9 H, m). Anal. Calcd for $C_{33}H_{32}N_2O_4S_2$: C, 67.78; H, 5.52; N, 4.79. Found: C, 67.49; H, 5.44; N, 4.79.

1-[(*p*-Methoxyphenyl)sulfonyl]-11β-[phenyl-(*R-rel*)-sulfinyl]kopsan-10-one (46) and Its Sulfinyl Epimer, 47. A solution of **45** (500 mg, 0.856 mmol) in CH_2Cl_2 (3.0 mL) was cooled to −78 °C, and a solution of 3-chloroperoxybenzoic acid (208 mg, 80–90% pure) in CH_2Cl_2 (10 mL) was added over 1.5 h. After this time 10% aqueous $NaHCO_3$ (35 mL) was added and the mixture warmed to room temperature with rapid stirring. The organic phase was then separated and dried (Na_2SO_4). Removal of solvent followed by flash chromatography gave the following:

(i) **46** (347 mg, 68%) mp 205–207 °C (EtOAc–hexane); NMR ($CDCl_3$) δ 8.20 (2 H, d, J = 10 Hz), 7.50–7.02 (11 H, m), 4.05 (1 H, m), 3.86 (3 H, s), 3.66 (1 H, s), 3.50 (1 H, dd, J = 9, 5 Hz), 3.00–2.64 (3 H, m), 1.95 (1 H, m), 1.75–1.23 (9 H, m); MS *m/e* calcd for $C_{33}H_{32}N_2O_5S_2$ 600.175, found 600.176.

(ii) **47** (95 mg, 19%) mp 248–250 °C (EtOAc); NMR ($CDCl_3$) δ 8.02 (2 H, d, J = 10 Hz), 7.68–7.05 (11 H, m), 4.25 (1 H, m), 3.91 (3 H, s), 3.66 (1 H, s), 3.34 (1 H, m), 2.86 (1 H, m), 2.55 (1 H, m), 2.07–1.20 11 H, m); *m/e* MS, calcd for $C_{33}H_{32}N_2O_5S_2$ 600.175, found 600.176.

Sulfoxide **47** was recycled by quantitative reduction back to **45** (trifluoroacetic anhydride/sodium iodide/acetone) followed by reoxidation using the above procedure.

1-[(*p*-Methoxyphenyl)sulfonyl]-22β-[phenyl-(*S-rel*)-sulfinyl]kopsan-10-one (49) and the Adduct 50. A solution of **46** (100 mg, 0.167 mmol) in dry toluene (5 mL) was heated in a resealable tube at ca. 215 °C for 1.25 h. Removal of solvent followed by flash chromatography gave **46** (12 mg) and **49** (55 mg 55%, 67% based on recovered **46**, which was recycled): mp 271–272 °C (EtOAc); IR ($CHCl_3$) 1682, 1595 cm^{-1}; NMR ($CDCl_3$) δ 8.11–8.03 (4 H, m), 7.56–7.50 (3 H, m), 7.28–7.16 (2 H, m), 7.04 (1 H, t, J = 7 Hz), 6.96 (2 H, d, J = 10 Hz), 4.19 (1 H, dd, J = 13, 5 Hz), 3.85 (3 H, s), 3.59 (1 H, s), 3.46 (1 H, s), 3.37 (1 H, d, J = 10 Hz), 3.22 (1 H, s), 2.82 (1 H, m), 2.22 (1 H, m), 1.78–1.16 (9 H, m); MS, *m/e* calcd for $C_{33}H_{32}N_2O_5S_2$ 600.175, found 600.173.

In the above reaction, lower yields of **49** were obtained if the reaction was allowed to proceed until all trace of **46** was lost.

