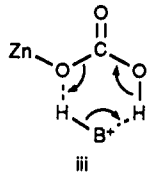
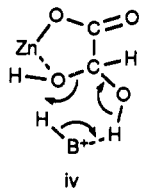


iii



iv

Thus, the present pH–rate studies suggest that the enzymatically catalyzed dehydration of glyoxylate hydrate is mechanistically similar to the dehydration of bicarbonate ion, and given the structural similarities between the two anionic substrates, glyoxylate hydrate may serve as a useful mechanistic probe for CA II.

In summary, we have demonstrated the validity of the assumption that unhydrated glyoxylate is the preferential substrate for its reduction to glycolate. This information has allowed a meaningful interpretation of the Michaelis constants for the LDH-catalyzed reduction of glyoxylate and the corresponding oxidation of glyoxylate hydrate. At the same time, the rate-limiting dehydration of glyoxylate hydrate at high concentrations of LDH allowed us to determine the catalytic rate coefficients for general acids, general bases, transition-metal ions, and carbonic anhydrase, providing an extension of our earlier work on the catalysis of the reversible hydration reactions of other carbonyl compounds. Aided by comparisons of the kinetic parameters between chemical catalysis and catalysis by CA II, we have shown that glyoxylate and its conjugate hydrate serve as a novel substrate pair for carbonic anhydrase. The glyoxylate substrate has provided a natural and important continuation of our earlier work involving acetaldehyde,[8] pyruvate,[9] and bicarbonate[10] as substrates of CA II, demonstrating the catalytic versatility of this enzyme.

Acknowledgment. We thank Greg Spyridis and Doris Sidrovich for their expert assistance in the preparation of this manuscript.

Registry No. Zn^{2+}, 23713-49-7; Cu^{2+}, 15158-11-9; Co^{2+}, 22541-53-3; Ni^{2+}, 14701-22-5; Cd^{2+}, 22537-48-0; Mn^{2+}, 16397-91-4; NADH, 58-68-4; LDH, 9001-60-9; BCA, 9001-03-0; glyoxylate, 298-12-4; glyoxylate hydrate, 563-96-2.

(23) Pocker, Y.; Janjic, N. *J. Am. Chem. Soc.* **1989**, *111*, 731.
(24) Pedersen, K. J. *Acta Chem. Scand.* **1948**, *2*, 385.

Unified Strategy for Synthesis of Indole and 2-Oxindole Alkaloids

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Abstract: A concise and general entry to representative indole alkaloids of the yohimboid, heteroyohimboid, corynantheoid, and 2-oxindole classes has been developed exploiting a strategy that features intramolecular Diels–Alder reactions for the facile construction of the D/E ring subunits of the target alkaloids. The efficacy of the approach is first illustrated by a two-step total synthesis of the yohimboid alkaloid oxogambirtannine (**2**) from **22**. Thus, the Diels–Alder substrate **25**, which was prepared by nucleophilic addition of vinyl ketene acetal **24** to the intermediate *N*-acyliminium salt formed in situ upon reaction of **22** with **23**, was heated in the presence of benzoquinone to give a mixture of diastereoisomeric cycloadducts **26** and **27**; these adducts underwent spontaneous oxidation to furnish **2**. In another application of the strategy, the [4+2] heterocyclization of **34a**, which was formed upon nucleophilic addition of 1-[(trimethylsilyl)oxy]butadiene to the *N*-acyliminium salt generated in situ upon treatment of **22** with crotonyl chloride, afforded a mixture (ca. 9:1) of cycloadducts **35a** and **36a**. The major adduct **35a** was converted to **42a** using a general procedure for effecting β-carbomethoxylation of enol ethers to give vinylogous carbonates. Subsequent reduction of **42a** to the heteroyohimboid alkaloids (±)-tetrahydroalstonine (**3**) and (±)-cathenamine (**4**) was achieved by selective delivery of 2 or 1 equiv of hydride, respectively. When **42a** was treated with sodium amide, stereoselective β-elimination ensued to give **49**, which was converted by chemoselective hydride reduction into the corynantheoid alkaloid (±)-geissoschizine (**5**). Facile access to alkaloids of the 2-oxindole family was realized by using a new protocol for achieving stereoselective, oxidative rearrangements of β-carboline N_b lactams into 3,3-disubstituted 2-oxindoles. Thus, exposure of **42a** to *tert*-butyl hypochlorite followed by acid and silver ion induced rearrangement of the intermediate 3-chloroindolenine gave **50**, with only traces of the C(7) epimer being detected. Hydride reduction of **50** gave (±)-isopteropodine (**6**), acid-catalyzed isomerization of which furnished an equilibrium mixture (1:3) of **6** and (±)-pteropodine (**51**). The stereochemical course of the intramolecular hetero-Diels–Alder reaction of **34a** to give **35a** and **36a** as the only isolable cycloadducts was examined by computational analysis. The geometry of the six-atom transition state was established by semiempirical methods by using the standard closed-shell, restricted Hartree–Fock (RHF) version of the AM1 method. With use of this constrained geometry for the six-membered pericyclic array, the overall conformational energies for the four possible transition states **52–55** were minimized by MM2 calculations (MacroModel). The calculated relative energies of these transition states were in the order **52** < **53** < **54** < **55**. Since the cyclization of **34a** produced only **35a** and **36a** in an approximately 9:1 ratio via the respective transition states **52** and **53**, these calculations correlated qualitatively with the experimental results.

Introduction

Members of the indole family of alkaloids have long been subjects of scientific investigations.[1] These inquiries have been stimulated not only by the structural diversity of this family of alkaloids but also because the physiological and biological properties of some are legendary. The yohimboid, heteroyohimboid, and corynantheoid alkaloids, which are biosynthetically derived from the union of tryptophan and an unrearranged secologanin skeleton, constitute three major subgroups of the indole class. Typical of the yohimboid alkaloids is the presence of either a *cis*- or *trans*-hydroisoquinoline ring system, and in no known alkaloid is this fragment endowed with greater complexity than in reserpine (**1**).[2] At the other end of the spectrum lies oxogambirtannine

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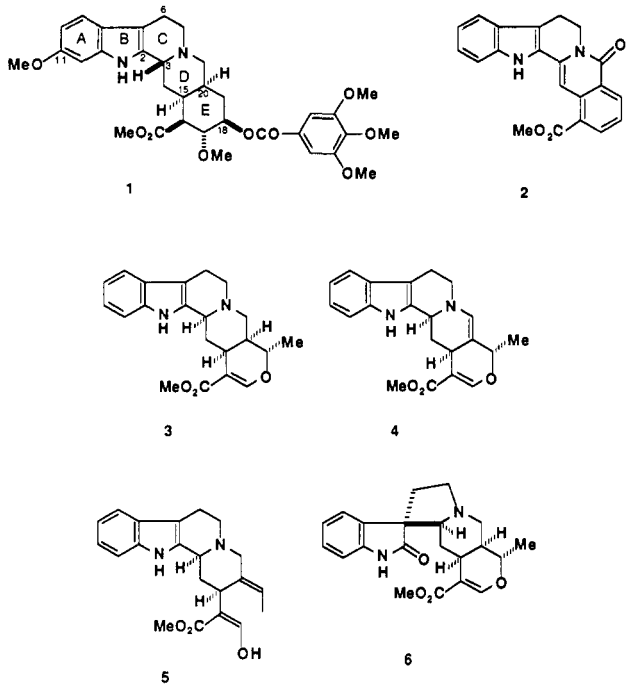
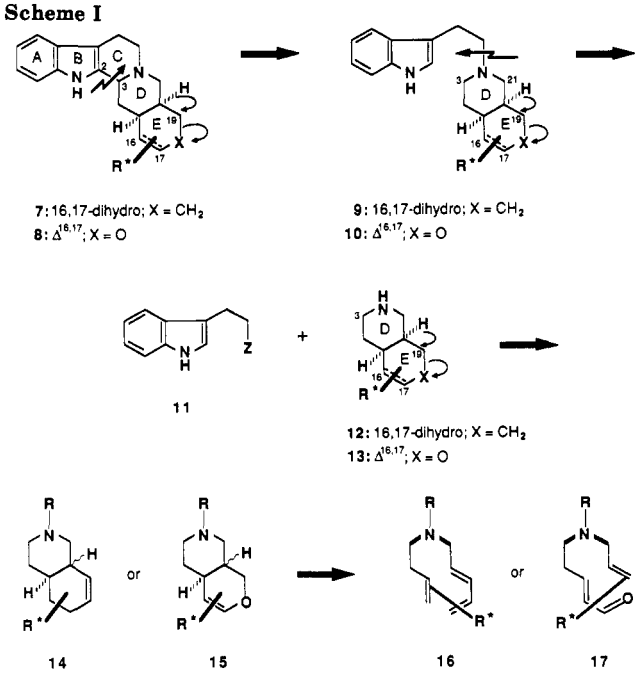
(2),[3] which possesses an aromatic 1-isoquinolone as the DE ring subunit. Heteroyohimboid alkaloids such as tetrahydroalstonine (3)[4,5] and cathenamine (4)[6] incorporate a hydro-7-oxaisoquinoline as the DE moiety. The corynantheoid subgroup to which geissoschizine (5)[7,8] belongs is characterized by a substituted piperidine D ring bearing variously functionalized alkyl appendages at C(15) and C(20) as remnants of the original E ring. Related to the heteroyohimboid and corynantheoid alkaloids by an oxidative rearrangement are the respective 2-oxindole alkaloids[9] of which isopteropodine (6) is a characteristic example.



Scheme I



The indole alkaloids provide an exceptional opportunity for the design and development of new strategies for the elaboration of complex molecular frameworks and for the invention of new methods for carbon–carbon bond construction and selective functional group interconversions. With respect to the former issue, strategies that have been devised to address the challenges posed by the naturally occurring bases **1–6** have had broad applicability in the arena of indole alkaloid synthesis. One common entry to alkaloids related to **1–4** has evolved according to the sequence ABDE ⇒ ABCDE in which the C ring is formed at a late stage of the synthesis. This fundamental strategy may be generally illustrated for the case of the hypothetical pentacyclic yohimboid and heteroyohimboid models **7** and **8** (Scheme I), wherein R* collectively represents the requisite substituent and

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(3) (a) Merlini, L.; Gianluca, N. *Gazz. Chim. Ital.* **1967**, *97*, 1915. (b) Beisler, J. A. *Tetrahedron* **1970**, *26*, 1961. (c) Irie, H.; Fukudome, J.; Ohmori, T.; Tanaka, J. *J. Chem. Soc., Chem. Commun.* **1975**. 63. (d) Ninomiya, I.; Naito, T.; Tada, Y. *Heterocycles* **1983**, *20*, 853. (e) Ninomiya, I.; Naito, T.; Doi, E.; Miyata, O. *Ibid.* **1986**, *24*, 903.

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(8) For other leading references to approaches to corynantheoid alkaloids, see: (a) Wenkert, E.; Dave, K. G.; Lewis, R. G.; Sprague, P. W. *J. Am. Chem. Soc.* **1967**, *89*, 6741. (b) Autrey, R. L.; Scullard, P. W. *Ibid.* **1968**, *90*, 4917. (c) Szántay, C.; Barczai-Beke, M. *Tetrahedron Lett.* **1968**, 1405. (d) van Tamelen, E. E.; Hester, J. B., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 7342. (e) van Tamelen, E. E.; Wright, I. G. *Ibid.* **1969**, *91*, 7349. (f) Ziegler, F. E.; Sweeny, J. G. *Tetrahedron Lett.* **1969**, 1097. (g) Kametani, T.; Kanaya, N.; Hino, H.; Huang, S.-P.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3168. (h) Takano, S.; Shibuya, K.; Takahashi, M.; Hatakeyama, S.; Ogasawara, K. *Heterocycles* **1981**, *16*, 1125. (i) Suzuki, T.; Sato, E.; Unno, K. *Ibid.* **1985**, *23*, 835. (j) Ihara, M.; Taniguchi, N.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1438. (k) Ninomiya, I.; Naito, T.; Winterfeldt, E.; Freund, R.; Ishida, T. *Heterocycles* **1990**, *30*, 1031 and references therein.

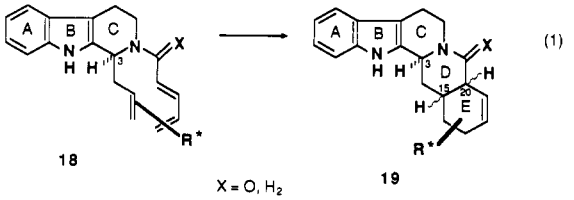
(9) For previous syntheses of 2-oxindole alkaloids, see: (a) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 3871. (b) Chan, K. C.; Morsingh, F.; Yeoh, G. B. *J. Chem. Soc. C* **1966**, 2245. (c) Chan, K. C. *Phytochemistry* **1969**, *8*, 219. (d) Ban, Y.; Seto, M.; Oishi, T. *Tetrahedron Lett.* **1972**, 2113. (e) Ban, Y.; Taga, N.; Oishi, T. *Tetrahedron Lett.* **1974**, 187. (f) Brown, R. T.; Chapple, C. L.; Platt, R. *Tetrahedron Lett.* **1976**, 1401.

