The Indole-2,3-quinodimethane Strategy for the Synthesis of Indole Alkaloids

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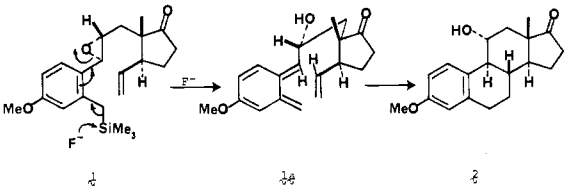
The chemistry of alkaloids has been historically central to the development of classical methods of structural elucidation and synthesis in organic chemistry. Many well-known and important reactions, such as the Hofmann elimination, were discovered during the era of classical chemical degradation. The first major achievements in organic synthesis involved the planned, rational synthesis of quinine and later reserpine and strychnine.[1] These syntheses inspired subsequent generations of organic chemists to design and carry out the syntheses of increasingly complex natural products.

A major preoccupation of synthesis has been the development of new methodology or synthetic methods. Frequently, this has led to short efficient syntheses of natural products, which serve to emphasize and illustrate the value of such research. However, this is not always the case, since some methods can be contrived into awkward strategies that are less than convincing in their design and efficiency. The method must fit the problem and not the other way around.

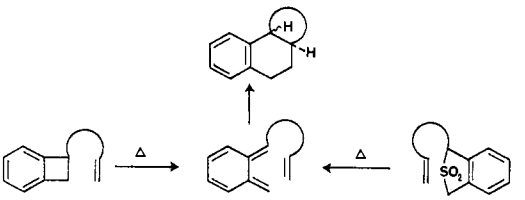
Recently in our own research, one of the central themes has been the development of synthetic methods based upon organosilicon chemistry.[2] We have been cautious to make sure that the silicon component, usually a trimethylsilyl group, is actually necessary. It would be somewhat perverse to have a $SiMe_3$ group play a directing or activating role that, in fact, was not necessary. The research described here owes its existence to this very point.

Previous methods for the generation of quinodimethanes for the synthesis of estrogenic steroids have involved temperatures in excess of 180 °C (Scheme I).[3] We were interested in using a 1,4-elimination reaction, initiated by fluoride ion attack on silicon, to provide the driving force (Si–F bond strength ca. 140 kcal mol^{-1}) to generate a monobenzenoid-derived quinodimethane intermediate under considerably milder conditions, hopefully at room temperature (20 °C). This proved to be readily translated into experimental reality when we found that the benzyltrimethylsilane **1** on treatment with CsF in diglyme at 20 °C gave 11α-hydroxyestrone *O*-methyl ether **2** in 70% yield.[4] The features of this

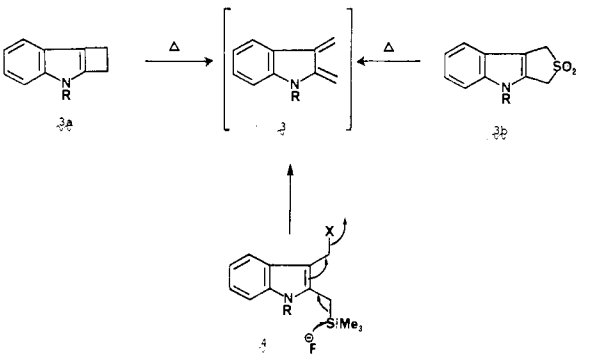


reaction that are typical of most *o*-quinodimethane approaches to estrone synthesis are the exo-type transition-state **1a**, combined with the *E*-diene geometry (always assumed), to give the B/C trans ring fusion

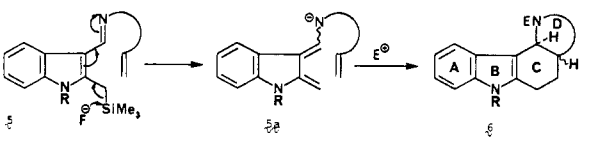
Scheme I



Scheme II



Scheme III



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Paul Pappalardo was born in Michigan in 1956. He received his B.Sc. from the University of Michigan; he is now a doctoral candidate at Indiana University, Bloomington.

(1) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 849. Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749.

(2) Magnus, P. *Aldrichimica Acta* **1980**, *13*, 43.

(3) For a comprehensive review of quinodimethanes in synthesis, see: Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, 41.

(4) Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6885.

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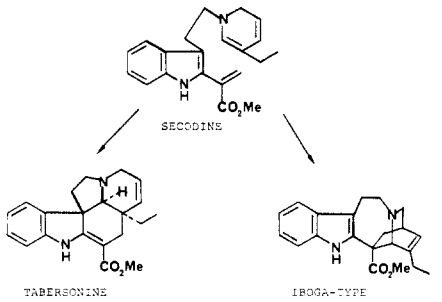
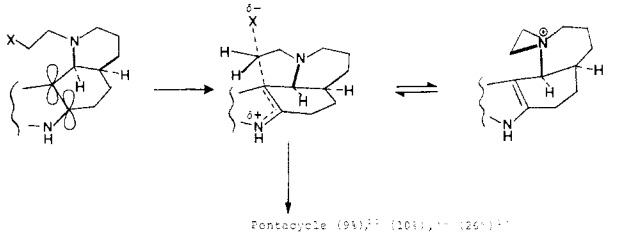
Scheme IV



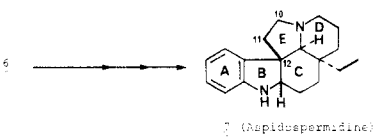
Scheme V



(natural relative stereochemistry).