In a separate experiment the mixture of sulfoxides **46** and **47** was subjected to thermolysis. Again the best yield was obtained by not allowing the thermolysis to go to completion. In this case, a virtually quantitative yield of **49** was observed (for ca. 66% conversion of **46** to **49**). In another experiment a solution of **46** (10 mg) in 2,3-dimethylbuta-1,3-diene (2 mL) was heated at 220 °C in a sealed tube for 2 h. Removal of the solvent and purification of the residue using 1:2 Et-

OAc/hexane as eluant afforded **50** as a gum (3.3 mg, 36%): NMR ($CDCl_3$) δ 8.10–6.90 (8 H, m), 4.23 (1 H, m), 3.87 (3 H, s), 3.50 (2 H, m), 3.26 (2 H, d), 2.77 (2 H, dt), 2.63 (2 H, br t), 2.18 (6 H, m), 2.00–1.20 (10 H, m); MS, *m/e* calcd. for $C_{33}H_{36}N_2O_4S$ (M^+) 556.2395, found 556.2371, calcd for $C_{26}H_{29}N_2O$ ($M^+ - SO_2C_6H_4OMe$) 385.2279, found 385.2277.

1-[(*p*-Methoxyphenyl)sulfonyl]-10,22-dioxokopsane (52). A solution of **49** (75 mg, 0.125 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C and trifluoroacetic anhydride (200 μL) was added. After 10 min chlorobenzene (10 mL) was added and the solution heated to 135 °C during which time the CH_2Cl_2 was allowed to boil out in a stream of argon. After 20 min TLC indicated a mixture (ca. 1:1) of **49** and a slightly more polar product, shown to be **51** (see below). The reaction mixture was cooled to ca. 80 °C, and trifluoroacetic anhydride (400 μL) was added and heating (135 °C) resumed. Complete conversion of both **49** and **51** to a less polar product was observed within a few minutes. The solution was cooled, 10% aqueous $NaHCO_3$ (10 mL) was added, and the mixture was rapidly stirred for 45 min. CH_2Cl_2 (10 mL) was added, the organic layer separated, and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried (Na_2SO_4), and after removal of the solvent, purification of the residue by PLC (1:1 EtOAc–petroleum ether) gave **52** (43 mg, 70%) as a colorless foam. A sample was recrystallized from methanol: mp 173–175 °C; IR ($CHCl_3$) 1758, 1685, 1595 cm^{-1}; NMR ($CDCl_3$) δ 7.86 (2 H, d, *J* = 10 Hz), 7.34–7.16 (3 H, m), 7.09–6.93 (3 H, m), 4.23 (1 H, m), 3.91 (1 H, m), 3.86 (3 H, s), 3.82 (1 H, s), 2.93 (1 H, m), 2.64 (1 H, m), 2.00 (1 H, m), 1.86–1.34 (8 H, m); MS, *m/e* calcd for $C_{27}H_{26}N_2O_5S$ 490.156, found 490.156.

In a separate experiment **49** was treated with TFAA/CH_2Cl_2 at 20 °C for 2 h to give a mixture of **49** and **51** from which **51** was isolated as a colorless solid in 30% yield: NMR ($CDCl_3$) 4.16 (1 H, d, *J* = 10 Hz), 4.00 (1 H, dd, *J* = 13, 5 Hz), 4.52 (1 H, s), 3.25 (1 H, d, *J* = 2.5 Hz), 2.75 (1 H, m), 2.51 (1 H, m), 1.18 (1 H, s).

Other experimental evidence in support of the assignment of **51** included (i) oxidation of both **49** and **51** separately using MCPBA to the same sulfone (by TLC) and (ii) reduction of **49** and **51**, using TFAA/NaI/acetone to the same sulfide (again by TLC).

(±)-10,22-Dioxokopsane (2). A solution of **52** (30 mg, 0.06 mmol) in THF (3 mL) was added to liquid ammonia (5 mL, distilled from sodium) at −33 °C. Clean lithium wire (3 × ca. 1-mm sections) was added, and after 10 min a blue color formed. The mixture was then cooled to −78 °C and stirred for an additional 5 min. Solid ammonium acetate was added whereupon the blue color was immediately discharged. Water (5 mL) was added and after warming to room temperature the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined extracts were dried (Na_2SO_4) and purification by PLC (3:97 MeOH: EtOAc) gave two isomeric alcohols: (i) kopsanol 10-lactam **53** (13 mg, 66%) as a colorless glass and (ii) epikopsanol 10-lactam **53** (5.2 mg, 25%) as a colorless glass, assigned on the basis of the multiplicity of protons at C-11, C-22, and C-3 as described by Gilbert et al.[5] (**53**, X = H, OH; R = H, epimers).