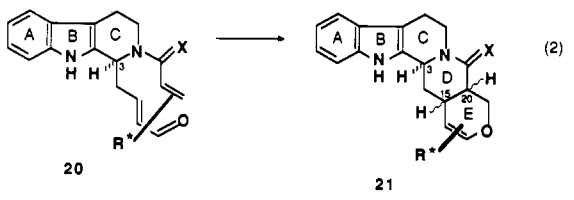
functional groups on the E ring. According to this approach, the seco derivatives **9** and **10** were typically elaborated by coupling functionalized DE fragments **12** and **13** with a suitable tryptophyl synthon **11** (Z = leaving group). This operation set the stage for the oxidative cyclization[10] of **9** and **10** to deliver the targeted alkaloids **7** and **8**. Extension of this plan to the syntheses of corynantheoid alkaloids as represented by **5** required an additional operation to cleave the E ring by scission of the C(19)–O bond either before (e.g., in **10** or **13**) or consequent to (e.g., in **8**) formation of the C ring.

In the general context of formulating novel routes to the indole alkaloids according to the ABD(E) ⇒ ABCD(E) strategy, one of the major challenges lay in devising effective tactics to fashion substituted DE bicyclics related to **12** and **13**. Although numerous creative approaches have been marshalled to address this problem, opportunities for the design of more concise strategies remained. Toward this end, our interest in intramolecular Diels–Alder reactions[11,12] prompted us some years ago to examine the feasibility of deploying the cyclizations **16** → **14** and **17** → **15**, respectively, as pivotal steps in the elaboration of the corresponding DE ring subunits **12** and **13**.[13] Fabrication of the requisite trienic substrates **16** and **17** was readily achieved in a convergent fashion by one of two connective modes (darkened bonds) involving coupling the dienic and dienophilic synthons via facile carbon–nitrogen bond formation. In the early exploratory work,[13a] we discovered that heating **16** and **17** led preferentially to the cis cycloadducts, but the degree of stereoselectivity of the cyclization varied somewhat according to the substitution and functionality on **16** and **17**. In order to demonstrate the efficacy of this intramolecular Diels–Alder approach to the preparation of representative indole alkaloids, we then implemented the intramolecular [4+2] cycloadditions of substituted derivatives of **16** and **17** as key constructions in the total syntheses of reserpine (**1**)[2d] and tetrahydroalstonine (**3**).[4f]

Despite their extensive use, ABD(E) ⇒ ABCDE based strategies for the syntheses of indole alkaloids of the yohimboid and heteroyohimboid families suffer some deficiencies. Perhaps the major drawback, which is not universally acknowledged, is that the mercuric ion induced oxidation[10] of the piperidine nitrogen in seco derivatives as **9** and **10** rarely proceeds with high regioselectivity. Thus, not only are the desired C(3)–N(4) iminium salts produced upon oxidation of tertiary amines **9** and **10**, but significant quantities of the isomeric C(21)–N(4) iminium salts are also generated, thus leading to the formation of the corresponding "inside" analogues.[14] Furthermore, under the typical conditions of this reaction, the initial products **7** and **8** undergo rapid oxidation to furnish the corresponding $\Delta^{3,4}$-dehydro derivatives that must then be reduced to provide the desired targets, but the stereoselectivity of this reduction may be problematic. For example, whereas normal and allo products are usually formed with high levels of selectivity, reductions leading to the C(3) epimeric pseudo and epiallo isomers often give mixtures of C(3) diastereoisomers. One useful modification of the ABD(E) ⇒ ABCD(E) approach that avoids formation of skeletal isomers in the cyclization step involves the Bischler–Napieralski cyclization of an ABD(E) precursor (**9** or **10**) bearing a lactam function at C(3); however, as noted above, there remains a potential problem associated with the stereoselectivity of reduction of the $\Delta^{3,4}$-dehydro intermediates.

Genesis of a New Strategy. In order to address the aforementioned inadequacies of the ABD(E) ⇒ ABCD(E) entry to the indole alkaloids, we were intrigued by the possibility of devising a variant of the ABC ⇒ ABCD(E)[15] route that featured intramolecular Diels–Alder reactions. According to this plan, substrates **18** and **20** would be assembled in the first phase of the effort, and cyclization via intramolecular cycloaddition would then deliver the pentacyclic adducts **19** and **21**, respectively (eqs 1 and 2). Since the C ring is formed prior to elaboration of the D and E rings, this strategy does not suffer the regiochemical ambiguity that may attend construction of the framework via the ABD(E) ⇒ ABCD(E) approach.





Despite the significant prior contributions to the development of the ABC ⇒ ABCD(E) strategy,[15] there were several challenges and scientific questions that remained unsettled at the outset of our inquiry. The first obstacle that would have to be surmounted was the development of a concise route to the 3-substituted tetrahydrocarbolines **18** and **20**. Tactics based upon known chemistry in the indole arena were considered too lengthy. Another issue to be answered was the extent to which the stereochemistry at C(3) of the Diels–Alder precursors **18** and **20** would control the relative stereochemistry at C(15) and C(20) in the pentacyclic adducts **19** and **21**. We were also interested in extending these studies to the development of concise entries to the 2-oxindole alkaloids of the heteroyohimboid and corynantheoid classes as a prelude to future efforts directed toward the *Strychnos* alkaloids. In this context, another challenge lay in the invention of tactics to effect the oxidative reorganization of the heteroyohimboid or corynantheoid framework into the corresponding 2-oxindole skeleton with a high level of stereochemical control.

We now record some of the results of these investigations and their culmination in the development of facile total syntheses of the yohimboid alkaloid oxogambirtannine (**2**), the heteroyohimboid alkaloids (±)-tetrahydroalstonine (**3**) and (±)-cathenamine (**4**), the corynantheoid alkaloid (±)-geissoschizine (**5**), and the 2-oxindole alkaloid (±)-isopteropodine (**6**).[16]

(10) For examples of such oxidative cyclizations, see: (a) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1962**, *84*, 4914. (b) Morrison, G. C.; Cetenko, W.; Shavel, J., Jr. *J. Org. Chem.* **1967**, *32*, 4089. (c) Husson, H.-P.; Chevolot, L.; Langlois, Y.; Thal, C.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1972**, 930. (d) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.-I.; Haginiwa, J. *Tetrahedron Lett.* **1972**, *11*, 1081. (e) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109. (f) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron* **1973**, *29*, 2015. (g) Sakai, S.; Ogawa, M. *Heterocycles* **1978**, *10*, 67. (f) Fujii, T.; Ohba, M.; Sasaki, N. *Heterocycles* **1984**, *22*, 1805. (h) See also refs 2c,d, 4d,e, and 5e.

(11) For excellent reviews of the intramolecular Diels–Alder reaction, see: (a) Ciganek, E. *Org. React. (N.Y.)* **1984**, *32*, 1. (b) Taber, D. F. *React. Struct.: Concepts Org. Chem.* **1984**, *18*, 1. (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (d) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

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(14) For a recent discussion of the scope and limitations associated with the use of oxidative cyclizations of seco derivatives for the elaboration of yohimboid and heteroyohimboid alkaloids, see ref 2d and citations therein.

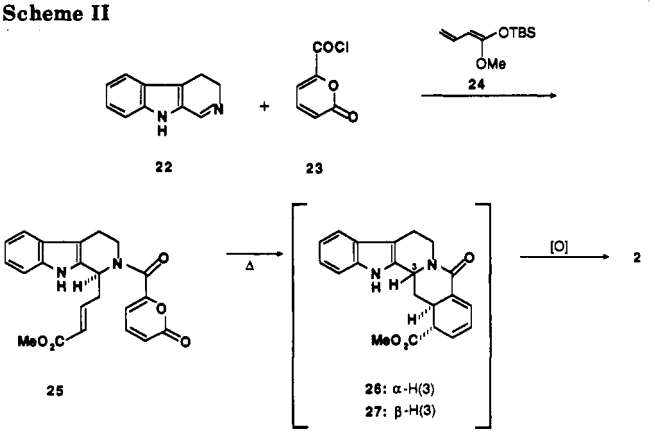
(15) For leading examples of the ABC → ABCD(E) approach to indole alkaloids, see: (a) Szántay, C.; Honty, K.; Töke, L.; Szabó, L. *Chem. Ber.* **1976**, *109*, 1737. (b) Szántay, C.; Blaskó, G.; Honty, K.; Baitz-Gács, E.; Tamás, J.; Töke, L. *Liebigs Ann. Chem.* **1983**, 1292. (c) Miyata, O.; Hirata, Y.; Naito, T.; Ninomiya, I. *Heterocycles* **1984**, *22*, 1041. (d) Danishefsky, S.; Langer, M.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983. (e) Yamaguchi, R.; Hamasaki, T.; Utimoto, K.; Kozima, S.; Takaya, H. *Chem. Lett.* **1990**, 2161. (f) Meyers, A. I.; Highsmith, T. K.; Buonora, P. T. *J. Org. Chem.* **1991**, *56*, 2960. See also refs 5n, 7g, and 8g,h,k.

(16) For preliminary accounts of portions of this work, see: (a) Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 5925. (b) Martin, S. F.; Geraci, L. S. *Tetrahedron Lett.* **1988**, *29*, 6725. (c) Martin, S. F.; Mortimore, M. *Ibid.* **1990**, *31*, 4557.

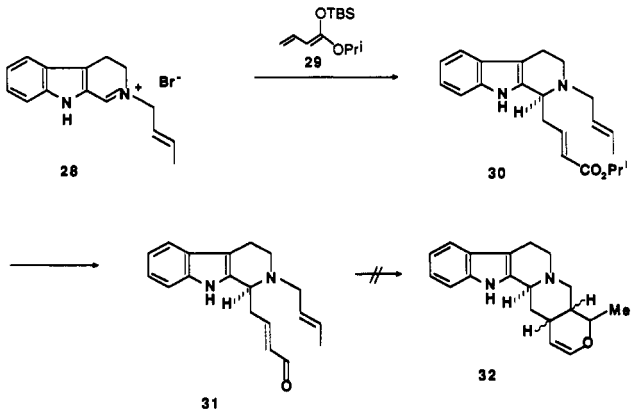
Discussion

Total Synthesis of Oxogambirtannine (2). The critical elements of our ABC ⇒ ABCD(E) approach to indole alkaloids using intramolecular [4+2] cycloaddition reactions may be exemplified by its application to a short synthesis of the yohimboid alkaloid oxogambirtannine (**2**) (Scheme II). The Diels–Alder substrate **25** was prepared by a vinylogous Mannich-type reaction involving nucleophilic addition of a *O*-silylvinylketene acetal[17] to an *N*-acyliminium salt.[18,19] Thus, reaction of the 1,1-dioxygenated butadiene **24**[20] (2 equiv) with the *N*-acyliminium salt that was generated in situ upon reaction of 3,4-dihydro-β-carboline (**22**)[21] with 2-pyrone-6-carbonyl chloride (**23**)[22] provided the 3-substituted β-carboline **25** (86%). No products derived from reaction at the α-position of **24** were isolated,[20a] nor was there any evidence of cyclocondensation between **22** and **24**.[23] Heating **25** in refluxing mesitylene in the presence of benzoquinone delivered oxogambirtannine (**2**) in 91% yield. A mixture (ca. 1:2.3) of the intermediate cycloadducts **26** and **27** could be isolated when the cyclization was conducted in the absence of benzoquinone, but the E ring of these substances was only modestly stable toward aerial oxidation.

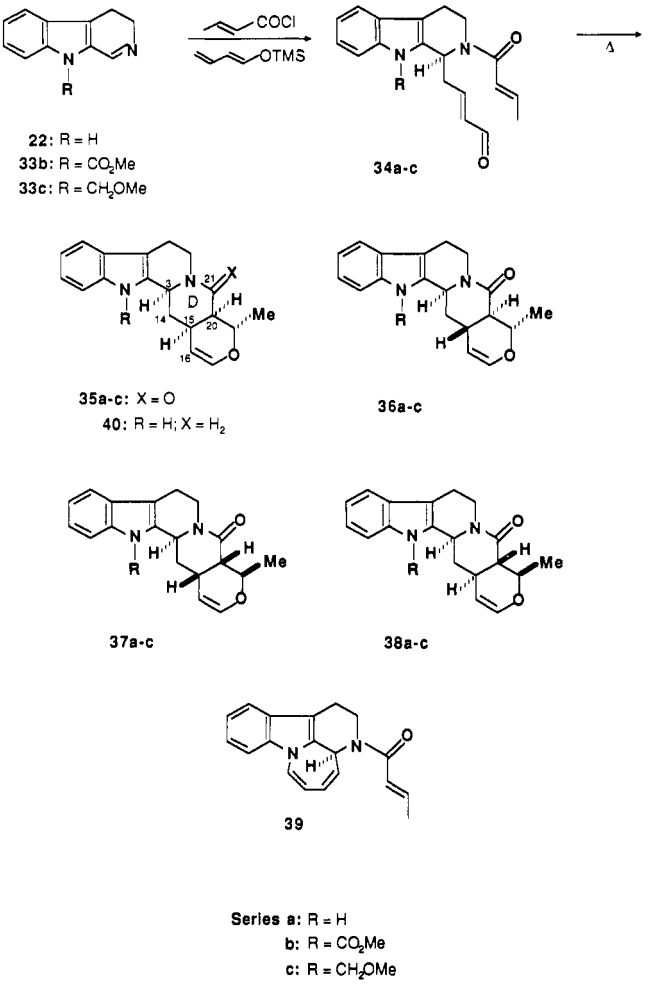
Scheme II



Scheme III



Scheme IV



Generalization of the Plan and Synthesis of Heteroyohimboid Alkaloids. The extraordinarily concise nature of the preceding synthesis of oxogambirtannine (**2**) provided the impetus to probe the generality of this novel approach to indole alkaloids. It first occurred to us that an ABC ⇒ ABCDE strategy might be advantageously combined in tandem with a hetero-Diels–Alder reaction eventuating in a succinct entry to the heteroyohimboid alkaloids. However, our initial foray (Scheme III) in this direction was not encouraging as evidenced by the following experience. N-alkylation of **22** with crotyl bromide provided the intermediate iminium salt **28** that underwent nucleophilic addition by the vinylketene acetal **29** to give the tetrahydro-β-carboline **30**. Although subsequent overreduction of the ester function (DIBAL) of **24** followed by Swern oxidation of the intermediate allylic alcohol furnished **31**, all attempts to effect its cyclization via an

(17) For reviews of silyl enol ethers and silyl dienol ethers, see: (a) Rasmussen, J. K. *Synthesis* **1977**, 91. (b) Brownbridge, P. *Ibid.* **1983**, *1*, 85.