Rather than pursue variations of this type of strategy in monobenzenoid systems, it was apparent that this methodology should be amenable to heteroaromatic *o*-quinodimethanes, whereas adaptation of the previous strategies (Scheme I) would be a formidable task.[5] Indeed, for the indole-2,3-quinodimethane system (Scheme II) it would involve the synthesis of the precursors **3a** or **3b**, itself a difficult problem. With the benzyltrimethylsilane strategy in mind, the indole derivative **4** should on treatment with fluoride ion undergo 1,4-fragmentation to give the desired indole-2,3-quinodimethane **3**. Extension of this simple idea to an intramolecular version would, in principle, provide a highly convergent way for making indole alkaloids, especially those of the *Aspidosperma* type (Scheme III).[6]

We planned to prepare the imine **5** and treat it with fluoride ion with the anticipation that **5a** would be formed and result in **6** through intramolecular [2 + 4] cycloaddition. It is possible that compounds of the type **6** could be converted into *Aspidosperma* alkaloids.



While many routes have been developed for the synthesis of these types of indole alkaloids, the most interesting being based upon the provocative so-called secodine route (Scheme IV),[7] a route based on an indole-2,3-quinodimethane would offer a high degree of flexibility and convergency. It should be noted that the biosynthetic pathway (Scheme IV) has only been synthetically realized at the dihydro-oxidation level.[8]

Our early results in attempting to make Scheme III reality resulted in two very important observations. First, treatment of the imine **8** with *n*-BuLi/THF/−78 °C followed by $ClSiMe_3$ gave the required 2-[(trimethylsilyl)methyl]indole derivative **9**, but all attempts to hydrolyze the imine **9** gave the desilylated aldehyde **10**. This suggested that the 2-methyl group in **10** is sufficiently acidic to promote the protodesilylation reaction, and more important that this reaction could proceed via an indole-2,3-quinodimethane intermediate **11**. Secondly, the indolic nitrogen lone pair of electrons must be inductively deactivated by an arylsulfonyl group.[6]

As a result of these two observations, a key experiment was carried out. Treatment of the imine **12** (R = $SO_2C_6H_4OMe$-*p*, throughout) with acetic anhydride at reflux gave the tetracyclic amide **13** (E = Ac, 64%).

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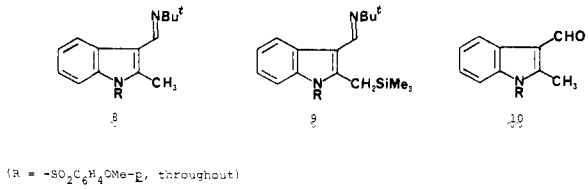
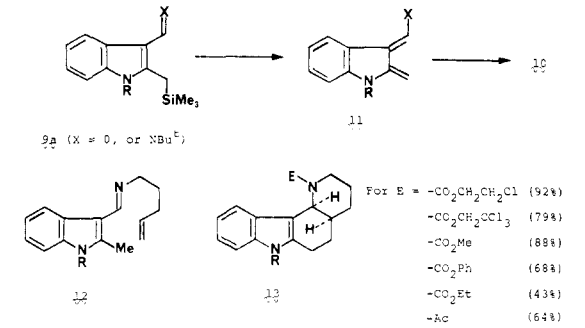
(8) For leading references to attempts to carry out both *inter*- and *intramolecular* versions, Scheme IV, both in the oxidation level depicted (dehydrosecodine) and the dihydro system (secodine), consult: (a) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705. Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Kirkemo, C. L. *Ibid.* **1979**, *44*, 1063. Kuehne, M. E.; Huebner, J. A.; Matsko, T. H. *Ibid.* **1979**, *44*, 2477. Kuehne, M. E.; Kirkemo, C. L.; Matsko, T. H.; Bohnert, J. C. *Ibid.* **1980**, *45*, 3259. Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *Ibid.* **1981**, *46*, 2002. (b) Weinstein, B.; Chang Lin, L.; Fowler, F. W. *J. Org Chem.* **1980**, *45*, 1657. (c) Kutney, J. P.; Badger, R. A.; Beck, J. F.; Bosshardt, H.; Matough, F. S.; Ridaura-Sanz, V. E.; So, Y. H.; Sood, R. S.; Worth, B. R. *Can. J. Chem.* **1979**, *57*, 289. Wilson, R. M.; Farr, R. A.; Burlett, D. J. *J. Org. Chem.* **1981**, *46*, 3293. Beeken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677. (d) Secodine via Claisen rearrangement: Raucher, S.; Macdonald, J. E.; Lawrence, R. F. *J. Am. Chem. Soc.* **1981**, *103*, 2419. (e) Marazano, C.; Fourrey, J-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1977**, 742. Marazano, C.; Fourrey, J-L.; Das, B. C. *Ibid.* **1981**, 37. Marazano, C.; LeGoff, M-T.; Fourrey, J-L.; Das, B. C. *Ibid.* **1981**, 389. Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382. Hasan, I.; Marinelli, E. R.; Chang Lin, L-C.; Fowler, F. W.; Levy, A. B. *Ibid.* **1981**, *46*, 157. (f) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1966**, *88*, 3099. Many other approaches have been developed. For a general review of indole alkaloid synthesis, see: Kutney, J. P. "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1977; Vol. 3, p 273. Cordell, G. A. *Alkaloids* **1979**, *17*, 200. (a) Oxindole approach: Ban, Y.; Ohnuma, T.; Nagai, M.; Sendo, Y.; Oishi, T. *Tetrahedron Lett.* **1972**, 5032. Seki, K.; Ohnuma, T.; Oishi, T.; Ban, Y. *Ibid.* **1975**, 723. Ohnuma, T.; Oishi, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 301. (b) Nine-membered-ring intermediates: Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708. Kutney, J. P.; Cretney, W. J.; LeQuesne, P.; McKague, B.; Piers, E. *J. Am. Chem. Soc.* **1970**, *92*, 1712. Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Leutwiler, A.; Neilson, V. R.; de Souza, J. P. *Helv. Chim. Acta* **1975**, *58*, 1648. (c) Rearrangement route: Barton, J. E. D.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1965**, 298. Harley-Mason, J.; Kaplan, M. *Ibid.* **1967**, 915. (d) *N*-Acyliminium cyclization: Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (e) Heteroatom-directed photoarylation: Schultz, A. G.; Chiu, I-C. *J. Chem. Soc., Chem. Commun.* **1978**, 29. (f) For other notable approaches: Ando, M.; Büchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880. Büchi, G.; Matsumoto, K. E.; Nishimura, H. *Ibid.* **1971**, *93*, 3299. Giri, V. S.; Ali, E.; Pakrashi, S. C. *J. Heterocycl. Chem.* **1980**, *17*, 1133. Laronze, J. Y.; Laronze-Fontaine, J.; Lévy, J.; LeMen, J. *Tetrahedron Lett.* **1974**, 491. Takano, S.; Shishido, K.; Matsuzaka, J-I.; Sato, M.; Ogasawara, K. *Heterocycles* **1979**, 307. Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. For various stereochemical points concerning a retro-Mannich/Mannich reaction in the synthesis of aspidospermine and quebrachamine: Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kamaoka, Y. *Tetrahedron Lett.* **1965**, 2261. Many subsequent syntheses have been based upon the original Stork strategy: Stevens, R. V.; Fitzpatrick, J. M.; Kaplan, M.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1971**, 857. Inoue, I.; Ban, Y. *J. Chem. Soc. C* **1970**, 602. Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, 727. Ohnuma, T.; Oishi, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 301. Saxton, J. E.; Smith, A. J.; Lawton, G. *Tetrahedron Lett.* **1975**, 4161. Lawton, G.; Saxton, J. E.; Smith, A. J. *Tetrahedron* **1977**, *33*, 1641. Martin, S. F.; Desai, S. R.; Phillips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294. Pearson, A. J.; Rees, D. C. *Ibid.* **1982**, *104*, 1118. Klioze, S. S.; Darmory, F. P. *J. Org. Chem.* **1975**, *40*, 1588. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, 4041.