(±)-Kopsanol 10-lactam **53** (8 mg, 0.016 mmol) in benzene (1 mL) and Me_2SO (400 μL) was cooled (ice bath), and pyridine (5 μL) and trifluoroacetic acid (3 μL) were added followed by 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (60 mg). The mixture was warmed to room temperature and then heated at 60 °C for 1 h. The mixture was then concentrated in vacuo, 10% aqueous $NaHCO_3$ (2 mL) was added, and the product was extracted with CH_2Cl_2 (4 × 4 mL). The combined extracts were dried (Na_2SO_4), and PLC (3:97 MeOH:EtOAc) gave (±)-10,22-dioxokopsane (5.3 mg, 66%) as a colorless solid.

This material had superimposible IR and ^1H NMR spectra and identical R_f values (5:95 EtOAc:MeOH R_f 0.41; 3:2 $CHCl_3$:EtOAc R_f 0.77; 9:1 EtOAc:EtOH R_f 0.38; 3:2 $CHCl_3$:acetone R_f 0.66—10,22-dioxokopsane gave a very characteristic pink color when sprayed/heated with phosphomolybdic acid), when compared with those of an authentic sample.

IR ($CHCl_3$) 1752, 1677 cm^{-1}; NMR ($CDCl_3$) δ 7.16 (1 H, d, *J* = 7 Hz), 7.11 (1 H, t, *J* = 7 Hz), 6.82 (1 H, t, *J* = 7 Hz), 6.71 (1 H, d, *J* = 7 Hz), 4.25 (1 H, dd, *J* = 13, 5.5 Hz), 3.74 (1 H, d, *J* = 1.5 Hz), 3.66 (1 H, br s), 2.94 (1 H, td, *J* = 13, 4.3 Hz), 2.90 (1 H, t, *J* = 1.5 Hz), 2.83 (1 H, d, *J* = 11 Hz), 2.0–1.38 (10 H, m).

(±)-Epikopsanol 10-lactam **53** was similarily converted to (±)-10,22-dioxokopsane in 40% yield.

(±)-Kopsanone (3, X = O). A solution of **52** (20 mg, 0.041 mmol) in THF (1 mL) was added dropwise to a rapidly stirred slurry of $LiAlH_4$ (60 mg) in THF (5 mL). The mixture was then heated at reflux for 4 h. After this time TLC showed complete conversion to a mixture of kopsanol and epikopsanol (prepared by $NaBH_4$ reduction of an authentic sample of kopsanone). The mixture was cooled to 0 °C and quenched with 1 H NaOH. The resulting mixture was thoroughly extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4).

After removal of the solvent, the residue (10 mg) was dissolved in benzene (1 mL) and Me_2SO (1 mL) and cooled (ice-bath), and pyridine (6 μL) and trifluoroacetic acid (4 μL) were added followed by 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (60 mg). The mixture was allowed to slowly warm to 20 °C and then heated at 60 °C for 1 h. The mixture was concentrated in vacuo and quenched with 10% aqueous $NaHCO_3$, and the product was extracted with CH_2Cl_2 (4 × 5 mL). The combined extracts were dried (Na_2SO_4). *Removal of solvent and purification by PLC* (95:5 $CHCl_3$:MeOH) gave (±)-kopsanone (**3**) (6.2 mg. 50% from **52**) as a colorless glass.

This material had superimposible IR and ^1H NMR spectra and identical R_f values (5:95 MeOH:EtOAc R_f 0.35; 3:2 $CHCl_3$:EtOAc R_f 0.62; 9:1 EtOAc:EtOH R_f 0.27; 3:2 $CHCl_3$:acetone 0.51—Kopsanone gave a very characteristic pink color when sprayed/heated with phosphomolybdic acid) when compared with those of an authentic sample.

IR ($CHCl_3$) 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.29 (1 H, d, *J* = 7 Hz), 7.06 (1 H, t, *J* = 7 Hz) 6.79 (1 H, t, *J* = 7 Hz), 6.67 (1 H, d, *J* = 7 Hz), 3.58 (1 H, br s), 3.51 (1 H, t, *J* = 10 Hz), 3.37 (1 H, d, *J* = 1.5 Hz), 3.14 (1 H, dd, *J* = 9, 5 Hz), 3.06–3.00 (2 H, m), 2.69 (1 H, d, *J* = 11 Hz), 2.58 (1 H, ddd, *J* = 10, 4.5, 1.5 Hz), 2.04 (1 H, d, *J* = 16 Hz), 1.90–1.20 (9 H, m).

