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An Efficient Approach to *Aspidosperma* Alkaloids via [4 + 2] Cycloadditions of Aminosiloxydienes: Stereocontrolled Total Synthesis of (±)-Tabersonine. Gram-Scale Catalytic Asymmetric Syntheses of (+)-Tabersonine and (+)-16-Methoxytabersonine. Asymmetric Syntheses of (+)-Aspidospermidine and (−)-Quebrachamine

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Abstract: Described is a concise, highly stereocontrolled strategy to the *Aspidosperma* family of indole alkaloids, one that is readily adapted to the asymmetric synthesis of these compounds. The strategy is demonstrated by the total synthesis of (±)-tabersonine (*rac*-**1**), proceeding through a 12-step sequence. The basis for this approach was provided by a highly regio- and stereoselective [4 + 2] cycloaddition of 2-ethylacrolein with 1-amino-3-siloxydiene developed in our laboratory. Subsequent elaboration of the initial adduct into the hexahydroquinoline DE ring system was accomplished efficiently by a ring-closing olefin metathesis reaction. A novel ortho nitrophenylation of an enol silyl ether with (*o*-nitrophenyl)phenyliodonium fluoride was developed to achieve an efficient, regioselective introduction of the requisite indole moiety. The final high-yielding conversion of the ABDE tetracycle into pentacyclic target *rac*-**1** relied on intramolecular indole alkylation and regioselective C-carbomethoxylation. Our approach differs strategically from previous routes and contains built-in flexibility necessary to access many other members of the *Aspidosperma* family of indole alkaloids. The versatility of the synthetic strategy was illustrated through the asymmetric syntheses of the following *Aspidosperma* alkaloids: (+)-aspidospermidine, (−)-quebrachamine, (−)-dehydroquebrachamine, (+)-tabersonine, and (+)-16-methoxytabersonine. Of these, (+)-tabersonine and (+)-16-methoxytabersonine were synthesized in greater than 1-g quantities and in enantiomerically enriched form (∼95% ee). The pivotal asymmetry-introducing step was a catalyzed enantioselective Diels−Alder reaction, which proceeded to afford the cycloadducts in up to 95% ee. Significantly, the synthetic sequence was easy to execute and required only four purifications over the 12-step synthetic route.

Introduction

The field of alkaloid synthesis, pioneered more than half a century ago, remains an active and exciting area of chemistry and provides a fertile ground for innovation. The pharmacological significance of naturally occurring alkaloids along with the challenge posed by their diverse and intricate structures has inspired much new chemistry. Efficient and elegant routes to these often daunting molecular frameworks have been developed. The unique problems incurred during the studies have, in turn, fueled the development of new synthetic methods that have proven to be of general use.

Over the past few years, we have been actively studying the chemistry of 1,3-butadienes that have a nitrogen attached at the 1-position and an oxygen at the 3-position (**I**).[1] Such aminosiloxydienes are highly reactive and readily undergo Diels−Alder (DA) cycloadditions with a variety of dienophiles. The cycloadditions proceed with complete regiocontrol and in some cases with exceptional diastereoselectivity. Indeed, recently we developed a catalyzed asymmetric DA reaction of aminosiloxydienes that affords the cycloadducts in high yields and with excellent enantiomeric excesses.[1i,k] Overall, the broad scope of the DA reaction of these dienes provides an attractive foundation for the development of new strategies to natural products, especially alkaloids. We recognized that the product of the DA reaction with an α-substituted acrolein, cycloadduct **II**, incorporates and perfectly positions an amine, a silyl enol ether, and an aldehyde functionality for further elaboration into tetrahydroindoline (**III**) and hexahydroquinoline (**IV**) substructures, which are found in many natural alkaloids (Scheme 1). We

† Recipient of Abbott Laboratories Graduate Fellowship.

(1) (a) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252−5253. (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165−7166. (c) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039−3052. (d) Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045−8047. (e) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562−9573. (f) Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2000**, *78*, 160−168. (g) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059−9068. (h) Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321−3323. (i) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843−7844. For preparation of 1-(dimethylamino)-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene, see: (j) Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2000**, *78*, 152−159. (k) Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 1163−1166.

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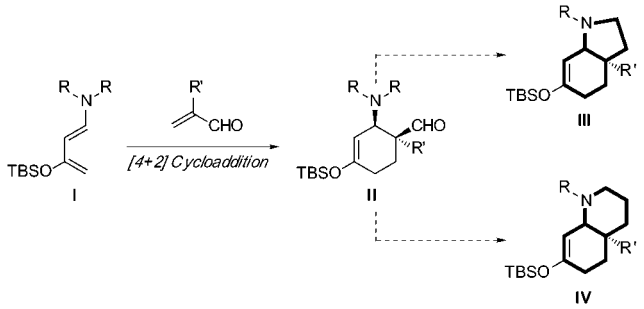
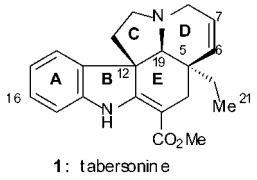
Scheme 1



describe here the realization of this principle through the development of a conceptually novel strategy to the *Aspidosperma* family of alkaloids. The strategy is illustrated through the concise, stereocontrolled synthesis of (±)-tabersonine (*rac*-**1**), as well as the asymmetric syntheses of (+)-tabersonine (*ent*-**1**), (+)-16-methoxytabersonine, (+)-aspidospermidine, (−)-quebrachamine, and (−)-dehydroquebrachamine.[2]

Background and Biological Significance

The *Aspidosperma* family represents one of the largest groups of indole alkaloids, with more than 250 compounds isolated from various biological sources.[3] The basic skeletal features of these compounds, particularly the complex pentacyclic ABCDE framework, can be seen in the namesake of the family, aspidospermine. In our development of a new strategy to these alkaloids, we selected as the target the slightly more elaborate and significant member of this family, tabersonine (**1**), which

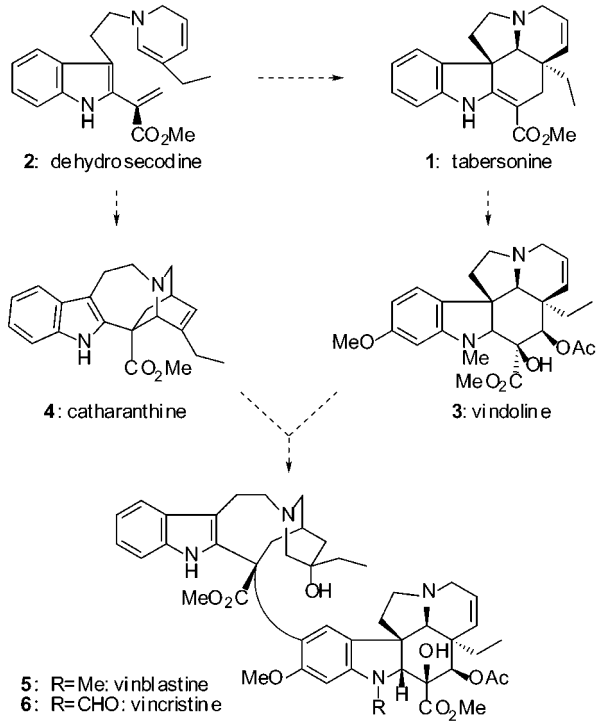


1: tabersonine

plays a central role in the biosynthesis and the synthetic chemistry of *Aspidosperma* alkaloids.

Tabersonine was first isolated in 1954 from *Amsonia tabernaemontana* by Le Men et al. Soon after the initial report, the alkaloid was isolated from several other natural sources, indicating its relative biological abundance.[4] Wenkert had proposed in 1962 that tabersonine could arise biosynthetically via the intramolecular DA reaction of dehydrosecodine **2** (Scheme 2).[5] Support for this hypothesis came from subsequent labeling experiments and by the isolation of secodine from natural sources.[6] Tabersonine serves as the biosynthetic predecessor to several members of the *Aspidosperma* family, most notably vindoline (**3**).[7] The importance of vindoline stems from

Scheme 2



the fact that its coupling with catharanthine (**4**) leads to the pharmacologically significant *Vinca* alkaloids, such as vinblastine (**5**) and vincristine (**6**).[8] It is interesting to note that catharanthine, a member of the *Iboga* family of alkaloids, also appears to arise from an intramolecular DA reaction of dehydrosecodine **2**, but by an alternate mode of cyclization.[9] Vinblastine, vincristine, and some closely related derivatives display potent anticancer activity, and these compounds are used currently for the treatment of several types of tumors. Vincristine, for example, when used in combination with other anticancer agents, is remarkably effective for the treatment of pediatric leukemia, with a success rate of >90%. Tabersonine is important not only for its biosynthetic relationship to the *Vinca* alkaloids but also because it is the chemical progenitor of these alkaloids. The chemical conversion of tabersonine to vindoline and then to different bisindole alkaloids is well documented.[9] For these reasons, tabersonine represents an attractive target for synthesis.[10] A stereocontrolled, concise, and high-yielding route to tabersonine would open up the possibility of synthesizing not only vinblastine and vincristine but also numerous structural analogues that would be difficult to obtain via the natural compounds. Finally, since the biosynthesis and most chemical syntheses of vindoline go through 16-methoxytabersonine (**7**)