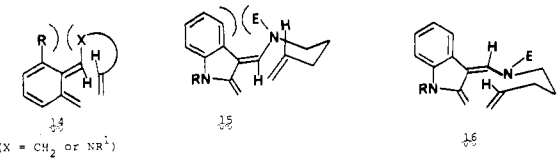
(R = -$SO_2C_6H_4OMe$-p, throughout)



In this and all the subsequent cyclizations, the newly formed ring junction is cis. We have not been able to detect any trans-ring-fused tetracyclic adducts. Obviously, other more useful electrophiles can react with **12** to provide a range of tetracyclic adducts. Since we required the adduct **13** (E = H) and could not hydrolyze **13** (E = Ac), **12** was treated with a series of chloroformates to give the tetracyclic exocyclic carbamates **13** [E = $CO_2CH_2CH_2Cl$ (92%), $CO_2CH_2CCl_3$ (79%), CO_2Me (88%), CO_2Ph (68%), CO_2Et (43%)]. It is vital that the electrophile used to initiate formation of the tetracyclic adduct be readily removed. Of the series above, the β,β,β-trichloroethyl carbamate proved to be the most useful, since only mild zinc–acetic acid reduction gave **13** (E = H). Before proceeding to the direct application of these results to indole alkaloid synthesis, a few brief comments about the stereochemical outcome of these cyclizations are instructive.[9]

The intramolecular trapping of a monobenzenzoid-derived *o*-quinodimethane has been generally assumed to have the geometry indicated in **14**.[10] At first sight this seems reasonable since the products formed, in particular those that have subsequently been converted into estrone, have the newly formed ring junction (B/C for steroids) predominantly trans fused. For the indole-2,3-quinodimethane system **15**, the steric repulsion between the substituent at the 3-position and the benzenoid ring (C-4 hydrogen atom) makes this configuration less likely. We favor the transition state **16**, designated as exo-E, since, without exception, we have only observed cis-fused tetracyclic compounds. It should be noted that all *Aspidosperma* alkaloids have the C/D ring junction cis fused.

With these initial, highly encouraging results in hand, we proceeded to examine two complementary syntheses of the alkaloid aspidospermidine **7**, primarily to learn



(X = CH_2 or NR^1)

about key transformations that will be needed in the construction of the more complicated and highly condensed indole alkaloids.

Since nearly all the *Aspidosperma* alkaloids have an ethyl group at the C/D ring fusion, it is important that the intramolecular trapping of an indole-2,3-quinodimethane tolerate 2,2-dialkyl substitution in the dienophile component. But perhaps the most vital question that has to be answered is how the sterically congested C-11–C-12 bond (quaternary at C-12 and part of a relatively strained five-membered ring) is to be made. Both molecular models and the literature demonstrate that an intramolecular S_N2 displacement process, using the indole 2,3-double bond as the nucleophile toward a leaving group attached to C-11, would be difficult since the pseudopentacoordinate transition state is severely sterically impeded. Previous experience with this situation has been documented by Ziegler,[11] Wenkert and Potier,[12] and most recently by Natsume.[13] Their joint findings are summarized in Scheme V, which shows that while it is possible to make the C-11–C-12 bond in the manner described, it is not a high-yielding process. We were especially interested in the possibility of having a functional handle at C-11 to enable the more highly condensed members of the *Aspidosperma* alkaloids, such as the kopsanes **37**/**38**, to be made.