(*R*)-(+)-(*p*-Tolylsulfinyl)acetic Acid 34. (*R*)-(+)-4-(Methylsulfinyl)toluene (3.5 g, 22.7 mmol) in dry THF (30 mL) was added to a solution of LDA (25 mmol) in dry THF (100 mL) at 0 °C, and the mixture was stirred for 0.25 h. CO_2 gas was bubbled through the solution for 1 h, and the reaction was quenched with NH_4Cl (50 mL). The solvent was removed by evaporation and the residue subjected to an acid–base workup. The neutral fraction afforded starting material (1.60 g, 46%) while the acidic fraction was crystallized from EtOAc/hexane to afford **34** as white crystals (1.55 g, 34%): mp 105–106 °C; IR ($CHCl_3$) 3000 (br), 1720, 1125, 1040 cm^{-1}; NMR ($CDCl_3$) δ 11.20 (1 H, br s), 7.70–7.30 (4 H, m), 3.90 (2 H, AB system, J_{AB} = 15 Hz), 2.42 (3 H, s); $[\alpha]^{25}_D$ +192.4° (c 11.8, Me_2CO). Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08. Found: C, 54.50; H, 5.19.

(+)-1-[(*p*-Tolyl-(*R*)-sulfinyl)acetyl]-*cis*-2,3,4,4a(*R*),5(*R*),6,7,11c-(*S*)-octahydro-5α(*R*)-chloro-7-[(*p*-methoxyphenyl)sulfonyl]-1*H*-pyrido-[3,2-*c*]carbazole (35) and Its 4a(*S*),5(*S*),11c(*R*) Diastereomer 36. A solution of the tetracyclic amine **22** (1.25 g, 2.9 mmol), (*R*)-(+)-(*p*-tolylsulfinyl)acetic acid **34** (750 mg, 3.70 mmol), and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (1.8 g, 4.25 mmol) in dry CH_2Cl_2 (100 mL) was stirred at 25 °C for 12 h. Water (50 mL) was added and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica using EtOAc as eluant to afford a foam (1.75 g, 99%). Separation of the diastereoisomers by preparative HPLC using EtOAc/hexane (3:1) as eluant furnished **35** (830 mg, 47%) as a foam: IR ($CHCl_3$) 1640, 1260, 1025 cm^{-1}; NMR ($CDCl_3$) δ 8.30–6.80 (12 H, m), 3.80 (3 H, m), 2.42 (3 H, m), spectrum complicated by amide resonance; $[\alpha]^{25}_D$ +80.8° (*c* 11.2, $CHCl_3$); MS, *m/e* calcd for $C_{31}H_{31}N_2ClO_5S_2$ 610.136, found 610.139.

Further elution afforded **36** (838 mg, 47%) as a foam: IR ($CHCl_3$) 1640, 1260, 1025 cm^{-1}; NMR ($CDCl_3$) δ 8.20–6.70 (12 H, m), 3.80 (3 H, m), 2.47 and 2.42 (3 H, 2 × s), spectrum complicated by amide resonance; $[\alpha]^{25}_D$ +94.0° (*c* 11.6, $CHCl_3$); MS, *m/e* calcd for $C_{31}H_{31}N_2ClO_5S_2$ 610.136, found 610.137.