(18) For reviews of *N*-acyl- and *N*-alkyliminium salts, see: (a) Zaugg, H. E. *Synthesis* **1984**, *85*, 181. (b) Govindachari, T. R.; Chinnasamy, P.; Rajeswari, S.; Chandrasekaran, S.; Premila, M. S.; Natarajan, S.; Nagarajan, K.; Pai, B. R. *Heterocycles* **1984**, *22*, 585. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (d) See also: Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243.

(19) For selected examples of nucleophilic additions to iminium salts, see: (a) Oppolzer, W.; Hauth, H.; Pfäffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801. (b) Torii, S.; Inokuchi, T.; Takagishi, S.; Akahoshi, F.; Uneyama, K. *Chem. Lett.* **1987**, 639. (c) Shono, T.; Matsumura, Y.; Uchida, K.; Tagami, K. *Ibid.* **1987**, 919. (d) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (e) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118. (f) Yamaguchi, R.; Otsuji, A.; Utimoto, K. *J. Am. Chem. Soc.* **1988**, *110*, 2186. (g) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345. (h) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Yoshioka, K. *Tetrahedron Lett.* **1989**, *30*, 1253. (i) Mooiweer, H. H.; Ettema, W. A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1990**, *46*, 2991.

(20) (a) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, *34*, 3205. (b) Makin, S. M.; Kruglikova, R. I.; Shavrygina, O. A.; Chernyshev, A. I.; Popova, T. P.; Tung, N. F. *J. Org. Chem. USSR (Engl. Transl.)* **1982**, *18*, 250.

(21) Whittaker, N. *J. Chem. Soc. C* **1969**, 85.

(22) Dreiding, A. S.; Allain, R.; Rey, M.; Dunkelblum, E. *Helv. Chim. Acta* **1970**, *53*, 2159.

(23) (a) For a review of cyclocondensations of imines with electron-rich dienes, see: Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; pp 34–93. See also: (b) Danishefsky, S.; Langer, M.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983. (c) Grieco, P.; Fobare, W. F. *J. Chem. Soc., Chem. Commun.* **1987**, 185. (d) Grieco, P.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 1378. (e) Brandstadter, S. M.; Ojima, I. *Tetrahedron Lett.* **1987**, *28*, 613. (f) Ryan, K. M.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Ibid.* **1987**, *28*, 2103. (g) Midland, M. M.; McLoughlin, J. I. *Ibid.* **1988**, *29*, 4653.

intramolecular hetero [4+2] cycloaddition[12,24,25] to generate cycloadducts of constitution **32** were unavailing. Decomposition pathways seemed to dominate the thermal chemistry of **31**, an observation reminiscent of earlier work in our laboratories involving other olefinic amino α,β-unsaturated aldehydes.[4f]

We reasoned at this juncture that replacement of the basic nitrogen atom N_b in **31** with an amide nitrogen might lend enhanced stability to the intermediate hetero-Diels–Alder substrate. Whereas this decision to protect and incorporate N_b as an amide nitrogen was soundly based upon our own experiences, it was not obvious a priori whether it would be necessary to protect N_a of the indole nucleus. Consequently, we conducted a series of three parallel investigations in which the nitrogen atom of the indole ring was unprotected (series a) or protected with an electron-withdrawing substituent (CO_2Me) (series b) or with a removable alkyl group (CH_2OMe) (series c) (Scheme IV). A variety of stepwise entries to the key substrates **34a–c** for the hetero-Diels–Alder reactions might be envisaged, but after considerable experimentation with longer routes, the tactic that was adopted owed its inspiration to chemistry previously exploited for the synthesis of **25**. In the event, treatment of **22** with crotonyl chloride generated an *N*-acyliminium salt in situ that underwent nucleophilic addition of 1-[(trimethylsilyl)oxy]butadiene to provide the hetero-Diels–Alder substrate **34a** (78%) in a single operation (Scheme IV). In a similar fashion, **33b** and **33c**, which were prepared in situ by reaction of **22** with either methyl chloroformate or bromomethyl methyl ether in the presence of potassium *tert*-butoxide and 18-crown-6,[26] were converted into the corresponding hetero-Diels–Alder substrates **34b** and **34c** in good overall yields.

Assemblage of the heteroyohimboid skeleton was then achieved upon thermal cyclization of **34a** to afford an easily separable mixture (ca. 9:1) of the cis and trans cycloadducts **35a** and **36a** in a combined yield of 89%. Neither of the other possible diastereomeric cycloadducts **37a** and **38a** was isolated from this reaction. *Thus, the pentacyclic framework of the heteroyohimboid alkaloids was accessible by a linear sequence requiring only four synthetic operations from commercially available tryptamine.* Further discussion of the stereochemical aspects of this cyclization will be deferred until later. It might be noted that in the early phases of this work we found it necessary to heat **34a** in the absence of traces of acid and oxygen by using carefully purified starting material. For example, in the presence of acid, variable and significant quantities of the tetracyclic dienamine **39** were isolated. The N_a-protected hetero-Diels–Alder substrates **34b** and **34c** also underwent cyclization upon heating to give mixtures of the corresponding cycloadducts **35b,c** and **36b,c** in good yields and similar ratios as was observed for the cyclization of **34a**. Since we ultimately discovered that there was no need to protect the indole ring or the indolic N–H bond in subsequent reactions, these conversions were not optimized. The ensuing discussion will accordingly be focused upon the transformations of unprotected indoles of series a with specific comment regarding the N_a-protected intermediates when chemically justified.

The initial stereochemical assignments of the cycloadducts **35a** and **36a** were based primarily upon analyses of their ^{1}H NMR spectra, and a few comments are in order. The axial nature of the proton at C(3) in **35a** was indicated by its coupling (J = 4.5, 11.7 Hz) with the two adjacent protons at C(14); the proton at C(15) was surmised to be in an axial orientation on the D ring on the basis of its coupling (J = 2.1, 11.7 Hz) with the methylene group at C(14). The anticipated trans relationship between the protons at C(19) and C(20) was supported by a coupling of 8.9 Hz. Since the signals for the protons at C(15) and C(20) overlapped with other signals in the ^{1}H NMR spectrum of **35a**, the cis stereochemistry of the DE ring fusion was ascertained from the derived tertiary amine **40**, which was prepared by reduction of **35a** with alane (2 equiv; THF; −78 °C → room temperature; 10 min; 92%) ($J_{15,20}$ = 5.0 Hz; $J_{19,20}$ = 10.1 Hz). For the minor cycloadduct **36a**, all of the requisite coupling constants could be observed. The equatorial orientation on the D ring of the proton at C(3) was indicated by its coupling (J = 3.6, 7.1 Hz) with the methylene group at C(14), whereas the axial orientation with respect to the D ring of the proton at C(15) was supported by couplings (J = 3.6, 12.0 Hz) with the adjacent protons at C(14). The trans-ring fusion of the DE ring junction was assigned on the basis of a coupling constant of 11.5 Hz between the two protons at C(15) and C(20), and the trans relationship between the protons at C(19) and C(20) was supported by J = 9.7 Hz. The veracity of these structural assignments was later established unequivocally by the subsequent transformations of **35a** and **36a** into the known natural products **3** and **44** (vide infra).

Only two functional group manipulations remained to complete the total syntheses of the heteroyohimboid alkaloids (±)-tetrahydroalstonine (**3**) and (±)-cathenamine (**4**), an unstable alkaloid not previously prepared by total synthesis,[6] from the pentacyclic cycloadduct **35a**. The first task to be undertaken was carbomethoxylation of the enol ether moiety at C(16). Treatment of **35a** with trichloroacetyl chloride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine at room temperature for 3 days gave **41a**, which was subjected to a modified haloform-type cleavage reaction by heating in methanol in the presence of triethylamine to deliver **42a** in 87% overall yield.[4f,27] Attempts to accelerate the initial C-acylation step by heating **35a** with trichloroacetyl chloride provided only traces of **41a**, with decomposition pathways prevailing. Interestingly, when the N-acylated indole **35b** was heated with neat trichloroacetyl chloride at 55 °C followed by reaction of the intermediate **41b** with methanol in the presence of triethylamine, **42b** was obtained in 86% overall yield. Thus, the presence of the *N*-carbomethoxy group on the indole nitrogen stabilized the indole moiety, thereby permitting the use of more vigorous conditions for acylation of the enol ether moiety. Attempts to effect C-acylation at C(16) of the tertiary amine **40** with trichloroacetyl chloride under a variety of conditions provided only complex mixtures of unidentified products. This protocol for installing the carbomethoxy group on the enol ether moiety at C(16) of **35a** to give **42a** should be generally applicable to the construction of vinylogous carbonates, a structural subunit found in a variety of natural products.[27b]

Completion of the syntheses of (±)-tetrahydroalstonine (**3**) and (±)-cathenamine (**4**) merely required selective addition of 2 or 1 equiv of hydride, respectively, to the lactam carbonyl at C(21) of **42**. We discovered in preliminary experiments that controlled reduction of **42a** with alane could be executed without concomitant reduction of the C(16) ester moiety, but variable mixtures of (±)-tetrahydroalstonine (**3**) and (±)-cathenamine (**4**) were typically produced upon workup. Two modified protocols were therefore devised to provide either **3** or **4**. In the event, treatment of **42a** with alane at −52 °C followed by sequential addition of MeOH, glacial acetic acid, and then excess $NaBH_3CN$ furnished **3** in 90% yield. This synthetic (±)-tetrahydroalstonine was identical except with respect to optical rotation with an authentic sample of the natural alkaloid.[28] Alternatively, delivery of 1 equiv

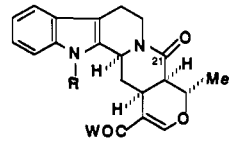
(24) For examples of intramolecular [4+2] cycloadditions involving simple α,β-unsaturated aldehydes as the 4π components, see: (a) Snider, B. B.; Dunčia, J. V. *J. Org. Chem.* **1980**, *45*, 3461. (b) Schreiber, S. L.; Meyers, H. V.; Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 8274. (c) Denmark, S. E.; Sternberg, J. A. *Ibid.* **1986**, *108*, 8277. (d) See ref 4f.

(25) For other examples of intramolecular hetero-Diels–Alder reactions involving unsaturated carbonyl compounds as dienic partners, see: (a) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696. (b) Hug, R.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1675. (c) Begley, M. J.; Crombie, L.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2402. (d) Snider, B. B.; Roush, D. M.; Killinger, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 6023. (e) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1981**, *22*, 4437. (f) Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671. (g) Takano, S.; Satoh, S.; Ogasawara, K. *Heterocycles* **1985**, *23*, 41; *J. Chem. Soc., Chem. Commun.* **1988**, 59. (h) Tietze, L. F.; Brumby, T.; Pretor, M.; Remberg, G. *J. Org. Chem.* **1988**, *53*, 810 and previous work. (i) Dolle, R. E.; Armstrong, W. P.; Shaw, A. N.; Novelli, R. *Tetrahedron Lett.* **1988**, *29*, 6349.

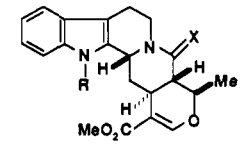
(26) (a) Meyers, A. I.; Hellring, S. *J. Org. Chem.* **1982**, *47*, 2229. (b) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *J. Org. Chem.* **1985**, *50*, 961.