Changing the hybridization at C-11 from sp^3 to sp^2 means that intramolecular participation of the indole 2,3-double bond leads directly to the establishment of the C-11–C-12 bond. A sulfonium ion, generated from the corresponding sulfoxide via the Pummerer rearrangement, is ideal and also provides a useful functional group at C-11.[14]

The imine **17** (prepared from **10** and the corresponding amine) was cyclized to the cis-fused tetracyclic carbamate **18** by treatment with Cl_3CCH_2OCOCl at 135 °C in 46% yield. In general, the ethyl substitution reduces the yields of tetracyclic adducts by about 20%. The carbamate **18** was converted into the sulfoxide **20** by standard methods (Zn/AcOH to give **19**, followed by $PhSCH_2COCl$ and MCPBA oxidation), which was exposed to trifluoroacetic anhydride at 0 °C and then heated to 130 °C to effect an intramolecular Pummerer-type reaction to give the pentacyclic amide **21** (91%). Final conversion to (±)-aspidospermidine (**7**) was readily carried out by desulfurization (Raney nickel) to **22**, followed by $LiAlH_4$ to give **7** (71%) (Scheme VI).

The α-phenylthio amide **21** serves to provide a useful means of introducing functionality at C-11 that will enable the more highly condensed alkaloids to be made.

While the above synthesis is reasonably concise, it should be noted that the chloroformate electrophile is

(9) Dr. Peter Gund (Merck) using the Merck Molecular Modeling System demonstrated that there is virtually no energy difference between **15** and **16** and that steric interactions twist the nitrogen atom of the dienamine out of conjugation with the diene system for both isomers.

(10) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833, 3834. Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1972**, 1031. Oppolzer, W. *Tetrahedron Lett.* **1974**, 1001. For a comprehensive review of the intramolecular Diels–Alder reaction, see: Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. For an extensive compilation of references to quinodimethanes (*o*-xylylenes) in synthesis, see: Moder, K. P.; Leonard, N. J. *J. Am. Chem. Soc.* **1982**, *104*, 2613. Oppolzer, W. *Synthesis* **1978**, 793.

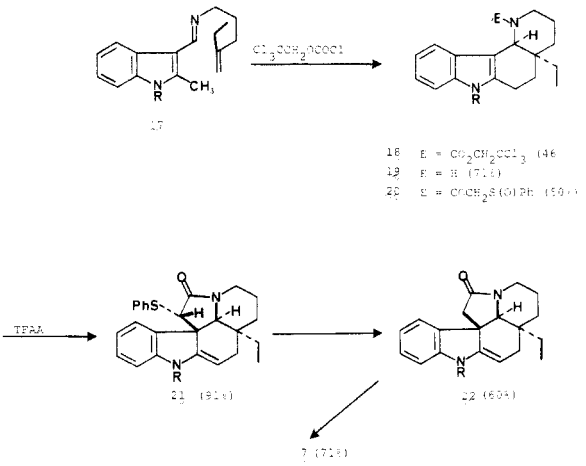
(11) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. Ziegler, F. E.; Bennett, G. B. *Ibid.* **1973**, *95*, 7458.

(12) Husson, H-P.; Thal, C.; Potier, P.; Wenkert, E. *J. Chem. Soc., Chem. Comm.* **1970**, 480. Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271.

(13) Natsume, M.; Utsunomiya, I. *Heterocycles* **1982**, 111.

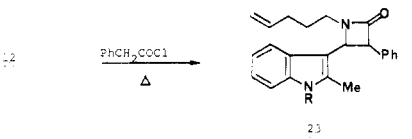
(14) Pummerer reaction applied to indoles: Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118.

Scheme VI
Exocyclic Carbamate Route to (±)-Aspidospermidine[a]



[a] The number of steps from 1-[(*p*-methoxyphenyl)-sulfonyl]-2-methyl-3-formylindole to (±)-aspidospermidine is eight, proceeding in an overall yield of 6.3%.

needed to effect cyclization and then it is removed and replaced by another electrophile, namely, the (phenylthio)acetyl group. Why not conduct the initial cyclization with say, (phenylthio)acetyl derivatives and make **20** directly? Unfortunately, whenever the acetylating species can easily enter into ketene pathways, β-lactams **23** become the major, if not the only, product.



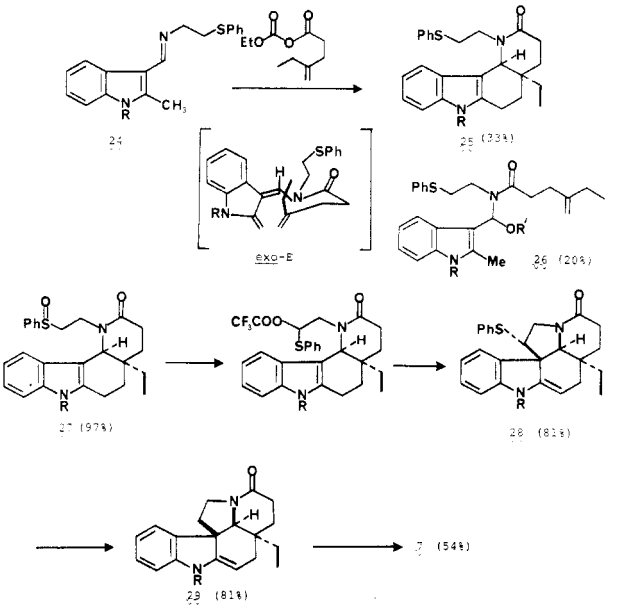
The second approach to the synthesis of (±)-aspidospermidine incorporates the two-carbon C-10–C-11 tryptamine bridge into the imine portion from the beginning of the synthesis. We have designated this second route as the endocyclic amide route. It will offer the opportunity to introduce functionality into the D ring.