(−)-2,3,4,5-Tetradehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(*p*-tolylthio)-20,21-dinoraspidospermidin-10-one (37) and (+)-2,3,4,5-Tetradehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11α-(*p*-tolylthio)-20,21-dinoraspidospermidin-10-one (39). A solution of the tetracyclic sulfoxide **35** (more mobile diastereomer; 650 mg, 1.065 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C was treated with $(CF_3CO)_2O$ (595 mg, 2.83 mmol) and allowed to warm up to 25 °C over 0.5 h. Chlorobenzene (50 mL) was added, the CH_2Cl_2 removed by distillation, and the resulting solution heated at 120 °C for 6 h. Removal of the solvent followed by purification of the residue on silica using EtOAc/hexane (3:7) as eluant afforded a mixture of **37** and **39**. Separation by preparative HPLC using EtOAc/hexane (1:2) as eluant afforded **39** (47 mg, 8%): IR ($CHCl_3$) 1690, 1595, 1258 cm^{-1}; NMR ($CDCl_3$) δ 7.90–6.40 (13 H, m), 5.81 (1 H, d, *J* = 6 Hz), 4.38 (1 H, s), 4.30 (1 H, m), 3.60 (3 H, s), 3.13 (1 H, s), 2.95 (1 H, m), 2.59 (1 H, m), 2.27 (3 H, s), 2.20 (1 H, m), 1.76 (1 H, m), 1.58 (1 H, m); $[\alpha]^{25}_D$ +86.3° (*c* 4.8, $CHCl_3$); MS, *m/e* calcd for $C_{31}H_{28}N_2O_4S_2$ 556.149, found 556.149.

Further elution afforded **37** (408 mg, 69%): IR ($CHCl_3$) 1690, 1595, 1258 cm^{-1}; NMR ($CDCl_3$) δ 8.00–6.70 (12 H, m), 6.17 (1 H, d, *J* = 6 Hz), 5.74 (1 H, d, *J* = 6 Hz), 4.33 (2 H, m), 4.04 (1 H, s), 3.70 (3 H, s), 2.94 (1 H, dt, *J* = 2.9 Hz, J = 12.6 Hz), 2.50 (1 H, m), 2.27 (3 H, s), 2.15 (1 H, m), 1.78 (1 H, m), 1.57 (1 H, m); $[\alpha]^{25}_D$ −47.2° (*c* 4.6, $CHCl_3$); MS, *m/e* calcd for $C_{31}H_{28}N_2O_4S_2$ 556.149, found 556.148.

(+)-2,3,4,5-Tetradehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11β-(*p*-tolylthio)-20,21-dinoraspidospermidin-10-one (38) and (−)-2,3,4,5-Tetradehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11α-(*p*-tolylthio)-20,21-dinoraspidospermidin-10-one (40). A solution of the tetracyclic sulfoxide **36** (more polar diastereomer; 650 mg, 1.065 mmol) was treated as described for **35**. Purification by preparative HPLC using EtOAc/hexane (1:2) as eluant afforded **40** (29 mg, 5%): NMR and IR identical with **39**; $[\alpha]^{25}_D$ −53.3° (*c* 3, $CHCl_3$); MS, *m/e* calcd for $C_{31}H_{28}N_2O_4S_2$ 556.149, found 556.151.

Further elution afforded **38** (402 mg, 68%): NMR and IR identical with **37**; $[\alpha]^{25}_D$ +42.9° (*c* 3.4; $CHCl_3$); MS, *m/e* calcd for $C_{31}H_{28}N_2O_4S_2$ 556.149, found 556.147.

(+)-2,3,4,5-Tetradehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11α-(prop-2-en-1-yl)-11β-(*p*-tolylthio)-20,21-dinoraspidospermidin-10-one (41). (a) From (+)-11β-(Tolylthio)pentacycle 38. **38** (43.3 mg, 0.078 mmol) in THF (2 mL) was added to a solution of LDA (0.39 mmol) in THF (5 mL) and the solution stirred for 10 min at 0 °C. Allyl bromide (400 mg, 3.3 mmol) was added and the mixture stirred for 0.25 h at 0 °C. Saturated NH_4Cl (5 mL) was added and the solvent removed by evaporation. The residue was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and evaporated. Purification of the residue by preparative TLC using EtOAc/hexane (7:13) as eluant afforded a gum (27 mg, 58%): IR ($CHCl_3$) 1687, 1595, 1160 cm^{-1}; NMR ($CDCl_3$) δ 8.00–6.15 (12 H, m), 6.24 (1 H, d, *J* = 6 Hz), 5.86 (1 H, ddt, *J* = 6.4, 10.2, 17.1 Hz), 5.70 (1 H, d, *J* = 6 Hz), 4.90 (1 H, dd, *J* = 1.7, 10.2 Hz), 4.70 (1 H, dd, *J* = 1.7, 17.1 Hz), 4.37 (2 H, m), 3.83 (3 H, s), 2.94 (1 H, dt, *J* = 2.9, 12.8 Hz), 2.84 (1 H, A part of ABX, J_{AB} = 16, J_{AX} = 7 Hz), 2.55 (1 H, B part of ABX, J_{AB} = 16, J_{BX} = 6 Hz), 2.52 (1 H, m), 2.25 (3 H, S), 2.17 (1 H, m), 1.82 (1 H, m), 1.60 (1 H, m); $[\alpha]^{25}_D$ +74.5° (*c* 4.3; $CHCl_3$); MS, *m/e* calcd for $C_{34}H_{32}N_2O_4S_2$ 596.180, found 596.179.