(2) Preliminary communication: Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523−13524.
(3) (a) Saxton, J. E. *Indoles, Part 4: The Monoterpenoid Indole Alkaloids*; Wiley: Chichester, 1983. (b) Herbert, R. B. In *The Monoterpenoid Indole Alkaloids*; supplement to Vol. 25, part 4, of *The Chemistry of Heterocyclic Compounds*; Saxton J. E., Ed.; Wiley: Chichester, 1994; Chapter 1. (c) Saxton, J. E. *The Monoterpenoid Indole Alkaloids*; supplement to Vol. 25, part 4, of *The Chemistry of Heterocyclic Compounds*; Saxton J. E., Ed.; Wiley: Chichester, 1994; Chapter 8. (d) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50. (e) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter 1. (f) Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, 327−340 and references therein.
(4) Janot, M.-M.; Pourrat, H., Le Men, J. *Bull. Soc. Chim. Fr.* **1954**, 707−708.
(5) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98−102.
(6) (a) Evans, D. A.; Smith, G. F.; Smith, G. N.; Stapleford, K. S. *J. Chem. Soc., Chem. Commun.* **1968**, 859−861. (b) Sakai, S.; Aimi, N.; Kato, K.; Ido, H.; Watanabe, Y.; Haginiva, J. *Chem. Pharm. Bull.* **1971**, *19*, 1503−1505. (c) Battersby, A. R.; Bhatnagar, A. K. *J. Chem. Soc., Chem. Commun.* **1970**, 193−194.
(7) (a) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Chem. Commun.* **1984**, 909−911. (b) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 155−161.
(8) (a) Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, G. *J. Chem. Soc., Chem. Commun.* **1975**, 670−671. (b) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Heterocycles* **1975**, *3*, 639−649. (c) Langlois, N.; Gueritte, G.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017−7024. (d) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243−2245.
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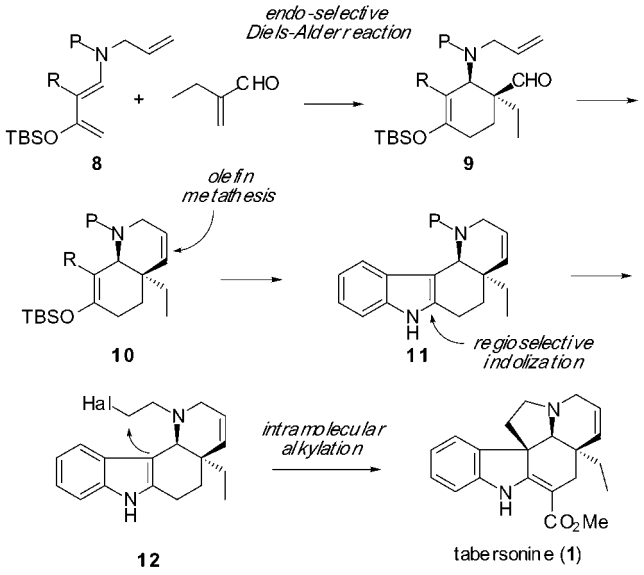
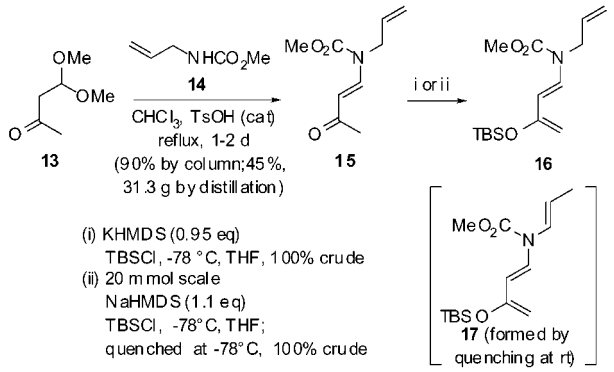
Scheme 3



Scheme 4



as an intermediate, the development of a direct synthesis of this alkaloid was an important objective.[11]

Synthetic Strategy. The highly compact but intricate pentacyclic skeleton of tabersonine (**1**) represents a significant synthetic challenge. The central cyclohexene ring (E) is substituted at five of the six carbons and possesses two quaternary chiral centers. The cis relationship of the three contiguous stereocenters at C-12, C-19, and C-5 is responsible for the overall conformational rigidity of the molecule. The combination of these structural challenges and the potent pharmacological properties exhibited by several members has made these alkaloids attractive targets for chemical synthesis.[10]

Our strategy to the *Aspidosperma* pentacycle is based on the recognition that control of the cis relationship of the two stereogenic centers at C-5 and C-19 is tantamount to solving the stereochemical problems posed by these alkaloids (Scheme 3). A particularly attractive solution was possible through a Diels–Alder reaction of our aminosiloxydienes.[1] The Diels–Alder reaction of an appropriately functionalized aminosiloxydiene **8** with ethylacrolein would give cycloadduct **9** with complete regioselectivity and excellent endo selectivity. This simple transformation would orient the amino group and the aldehyde functionality in a cis relationship and position the enol ether for formation of the indole ring, thus addressing all the issues associated with these alkaloids (vide infra). The six-membered ring containing the C-6–C-7 double bond could be constructed via ring-closing metathesis reaction. Conversion of **10** into tetracycle **11** would rely on indolization. In this context, it is noteworthy that there was no good precedent for accomplishing this transformation in a regiocontrolled manner. We planned either to use the known methods of indole syntheses—i.e., Gassman's or Fischer's protocols—or to develop a new method for regioselective indolization.

The assembly of the spiroindolenine portion of the pentacyclic skeleton would be accomplished by an intramolecular alkylation. Whereas this construction had precedent, the reported yields were low, so a more effective solution would have to be developed. Regioselective incorporation of carbomethoxy group, also an unsolved problem in the alkaloids field, would then furnish tabersonine (**1**).

Results and Discussion

(I) Total Synthesis of (±)-Tabersonine. The Pivotal Diels–Alder Reaction. The synthesis of racemic tabersonine began with the preparation of 1-amino-3-siloxy-1,3-butadiene **16**, which was equipped with the carbomethoxy group, to temper the reactivity of the amino group, and the allyl group, chosen to provide the necessary handle for constructing the piperidine ring. We expected to prepare diene precursor **15** by the reported acid-catalyzed condensation of a secondary amide with the commercially available monoacetal **13**.[12] The required *N*-allylcarbamate **14** was prepared in 96% crude yield by the reaction of 2 equiv of allylamine with methyl chloroformate in dichloromethane. For the condensation reaction, we utilized a slightly modified protocol, which included the use of chloroform, as a higher boiling solvent, to facilitate the product formation (Scheme 4). Under these conditions, the reaction reached completion within 24 h and furnished the desired vinylogous imide **15** in 90% yield.[13] On large scales, although the condensation of **14** with acetal **13** to provide vinylogous imide **15** proceeded cleanly, the isolated yield of the product

(10) (a) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1971**, *93*, 5930–5931. (b) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458–7464. (c) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1979**, *101*, 6414–6420. (d) Lévy, J.; Laronze, J.-Y.; Laronze, J.; Le Men, J. *Tetrahedron Lett.* **1978**, 1579–1580. (e) Kuehne, M. E.; Okuniewitcz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335–1343. (f) Kuehne, Martin E.; Podhorez, David E. *J. Org. Chem.* **1985**, *50*, 924–929. (g) Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 1, 2913–2927. (h) Kuehne, M. E.; Podhorez, D. E.; Mulamba, T.; Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347–353. (i) Kuehne, M. E.; Hugel, G.; Cartier, D.; Levy, J. *Tetrahedron Lett.* **1989**, *30*, 4513–4516. (j) Kalaus, G.; Greiner, I.; Kajtar-Peredy, M.; Brlik, J.; Szabo, L.; Szantay, C. *J. Org. Chem.* **1993**, *58*, 1434–1442. (k) Kuehne, M. E.; Wang, T.; Seaton, P. J. *J. Org. Chem.* **1996**, *61*, 6001–6008. (l) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y.-L.; Wang, T. *J. Org. Chem.* **1998**, *63*, 2172–2183. (m) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519–1522.

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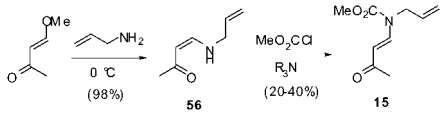
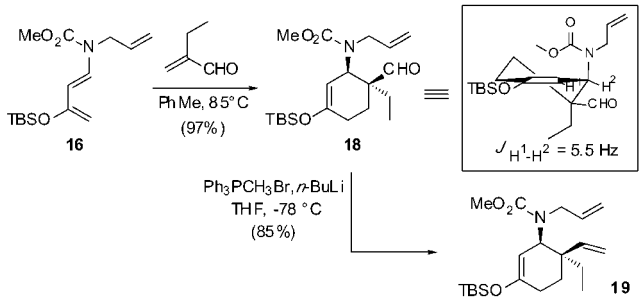
(12) Khokhlov, P. S.; Savenkov, N. F.; Sokolova, G. D.; Strepikheev, Yu. A.; Kolesova, V. A. *J. Org. Chem. USSR* **1982**, 875.