Treatment of **24** with the mixed anhydride derived from 4-ethylpent-4-enoic acid in chlorobenzene at 140 °C for 2.75 h gave **25** (33%) after chromatography and crystallization. The major byproduct from this reaction is the ethoxy adduct **26** (ca. 20%), which was *not* converted into **25** on further heating. The relative stereochemistry of **25** was demonstrated by single-crystal X-ray crystallography to be cis. Oxidation of **25** with $MCPBA/CH_2Cl_2/NaHCO_3$ at 0 °C gave the sulfoxide **27** (97%) as a mixture of diastereoisomers. When this sulfoxide was treated with $TFAA/CH_2Cl_2/0$ °C and then rapidly heated to 130 °C (addition of PhCl), the pentacycle **28** (81%) was formed. The relative stereochemistry of the phenylthio group at C-11 was confirmed by single-crystal X-ray crystallography. Desulfurization (Raney nickel) of **28** followed by $LiAlH_4$ reduction gave (±)-aspidospermidine (**7**) (Scheme VII).[15]

Both syntheses of (±)-aspidospermidine serve as a model study for the synthesis of the more complicated indole alkaloids. Scheme VIII summarizes the progress and future possibilities.

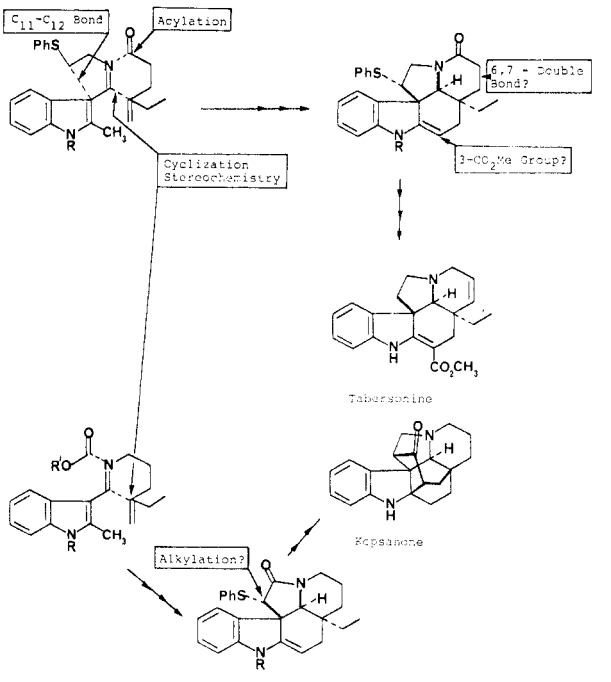
(15) Gallagher, T.; Magnus, P.; Huffman, J. *J. Am. Chem. Soc.* **1982**, *104*, 1140.

Scheme VII
Endocyclic Amide Route to (±)-Aspidospermidine[a]



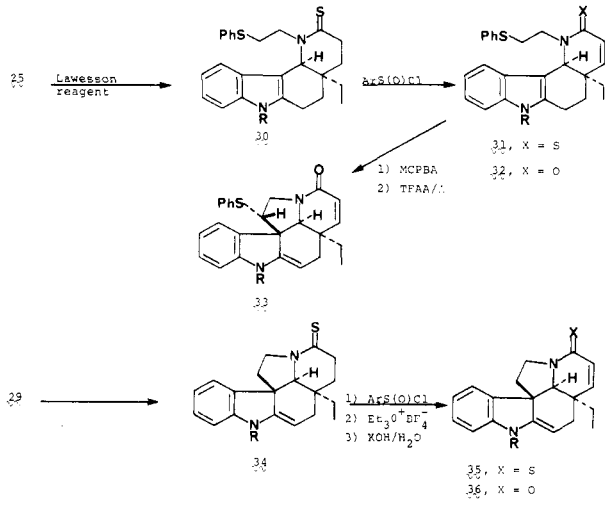
[a] The number of steps from 1-[(*p*-methoxyphenyl)-sulfonyl]-2-methyl-3-formylindole to (±)-aspidospermidine is six, proceeding in an overall yield of 11.7%.

Scheme VIII



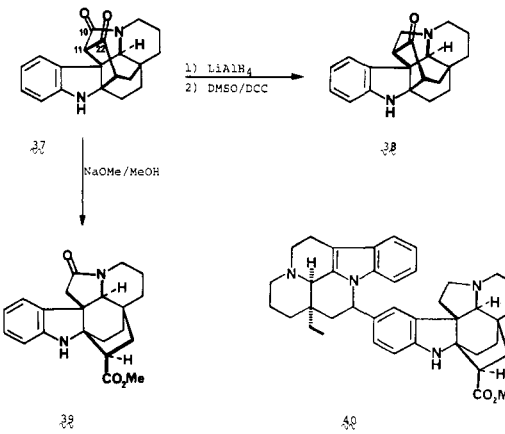
A particularly interesting problem, not only in the synthesis of tabersonine and vinblastine but in a quite general sense, is the conversion of amides into α,β-unsaturated amides. The structures of these complex alkaloids demand that the 6,7-double bond be introduced under very mild conditions into appropriate precursors. With use of the conventional methodology of amide bases (LDA, etc.) followed by electrophiles such as $(PhSe)_2$, PhSeBr, or $(PhS)_2$, the substrate **25** (and *N*-alkyl analogues) either gave complex mixtures [which on oxidation (MCPBA) and heating gave no indication of the α,β-unsaturated amide] or no reaction at all. One way around this dilemma is to increase the acidity of the protons adjacent to the C-8 carbonyl