(27) (a) Effenberger, F.; Maier, R.; Schönwälder, K.-H.; Ziegler, T. *Chem. Ber.* **1982**, *115*, 2766. (b) For an independent application, see: Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6755; **1986**, *108*, 4974.

of hydride to the lactam function of **42a** by treatment with lithium diethoxyaluminum hydride at −45 °C gave in 70% yield (±)-cathenamine (**4**), which had spectral properties identical with those reported in the literature.[29] In a parallel sequence of experiments, the minor cycloadduct **36a** was converted into racemic **43a**; hydride reduction of **43a** then provided (±)-19-*epi*-3-isoajmalicine (**44**),[5i] which exhibited spectral characteristics identical with those reported in the literature.[4b]

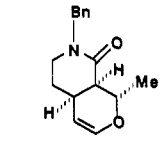


41a,b: W = CCl_3
42a,b: W = OMe

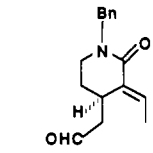


43a,b: X = O
44: R = H; X = H_2

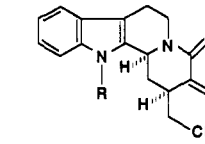
Series **a**: R = H
b: R = CO_2Me



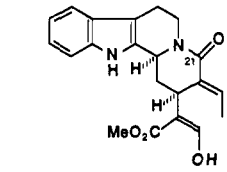
45



46



47: R = H
48: R = CH_2OCH_3



49

Extension to the Corynantheoid Alkaloids. Synthesis of (±)-Geissoschizine (5). Comparison of structures **35a** and **42a** with that of the corynantheoid alkaloid geissoschizine (**5**) reveals the tantalizing possibility that one or both of these intermediates might serve as precursors of **5**. Since control of the relative stereochemistry at C(3) and C(15) was one problem commonly encountered during previous approaches to **5**, it is notable that these centers are correctly established by the cycloaddition that provided **35a**. The critical question at this juncture regarded the feasibility of effecting stereoselective β-elimination of the hydropyran oxygen atom of either **35a** or **42a** to provide a tetracycle bearing the requisite (*E*)-ethylidene array at C(20).[30] This seemed a reasonable tactic, since we had previously discovered that **45** was converted into **46** upon reaction with sodium amide.[4f,31] In view of this precedent, it was somewhat surprising that, upon treatment of **35a** with a variety of bases, only starting material was recovered; there was no evidence for the formation of any of the desired elimination product **47**. On the other hand, reaction of **35b** with sodium amide gave a mixture (1:2–3) of the N-deprotected indole **35a** together with the ring-opened product **47**, whereas the N-alkylated analogue **35c** was smoothly converted into the tetracycle **48** by exposure to sodium amide. On the basis of examination of the ^1H NMR spectra of the crude reaction mixtures, none of the (*Z*)-ethylidene isomer of either **47** or **48** was formed in these processes.

One of our principal overall goals was to develop a concise entry to representative corynantheoid alkaloids. Consequently, protecting the indolic nitrogen in order to realize efficient cleavage of the E ring was ruled as a method of last resort, and we sought a more direct protocol. Given the above findings, we reasoned that scission of the E ring via β-elimination of a strong base or a weak leaving group (i.e., an aldehyde enolate) would not occur if the indole nitrogen atom simultaneously bore a negative charge. In this context, it seemed likely that **42a** should undergo β-elimination of the E-ring oxygen more readily than **35a**. This supposition was founded upon the premise that the leaving group in **42a** would be the stabilized enolate of an α-formyl ester rather than the considerably more basic enolate of an aldehyde as in the cases of **35a–c**. In agreement with this hypothesis, we were gratified to discover that treatment of **42a** with excess sodium amide resulted in facile β-elimination of the E-ring oxygen to give the (*E*)-ethylidene lactam **49** in excellent yield; there was no evidence for formation of the *Z* double bond isomer. This stereoselective route to the (*E*)-ethylidene array of geissoschizine represents a solution to one of the problems encountered in some previous approaches to this alkaloid, and it seems likely that this tactic may be more broadly exploited to access other corynantheoid alkaloids.

With **49** thus secured, only the superficially straightforward task of reducing the D-ring lactam function into a tertiary amine remained to complete the total synthesis of (±)-geissoschizine (**5**). However, owing to the highly functionalized nature of **49**, considerable difficulty was encountered in defining suitable conditions to achieve this deceptively simple transformation. For example, attempted reduction of **49** with a variety of aluminum-derived hydride reducing agents including diisobutylaluminum hydride and alane under a variety of conditions gave horrendous mixtures of products. Typical of the kinds of problems that were encountered during these attempts were reduction of the hydroxymethylene group and 1,4-reduction of the α,β-unsaturated lactam moiety. Several stepwise methods that were previously developed for converting a lactam to a more reactive intermediate such as an imidate, imidoyl chloride, or a thiolactam followed by reduction with $NaBH_4$ or Raney nickel also failed to effect reduction of **49** and gave instead complex mixtures of products.[32]

After considerable experimentation, we discovered two tactics, each of which involved prior protection of the hydroxymethylene moiety of **49** followed by selective hydride reduction of the lactam function, that reproducibly delivered geissoschizine (**5**). For example, protection of the hydroxymethylene group in situ as an enolate was achieved by deprotonation of **49** with lithium hexamethyldisilazide. Subsequent serial addition of Et_3Al and DIBAL-H under strictly controlled conditions provided **5** in 35% recrystallized yield together with recovered starting material (52% yield of **5** based on recovered starting material). Alternatively, the hydroxymethylene function in **49** was protected as its *tert*-butyldimethylsilyl enol ether, and this substance was converted without purification into **5** in 40% overall yield by sequential O-methylation of the lactam carbonyl oxygen atom in the presence of activated 4-Å molecular sieves followed by reduction of the intermediate imidate salt with $NaBH_4$. Use of molecular sieves was absolutely essential to the success of this reductive sequence.[32f] The (±)-geissoschizine (**5**) thus obtained by both of these procedures was spectroscopically identical with an authentic sample.[33]

Application to 2-Oxindole Alkaloids. Synthesis of (±)-Isopteropodine (6). The final challenge before us was to extend these investigations into the synthetic arena of the 2-oxindole alkaloids.

(28) We thank Professor E. Wenkert (University of California, San Diego) and Dr. M. R. Uskoković (Hoffmann-LaRoche) for providing authentic samples of natural tetrahydroalstonine (**3**).

(29) (a) Lounasmaa, M.; Kan, S.-K. *Tetrahedron* **1980**, *36*, 1607. (b) Lounasmaa, M.; Tolvanen, A. *Heterocycles* **1986**, *24*, 3229. See also ref 6a,d.

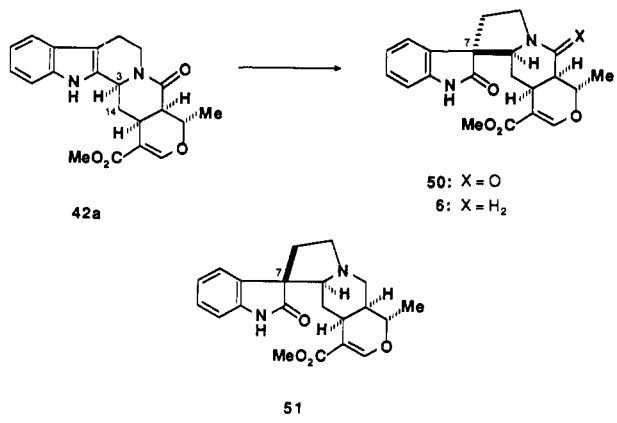
(30) For a review of methods to elaborate the ethylidene substituent in indole alkaloids, see: Bosch, J.; Bennasar, M. L. *Heterocycles* **1983**, *20*, 2471.

(31) For a related transformation to generate the ethylidene substituent, see ref 7e.

(32) For example, see: (a) Borch, R. F. *Tetrahedron Lett.* **1968**, 61. (b) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061. (c) Sundberg, R. J.; Walters, C. P.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 3730. (d) Naito, T.; Kojima, N.; Miyata, O.; Ninomiya, I. *Heterocycles* **1986**, *24*, 2117. (e) Mandal, S. B.; Giri, V. S.; Pakrashi, S. C. *Ibid.* **1988**, *27*, 11. (f) Freund, R.; Winterfeldt, E. *Liebigs Ann. Chem.* **1988**, 1007.

(33) We thank Professor H. Rapoport (University of California, Berkeley) for an authentic sample of natural geissoschizine (**5**).

Scheme V



42a

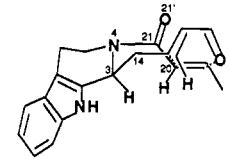
50: X = O
6: X = H_2

51

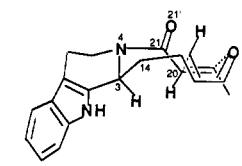
In this context, it occurred to us to examine the feasibility of effecting the oxidative transformation of **42a** into the spiro indole **50**, since this latter substance appeared to be an ideal precursor of the 2-oxindole alkaloid (±)-isopteropodine (**6**). The oxidative reorganization of indoles to 2-oxindoles for substrates in which N_b is unacylated is well documented, and a number of reliable methods are available.[34] On the other hand, such conversions involving N_b-acylated analogues have received only limited attention,[35] there being only one such account prior to the initiation of our inquiry. We therefore undertook a study to probe the synthetic potential of such rearrangements using pentacyclic and tetracyclic carbolines wherein N_b was incorporated as part of a D-ring lactam.[16c]

Our initial efforts to induce the oxidative reorganization of **42a** into **50** were most discouraging, and the $\Delta^{3,14}$-didehydro derivative of **42a** was the major product isolated from these early attempts. Ultimately, we discovered that treatment of **42a** with *tert*-butyl hypochlorite and triethylamine followed by solvolysis of the intermediate 3-chloroindolenine in aqueous methanol containing perchloric acid and silver perchlorate furnished the desired 2-oxindole **50** in 87% yield; no rearrangement occurred in the absence of acid (Scheme V). Only trace amounts (<5%) of the diastereoisomer epimeric with **50** at C(7) were detected in the crude reaction mixture. The structure of **50** was unambiguously established by single crystal X-ray analysis.[36] The high level of stereoselectivity in this process is significant since it stands in stark contrast to those oxidative rearrangements involving analogues in which N_b is not part of an amide function. As a consequence of the ready interconversion of 2-oxindole bases of types A and B by heating under basic and acidic conditions, the corresponding oxidative skeletal reorganizations involving N_b-unacylated intermediates invariably afford mixtures of stereoisomers epimeric at the C(7) spiro carbon atom.[9,34] Selective reduction of **50** with alane followed by $NaBH_3CN$ delivered in 83% yield the type A 2-oxindole alkaloid (±)-isopteropodine (**6**),[9b] which with the exception of optical properties was identical with an authentic sample.[37,38] Heating **6** in glacial acetic acid furnished an equilibrium mixture (1:3) of **6** together with the type B 2-oxindole alkaloid (±)-pteropodine (**51**).

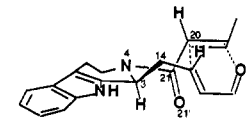
Computational Analysis of the Intramolecular Hetero-Diels–Alder Reaction. Although the cyclization of triene **34a** could have provided any of the four possible diastereoisomeric cycloadducts **35a–38a** (Scheme IV), only **35a** and **36a** were isolated. Preliminary examination of Dreiding molecular models revealed that **35a** and **36a** were likely produced via a transition state in which the chain connecting the dienic and dienophilic moieties resided in a boatlike conformation as depicted in **52** and **53**, respectively.[39] The two cycloadducts **37a** and **38a** that were not detected in the reaction mixture would have arisen from transition states wherein the connecting chain resembled a half-chairlike array corresponding to **54** and **55**. Orbital overlap for the [4+2] cycloaddition is poor in those alternative transition states in which the dienophile resides in an s-trans conformation.



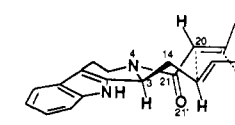
52



53



54



55

In view of the then unexpected involvement of a boatlike conformation of the D ring in the cyclization of **34a**, we sought a better understanding of the energetic and conformational factors that controlled the stereochemical course of this intramolecular cycloaddition. Toward this end, we performed a computational study that derived its inspiration from the work of Houk[40a] and employed a protocol involving a combination of semiempirical and molecular mechanics calculations.[40] Determination of the optimal geometry of the six atoms in the pericyclic transition state for the hetero-Diels–Alder reaction of **34a** was the first task, and the hetero-Diels–Alder dimerization of acrolein was selected as a simple computational model. Since no calculations of the transition-state geometry for the dimerization of acrolein had been reported, semiempirical calculations were conducted with use of the standard closed-shell, restricted Hartree–Fock (RHF) version of the AM1[41] method as implemented in the AMPAC program[42] for the eight possible pericyclic transition states for this cycloaddition.[43] The calculated heats of formation and the geometric parameters (bond lengths, bond angles, and torsional angles) are

(34) For examples of conversions of indoles to 2-alkoxyindolenines and 2-oxindoles, see: (a) Gaskell, A. J.; Radnunz, H.-E.; Winterfeldt, E. *Chem. Ber.* **1970**, *26*, 5353. (b) Ikeda, M.; Tamura, Y. *Heterocycles* **1980**, *14*, 867. (c) Awang, D. V. C.; Vincent, A.; Kindack, D. *Can. J. Chem.* **1984**, *62*, 2667. (d) Wenkert, E.; Shi, Y.-J. *Synth. Commun.* **1989**, *19*, 1071. See also ref 9a.

(35) (a) Laronze, J.-Y.; Laronze, J.; Royer, D.; Lévy, J.; Le Men, J. *Bull Soc. Chim. Fr.* **1977**, 1215. (b) Hollinshead, S. P.; Grubisha, D. S.; Bennett, D. W.; Cook, J. M. *Heterocycles* **1989**, *29*, 529. (c) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327.