(13) Initially, we attempted the preparation of the diene precursor **15** by a two-step sequence exploiting the acylation of secondary vinylogous amide **56**. While the reaction of allylamine with methoxybutenone occurred to give **56**, the second step turned out to be troublesome. The desired vinylogous imide **15** was typically obtained in 20–40% yield under the different conditions examined.



Scheme 5



after vacuum distillation was lower (45%, 31.3 g). The lower yield is ascribed to the thermal instability of the vinylogous imide. Since a large amount of imide **15** was easily prepared, further effort was not expended on optimizing the large-scale preparation.

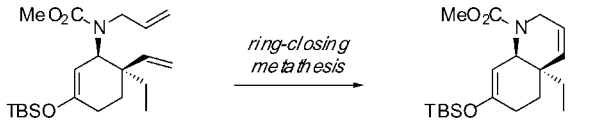
Vinylogous imide **15** was converted to the desired diene **16** via a modification of our established protocol. Initially, the presence of the allyl group in **15** proved to be problematic for the diene formation. The use of 1.1 equiv of KHMDS (0.5 M in toluene), according to our standard protocol,[2] resulted in partial isomerization of the double bond to form **17**, especially when the reaction was quenched at room temperature. The isomerization was less of a problem at lower temperature, but the silylation was incomplete. Two solutions to this problem were found. The double bond isomerization was avoided by using the vinylogous amide in slight excess. An even better result was obtained when we used the base NaHMDS, which is available in a more convenient form, as a 1.0 M solution in THF. The deprotonation was accomplished using a slight excess of NaHMDS followed by treatment of the resulting enolate with TBSCl. The reaction was then quenched at −78 °C to afford a quantitative crude yield of diene **16**, which was sufficiently pure for use in the cycloaddition step.

Diene **16** was expected to display diminished reactivity compared to the previously described 1-(dialkylamino)-3-siloxy-1,3-dienes, since the electron-donating ability of the nitrogen atom is diminished by the presence of the carbomethoxy group. In accord with this expectation, no reaction occurred at room temperature between **16** and ethylacrolein. However, the cycloaddition proceeded readily upon heating the reaction mixture to 65−85 °C in toluene for 48 h. Despite the higher temperature, the reaction was completely regioselective and very highly endo selective,[14] affording the desired adduct **18** in >95% isolated yield (Scheme 5). The relative stereochemistry of **18** was tentatively assigned at this stage from its high-temperature ^{1}H NMR spectrum. The compound displayed a very characteristic pattern, in which both H^1 and H^2 were observed as doublets with a vicinal coupling constant of 5.5 Hz, consistent with a conformation in which the nitrogen substituent occupies a pseudoaxial position and the aldehyde functionality, an equatorial orientation. This arrangement of the substituents was in a good agreement with previously described conformational analysis of endo adducts of aminosiloxydienes.[1c]

Ring-Closing Metathesis. Having achieved the cis relative stereochemistry required for *Aspidosperma* alkaloids, we then proceeded to construct the hexahydroquinoline (DE) ring system

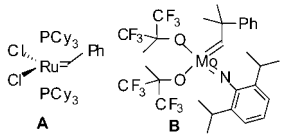
(14) A small amount (<5%) of a diastereomeric adduct, tentatively assigned as exo, was observed in the NMR spectrum of the crude product mixture.

Table 1. Ring-Closing Metathesis of Carbamate 19



entry	solvent (M)	catalyst (mol %)	temp (°C)	time (h)	conversion[a] (%)	yield[b] (%)
1	C_6H_6 (0.03)	**A**[e] (5)	20	40	60	nd[c]
2	C_6H_6 (0.03)	**A**[e] (10)	60	20	80	67
3	PhMe (0.09)	**A**[e] (5)	80	10	60[d]	58
4	CH_2Cl_2 (0.10)	**A**[e] (7)	40	2	85	75
5	C_6H_6 (0.09)	**B**[e] (5)	60	1	100	88

[a] The extent of conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield after chromatographic purification. [c] The isolated yield was not determined in this case. [d] The other 40% corresponded to the byproduct formed by isomerization of the allyl group. [e] Catalysts employed:



using a ring-closing metathesis (RCM) reaction.[15] The aldehyde was first converted into the diene **19** via a standard Wittig olefination protocol. No hydrolysis of the silyl enol ether moiety was observed under these conditions.

The RCM reaction was investigated next using both Grubbs' ruthenium[16] catalyst and Schrock's molybdenum[17] catalyst. The results of this study are summarized in Table 1. The reaction was carried out in benzene at room temperature in the presence of Grubbs catalyst. NMR analysis after 16 h indicated clean formation of the cyclized product **20**, but the reaction only progressed to ∼60% conversion (entry 1). The amount of the desired product did not significantly increase over the next 24 h, suggesting that the catalyst had decomposed. At higher temperature, the reaction progressed to ∼80% conversion and afforded **20** in 67% isolated yield (entry 2). The mildest conditions for the RCM using this catalyst involved the use of dichloromethane as the solvent (40 °C, 2 h) and gave a 75% yield of **20** (entry 3). The reaction proceeded even more cleanly using Schrock's catalyst, although greater care was required to exclude oxygen while the catalyst was handled and during the reaction. The cyclization was essentially complete after 1 h at 60 °C in benzene and afforded the desired product **20** in 88% yield (entry 4). Dimeric byproducts were not observed in any of the olefin metathesis experiments described above.[18]

To simplify the NMR spectra of carbamate **20**, which exists as a 1:1 mixture of rotomers at ambient temperature, the carbamate was reduced to the corresponding tertiary amine **21**. The structure of **21**, established by a combination of the DQF

(15) Recent reviews on the application olefin metathesis to organic synthesis: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (d) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89. (e) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153. (f) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211−240. (g) Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565−588. (h) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013−3043.

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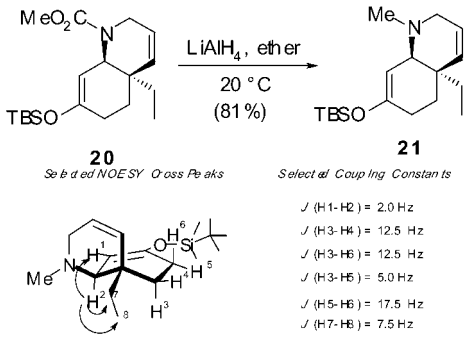
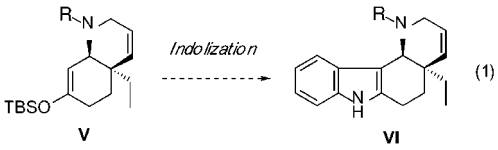


Figure 1. Structural assignment of **21**.

COSY and NOESY experiments, is shown in Figure 1, in what is believed to be the preferred conformation. The pseudoequatorial orientation assigned for the amine is consistent with the small coupling observed between H^1 and H^2 ($J_{H1-H2} = 2.0$ Hz). The cis stereochemistry of the hexahydroquinoline (**21**) was evident from the strong NOESY cross-peaks between the proton adjacent to the nitrogen and the methylene unit of the ethyl group. This observation confirmed the endo selectivity of the key Diels−Alder reaction.