(b) From (−)-11α-(Tolylthio)pentacycle 40. **40** (21 mg, 0.038 mmol) was treated as described above for **38**. Purification by preparative TLC using EtOAc/hexane (7:13) as eluant afforded a gum (10 mg, 44%). Identical in all respects with **41**.

We were unable to obtain **39** and **40** completely uncontaminated by C-11 phenylthio epimers; consequently the rotations at the D line were not exactly opposite, although the CD curves (Scheme III) are reasonable mirror images. A similar situation prevailed for **37** and **38**, except the equal and opposite match at the D line was more accurate, presumably because of their greater abundance.

Kinetic Studies. Conversion of 28 into 30. The homoannular diene **28** (6 mg) was dissolved in 1-butanol (2 mL), and aliquots of this solution (250 μL) were added to 1-butanol (3 mL) previously equilibrated at the desired temperature. The mixture was mixed by vigorous shaking in a cuvette, and the absorbance at 330 nm was monitored. A plot of log absorbance vs. time enabled the following first-order rate constants to be determined: *k* (mol L^{-1} h^{-1}), *T* (°C); 5.993×10^{-6}, 60; 1.572×10^{-5}, 69; 4.169×10^{-5}, 79; 8.957×10^{-5} 88; 2.602×10^{-4}, 100. Fitting these data to the Arrhenius equation using a least-squares procedure (R = 0.999) enabled us to calculate the thermodynamic parameters. For further details see text.

(+)-2,3,4,5-Tetradehydro-1-[(*p*-methoxyphenyl)sulfonyl]-11α-methyl-11β-(*p*-tolylthio)-20,21-dinoraspidospermidin-10-one (43). A solution of the (+)-pentacycle **38** (100 mg, 0.18 mmol) in dry THF (2 mL) was added to a solution of LDA (0.43 mmol) in dry THF (2 mL) and the mixture stirred for 20 min at 0 °C. Methyl iodide (400 μL, 912 mg, 6.42 mmol) was added and the mixture stirred for 1 h at 0 °C. The reaction was quenched with 2 N HCl and the organic solvent removed by evaporation. The residue was extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography using 40% $CHCl_3$/hexane as eluant to furnish a foam (88 mg, 86%): IR ($CHCl_3$) 1685, 1595, 1260 cm^{-1}; NMR ($CDCl_3$) δ 8.00–6.90 (12 H, m), 6.33 (1 H, d, *J* = 6 Hz), 5.69 (1 H, d, *J* = 6 Hz), 4.49 (1 H, s), 4.31 (1 H, m), 3.86 (3 H, s), 2.95 (1 H, dt, *J* = 3, 12.8 Hz), 2.48 (1 H, m), 2.29 (3 H, s), 2.17 (1 H, m), 1.78 (1 H, m), 1.48 (1 H, m), 1.23 (3 H, s); $[\alpha]^{25}_D$ +100.6° (*c* 12.6, $CHCl_3$); MS, *m/e* calcd for $C_{32}H_{30}N_2O_4S_2$ 570.166, found 570.165.

Thermolysis of **43** at temperatures as high as 230 °C only resulted in extensive decomposition, with no evidence for epimerization at C-11 or enantiomerization (carried out in the chiral series), thus excluding the possibility of a cycloreversion pathway.

Acknowledgment. The National Institutes of Health (GM 29801) are gratefully thanked for their financial support. The National Science Foundation (CHE 81-05004) is thanked for funds to purchase a 360-MHz NMR spectrometer. Professor Manfred Hesse is thanked for samples of 10,22-dioxokopsane (**2**) and kopsanone (**3**, X = O). Professor K. Biemann (MIT) is thanked for MS comparison.