(36) Lynch, V. M.; Mortimore, M.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1991**, *C47*, 234.

(37) Martin, G. E.; Sanduja, R.; Alam, M. *J. Nat. Prod.* **1986**, *49*, 406.

(38) We thank Professor M. Alam (University of Houston) for a generous sample of natural isopteropodine (**6**) for comparison.

(39) The preferential involvement of boatlike transition states in the cyclizations of related, all-carbon 1,7,9-decatrienones has been documented. See: Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915.

(40) (a) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297. See also: (b) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186. For a different perspective on the use of transition state modeling, see: (c) Menger, F. M.; Sherrod, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8071.

(41) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(42) AMPAC is available from the Quantum Chemistry Program Exchange (QCPE), Program No. 506; Indiana University: Bloomington, IN 47405.

(43) We thank Dr. Eammon Healy and Dr. James Ruiz for rendering invaluable advice and assistance during the execution of these calculations. It is noteworthy that the theoretically predicted regiochemistry for the dimerization of acrolein according to these AM1-RHF calculations, which predicted concerted transition states, is opposite to that observed experimentally.[44] An alternative method (AM1-CI),[45] which allows for biradical configurations to be included in the wave function, was then used to study the dimerization reaction. Although these AM1-CI calculations overestimated the stability of the biradical species and predicted a two-step reaction with a biradical intermediate, they did predict the correct regiochemical course of the reaction.[46] However, because of the errors associated with the large biradical character in these transition states, their geometries cannot be reliably used for modeling purposes.

(44) Alston, P. V.; Shillady, D. D. *J. Org. Chem.* **1974**, *39*, 3402 and references therein.

(45) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771.

(46) For a related account of AM1-CI calculations of the Diels–Alder reaction of acrolein and ethylene, see: Tietze, L. F.; Fennen, J.; Anders, E. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1371.

summarized in the supplementary material. These calculations indicated that each of these cycloadditions was concerted but asynchronous. It may be noted that the angle of approach for the dimerization of acrolein was found to be approximately the same as the angle of approach calculated using MINDO/3 for the cycloaddition of acrolein and ethylene.[47]

There are eight possible arrangements of two acrolein molecules in the transition state for the hetero-Diels–Alder dimerization of acrolein. However, owing to the various geometric constraints in the chain linking the diene and dienophile, only one of the four endo orientations, which corresponds to that shown in **52** and **54**, and one of the four possible exo orientations, which correlates with **53** and **55**, are applicable to the cyclization of **34a**. The geometric parameters obtained from the aforementioned AM1 calculations for these two six-center transition states were then used to constrain the corresponding six atoms of the dienophilic and dienic subunits of **34a** in the endo and exo orientations **52**/**54** and **53**/**55**, respectively. The overall conformational energies for these four possible transition states were then minimized by utilizing the default values of the normal MM2[48] force field that are preset in the MacroModel (Ver 2.0) program package.[49,50] The calculated total strain energies for the transition states thus minimized were as follows: **52** (64.1 kcal/mol); **53** (68.8 kcal/mol); **54** (71.4 kcal/mol); and **55** (75.2 kcal/mol).

An examination of the geometries produced by these molecular mechanics calculations revealed that slight distortions of the dihedral angle (ca. 2–6°) about the single bond of the diene were occurring during the calculations. We surmised that the deviations of this dihedral angle from that defined by the AM1 calculations were in response to significant torsional strain factors in the intramolecular reaction. Consequently, the initial geometries obtained for the four transition states **52**–**55** were then employed as starting geometries for a final minimization in which the dihedral angle about the s-cis bond of the heterodiene moiety was not constrained, thereby allowing atoms of the diene to alleviate any significant torsional interactions. The dihedral angle about the s-cis diene bond for the resulting transition states **52** and **54** now differed by some 4–6° from that determined by AM1 calculations, whereas for transition states **53** and **55** the deviation was 13–15°. The calculated total strain energies for these minimized transition states were in the order **52** (62.5 kcal/mol) < **53** (64.7 kcal/mol) ≪ **54** (70.9 kcal/mol) < **55** (71.3 kcal/mol). Although there were slight differences (ca. 0.5 kcal/mol) in the van der Waal and bend terms for these two sets of calculations, the major changes were in the torsional energy terms, which decreased by about 4.5 kcal/mol for transition states **53** and **55**. On the basis of these later calculations, one would predict that only **35a** and **36a** would be produced in significant amounts from the cyclization of **34a**. Moreover, the expected ratio of **35a** and **36a** would be approximately 6:1, a value not very different from the experimentally observed ratio of 8.8:1. Since the energy differences thus calculated for the transition states **52**–**55** correspond closely to our experimental results, it seems likely that the geometries for **52**–**55** so derived are reasonable.

Examination of the individual force field energies for each of the minimized transition states **52**–**55** (Table 5, supplementary material) reveals some geometric factors that seem to account for the stereochemical course of the cyclization of **34a**. The major differences between the boat/boat transition states **52** and **53** and the half-chair/boat transition states **54** and **55** lay in the torsion and bend terms with smaller discrepancies in the van der Waal terms. In this context, the boat/boat geometries **52** and **53** required minimal rotation of some 3–11° about the amide N–CO bond, whereas the half-chair/boat geometries **54** and **55** required more substantial rotations of approximately 25–35° about the N–CO bond. Thus, greater loss of amide resonance is apparently required to attain the three-dimensional array in the half-chair/boat transition states **54** and **55** relative to the boat/boat geometries **52** and **53**, thereby favoring the latter. One possible cause of the significant dissimilarity in the bending energy terms for the boat/boat and the half-chair/boat transition-state geometries was evident upon examination of the N(4)–C(3)–C(14) bond angle, which was about 110° in **52** and **53** compared to approximately 122° in **54** and **55**. Thus, the half-chair/boat transition states **54** and **55** incorporate more angle strain than the alternative boat/boat arrays **52** and **53**. The major energetic differences between the transition states **52** and **53** appear in the van der Waal and bend terms, but these deviations are too small (<0.5 kcal/mol) to allow specific comment on their relative importance. Moreover, secondary orbital interactions, which are possible in **52** but not **53**, may also play a role.[51]

Conclusions

Intramolecular hetero-Diels–Alder reactions were marshalled in the design of a unified ABC ⇒ ABCD(E) strategy for the highly stereoselective syntheses of alkaloids of the yohimboid, heteroyohimboid, and corynantheoid classes. The efficacy of the approach was convincingly established by its application to concise total syntheses of the representative indole alkaloids oxogambirtannine (**2**), (±)-tetrahydroalstonine (**3**), (±)-cathenamine (**4**), (±)-geissoschizine (**5**), and (±)-isopteropodine (**6**) in which no protective and deprotective maneuvers were required. During these investigations, useful protocols were developed for (1) installing a carbomethoxy group onto an enol ether moiety to give a vinylogous carbonate; (2) introducing the (*E*)-ethylidene array at C(20) of the corynantheoid alkaloids; and (3) inducing the stereoselective oxidative reorganization of indoles to 2-oxindoles. Not only did this latter discovery result in an efficacious route to the 2-oxindole alkaloids isopteropodine (**6**) and pteropodine (**51**), but such a procedure might also be exploited as a useful tactic in designing new entries to the more complex indole alkaloids of the *Strychnos* family. Further applications of intramolecular hetero-Diels–Alder reactions to the total synthesis of indole alkaloids constitute the subject of current investigations, the results of which will be reported in due course.

Experimental Section

General Procedures. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Diethyl ether (ether), tetrahydrofuran (THF), toluene, xylenes, and mesitylene were distilled from either sodium or potassium benzophenone ketyl immediately prior to use. Triethylamine, diisopropylamine, dimethyl sulfoxide (DMSO), and methylene chloride were distilled from calcium hydride and stored over 4-Å molecular sieves under nitrogen. All reactions involving organometallic reagents or other air-sensitive reagents were executed under an atmosphere of dry nitrogen or argon, by using oven or flame-dried glassware. Spectra were recorded on compounds that were ≥95% pure by HPLC or ^{1}H NMR spectroscopy. IR spectra of oils were recorded as thin films (NaCl plates), whereas the IR spectra of solids were determined as solutions in $CHCl_3$. The ^{1}H and ^{13}C NMR spectra were determined unless otherwise indicated as solutions in $CDCl_3$ at the indicated field; chemical shifts are expressed in parts per million (δ units) downfield from tetramethylsilane. Splitting patterns are designated as

(47) Lee, I.; Han, E. S.; Choi, J. Y. *J. Comput. Chem.* **1984**, *5*, 606.
(48) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; Caserio, M. C., Ed.; American Chemical Society: Washington, DC, 1982; see also references therein.
(49) Still, W. C. Columbia University. We thank Prof. Still for making the MacroModel (Ver. 2.0) program available.
(50) During the transition-state calculations using MacroModel, the TA-Mov button was inactive because a terminal atom (the oxygen atom) was being constrained. A geometry was considered to be "minimized" when the first derivative RMS value was ≤0.0025 kJ/Å. The block diagonal Newton–Raphson minimization method was initially employed until a first derivative RMS value of ≤0.01 kJ/Å was achieved, and then the full-matrix Newton–Raphson method was used to provide the final geometry. The force field calculations were not parameterized to include secondary orbital interactions that occur in the *endo* transition states **52** and **54** but not in the *exo* transition states **53** and **55**. Such interactions have been estimated experimentally to stabilize the *endo* transition state of an all-carbon Diels–Alder cycloaddition by 0.35–1.20 kcal.[51]
(51) (a) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297. (b) Houk, K. N. *Tetrahedron Lett.* **1970**, 2624. (c) Stephenson, L. M.; Smith, D. E.; Current, S. P. *J. Org. Chem.* **1982**, *47*, 4170. (d) Ripka, W. C.; Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186.

s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet; comp, complex multiplet; br, broad.

Methyl (±)-(*E*)-4-[2,3,4,9-Tetrahydro-2-[(2-oxo-2*H*-pyran-6-yl)carbonyl]-1*H*-pyrido[3,4-*b*]indol-1-yl]-2-butenoate (25). To a solution containing 3,4-dihydro-β-carboline (**22**)[21] (0.207 g, 1.22 mmol) and 1-(*tert*-butyldimethylsiloxy)-1-methoxybutadiene (**24**)[20] (0.450 g, 2.10 mmol) in THF (2 mL) at −78 °C was added via cannula 2-pyrone-6-carbonyl chloride[22] (0.195 g, 1.23 mmol) dissolved in THF (1 mL) precooled to −78 °C. The mixture was stirred at −78 °C for 15 min and then at room temperature for 15 min. The reaction was recooled to −78 °C, and the white precipitate was removed by suction filtration and washed with cold THF (2 × 0.5 mL) to give **25** (0.412 g, 86%), which was recrystallized from EtOH to give light lime granular crystals: mp 192–193.5 °C (dec); IR ν 3455, 2970–2910, 2855, 1750, 1730, 1650 cm^{-1}; ^{1}H NMR (500 MHz) δ 8.06 (br s, 1 H), 7.48 (d, *J* = 7.7 Hz, 1 H), 7.43 (dd, *J* = 9.5, 6.5 Hz, 1 H), 7.35 (d, *J* = 7.7 Hz, 1 H), 7.20 (br t, *J* = 7.7 Hz, 1 H), 7.15–7.04 (comp, 2 H), 6.68 (d, *J* = 6.5 Hz, 1 H), 6.45 (d, *J* = 9.5 Hz, 1 H), 5.98 (d, *J* = 15.5 Hz, 1 H), 5.75 (t, *J* = 6.6 Hz, 1 H), 4.16 (dd, *J* = 4.9, 13.9 Hz, 1 H), 3.74 (s, 3 H), 3.59–3.51 (comp, 1 H), 3.19–2.51 (comp, 4 H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 165.6, 161.0, 159.4, 154.5, 144.4, 143.8, 136.0, 132.3, 126.0, 123.0, 121.2, 118.6, 117.8, 116.8, 111.1, 106.7, 105.7, 51.1, 48.8, 41.4, 36.4, 21.6; mass spectrum, *m/z* 392.1378 ($C_{22}H_{20}N_2O_5$ requires 392.1372), 348, 293, 169, 156, 144 (base). Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.01; H, 5.37; N, 6.95.