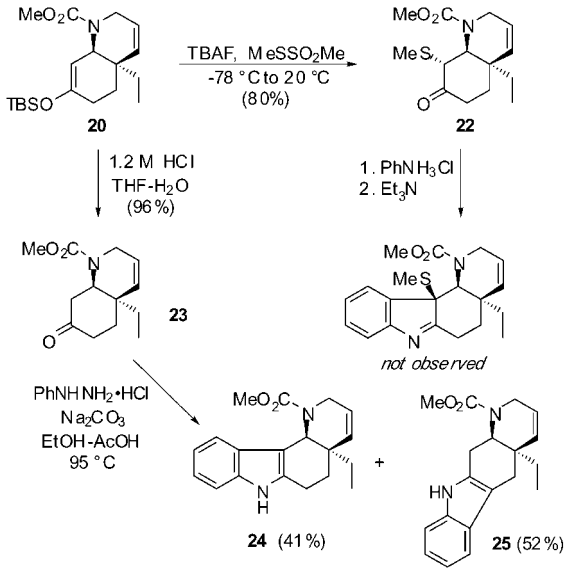
Attempted Gassman Indolization. The next major hurdle in the synthesis was the conversion of bicyclic compound **V** to the "angular" tetracyclic intermediate **VI** (eq 1). Formation of



the indole ring in a regiocontrolled manner was critical. To this end, it is noteworthy that the Diels−Alder reaction had not only positioned the amine and the sp^2 hybridized carbon in the required cis arrangement, but it had also correctly set up the enol ether for formation of the desired indole. The problem was that despite the plethora of methods for indole synthesis—and numerous applications of these—there did not appear to be a way to convert an enol ether regiospecifically to the corresponding indole.[19]

A solution to the regiocontrolled indole synthesis was envisioned through the Gassman indole synthesis.[20] The plan was to convert the enolsilyl ether to the corresponding thiomethyl ketone, which would lock the system into producing the desired regioisomer of the final indole. The required thiomethyl ketone **22** was prepared directly from the silyl enol ether **20** upon its treatment with methylthiomethanesulfonate and TBAF at −78 °C (Scheme 6).[21] As expected, this reaction gave the thiomethyl ketone **22**, which was isolated in 80% yield. The thiomethyl compound was present as a single diastereomer,

Scheme 6

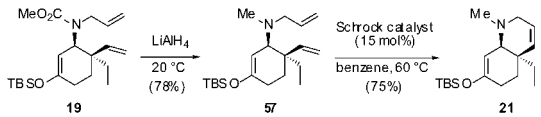


assigned the α-stereochemistry for the thiomethyl substituent based on the large diaxial coupling between H^1 and H^2 ($J = 10$ Hz). Disappointingly, the Gassman indolization of **22** proved problematic. Neither the desired imine nor the corresponding anilinoketone were detected under the standard Gassman indolization protocols examined. The lack of success of this reaction can be understood in light of the congested steric environment around the sulfur atom, as well as the possibility of competing [1,2] rearrangement of the intermediate ylide, a known side reaction of the Gassman method.[20]

Fischer Indolization. We next turned our attention to the venerable Fisher indolization method for the synthesis of the desired "angular" tetracycle. The hope was that either there would be inherent preference for the desired, angular tetracycle or that we could exploit a modification of the Fisher reaction to accomplish the desired indole formation.[22] Treatment of the silyl enol ether **20** with dilute hydrochloric acid accomplished a clean hydrolysis to bicyclic ketone **23**, with the cis stereochemistry intact. This conversion, of course, sacrificed the double bond position that was achieved through the initial cycloaddition (Scheme 6).

In preparation for Fischer indolization, ketone **23** was converted to the phenylhydrazone by heating it with phenylhydrazine hydrochloride in the presence of sodium carbonate. The crude hydrazone was then heated at 95 °C in glacial acetic acid, a weakly acidic medium known to favor idolization toward the more substituted carbon.[22] Under these conditions, the indolization proceeded cleanly and in high yield (93% overall) but afforded both possible indole isomers, in roughly equal

(18) We were interested in assessing the ring-closing metathesis capability of a tertiary amine, such as **57,** compared to carbamate **19**. The required amine (**57**) was prepared by reduction of **19** with lithium aluminum hydride. Although no reaction occurred when **57** was treated with Grubbs catalyst **A**, a clean cyclization occurred in the presence of the Schrock carbene **B**, affording bicyclic amine **21** in 75% yield. This compound was determined to be identical to the one previously obtained from reduction of carbamate **20**.



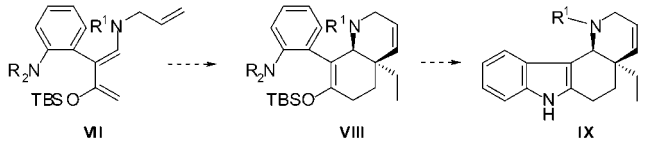
(19) Recent reviews of indole synthesis: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075. (b) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (c) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. 2, pp 119−206. (d) Döpp, H.; Döpp, D.; Langer, U.; Gerding, B. In *Methoden der Organischen Chemie*; Kreher, R., Ed.; Georg Thieme Verlag: Stuttgart, 1994; Hetarene I, Teil 2, pp 546−1336 and references therein.

(20) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Berkeley, W. C. *J. Am. Chem. Soc.* **1974**, *96*, 5495−5508.

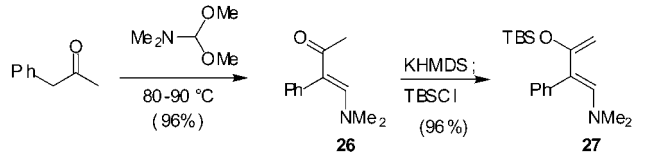
(21) Takeuchi, K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 5, pp 3538−3541.

(22) Fischer Indole synthesis: (a) Robison, B. *The Fischer Indole Synthesis*; J. Wiley & Sons: New York, 1982. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1993**, *25*, 607−632. See also: (c) Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106−7115.

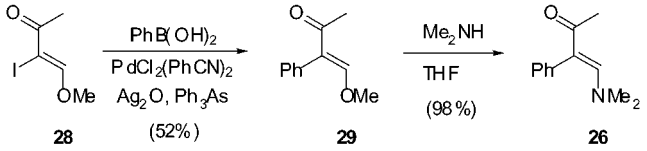
Scheme 7



Scheme 8



Scheme 9



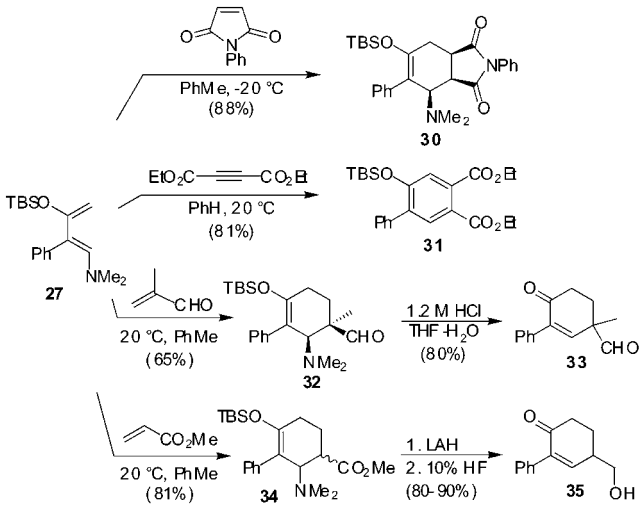
amounts. The two isomers were readily separated by column chromatography and assigned the structures indicated. Some variations of the above reaction conditions were examined, but these did not significantly alter the ratio of the two isomeric indoles.

Incorporation of Aromatic Fragment into Aminosiloxydienes. Given the difficulties encountered with the Gassman and Fischer indolization methods, we decided to tackle the problem by a different strategy, one in which the indole aromatic ring was incorporated in the starting material. To this end, we considered the use of appropriately functionalized 2-aryl-substituted aminosiloxydiene **VII** (Scheme 7). According to this plan, an endo-selective cycloaddition of **VII** with ethylacrolein would furnish **VIII**; unmasking of aniline and hydrolysis of silyl enol ether would be followed by imine formation and indolization to give tetracycle **IX**.

Since 2-aryl-substituted aminosiloxydiene had not been prepared previously, we decided to first construct the 2-phenyl-substituted derivative **27** in order to test its chemical reactivity. The diene precursor **26** was prepared as reported in 96% yield simply by heating phenylacetone and DMF−dimethylacetal at 80−90 °C (Scheme 8).[23] Vinylogous amide **26** was then subjected to our standard silylation procedure, which afforded the corresponding diene **27** in 96% isolated yield. This diene was found to be relatively stable in solution in either benzene or toluene, however, attempts to dissolve it in $CDCl_3$ led to significant hydrolysis to the vinylogous amide **26**.

A second route to 2-aryl-substituted aminosiloxydienes was developed, one based on the Suzuki cross-coupling reaction[24] between 2-iodo-3-methoxybutenone (**28**) and the appropriate arylboronic acid (Scheme 9). This method promised to be more versatile given the ready availability of a variety of substituted arylboronic acids. Indeed, it was found that the reaction between iodide **28**[25] and phenylboronic acid proceeded well under the conditions developed by Johnson et al.,[26] to give the corresponding cross-coupling product **29** in 52% yield. Subsequent treatment of **29** with dimethylamine afforded vinylogous amide **26** in nearly quantitative yield.

Scheme 10

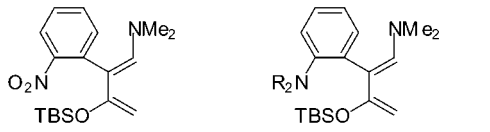


A brief study was carried out to assess the reactivity of diene **27** with activated dienophiles. Diene **27** reacted readily with *N*-phenylmaleimide at −20 °C to afford the endo adduct **30** in 88% yield (Scheme 10). The reaction of diene **27** with diethylacetylene dicarboxylate also proceeded smoothly to afford in 81% yield the tetra-substituted benzene derivative **31**, wherein the cycloadduct had aromatized through the loss of dimethylamine.[27] The reaction conditions used for the phenyl-substituted diene are comparable to that used earlier for the parent dimethylaminosiloxydienes, indicating a similar reactivity profile for the two dienes.