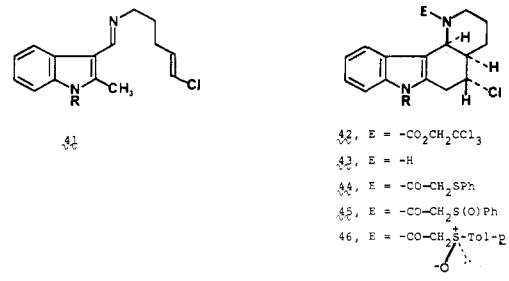
group, so that an electrophile can be introduced under very mild conditions. The pK_a of a methylene group adjacent to an amide is approximately 32, whereas that adjacent to a thioamide is 16. Treatment of **25** with the Lawesson reagent ($PhCH_3$/90 °C/2 h) gave **30** (75%).



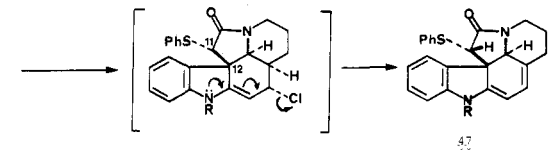
When **30** was treated with *p*-TolS(O)Cl/CH_2Cl_2/EtNPr-i_2 at 0 °C, followed by aqueous workup, the α,β-unsaturated thioamide **31** was isolated in 81% yield. Treatment of **31** with $Et_3O^+BF_4^-$/CH_2Cl_2, followed by aqueous KOH, gave the α,β-unsaturated amide **32** (58%). Oxidation of **32** (MCPBA) followed by the intramolecular Pummerer reaction gave the pentacyclic system **33** (65%). Extension of this new mild procedure to the pentacyclic amide **29** required slightly more vigorous conditions. The thioamide **34** (from **29** and Lawesson's reagent; 73% yield) was treated with *p*-TolS(O)Cl/NPr_2^iEt/CH_2Cl_2 at 40 °C, followed by aqueous workup, to give the α,β-unsaturated thioamide **35** (92%). Conversion into the α,β-unsaturated amide **36** using $Et_3O^+BF_4^-$ proceeded in 80% yield. The mechanism and extension of this unusual dehydrogenation procedure is currently being investigated.[16]

A point alluded to earlier is the possibility of manipulating C-11, especially in substrates such as **21**. In this context, a most attractive class of alkaloids that defied classical structural elucidation by chemical degradation, but eventually submitted to mass spectrometry and subsequently single-crystal X-ray crystallography, are the kopsanes.[17] 10,22-Dioxokopsane (**37**) is a central member of this class of alkaloids since it can be readily converted into other members of this group. Exposure of **37** to $LiAlH_4$, followed by oxidation (Me_2SO/DCC), gave kopsanone (**38**). Treatment of **37** with NaOMe/MeOH gave pleiocarpinilam, a potential component of the dimeric indole alkaloid pleiomutine (**40**). Using the indole-2,3-quinodimethane strategy, we treated the imine **41** with β,β,β-trichloroethyl chloroformate/NPr_2^iEt/PhCl at 120 °C to give the tetracycle **42**. Under these conditions the secondary equatorial Cl atom in **42** is quite stable. The trichloro carbamate group is readily removed (Zn/AcOH) to give the secondary amine **43** (95%). At this stage we have the opportunity to resolve **43**, which is necessary if the dimeric systems are to be synthesized. Since the amine **43** has to be converted into the (phenylsulfinyl)acetamide derivative **45** in order to make the C-11–C-12 bond using the Pummerer reaction, we were attracted to the idea that a chiral (phenylsulfinyl)acetyl group (chiral at sulfur) might effect resolution. This notion is particularly attractive because the resolving agent becomes the tryptamine bridge (C-11–C-12) and is not discarded. Furthermore, as will be seen later, having chiral systems enables a ready solution to some mechanistic problems that arose, but first we worked out the sequence of transformation to 10,22-dioxokopsane (**37**) in the achiral series.[18]





When **45** was exposed to the Pummerer-type conditions, previously used for the formation of the C-11–C-12 bond (**20** → **21** and **27** → **28**), the homoannular diene **47** was formed directly. The formation of the C-11–C-12 bond (**45** → **47**) must precede the elimination of HCl, since we know that the 1,4-dihydrocarbazole that would result from the prior elimination of HCl aromatizes (1,4-elimination) to a carbazole under the conditions of this reaction.[19]



We considered in some detail the stereochemical outcome of allylation of the C-11 carbanion from **47**. It is, of course, essential that the allyl group eventually end up on the concave face of the homoannular diene so that an intramolecular [2 + 4] cycloaddition can

(16) Pappalardo, P.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 6525.
(17) Greshoff, M. *Ber.* **1890**, *23*, 3537. Bycroft, B. W.; Schumann, D.; Patel, M. B.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1147. Schumann, D.; Bycroft, B. W.; Schmid, H. *Experientia* **1964**, *20*, 202. Kump, C.; Schmid, H. *Helv. Chim. Acta* **1962**, *45*, 1090. Battersby, A. R.; Gregory, H. *J. Chem. Soc.* **1963**, 22. 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. Craven, B. M.; Gilbert, B.; Paes Leme, L. A. *Chem. Commun.* **1968**, 955; see also *J. Chem. Soc. C* **1966**, 1260.