Methyl 5,7,8,13-Tetrahydro-5-oxobenz[*g*]indolo[2,3-*a*]quinolizine-1-carboxylate (Oxogambirtannine) (2). A solution of **25** (54 mg, 0.138 mmol) and benzoquinone (0.031 g, 0.283 mmol) in degassed (freeze/thaw, 3 cycles under vacuum) mesitylene (10 mL) was heated in a sealed glass tube (oil bath, 180 °C) for 48 h. After removal of the solvent under vacuum, the residue was dissolved in EtOAc (10 mL) and the organic solution was washed with 5% NaOH (3 × 10 mL), 5% HCl (1 × 10 mL), H_2O (1 × 10 mL) and saturated NaCl (1 × 10 mL) and dried ($MgSO_4$). The crude material was purified by HPLC (1:4 EtOAc/hexanes) to give **2** (43 mg, 91%) as a yellow solid, which was recrystallized from MeOH to give fine yellow needles: mp 206–206.5 °C (dec) (lit.[52] mp 205 °C); IR ν 3465, 3020, 2970, 2870, 1725, 1670, 1630, 1160 cm^{-1}; ^{1}H NMR (300 MHz) δ 9.03 (br s, 1 H), 8.61 (d, *J* = 7.8 Hz, 1 H), 8.24 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.95 (s, 1 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.36–7.08 (comp, 4 H), 4.45 (t, *J* = 6.6 Hz, 2 H), 3.88 (s, 3 H), 3.06 (t, *J* = 6.6 Hz, 2 H); ^{13}C NMR (75 MHz) δ 167.1, 162.0, 138.1, 136.5, 135.7, 133.4, 133.3, 128.1, 126.4, 126.1, 124.8, 124.4, 124.0, 120.4, 119.3, 114.4, 111.5, 96.9, 52.1, 40.7, 19.7; mass spectrum, *m/z* 344.1153 (base) ($C_{21}H_{16}N_2O_3$ requires 344.1161), 329, 311, 284, 255, 169.

Methyl (±)-(3α,16α)-17,18,19,20-Tetradehydro-21-oxoyohimban-16-carboxylate (26) and Methyl (±)-(3β,16α)-17,18,19,20-Tetradehydro-21-oxoyohimban-16-carboxylate (27). A solution of **25** (0.202 g, 0.515 mmol) in degassed (freeze/thaw, 3 cycles under vacuum) xylenes (25 mL) in a sealed glass tube was heated at 145 °C (oil bath) for 12 h. After cooling, the tube was opened, the solvent was removed in vacuo, and the crude mixture (ca. 1:2.3) of cycloadducts **26** and **27** was separated by HPLC (1:2 EtOAc/hexanes) to give **26** (0.050 g, 27%) and **27** (0.113 g, 68%) as light yellow solids that were recrystallized from MeOH under nitrogen.

Data for **26**: mp 188–198 °C (dec); IR ν 3465, 3010, 2970, 2940, 2860, 1750, 1670, 1630, 1330, 1285 cm^{-1}; ^{1}H NMR (360 MHz) δ 8.04 (br s, 1 H), 7.51 (d, *J* = 7.5 Hz, 1 H), 7.31 (d, *J* = 7.5 Hz, 1 H), 7.23 (dd, *J* = 5.5, 2.5 Hz, 1 H), 7.18 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.12 (td, *J* = 7.5, 1.2 Hz, 1 H), 6.23 (ddd, *J* = 9.5, 5.5, 2.9 Hz, 1 H), 5.96 (br d, *J* = 9.5 Hz, 1 H), 5.26–5.19 (comp, 1 H), 4.90 (br d, *J* = 12.3 Hz, 1 H), 3.83 (s, 3 H), 3.35–3.17 (comp, 2 H), 2.98–2.80 (comp, 3 H), 2.63 (dt, *J* = 12.3, 3.6 Hz, 1 H), 1.68 (q, *J* = 12.3 Hz, 1 H); ^{13}C NMR (90 MHz) δ 173.5, 162.8, 136.5, 132.4, 129.4, 128.7, 128.0, 126.8, 125.6, 122.3, 119.9, 118.4, 110.9, 109.9, 52.6, 52.4, 47.1, 40.2, 35.3, 33.6, 20.9; mass spectrum, *m/z* 348.1472 (base) ($C_{21}H_{20}N_2O_3$ requires 348.1474), 289, 169, 156, 144. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.12; H, 5.84; N, 8.04.

Data for **27**: mp 188–198 °C (dec); IR ν 3440, 2980, 2935, 2920, 2840, 1730, 1650, 1610, 1460, 1265 cm^{-1}; ^{1}H NMR (360 MHz) δ 8.32 (br s, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.37 (d, *J* = 7.6 Hz, 1 H), 7.17 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.10 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.05 (dd, *J* = 5.5, 2.9 Hz, 1 H), 6.09 (ddd, *J* = 9.5, 5.5, 3.9 Hz, 1 H), 5.94 (br d, *J* = 9.5 Hz, 1 H), 5.19–5.01 (comp, 1 H), 4.96 (br s, 1 H), 3.81 (s, 3 H), 3.30 (dt, *J* = 17.7, 2.8 Hz, 1 H), 3.14–2.97 (comp, 3 H), 2.77–2.66 (comp, 1 H), 2.61 (dt, *J* = 13.8, 3.8 Hz, 1 H), 2.09 (ddd, *J* = 13.8, 11.7, 5.2 Hz, 1 H); ^{13}C NMR (90 MHz) δ 173.4, 164.0, 136.2, 133.0, 129.2, 128.5, 127.5, 127.2, 125.2, 122.1, 119.8, 118.2, 111.3, 110.9, 53.1, 52.4, 46.6, 43.6, 31.0, 30.7, 20.9; mass spectrum, *m/z* 348.1471 (base) ($C_{21}H_{20}N_2O_3$ requires 348.1474), 289, 169, 156, 144. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.28; H, 5.89; N, 8.05.

1-(4-Oxo-2-buten-4-yl)-2-crotonyl-1,2,3,4-tetrahydro-β-carboline (34a). To a solution of freshly recrystallized (from ether) 3,4-dihydro-β-carboline (**22**)[21] (0.97 g, 5.71 mmol) in THF (20 mL) at −78 °C was added 1-[(trimethylsilyl)oxy]butadiene[20] (4.75 g, 33.4 mmol) followed by crotonyl chloride (0.82 g, 7.83 mmol). The mixture was stirred at −78 °C for 10 min and at room temperature for 1.25 h, at which time it was added to saturated $NaHCO_3$ (300 mL) and EtOAc (400 mL). The layers were separated, and the organic layer was washed consecutively with H_2O (300 mL) and saturated NaCl (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), and silica gel (2.0 g) was added. The mixture was concentrated under reduced pressure, the residue was suspended in a minimum amount of CH_2Cl_2, and the slurry was applied to a column of silica gel (60 g) and eluted with hexanes/EtOAc (1:1) followed by 10% CH_2Cl_2 in hexanes/EtOAc (1:1) to give **34a** (1.37 g, 78%) as a light yellow solid, which was recrystallized from EtOH to give a white powder: mp 187–188.5 °C (dec); IR ν 3240, 1690, 1660, 1610, 1450, 1430 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.49 (br s, 1 H), 9.18 (d, *J* = 7.9 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.8 Hz, 1 H), 7.17–7.06 (comp, 2 H), 7.03–6.91 (m, 1 H), 6.78–6.68 (m, 1 H), 6.41 (br d, *J* = 15.0 Hz, 1 H), 6.09–6.05 (m, 1 H), 5.97 (dd, *J* = 15.5, 7.9 Hz, 1 H), 4.24–4.19 (m, 1 H), 3.49–3.39 (m, 1 H), 2.98–2.74 (comp, 4 H), 1.95 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, 3:1 DMSO-d_6/$CDCl_3$) δ 193.5, 166.6, 153.0, 142.6, 136.5, 134.8, 132.7, 126.6, 122.1, 121.7, 119.6, 118.1, 111.2, 108.1, 48.8, 40.6, 38.0, 22.2, 18.2; mass spectrum, *m/z* 308.1530 ($C_{19}H_{20}N_2O_2$ requires 308.1525), 289, 170 (base), 142, 69. Anal. Calcd for $C_{19}H_{20}N_2O_2 \cdot H_2O$: C, 72.38; H, 6.67; N, 8.89. Found: C, 72.78; H, 6.76; N, 8.64.

16-Decarbomethoxy-21-oxotetrahydroalstonine (35a) and 16-Decarbomethoxy-19-epi-3-iso-21-oxoajmalicine (36a). A solution of purified (recrystallized twice from EtOH) **35a** (0.553 g, 1.79 mmol) in degassed mesitylene (200 mL) was heated at reflux for 40 h, whereupon the solvent was removed under vacuum (5 mmHg). The residue was dissolved in CH_2Cl_2 (50 mL), and silica gel (1.0 g) was added. The solvent was removed under reduced pressure, and the residue was applied as a slurry in CH_2Cl_2 (5 mL) to a column of silica gel (25 g). The column was eluted with 2:1 hexanes/EtOAc followed by 1:1 hexanes/EtOAc to yield **35a** (0.445 g, 80%) and **36a** (0.051 g, 9%).

Data for **35a**: recrystallized from EtOH; mp 255–257 °C (dec); IR ν 3410, 1645, 1435, 1320, 1250 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.89 (br s, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.19 (td, *J* = 7.8, 1.0 Hz, 1 H), 7.13 (td, *J* = 7.6, 1.0 Hz, 1 H), 6.43 (d, *J* = 6.0 Hz, 1 H), 5.20–5.17 (m, 1 H), 4.77 (dd, *J* = 6.0, 4.5 Hz, 1 H), 4.76–4.74 (m, 1 H), 3.97 (dq, *J* = 8.9, 6.3 Hz, 1 H), 2.90–2.79 (comp, 3 H), 2.67–2.61 (comp, 2 H), 2.49–2.45 (m, 1 H), 1.78 (dt, *J* = 13.4, 11.7 Hz, 1 H), 1.45 (d, *J* = 6.3 Hz, 3 H); irradiation of resonances at δ 4.76 gave dd at δ 2.49 (*J* = 13.4, 2.1 Hz) and at δ 2.67 gave dd at δ 2.49 (*J* = 13.4, 4.5 Hz); ^{13}C NMR (125 MHz) δ 167.6, 144.8, 136.2, 132.9, 126.8, 122.3, 120.0, 118.4, 111.0, 109.5, 102.2, 69.9, 53.7, 46.6, 40.4, 34.4, 28.5, 21.1, 19.7; mass spectrum, *m/z* 308.1534 (base) ($C_{19}H_{20}N_2O_2$ requires 308.1525), 307, 265, 237, 169, 143. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.70; H, 6.55; N, 8.94.

Data for **36a**: recrystallized from toluene; mp 131.5–133 °C (dec); IR ν 3420, 2900, 1650, 1450, 1420, 1240, 1060 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (br s, 1 H), 7.37 (d, *J* = 7.7 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.96 (td, *J* = 7.4, 0.6 Hz, 1 H), 6.36 (dd, *J* = 6.0, 2.1 Hz, 1 H), 5.02 (m, 1 H), 4.78 (dd, *J* = 6.1, 1.4 Hz, 1 H), 4.55 (ddd, *J* = 12.8, 5.3, 1.4 Hz, 1 H), 3.90 (dq, *J* = 9.7, 6.1 Hz, 1 H), 2.96 (td, *J* = 12.8, 4.3 Hz, 1 H), 2.77–2.68 (m, 1 H), 2.61 (br d, *J* = 15.2 Hz, 1 H), 2.43 (dt, *J* = 12.0, 3.6 Hz, 1 H), 2.20 (dd, *J* = 11.5, 9.7 Hz, 1 H), 2.12 (br t, *J* = 12.0 Hz, 1 H), 2.04 (td, *J* = 12.0, 7.1 Hz, 1 H), 1.53 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz) δ 170.5, 144.1, 136.3, 133.0, 127.3, 122.4, 120.0, 118.4, 111.0 (2 C), 102.1, 72.5, 52.5, 48.2, 41.8, 35.1, 29.5, 21.4, 20.6; mass spectrum, *m/z* 308.1516 ($C_{19}H_{20}N_2O_2$ requires 308.1525), 293, 171, 143 (base), 69, 41.

16-Decarbomethoxytetrahydroalstonine (40). To a solution of alane (0.99 mmol) in THF (5 mL) at −78 °C was added dropwise a solution of **35a** (26 mg, 0.09 mmol) in THF (1.5 mL), and the solution was stirred at −78 °C for 40 min followed by 10 min at room temperature. After addition of THF/H_2O (1:1 v/v; 1 mL), ether (5 mL), EtOAc (10 mL), solid NaCl, and Na_2SO_4 were added and the resultant mixture was filtered through a plug of basic alumina. The filtrate was concentrated under reduced pressure to provide **40** (23 mg, 92%): IR ν 3440, 2900, 2800, 2750 cm^{-1}; ^{1}H NMR (300 MHz, 3:1 DMSO-d_6/$CDCl_3$) δ 7.84 (br s, 1 H), 7.44 (br d, *J* = 7.7 Hz, 1 H), 7.26 (br d, *J* = 8.0 Hz, 1 H), 7.14–7.04 (comp, 2 H), 6.32 (d, *J* = 6.0 Hz, 1 H), 4.74 (dd, *J* = 6.0, 5.0

(52) Merlini, L.; Mondelli, R.; Nasini, G.; Hesse, M. *Tetrahedron* **1967**, *23*, 3129.

Hz, 1 H), 4.29 (dq, J = 10.1, 6.1 Hz, 1 H), 3.15 (br d, J = 12.0 Hz, 1 H), 3.07 (br d, J = 12.4 Hz, 1 H), 2.96–2.86 (comp, 2 H), 2.67–2.45 (comp, 3 H), 2.19 (apparent dq, J = 12.0, 5.0 Hz, 1 H), 2.08–2.03 (m, 1 H), 1.78–1.75 (m, 1 H), 1.58 (q, J = 12.0 Hz, 1 H), 1.32 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, 3:1 DMSO-d_6/$CDCl_3$) δ 141.5, 134.2, 133.5, 124.8, 118.4, 116.4, 115.5, 109.1, 104.4, 103.1, 68.1, 58.0, 54.1, 51.3, 33.7, 29.1, 19.7, 16.7 (2 C); mass spectrum, m/z 294.1735 (base) ($C_{19}H_{22}N_2O$ requires 294.1732), 251, 223, 169, 156.