Cycloaddition of the phenyl-substituted diene **27** with methacrolein was particularly significant, since it allowed us to test not only the efficiency but also the diastereoselctivity of this reaction. To our delight, the reaction produced a single cycloadduct diastereomer, assigned the endo stereochemistry (**32**) based on its spectroscopic characteristics (Scheme 10). Treatment of **32** with an aqueous solution of HCl in THF accomplished the desired hydrolysis to enone **33** in good yield. The cycloaddition of **27** with methyl acrylate afforded a 1:1 mixture of the readily separable endo and exo isomers. Each diastereomer was efficiently converted to 4-(hydroxymethyl)-2-phenylcylohexenone (**35**) using lithium aluminum hydride reduction and an HF-mediated elimination sequence. These examples demonstrate the synthetic utility of 1-amino-2-phenyl-3-siloxydiene (**27**) for the assembly of substituted 2-phenyl-2-cyclohexenones, which are valuable intermediates for complex molecule synthesis. The present method represents a novel, more direct alternative to the currently available methods to such compounds, which involve a multistep arylation of a cyclohexenone precursor.[28]

Unfortunately, we were unable to extend the chemistry outlined above to the preparation of the dienes **36** and **37**, which

(23) (a) Bennett, G. B.; Mason, R. B., *Org. Prep. Proc. Int.* **1978**, *10*, 67−72. (b) Haefliger, W.; Hauser, D. *Synthesis* **1980**, 236−238.
(24) For reviews, see: (a) Miyaure, N., Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419−422.
(25) (a) Hodgson, D. M.; Witherington, J.; Moloney, B. A.; Richards, I. C.; Brayer, J.-L. *Synlett.* **1995**, 32−34. (b) Campos, P. J.; Tan, C.-Q.; Rodriguez, M. A. *Tetrahedron Lett.* **1995**, *36*, 5257−5260.
(26) Ruel, F. C.; Braun, M. P.; Johnson, C. R. *Org. Synth.* **1997**, *75*, 69−77.
(27) Dimethylaminomaleate was obtained as a byproduct in this reaction when 2 equiv of diethylacetylene dicarboxylate was employed. Presumably, the byproduct results from the Michael addition of the dimethylamine, which is produced by the elimination of the initially formed cycloadduct under the reaction conditions (see Supporting Information).
(28) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114−2116.

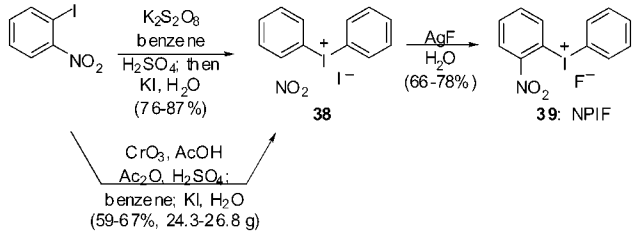


36 **37**: NR_2 = N(Bn)CO_2Me

possess, in a masked form, the amino group in the ortho position required for the indolization. The precursors to the diene were found to be incompatible with the silylation protocol.

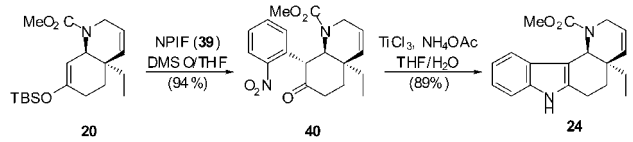
(*o*-Nitrophenyl)phenyliodonium Fluoride (NPIF): A New Reagent for Regiocontrolled Indole Synthesis. The difficulties encountered in attempting to selectively introduce the indole unit using available methodology prompted us to develop a new reagent capable of carrying out this transformation with high efficiency and complete regioselectivity. The objective was to find a reagent that would allow introduction of the *o*-nitrophenyl group—or some equivalent thereof—directly to an enol ether. The arylated ketone could then be converted to the desired indole in a regiospecific manner. Aryliodonium salts were particularly attractive as arylating agents, especially since Koser had shown that simple phenylation of ketone enol silyl ethers was possible.[29] The specific arylating agent that was required is NPIF (**39**),[30] which was synthesized by the two-step sequence outlined in Scheme 11. The oxidation of *o*-iodonitrobenzene with $K_2S_2O_8$ in benzene afforded a mixed diaryliodonium salt. Treatment of the crude hydrogen sulfate salt with aqueous KI gave (*o*-nitrophenyl)phenyliodonium iodide (**38**) as an orange solid in 76−87% yield. The exchange of the iodide counterion with a fluoride using aqueous AgF afforded the desired unsymmetrical nitrophenylating reagent (**39**) in 66−78% yield. These two compounds have been prepared on >25- and >10-g scales, respectively, without any complications. Iodonium iodide **38** can also be prepared using CrO_3 as the oxidant.[31]

Scheme 11



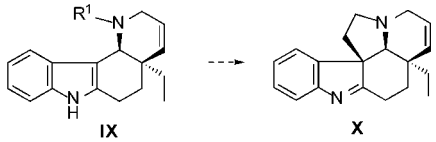
On the basis of the work of Beringer et al.,[32] the more electron deficient *o*-nitrophenyl group was expected to transfer during the arylation. To our delight, treatment of enol ether **20** with NPIF regiospecifically produced the desired α-arylated ketone **40** in 94% yield, as a single diastereomer (Scheme 12). The nitro group was then cleanly reduced with $TiCl_3$,[33] wherein the intermediate aniline underwent spontaneous condensation to yield the angular tetracyclic indole **24** in 89% yield. This

Scheme 12



o-nitrophenylation/reduction sequence represents a new synthesis of indoles, one that allows, for the first time, the regiospecific synthesis of indoles from the corresponding enol silyl ethers.[30] The generality of the sequence was evaluated and the results were recently published.[30] A clear advantage of this method is that it allows for the regiocontrolled synthesis of various substituted indoles by simply using the requisite aryliododonium salts. The formation of the 6-methoxy-substituted indole is illustrated through the asymmetric synthesis of 16-methoxytabersonine (vide infra).

Pentacycle Assembly and End Game. Having accomplished the stereocontrolled synthesis of the angular tetracycle, what remained was the development of an efficient end game to the *Aspidosperma* skeleton. Completion of the *Aspidosperma* pentacycle required the seemingly simple task of introducing a two-carbon unit to form the pyrrolidine ring that is spiro-fused to the indole (eq 2). This alkylation route to the spiroindolenine



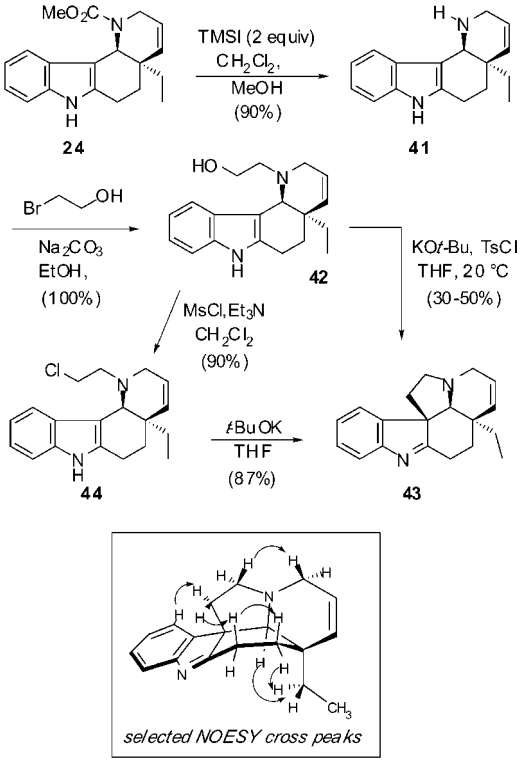
(2)

unit had been demonstrated early in the *Aspidosperma* alkaloids area through the groundbreaking work of Ziegler et al.,[34] but the reported efficiency of the process was variable. Indeed, to circumvent the difficulties associated with the alkylative introduction of the two-carbon unit, Magnus developed an elegant, Pummerer rearrangement-based sequence.[11b] Ultimately, since the most concise route to tabersonine was through the intramolecular S_N2 alkylation at the β-position of the indole, we examined variations of the Ziegler strategy. Additional precedent for this route came from the work of Natsume et al.,[34b] who had constructed the spiropyrrolidine ring by alkylative displacement of a mesylate upon deprotonation of indole with potassium *tert*-butoxide in DMSO or DMF. The reported yield for the process was, again, quite low (26−32%). The most encouraging precedent for this sequence was provided by Rubiralta and co-workers,[34d] who had accomplished the pyrrolidine ring closure in a related system in 70% yield by displacement of an in situ generated tosylate.