(18) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086.
(19) Exon, C.; Gallagher, T.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1982**, 613.

create the basic kopsane skeleton (48 → 49). First, it

48 49

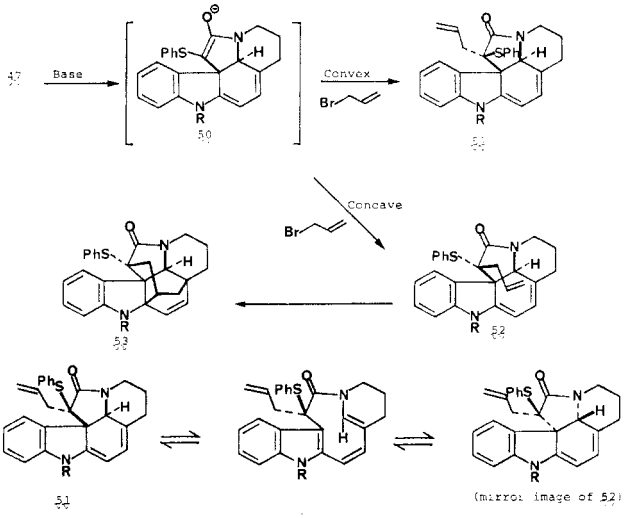
is not at all clear which face of a planar enolate species such as **50** is more accessible toward an allylating agent. Consequently it was predicted that an epimeric mixture at C-11 would result, **51** and **52**. The undesired product **51** has the inherent capability to be converted into the mirror image of **52** by a sequence of cycloreversion–recyclization transformations. This sequence, Scheme IX, inverts the configuration of both C-12 and C-19, which has the overall effect of turning the allyl group from the convex face of the diene to the concave face.[20] Once the dienophile is situated directly over the concave face of the diene, it should irreversibly cyclize to the basic kopsane structure **53**. One of the purposes of this analysis was to provide a pathway to the correct product **52**, even if the allylation initially gave **51**.

Treatment of **47** with $KN(SiMe_3)_2$/THF/0 °C followed by allyl bromide gave **52** (91%). The melting point of **52** is 158–160 °C, followed by conversion to **53**, mp 234–235 °C. Both the structures of **52** and **53** were confirmed by single-crystal X-ray crystallography. The thermodynamic parameters $\Delta H^{\ddagger} = 22.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -12.9$ eu for the transformation of **52** into **53** reflect the extremely small amount of organization needed to arrive at the transition state, and the transition state is late in the reaction pathway.

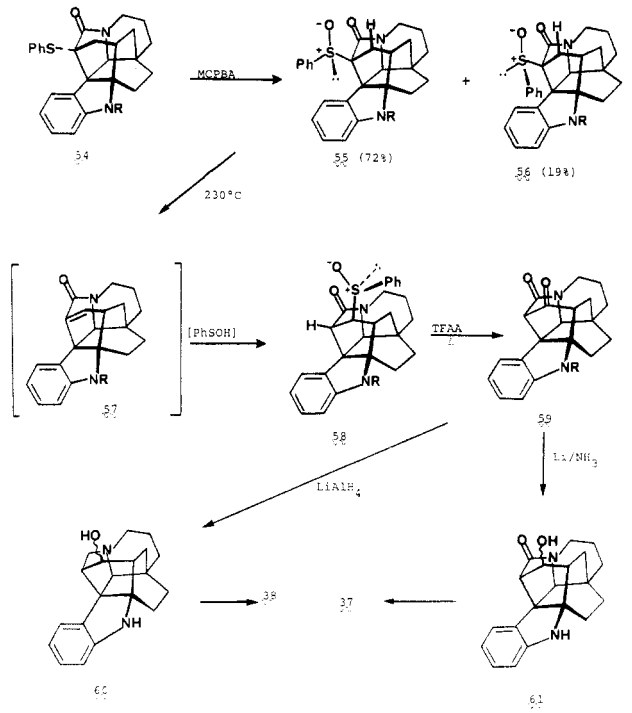
Reduction of the isolated double bond in **53** with diimide, generated in situ by treatment of $TsNHNH_2$ with NaOAc/EtOH, gave **54** (95%). Oxidation of the SPh group at C-11 with *m*-chloroperbenzoic acid at −70 °C gave a mixture of two diastereomeric sulfoxides **55** (72%) and **56** (19%). Only one of the sulfoxides can orientate the sulfur–oxygen bond in a syn coplanar fashion to the β-hydrogen atom to undergo syn elimination. The other enantiomer has to force the SPh group into the indoline ring in order to achieve the same conformation for syn elimination of benzenesulfenic acid. A priori we had no way of knowing whether the major or minor sulfoxide would lead to the torsionally strained α,β-unsaturated amide **57**. The mixture of sulfoxides **55**/**56** was heated in toluene at 230 °C (sealed tube). The major sulfoxide **55** disappeared and was replaced by a single new sulfoxide **58** (95%), and the minor sulfoxide remained unchanged. Assignment of the configuration at the sulfoxide sulfur atom in **58** is based upon the cis addition of benzenesulfenic acid to the torsionally strained α,β-unsaturated amide **57**. This unusual sequence transfers the PhS(O) group from C-11 to C-22. When the sulfoxide **58** was treated with TFAA/CH_2Cl_2/0 °C and then warmed to 130 °C (sealed tube), the β-keto amide **59** was formed. One

(20) While the diene/triene 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.