21-Oxotetrahydroalstonine (42a). A mixture of **35a** (0.20 g, 0.65 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.55 g, 2.68 mmol), and trichloroacetyl chloride (0.98 g, 5.37 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 3 days, at which point the solvent was removed under reduced pressure and the residual trichloroacetyl chloride was removed under vacuum (0.5 mmHg). To the resultant residue was added MeOH (8 mL) and Et_3N (8 mL), and this mixture was heated at 55 °C for 5 h. The solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel; 0 → 2% MeOH/$CHCl_3$ gradient) to give **42a** (0.21 g, 87%) as a light yellow solid, which upon recrystallization from toluene gave white needles: mp 245–246 °C (dec); IR ν 3410, 2890, 1720, 1660, 1450, 1325, 1240 cm^{-1}; ^{1}H NMR (360 MHz) δ 8.08 (br s, 1 H), 7.63 (s, 1 H), 7.49 (d, J = 7.6 Hz, 1 H), 7.30 (d, J = 7.6 Hz, 1 H), 7.18 (t, J = 7.6 Hz, 1 H), 7.12 (t, J = 7.6 Hz, 1 H), 5.20–5.14 (m, 1 H), 4.87–4.82 (m, 1 H), 4.10–4.02 (m, 1 H), 3.76 (s, 3 H), 3.11–3.06 (m, 1 H), 2.91–2.77 (comp, 4 H), 2.58 (dd, J = 10.1, 5.1 Hz, 1 H), 1.67 (q, J = 12.4 Hz, 1 H), 1.52 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (90 MHz) δ 167.4, 166.6, 156.0, 136.4, 132.8, 126.6, 122.0, 119.7, 118.2, 111.0, 108.9, 107.1, 71.6, 53.9, 51.1, 45.4, 40.4, 32.9, 28.3, 21.1, 19.4; mass spectrum, m/z 366.1576 ($C_{21}H_{22}N_2O_4$ requires 366.1580), 366, 263, 169, 149, 143, 129, 69 (base). Anal. Calcd for $C_{21}H_{22}N_2O_4$·0.5 H_2O: C, 67.20; H, 6.17; N, 7.46. Found: C, 66.86; H, 5.74; N, 7.16.

19-Epi-3-iso-21-oxoajmalicine (43a). With use of the procedure described in the previous experiment for preparation of **42a**, **36a** was converted to **43a** in 65% yield as a light yellow solid, which was recrystallized from MeOH to give white needles: mp 193–194.5 °C (dec); IR ν 3390, 2890, 1690, 1650, 1275, 1200, 1015 cm^{-1}; ^{1}H NMR (360 MHz) δ 8.40 (br s, 1 H), 7.56 (d, J = 1.5 Hz, 1 H), 7.45 (d, J = 7.5 Hz, 1 H), 7.30 (d, J = 7.8 Hz, 1 H), 7.16–7.06 (comp, 2 H), 4.89–4.86 (m, 1 H), 4.78–4.70 (m, 1 H), 4.02 (dq, J = 10.2, 6.0 Hz, 1 H), 3.68 (s, 3 H), 3.16 (dt, J = 13.7, 3.7 Hz, 1 H), 3.04–2.91 (comp, 2 H), 2.71–2.66 (m, 1 H), 2.46 (dddd, J = 11.6, 11.6, 3.9, 1.5 Hz, 1 H), 2.23 (dd, J = 11.6, 10.2 Hz, 1 H), 1.89 (ddd, J = 13.7, 11.6, 6.8 Hz, 1 H), 1.70 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz) δ 169.2, 167.0, 156.1, 136.2, 133.1, 127.1, 122.0, 119.7, 118.0, 111.2, 110.2, 106.7, 74.1, 53.1, 51.0, 48.2, 41.9, 32.2, 29.4, 21.0, 20.3; mass spectrum, m/z 366.1583 ($C_{21}H_{22}N_2O_4$ requires 366.1580), 366, 169, 156, 144, 143 (base), 69.

Tetrahydroalstonine (3). To a solution of **42a** (68 mg, 0.18 mmol) in THF (3.5 mL) at −52 °C was added alane (0.37 mmol) in THF (1.1 mL), and the solution was stirred at −52 °C for 50 min. After addition of MeOH (3.5 mL) at −52 °C, the mixture was stirred at room temperature for 10 min, whereupon $NaCNBH_3$ (353 mg, 5.62 mmol) and glacial acetic acid (0.05 mL) were added. The resultant mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was dissolved in 1:1 hexanes/EtOAc (25 mL), and this solution was washed with saturated $NaHCO_3$ (2 × 15 mL) and saturated NaCl (1 × 10 mL) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel; 1:4 hexanes/EtOAc) provided racemic **3** (58 mg, 90%) as a white solid. The ^{1}H and ^{13}C NMR spectra of this sample were superimposable with spectra taken of an authentic sample:[28] ^{1}H NMR (360 MHz) δ 7.87 (br s, 1 H), 7.56 (s, 1 H), 7.44 (d, J = 7.3 Hz, 1 H), 7.27 (d, J = 7.7 Hz, 1 H), 7.14–7.05 (comp, 2 H), 4.53–4.45 (m, 1 H), 3.75 (s, 3 H), 3.33–3.29 (m, 1 H), 3.10 (dd, J = 12.3, 1.8 Hz, 1 H), 2.97–2.87 (comp, 2 H), 2.87–2.66 (comp, 3 H), 2.57–2.45 (comp, 2 H), 1.71–1.68 (m, 1 H), 1.52 (q, J = 12.2 Hz, 1 H), 1.40 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz) δ 168.3, 155.9, 136.0, 134.4, 127.1, 121.2, 119.3, 118.0, 110.9, 109.3, 107.9, 72.4, 59.7, 56.1, 53.4, 51.2, 38.3, 34.1, 31.2, 21.6, 18.4.

19-Epi-3-isoajmalicine (44). To a solution of **43a** (63 mg, 0.17 mmol) in THF (3 mL) at −22 °C was added alane (0.70 mmol) in THF (1.4 mL). The resulting solution was stirred at −22 °C for 11 min, at which time MeOH (1.0 mL) was added. After the mixture was warmed to room temperature, it was filtered through a pad of neutral alumina by using EtOAc as the eluent. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (basic alumina, 0.5 g; 1:2 hexanes/EtOAc) to give **44** (19 mg, 32%). The ^{1}H and ^{13}C spectra of this compound corresponded to values reported in the literature:[4b] ^{1}H NMR (300 MHz) δ 8.17 (br s, 1 H), 7.52 (s, 1 H), 7.47 (d, J = 7.6 Hz, 1 H), 7.38 (d, J = 7.9 Hz, 1 H), 7.18–7.07 (comp, 2 H), 4.54–4.53 (m, 1 H), 3.73 (s, 3 H), 3.56 (dq, J = 9.9, 6.3 Hz, 1 H), 3.34 (apparent dd, J = 8.9, 3.0 Hz, 2 H), 3.13 (dt, J = 13.7, 2.5 Hz, 1 H), 3.07–2.95 (m, 1 H), 2.77 (dd, J = 10.8, 3.4 Hz, 1 H), 2.63–2.57 (m, 1 H), 2.49 (t, J = 10.8 Hz, 1 H), 2.00–1.92 (m, 1 H), 1.67–1.56 (comp, 2 H), 1.28 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz) δ 167.4, 156.0, 135.8, 132.8, 127.6, 121.5, 119.4, 117.9, 111.2, 108.0, 107.8, 75.4, 53.9, 51.0, 50.9, 47.0, 44.0, 31.3, 31.0, 18.0, 16.9.

Cathenamine (4). To a solution of **42a** (30 mg, 0.081 mmol) in THF (1.8 mL) at −78 °C under an argon atmosphere was added dropwise over 2 min, $LiAlH_2(OEt)_2$ (0.82 mL of 0.5 M, 0.41 mmol). The solution was warmed to −45 °C for 2 h and quenched with MeOH (1 mL). The mixture was poured into cold saturated NH_4Cl (3 mL) and extracted with EtOAc (4 × 5 mL). The combined organic phases were washed with saturated NaCl, dried (Na_2SO_4), filtered through Celite, and concentrated under reduced pressure, giving **4** (20 mg, 72%) as a pale yellow, viscous oil: IR ($CHCl_3$) ν 3470, 1680, 1615, 1438, 1375, 1298, 1190 cm^{-1}; UV (ethanol) λ 290.5, 280, 228 nm; ^{1}H NMR (360 MHz) δ 8.04 (s, 1 H), 7.54 (d, J = 1.3 Hz, 1 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.16 (ddd, J = 8.0, 7.1, 1.2 Hz, 1 H), 7.10 (ddd, J = 7.5, 7.1, 0.9 Hz, 1 H), 6.18 (d, J = 1.8 Hz, 1 H), 4.63 (q, J = 6.3 Hz, 1 H), 4.28 (dd, J = 11.5, 2.1 Hz, 1 H), 3.73 (s, 3 H), 3.52 (dd, J = 11.1, 5.6 Hz, 1 H), 3.31 (ddd, J = 11.2, 5.7, 2.4 Hz, 1 H), 3.27 (dd, J = 11.2, 4.1 Hz, 1 H), 3.20 (ddd, J = 12.8, 5.6, 2.1 Hz, 1 H), 2.89 (m, 1 H), 2.73 (br d, J = 14.9 Hz, 1 H), 1.46 (ddd, J = 12.8, 11.5, 11.1 Hz, 1 H), 1.42 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (90 MHz) 168.0, 154.6, 136.1, 133.9, 133.5, 127.0, 121.6, 119.4, 118.0, 110.9, 108.4, 107.7, 104.0, 76.5, 52.4, 50.9, 49.3, 33.6, 27.5, 22.2, 20.4; mass spectrum, m/z 350.16155 ($C_{21}H_{22}N_2O_3$ requires 350.16304), 350, 249, 190, 44 (base).

21-Oxogeissochizine (49). To a solution of sodium amide (492 mg, 12.62 mmol) in THF (18 mL) under an argon atmosphere was added via cannula **42a** (402 mg, 1.09 mmol) in THF (18 mL). The solution was stirred at room temperature for 2.5 h, cooled to 0 °C, and quenched with MeOH (4 mL). The mixture was poured into saturated NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with saturated NaCl, dried (Na_2SO_4), filtered through Celite, and concentrated under reduced pressure, giving **49** (386 mg, 96%) as a light yellow solid, which was recrystallized from EtOH to give a white powder: mp 161–162 °C; IR (Nujol) ν 3360, 3270, 1693, 1640, 1615, 1572, 1308, 1192, 1112, 744 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.90 (s, 1 H), 10.83 (d, J = 5.5 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.41 (d, J = 7.7 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 7.03 (ddd, J = 8.0, 7.5, 1.0 Hz, 1 H), 6.96 (ddd, J = 7.7, 7.5, 1.0 Hz, 1 H), 6.47 (qd, J = 7.3, 2.6 Hz, 1 H), 4.77 (dd, J = 12.1, 4.5 Hz, 1 H), 4.66 (d, J = 10.8 Hz, 1 H), 4.03 (m, 1 H), 3.51 (s, 3 H), 2.84 (ddd, J = 12.2, 12.1, 3.8 Hz, 1 H), 2.79 (m, 1 H), 2.64 (m, 1 H), 2.45 (ddd, J = 12.6, 6.9, 2.5 Hz, 1 H), 1.78 (ddd, J = 12.6, 12.2, 10.8 Hz, 1 H), 1.58 (dd, J = 7.3, 1.6 Hz, 3 H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 167.1, 166.3, 154.2, 136.2, 134.2, 133.8, 131.9, 126.1, 120.8, 118.4, 117.6, 110.9, 109.8, 107.1, 50.9, 50.4, 38.7, 34.8, 29.9, 20.5, 13.4; mass spectrum, m/z 366.1565 (base) ($C_{21}H_{22}N_2O_4$ requires 366.1580), 351, 334, 263, 169.