In preparation for the spiroindolenine synthesis, the methyl carbamate group on **24** was first removed with trimethylsilyl iodide in refluxing CH_2Cl_2.[35,36] Alkylation of the resulting secondary amine **41** with a 10-fold excess of bromoethanol in the presence of sodium carbonate in refluxing ethanol for 18 h afforded a quantitative yield of the desired tertiary amine **42**, poised for construction of the spiroindolenine (Scheme 13).[37]

(29) Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764−5767 and references therein.
(30) The scope of this two-step indole synthesis has been examined: Iwama. T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett*, **1999**, *1*, 673−676.
(31) (a) Kazmierczak, P.; Skulski, L. *Synthesis* **1995**, 1027−1032. (b) Kazmierczak, P.; Skulski, L. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 219−224.
(32) (a) Beringer, F. M.; Gindler, E. M.; Rapoport, M.; Taylor, R. J. *J. Am. Chem. Soc.* **1959**, *81*, 351−361. (b) Beringer, F. M.; Forgione, P. S.; Yudis, M. D. *Tetrahedron* **1960**, *8*, 49−63.
(33) (a) Ho, T.-L.; Wong, C. M. *Synthesis* **1974**, 45. (b) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 673−679.
(34) (a) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146−7149. (b) Natsume, M.; Utsunomiya, I. *Heterocycles* **1982**, *17*, 111−115. (c) Ogawa, M.; Kitagawa, Y.; Natsume, M. *Tetrahedron Lett.* **1987**, *28*, 3985−3986. (d) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882−7888 and references therein.
(35) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225−2277.

Scheme 13

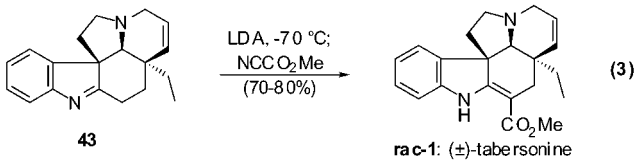


The cyclization protocol reported by Rubiralta and co-workers was examined first, but with unsatisfactory results. Treatment of **42** with *t*-BuOK followed by addition of *p*-toluenesulfonyl chloride afforded the desired pentacycle, (±)-didehydroaspidospermine (**43**), but in a variable yield (30−50%, Scheme 13).[34d] The poor reproducibility of the reaction was attributed to the competing tosylation of the indole nitrogen, which prevented the desired alkylative cyclization from taking place.

To improve the reliability of the protocol, we examined a two-step alternative, wherein first the alcohol would be selectively activated and then the ring closure would be accomplished. Treatment of amino alcohol **42** with Et_3N and methanesulfonyl chloride in CH_2Cl_2 resulted in clean formation of a single compound, which was found not to be the expected mesylate but the chloroamine **44**, isolated in 90% yield (Scheme 13). The formation of **44** is understandable based on related precedents. Displacement of the initially formed mesylate by the proximate nucleophilic nitrogen atom of the piperidine ring can produce aziridinium ion, which is then opened by the chloride ion.[38]

Since chloride **44** also represented a cyclization precursor, it was treated with a solution of *t*-BuOK in deuterated THF. The ^{1}H NMR analysis of the crude reaction mixture indicated a clean formation of (±)-didehydroaspidospermidine (**43**) as the sole reaction product.[39] The structure of **43** was determined by a combination of COSY, NOESY, and HMQC experiments. On the basis of the observed coupling constants between protons at C^1 and C^2, the central C ring is proposed to exist in the boat conformation. The selected NOESY cross-peaks are in full agreement with the proposed structure and cis stereochemistry at C^{12}, C^{19}, and C^5. The 500-MHz ^{1}H NMR and 125-MHz ^{13}C NMR spectra of our synthetic sample of **43** were identical to those recently reported in the literature.[39g] Significantly, a one-pot modification of this two-step procedure was subsequently developed (vide infra).

The selective introduction of the carbomethoxy group at C^1 was necessary at this stage in order to complete the total synthesis of tabersonine (**1**). As was true for the spiroindolenine formation, the introduction of the carbomethoxy group by direct acylation of the aza enolate had precedent,[11a] but the reaction was reported to give ∼1:1 mixture of the C-acylation and N-acylation products. Indeed, following Overman's protocol, when imine **43** was treated with an excess of LDA, followed by addition of methyl chloroformate at −78 °C, tabersonine (*rac*-**1**) was obtained in 37% yield, along with a significant amount of the expected N-acylation product. The C versus N selectivity issue was solved by using cyanomethyl formate (Mander's reagent),[40] which is known to be a "softer" acylating agent and to promote C-acylation over O-acylation. Deprotonation of **43** with LDA in THF followed by a quick injection of Mander's reagent[40] cleanly and selectively produced the C-acylated product, (±)-tabersonine (*rac*-**1**), isolated in 70−80% yield (eq 3). The 500-MHz ^{1}H NMR and 125-MHz ^{13}C



(3)

NMR spectra of our synthetic sample of tabersonine were identical to those previously reported in the literature.[10d,e,41]

Overall, this exercise established a novel, concise, and high-yielding route to *Aspidosperma* alkaloids, culminating in the synthesis of (±)-tabersonine, wherein the overall regio- and stereocontrol was predicated on the initial Diels−Alder reaction. In the course of validating the strategy, a new method for regioselective indole formation was developed, as were new protocols for spiroindolenine construction and carbomethoxylation α to imines.

(II) Gram-Scale Asymmetric Synthesis of (+)-Tabersonine. Installation of Chirality via Catalytic Asymmetric Diels−Alder Reaction. The success of the tabersonine synthesis motivated us to pursue our original, more ambitious goal, the synthesis of vinblastine and vincristine. However, the development of a meaningful synthesis of these bisindole alkaloids, which arise from the coupling of two chiral components, requires

(36) (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030−3031. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685−2686.

(37) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, S. *J. Org. Chem.* **1989**, *54*, 5591−5597.

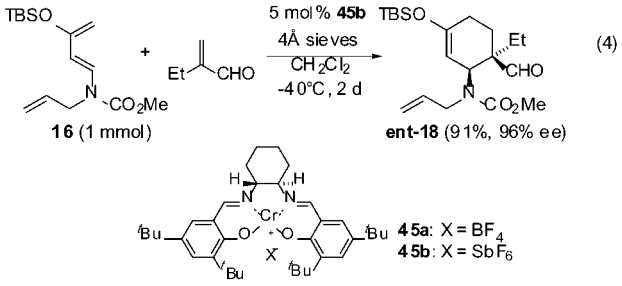
(38) Similar observations have been reported: (a) Lee, J. W.; Son, H. J.; Lee, J. H.; Yoon, G. J.; Park, M. H. *Synth. Commun.* **1996**, *26*, 89−94. (b) Springer, C. J.; Antoniw, P.; Bagshawe, K. D.; Searle, F.; Bisset, G. M. F.; Jarman, M. *J. Med. Chem.* **1990**, *33*, 677−681.

(39) (a) Plat, M.; Men, J. L.; Janot, M. M.; Wilson, J. M.; Budzikiewicz, H.; Durham, L. J.; Nakagawa, Y.; Djerassi, C. *Tetrahedron Lett.* **1962**, 271−276. (b) Zsadon, B.; Otta, K. *Acta Chim. (Budapest)* **1971**, *69*, 87−95. (c) Zsadon, B.; Horvath-Otta, K. *Herba Hung.* **1973**, *12*, 133−138. (d) Henriques, A.; Husson, H. P. *Tetrahedron Lett.* **1981**, *22*, 567−570. (e) Henriques, A.; Kan, C.; Chiaroni, A.; Riche, C.; Husson, H. P.; Kan, S. K.; Lounasmaa, M. *J. Org. Chem.* **1982**, *47*, 803−811. (f) Crippa, S.; Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Vecchietti, V. *Heterocycles* **1990**, *31*, 1663−1667. (g) Dupont, C.; Guenard, D.; Tchertanov, L.; Thoret, S.; Gueritte, F. *Bioorg. Med. Chem.* **1999**, *7*, 2961−2969.

(40) (a) Mander, L. N. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 5, pp 3466−3469. (b) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256−264 and references therein.

that we have access to both components in enantiomerically enriched form. With regard to the *Aspidosperma* component, the absolute stereochemistry of this piece is determined at the Diels−Alder step, so a method was required for carrying out this cycloaddition in an asymmetric fashion. Inspired by this objective, we investigated the possibility of carrying out the Diels−Alder reactions of aminosiloxydienes using a chiral Lewis acid.[42,43] We discovered that Jacobsen's chiral Cr(III)−salen complex[44] was very effective in catalyzing the Diels−Alder reactions of 1-amino-3-siloxy-1,3-butadienes with a wide range of α-substituted acroleins.[1i,k] In particular, the antimonate salt of the complex afforded the cycloadducts in excellent yields (>90%) and in high enantiomeric excesses (up to 97% ee).[1i,k] As such, this process was well suited for the asymmetric synthesis of *Aspidoperma* alkaloids.