Scheme IX



remaining problem needs to be solved: how to remove the (*p*-methoxyphenyl)sulfonyl group from the indoline nitrogen atom without destroying the rest of the molecule? Sulfonamides are notoriously difficult to remove, and there was no appropriate model system that could have provided a test for this crucial final reaction.

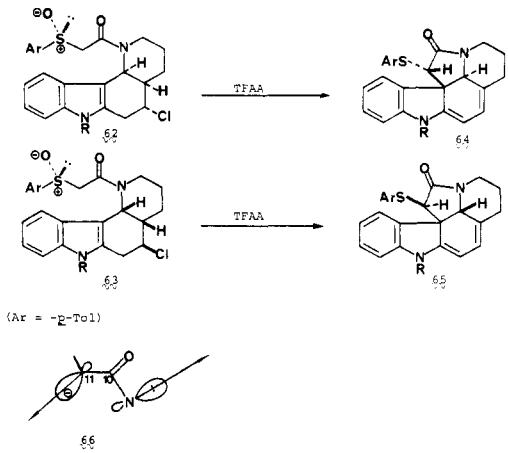


Reduction of **59** with $LiAlH_4$/THF gave an epimeric mixture of kopsanols **60**, which were oxidized by using a modification of the Moffatt oxidation (Me_2SO/MDCC) to give racemic kopsanone **36**. When **59** was treated with Li/NH_3/THF, it was cleanly converted into **61**. Reoxidation of **61** using the same procedure as before gave racemic 10,22-dioxokopsane (**37**).

To address the mechanistic question of alkylation of **47**, the optical resolution of **43** was required. Coupling of racemic **43** with (+)-*p*-TolS(O)CH_2CO_2H gave the diastereoisomers **62** and **63**, readily separated by standard chromatographic techniques. When the separate diastereoisomers **62** and **63** were treated with TFAA/CH_2Cl_2/130 °C, the enantiomers **64** and **65** resulted. When these separated enantiomers were ally-

lated (as for 47) and subsequently cyclized to optically active 53, examination of the CD curves of all of the products readily demonstrated that no crossover from one enantiomeric series into another had occurred. This unambiguously excludes the cycloreversion process (Scheme IX). To explain the stereochemical outcome of allylation at C-11 (methylation also gives the same stereochemistry, therefore excluding an O-allylation followed by [3.3] sigmatropic rearrangement), we favor the situation where the orbital coefficient at the C-11 anion is high on the endo face because it is trans coplanar to the amide nitrogen lone pair and therefore minimizes the dipole moment along the C-10–C-11 bond in 66. We are current exploring the generality of this phenomenon.

In summary, what started as an extension of our organosilicon research has rapidly developed into a separate program. The ready generation of an indole-2,3-quinodimethane intermediate through imine tautomerism, and its subsequent intramolecular trapping, provides a simple route to *Aspidosperma* alkaloids.



The ability of any strategy to cope with complicated problems and simplify them is the best measure of its value.

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Molecular Auger Spectroscopy†

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Auger electron spectroscopy, despite its widespread application in the area of surface studies,[1] has had only limited application to the study of molecular properties. Even in surface work its application has primarily been in qualitative and quantitative elemental identification. This limited application to molecular studies has largely resulted from the complex nature of the Auger process and the attendant difficulty of extracting detailed electronic information.

The Auger process and the experimental arrangement is illustrated in Figure 1 for the Auger spectroscopy of gas-phase molecules, the topic of this Account. The experimental arrangement involves the intersection of a high-energy (~2 keV) electron beam and a molecular jet diverging into a rapidly pumped chamber. This intersection occurs at the focal point of an electron-energy analyzer, in our case a retarding cylindrical mirror analyzer. The electron beam serves as a convenient way of producing an initial core-state ionization. The experimental arrangement in Figure 1 is limited to samples with vapor pressures $>10^{-3}$ torr, although low vapor pressure samples can be accommodated if necessary by heating the analyzer up to 100 °C. In general, the range of samples open to Auger spectroscopy is the same as that open to X-ray photoelectron spectroscopy. However, for solid samples where electron-beam damage is unacceptable, photon-beam excitation is the preferred mode. For initial core holes in states with less than several kiloelectron volts binding energy, the dominant mode of decay is the Auger process in which the core hole captures a higher lying electron and transfers its excess energy to ejecting a second electron, the Auger electron. As illustrated in Figure 1 for a two-state valence system, the Auger transition involves two electrons and three states,[2] the combination of which can yield three energetically distinct Auger electrons. For first row elements, these transitions are referred to as giving rise to the KVV Auger line. In general, the number of Auger transitions will be greater than the number of possible two-hole valence combinations because of multiplet combinations, and despite the fact that a typical spectrum covers 40–50 eV, one has little hope of resolving individual transitions for any molecule of appreciable size.

Thus, while the Auger process is more complicated than the usual one-electron spectroscopies, e.g., ultra-

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J. E. Houston received his Ph.D. degree in Physics from the Oklahoma State University in 1965. He joined Sandia National Laboratories after 2 years of teaching in the Physics Department at the South Dakota School of Mines. His research concerns the development and application of various electron spectroscopic techniques for obtaining an understanding of the nature of surfaces and the way in which their properties control the interaction of solids with their environment.

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(1) P. H. Holloway, *Adv. Electron. Electron Phys.*, 54, 241 (1980).
(2) T. A. Carlson, "Photoelectron and Auger Spectroscopy", Plenum Press, New York, 1975.

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