Geissoschizine (5). Method A. To a solution of hexamethyldisilazane (81 mg, 0.5 mmol) in THF (4 mL) at 0 °C under an argon atmosphere was added *n*-BuLi in hexane (0.22 mL of 2.5 M, 0.55 mmol). The mixture was stirred for 15 min and cooled to −78 °C, and a solution of **49** (91 mg, 0.25 mmol) in THF (4 mL) was added. After 30 min, triethylaluminum (0.27 mL of 1.9 M, 0.51 mmol) was added, the solution was maintained at −78 °C for 15 min, and then DIBAL (0.75 mL of 1 M, 0.75 mmol) was added. The solution was stirred for 10 min at −78 °C, 30 min at −45 °C, and 3 h at −10 °C, at which time the mixture was quenched with MeOH (1 mL), taken up into EtOAc (5 mL), and extracted with 10% HCl (3 × 10 mL). The organic phase was washed with saturated NaCl (10 mL), dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (silica gel, 3 g; 1:1 hexanes/EtOAc), giving recovered **49** (32 mg, 33%). The combined acid aqueous phases were basified with KOH and extracted with $CHCl_3$ (3 × 10 mL). The basic organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by recrystallization from MeOH and combined with **5** recovered after flash chromatography (silica gel, 2 g; 1:3 hexanes/EtOAc) of the mother liquor, giving **5** (32 mg, 35%; 52% based upon recovered starting **49**), which was spectroscopically identical with an authentic sample,[33] as a white solid: mp 184–185.5 °C (lit.[7e] mp 187–189 °C); IR (Nujol) ν 3185, 1695, 1590, 1300, 1260, 1100, 770, 738 cm^{-1}; UV (ethanol) λ 288.5, 264.5, 223.5, 203.5 nm; ^{1}H NMR (360 MHz) δ 7.84 (s, 1 H), 7.78 (br s, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.32 (d, J = 7.9 Hz, 1 H), 7.17 (dd, J = 7.9, 7.1 Hz, 1 H), 7.11 (dd, J = 7.8, 7.1 Hz, 1 H), 5.41 (q, J = 6.4 Hz, 1 H), 4.49 (d, J = 11.5 Hz, 1 H), 3.95 (dt, J = 13.5, 2.2 Hz, 1 H), 3.84 (dd, J = 11.2, 6.3 Hz, 1 H), 3.68 (s, 3 H), 3.21 (m, 2 H), 3.07 (m, 1 H), 2.82 (br d, J = 15.8 Hz, 1 H), 2.73 (td, J = 11.6, 4.0 Hz, 1 H), 2.62 (ddd, J = 13.0, 11.5, 6.3 Hz, 1 H), 2.11 (ddd, J = 13.0, 11.2, 1.9 Hz, 1 H), 1.82 (dd, J = 6.4 Hz, 3 H); ^{13}C NMR (90 MHz, DMSO-d_6) δ 168.9, 159.5, 136.2, 134.1 (2 C), 126.1, 120.8, 119.5, 118.5, 117.6, 110.9, 107.9,

105.8, 60.2, 55.4, 50.5, 50.1, 33.3, 30.4, 20.3, 12.6; mass spectrum, *m/z* 352.1784 ($C_{21}H_{24}N_2O_3$ requires 352.1787), 352, 337, 323, 251, 169 (base), 156.

Method B. To a stirred solution containing **49** (23 mg, 0.064 mmol) and 2,6-lutidine (0.023 mL, 0.20 mmol) in CH_2Cl_2 (1.5 mL) under argon at −20 °C was added dropwise *tert*-butyldimethylsilyl triflate (0.044 mL, 0.19 mmol), and the reaction mixture was stirred for 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1.5 mL) and then CH_2Cl_2 (10 mL), and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 × 3 mL), and the combined organic fractions were dried (Na_2SO_4/K_2CO_3, 1:1) and concentrated under reduced pressure. Without further purification, the intermediate 17-(silyloxy)-21-oxogeissoschizine was dissolved in CH_2Cl_2 (2 mL) under argon, and trimethyloxonium tetrafluoroborate (42 mg, 0.28 mmol) and freshly powdered 4-Å molecular sieves (0.15 gm) were added. The reaction mixture was stirred overnight at ambient temperature, whereupon it was cooled to 0–5 °C and diluted with MeOH (1.5 mL) followed immediately by the portionwise addition of $NaBH_4$ (11 mg, 0.28 mmol). The reaction was stirred for 15 min before being partitioned between saturated aqueous Na_2CO_3 solution (2 mL) and CH_2Cl_2 (10 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 3 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (130 × 20 mm silica gel using 4% MeOH in CH_2Cl_2 as elutant) to deliver **5** (9.0 mg, 40%) that had spectral properties identical with those of the above sample.

21-Oxoisopteropodine (50). To a solution containing **42a** (0.167 g, 0.45 mmol) and triethylamine (0.07 mL, 0.50 mmol) in CH_2Cl_2 (5 mL) at 0–5 °C under argon was added dropwise a solution of *tert*-butyl hypochlorite (0.071 mL, 0.60 mmol) in CCl_4 (0.8 mL) over 15 min. After the addition was complete, the reaction mixture was diluted with MeOH (6 mL) followed by the addition of silver perchlorate (0.147 g, 0.70 mmol) and aqueous perchloric acid (0.01 mL). The resulting mixture was allowed to warm slowly to room temperature and stirred overnight, whereupon CH_2Cl_2 (20 mL) was added and the mixture washed with saturated aqueous $NaHCO_3$ (1 × 5 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (95 × 40 mm neutral alumina (Brokmann Grade III) using 2% MeOH in CH_2Cl_2 as elutant) to deliver **50** as a pale yellow solid (0.139 g, 87%), which was recrystallized from benzene to provide **50** as a white solid: mp 246.5–247 °C (dec); IR ν 3400, 3180, 3040, 2960, 2940, 1710, 1630, 1470, 1440, 1220 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 12.07 (s, 1 H), 7.59 (s, 1 H), 7.33 (dt, J = 7.7, 1.2 Hz, 1 H), 7.14 (d, J = 7.7 Hz, 1 H), 7.09 (dt, J = 7.6, 0.8 Hz, 1 H), 7.02 (d, J = 7.1 Hz, 1 H), 4.18 (dd, J = 11.4, 4.4 Hz, 1 H), 4.08 (ddd, J = 12.5, 9.4, 9.1 Hz, 1 H), 3.91 (dq, J = 10.3, 6.2 Hz, 1 H), 3.83 (distorted t, J = 10.6 Hz, 1 H), 3.55 (s, 3 H), 3.04 (ddd, J = 12.5, 4.7, 3.1 Hz, 1 H), 2.60 (m, 1 H), 2.52 (dd, J = 10.2, 5.0 Hz, 1 H), 2.19 (dt, J = 13.0, 3.3 Hz, 1 H), 1.97 (ddd, J = 12.6, 8.4, 1.9 Hz, 1 H), 1.73 (d, J = 6.2 Hz, 3 H), 0.96 (dt, J = 12.6, 11.8 Hz, 1 H); ^{13}C NMR (75 MHz) δ 177.4, 167.1, 167.0, 155.5, 140.9, 130.3, 128.9 123.0, 122.9, 110.7, 107.7, 71.9, 64.4, 57.2, 51.2, 44.6, 44.2, 32.7, 29.7, 27.8, 19.9; mass spectrum, *m/z* 382.1514 ($C_{21}H_{22}N_2O_5$ requires 382.1529), 350 (base), 324, 281, 205, 159, 146, 130. Anal. Calcd for $C_{21}H_{22}N_2O_5 \cdot 0.5\ H_2O$: C, 64.44; H, 5.88; N, 7.16: Found: C, 64.83; H 5.58; N 7.23.

Isopteropodine (6). To a stirred solution of 2-oxindole **50** (56 mg, 0.14 mmol) in anhydrous THF (4 mL) under argon cooled to −70 °C was added dropwise a freshly prepared solution of alane (0.63 mL of a 0.51 M solution in THF, 0.32 mmol). The resulting pale yellow reaction mixture was allowed to warm slowly to −50 °C and stirred at that temperature for 30 min before addition of MeOH (1 mL). The reaction was stirred at room temperature for 10 min, whereupon sodium cyanoborohydride (48 mg, 0.76 mmol) and acetic acid (0.05 mL) were added. After stirring for 10 min, the reaction mixture was concentrated at reduced pressure. The residue was dissolved in EtOAc (25 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (6 mL); the organic layer was separated, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by chromatography (70 × 30 mm of neutral alumina (Brockmann Grade III), 1.5% MeOH in CH_2Cl_2 as elutant) to give oxindole **6** as a white solid (43 mg, 83%): mp 210–211 °C (lit.[9b] mp 209–211 °C); IR ν 3410, 3080, 3040, 2980, 2960, 2900, 1710, 1620, 1470, 1440, 1220 cm^{-1}; ^1H NMR (500 MHz) δ 7.80 (s, 1 H), 7.34 (s, 1 H), 7.20 (d, 1 H), 7.12 (dt, J = 1.2, 7.7 Hz, 1 H), 6.95 (dt, J = 0.8, 7.5 Hz, 1 H), 6.79 (d, J = 7.7 Hz, 1 H), 4.27 (dq, J = 10.4, 6.2 Hz, 1 H), 3.53 (s, 3 H), 3.21 (dd, J = 11.9, 1.8 Hz, 1 H), 3.14 (distorted t, J = 8.5 Hz, 1 H), 2.48 (dd, J = 11.6, 2.8 Hz, 1 H), 2.42 (dt, J = 11.9, 4.5 Hz, 1 H), 2.34 (comp, 3 H), 1.92 (m, 1 H), 1.53 (comp, 2 H), 1.34 (d, J = 6.2 Hz, 3 H), 0.79 (dt, J = 15.3, 12.4 Hz, 1 H); ^{13}C NMR (75 MHz) δ 181.4, 167.7, 155.1, 140.5, 133.9, 127.8, 124.7, 122.6, 110.1, 109.8, 72.3, 71.4, 57.2, 54.2, 53.7, 51.0, 38.2, 35.0, 30.8, 30.4, 18.8; mass spectrum, *m/z* 368.1729 (base) ($C_{21}H_{24}N_2O_4$ requires 368.1736), 351, 223, 180, 164.

Pteropodine (51). A solution of **6** (12.2 mg, 0.033 mmol) in anhydrous AcOH (2 mL) was heated at reflux under argon for 90 min. The AcOH was then removed under reduced pressure, and the residue was purified by flash chromatography (110 × 50 mm silica gel using 25–35% EtOAc in hexanes as a gradient elutant) to deliver first **6** (2.3 mg, 19%) as a white solid. Continued elution delivered pteropodine (**51**) (7.3 mg, 60%) as an opaque glass: IR ν 3410, 2960, 2900, 2780, 1710, 1620, 1470, 1440, 1225 cm^{-1}; ^1H NMR (500 MHz) δ 7.61 (s 1 H), 7.48 (s, 1 H), 7.20 (d, J = 7.4 Hz, 1 H), 7.18 (dt, J = 1.2, 7.7 Hz, 1 H), 7.04 (dt, J = 0.8, 7.5 Hz, 1 H), 6.81 (d, J = 7.7 Hz, 1 H), 4.34 (dq, J = 10.5, 6.1 Hz, 1 H), 3.60 (s, 3 H), 3.34–3.26 (comp, 2 H), 2.44–2.40 (comp, 1 H), 2.37 (dd, J = 7.2, 6.2 Hz, 1 H), 2.33 (dd, J = 11.5, 2.6 Hz, 1 H), 2.30 (dd, J = 11.9, 3.6 Hz, 1 H), 2.01 (dd, J = 12.1, 5.8 Hz, 1 H), 1.71 (m, 1 H), 1.68–1.56 (comp, 2 H), 1.47 (dt, J = 12.3, 11.8 Hz, 1 H), 1.40 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz) δ 180.7, 167.7, 155.3, 140.5, 133.4, 128.0, 123.2, 122.7, 109.3, 109.2, 74.4, 72.2, 56.1, 55.2, 53.6, 50.9, 37.9, 34.6, 31.0, 29.6, 19.0; mass spectrum, *m/z* 368.1737 (base), ($C_{21}H_{24}N_2O_4$ requires 368.1736), 310, 267, 223, 69.

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Registry No. 2, 18110-97-9; (±)-**3**, 20361-86-8; (±)-**4**, 116051-32-2; (±)-**5**, 25920-79-0; (±)-**6**, 134001-70-0; **22**, 4894-26-2; **23**, 75611-67-5; **24**, 107174-33-4; (±)-**25**, 122908-73-0; (±)-**26**, 122888-22-6; (±)-**27**, 122923-14-2; (±)-**34a**, 116005-83-5; (±)-**34b**, 133931-51-8; (±)-**34c**, 133931-55-2; (±)-**35a**, 116025-09-3; (±)-**35b**, 133931-52-9; (±)-**35c**, 133931-56-3; (±)-**36a**, 134001-71-1; (±)-**36b**, 134001-73-3; (±)-**36c**, 134001-75-5; (±)-**39**, 133931-53-0; (±)-**40**, 116025-09-3; (±)-**42a**, 20361-86-8; (±)-**42b**, 134001-74-4; (±)-**43a**, 134001-72-2; (±)-**43b**, 133931-54-1; (±)-**44**, 24196-06-3; (±)-**48**, 133931-57-4; (±)-**49**, 116025-45-7; (±)-**50**, 134002-29-2; (±)-**51**, 131725-45-6; CH_2=CHCH=CHOTMS, 63383-46-0; CH_3CH=CHCOCl, 10487-71-5; CH_2=CHCHO, 107-02-8.

Supplementary Material Available: Experimental details together with spectral characterization for compounds **34b,c**, **35b,c**, **36b,c**, **39**, **42b**, **43b**, **44**, and **48**, summary of the AM1 calculations (heats of formation and geometries) for the eight possible transition states for the hetero-Diels–Alder dimerization of acrolein, and a partial summary of the strain energies obtained from molecular mechanics calculations implemented by the MacroModel program (10 pages). Ordering information is given on any current masthead page.