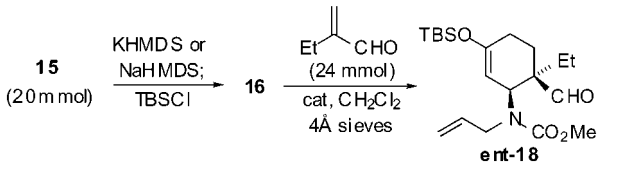
We were pleased to find that the desired cycloaddition proceeded well (eq 4). On a 1-mmol scale, the reaction between



(4)

diene **16** and ethacrolein, catalyzed by 5 mol % of the fluoroborate catalyst **45b**, afforded the cycloadduct (*ent*-**18**) in 91% yield and 96% ee (determined by the Mosher ester analysis of the corresponding alcohol).[1i,45] Several other conditions were examined to determine the optimum procedure for the multigram-scale catalytic enantioselective Diels−Alder reactions (Table 2). It was found that the cycloaddition could be carried out more conveniently—at room temperature and using less than 2 mol % of the catalyst—using the fluoroborate catalyst **45a**, but with a reduction in the ee to <90% (entries 1 and 2). The

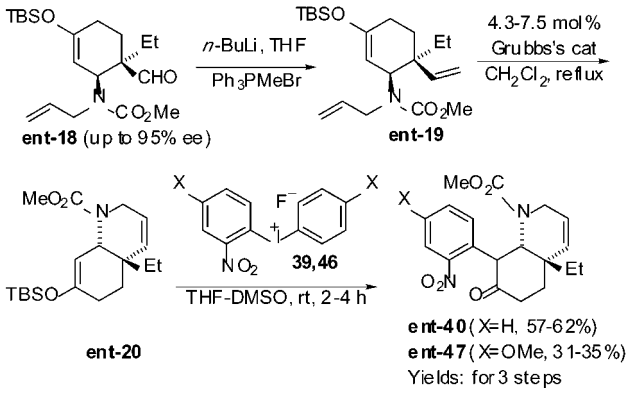
Table 2. Multigram-Scale Catalytic Enantioselective Diels−Alder Reactions



entry	catalyst (mol %)	temp (°C)	time (day)	yield (%)[a]	ee (%)[b]
1	**45a** (1.3)	rt	3	70	88
2	**45a** (1.9)	rt	2.5	81	88.5
3	**45b** (1.0)	−40	10	85	93
4	**45b** (2.0)	−40	4.5	81	93
5	**45b** (5.0)	−40	2	84	95
6[c]	**45b** (5.0)	−40	2	74	94

[a] Isolated yield in two steps from **15**. [b] Determined by Mosher ester analysis of the alcohol prepared by LAH reduction followed by hydrolysis. [c] 38 mmol of **15** was used.

Scheme 14

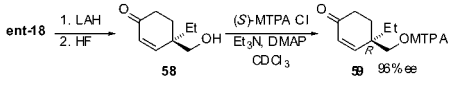


enantioselectivities were appreciably higher using the antimonate catalyst **45b**. The cycloadditions proceeded at −40 °C, in good yields and high ee's. The reactions were effective even at low catalyst loadings (1−2 mol % of **45b**), but the reaction times were rather long (entries 3 and 4). The best results were obtained using 5 mol % of catalyst **45b** (entries 5 and 6). The absolute stereochemistry of *ent*-**18** would afford the antipode of natural tabersonine.

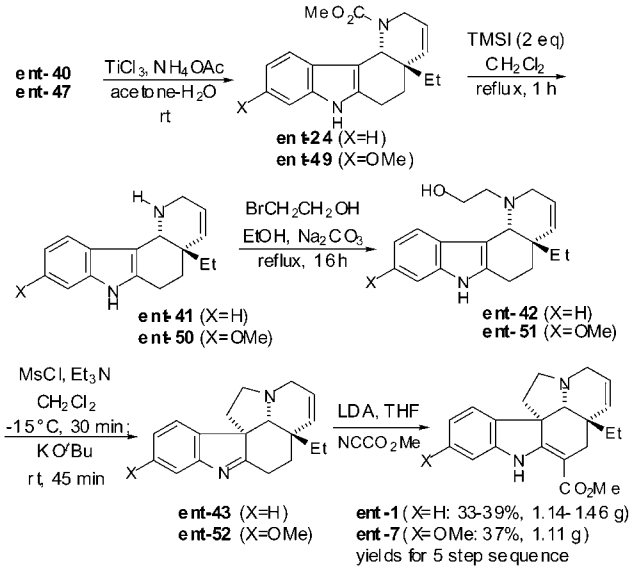
The remainder of the tabersonine synthesis closely paralleled the racemic synthesis, but practical improvements allowed multiple steps to be performed between purifications (Scheme 14). Thus, after the Witting methylenation, addition of hexane and filtration allowed facile removal of the insoluble triphenylphosphine oxide. The crude product was subjected to ring-closing metathesis using 4.3−7.5 mol % of Grubbs's catalyst.[16] After the metathesis was complete (by NMR and TLC), the reaction mixture was concentrated, and the resultant crude product (*ent*-**20**), without removal of Grubbs catalyst, was treated with phenyl(*o*-nitrophenyl)iodonium fluoride (**39**) in THF−DMSO. The product of this three-step sequence was purified by column chromatography to yield multigram quantities of the desired, enantiomerically enriched *o*-nitroarylated ketone (+)-*ent*-**40** in 57−62% overall yield.

As mentioned above, a strong point of the arylation protocol is that it provides ready access to various indoles. The use of substituted aryliodonium salts allows the preparation of indoles that are substituted on the aromatic ring. In the context of the present project, the synthesis of 16-methoxytabersonine was of

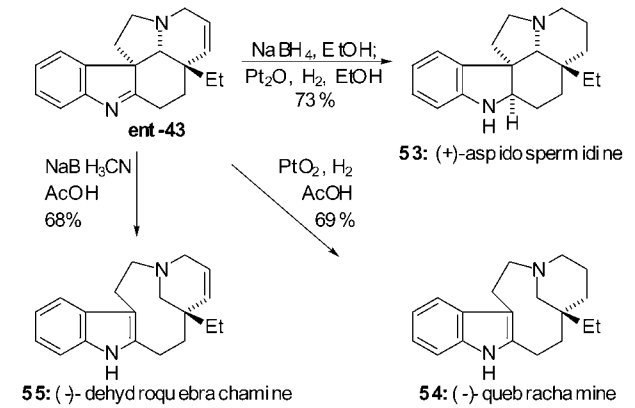
(41) Wen, R.; Laronze J.-Y.; Lévy, J. *Heterocycles* **1984**, *22*, 1061−1065.
(42) Reviews on chiral Lewis acids in organic synthesis: (a) Noyori, R. *Asymmetric Catalysts in Organic Synthesis*; Wiley: New York, 1994. (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497−526. (c) Oh, T. Reilly, M. *Org. Prep. Proc. Int.* **1994**, *26*, 129−158. (d) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl* **1998**, *37*, 388−401. (e) Dell, C. P. *J. Chem. Soc., Perkin Trans 1*, **1998**, 3873−3905. (f) Yamamoto, H. *Lewis Acid Reagents*; Oxford University Press: Oxford, 1999. (g) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: 1999; Vols. I−III. (h) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000. (i) Hisashi Yamamoto, H. *Lewis Acids in Organic Synthesis*; Wiley-VCH: New York, 2000.
(43) For reviews on the catalytic asymmetric Diels−Alder reactions, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007−1019. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741−761. (c) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289−332. (d) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. III, pp 1177−1235.
(44) (a) Martinez, L. E.; Leighton, J. M.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898. (b) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405. (c) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876−4877.
(45) The enantiomeric excess was determined by ^{1}H NMR analysis of the Mosher ester **59**, obtained through the sequence shown below. See Supporting Information for details. The absolute stereochemistry of the adduct was determined to be 6*R* by comparison of chemical shifts of the Mosher ester in ^{1}H NMR with the reported value.[1b,e,i]



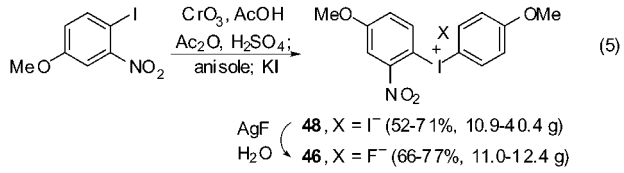
Scheme 15



Scheme 16



interest as it provided a more direct route to vindoline (and ultimately to vinblastine) than was possible through tabersonine. What was required was a modified diaryliodonium salt, one that could introduce the *p*-methoxy-*o*-nitrophenyl unit α to the carbonyl group. The necessary reagent, *p*-methoxy-*o*-nitrophenyl(*p*-methoxyphenyl)iodonium fluoride, was prepared on a multigram scale by the general procedure used for the preparation of **39**.[31] Thus, *p*-methoxy-*o*-nitroiodobenzene was oxidized with CrO_3 (the alternate procedure, vide supra) and the mixture treated with anisole. Subsequent addition of KI afforded iodonium iodide **48**, which was then converted to the corresponding iodonium fluoride **46** (eq 5).



(5)

The *p*-methoxy-*o*-nitrophenylation of *ent*-**20** using reagent **46** gave the expected arylation product *ent*-**47** in 31−35% isolated yields for the three-step sequence starting from *ent*-**18** (Scheme 14). The arylation with **46** was not fully optimized, and the reaction was accompanied by a considerable amount of hydrolyzed ketone *ent*-**23** (20−30%). The overall yield of *ent*-**47** was improved to 40% by using CH_2Cl_2−DMSO as cosolvents for the arylation steps.

The enantiomerically enriched arylated products *ent*-**40** and *ent*-**47** were transformed into (+)-tabersonine (*ent*-**1**) and (+)-16-methoxytabersonine (*ent*-**7**), respectively, by the five-step sequence shown in Scheme 15. Only the final products from the multistep sequence were purified. The reduction of *ent*-**40** and *ent*-**47** with $TiCl_3$ provided crude tetracyclic indoles *ent*-**24** and *ent*-**49**,[33] respectively, which were treated with 2 equiv of TMSI in refluxing CH_2Cl_2 to afford amines *ent*-**41** and *ent*-**50**.[35,36] The unpurified free amines were then treated with bromoethanol in EtOH in the presence of Na_2CO_3.[37] After standard workup, excess bromoethanol was removed under reduced pressure, and the resulting crude alcohols (*ent*-**42** and *ent*-**51**) were used in the subsequent step without purification.

In contrast to the original, two-step sequence, a one-pot procedure was developed for the transformation of alcohols *ent*-**42** and *ent*-**51** to pentacycles *ent*-**43** and *ent*-**52**, respectively. The treatment of *ent*-**42** and *ent*-**51** with MsCl and Et_3N in CH_2Cl_2 followed by addition of potassium *tert*-butoxide afforded the desired pentacycles. Finally, the crude pentacycles (*ent*-**43** and *ent*-**52**) were deprotonated with LDA, and the resultant anions reacted with methyl cyanoformate[40] to provide (+)-tabersonine (*ent*-**1**) and (+)-16-methoxytabersonine (*ent*-**7**), the antipodes of the natural products, in 33−39% (1.14−1.46-g quantities) and 37% (1.11-g quantity) yields, respectively, for the five steps from *ent*-**40** and *ent*-**47**.[46,47]

As stated in the Introduction, there are scores of alkaloids in the *Aspidosperma* family. One strength of our strategy is that it provides easy access to many different members of this family through advanced intermediates in the synthetic sequence. As a demonstration of this, the pentacyclic intermediate *ent*-**43** was converted into (+)-aspidospermidine (**53**),[34d,48] (−)-quebrachamine (**54**),[10c,48r,s,49] and (−)-dehydroquebrachamine (**55**) (Scheme 16).[10b,49d,50] The reduction of the imine double bond of *ent*-**43** with $NaBH_4$ in EtOH to dehydroaspidospermidine

(46) The 500-MHz ^{1}H NMR and 125-MHz ^{13}C NMR spectra of (+)-tabersonine (*ent*-**1**) were identical to those of (±)-tabersonine synthesized above. The 500-MHz ^{1}H NMR and 125-MHz ^{13}C NMR spectra of our synthetic sample of (+)-16-methoxytabersonine (*ent*-**7**) were identical to those previously reported in the literature. See: Lounasmaa, M; Kan, S.-K. *Acta Chem. Scand., B* **1980**, *34*, 379−381 for ^{1}H NMR and ref 11a for ^{13}C NMR.

(47) These compounds are enantiomers of the natural products. The natural compounds would be readily prepared using the other enantiomer of the chiral salen catalyst.

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followed by hydrogenation of the olefin with Pt_2O in EtOH afforded natural (+)-aspidospermidine (**53**) in 73% yield. Treatment of *ent*-**43** with $NaBH_3CN$ in AcOH accomplished the fragmentation of the C-7−C-21 bond and the chemoselective reduction of the resulting iminium ion to yield (−)-dehydroquebrachamine (**55**) in 68% yield. Hydrogenation of *ent*-**43** with Pt_2O in AcOH promoted the same fragmentation as well as reduction of both double bonds in the putative dihydropyridinium intermediate and afforded (−)-quebrachamine (**54**) in 69% yield.

Summary and Conclusions

We have described here a novel, highly stereocontrolled route to the *Aspidosperma* family of alkaloids. The strategy hinges on a highly regio- and stereoselective [4 + 2] cycloaddition of 2-ethylacrolein with 1-amino-3-siloxydienes. The effectiveness of the strategy was illustrated through the total synthesis of (±)-tabersonine, which was achieved by a concise sequence in ∼30% overall yield, the highest reported to date. The sequence demonstrated (a) the use of an olefin metathesis reaction to construct the *cis*-hexahydroquinoline ring system, having the double bond correctly positioned for these alkaloids, (b) a novel indole synthesis based on the regiocontrolled *o*-nitrophenylation of an enol silyl ether using (*o*-nitrophenyl)phenyliodonium fluoride, and (c) the high-yielding conversion of the ABDE tetracycle into the pentacyclic target (±)-**1** via an intramolecular indole alkylation and regioselective C-carbomethoxylation.

The strategy was readily adapted to the gram-scale asymmetric synthesis of *Aspidosperma* alkaloids. The pivotal asymmetry-introducing step was an enantioselective Diels−Alder reaction catalyzed by a chiral Cr(III)−salen complex. The cycloadduct was formed in high yield and with ∼95% ee, and it was then carried forward to (+)-tabersonine and (+)-16-methoxytabersonine, both of which were synthesized in >1-g quantities. The synthetic sequence was easy to execute and required only four purifications over the 12-step synthetic route. The versatility of the strategy was further illustrated through the asymmetric syntheses of (+)-aspidospermidine, (−)-dehydroquebrachamine, and (−)-quebrachamine.[47]

Experimental Section[51]

Methyl *N*-Allylcarbamate (14). Methyl chloroformate (30.9 mL, 0.40 mol) was added slowly to a chilled (0 °C) solution of allylamine (66 mL, 0.88 mol) in CH_2Cl_2 (600 mL). The reaction mixture was allowed to reach room temperature, stirred for 2 h, then washed successively with 2 M aqueous HCl (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL), and dried over $MgSO_4$. Concentration of the volatiles in vacuo gave 44.1 g (96%) of *N*-allyl carbamate (**14**) as a colorless oil, which was used without further purification.

Vinylogous Imide 15. **Method A.** A solution of methyl allylcarbamate (**14**; 230 mg, 2.0 mmol) and acetylacetaldehyde dimethylacetal (**13**; 0.57 mL, 4 mmol) in 5.0 mL of chloroform containing 20 mg of TsOH was heated at gentle reflux for 27 h. Concentration of the reaction mixture followed by direct flash chromatography on silica gel (50% EtOAc/hexanes) afforded 330 mg (90%) of the vinylogous imide **15** as a colorless oil.

Method B. A solution of **14** (44.1 g, 383 mmol) and acetal **13** (52 mL, 392 mmol) in 1 L of chloroform containing 2 g of TsOH was heated at gentle reflux for 44 h, during which time MeOH was removed using a Soxhlet apparatus packed with 4-Å molecular sieves. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled twice to give 31.3 g (45%) of vinylogous imide **15** as a yellow oil.

Aminosiloxydiene 16. **Method A.** A solution of KHMDS in toluene (0.5 M, 33.0 mL, 16.5 mmol) was diluted with THF (35 mL) and cooled to −78 °C. To the resulting solution was added the vinylogous imide **15** (3.15 g, 17.2 mmol) in THF (20 mL) over 30 min. The reaction was warmed to −50 °C over 2 h, cooled to −78 °C, and treated with TBSCl (2.64 g, 17.5 mmol) in THF (15 mL). The reaction mixture was warmed to room temperature, stirred for 30 min, diluted with ether (350 mL), filtered through dry Celite, and concentrated in vacuo to give essentially pure aminosiloxydiene **16** (∼100%) as an oil.

Method B. A solution of NaHMDS in THF (1 M, 22 mL, 22 mmol) was diluted with THF (40 mL) and cooled to −78 °C. To this stirred solution was added dropwise a solution of vinylogous imide **15** (3.66 g, 20 mmol) in THF (8.0 mL). After stirring at −78 °C for 1 h, the reaction mixture was treated with TBSCl (3.62 g, 24 mmol) in THF (4.0 mL). After 2 h, the cold reaction mixture was poured into ether (400 mL), filtered through Celite, and concentrated in vacuo. The residue was filtered again through Celite with hexanes (2 × 100 mL) to afford essentially pure aminosiloxydiene **16** (6.00 g, (∼100%) as a yellow oil, which was used without further purification for the next step.

Diels−Alder Adduct 18. A solution of the diene **16** (4.56 g, 15.4 mmol) and ethylacrolein (2.0 mL, 20 mmol) in toluene (10 mL) was heated first at 65 °C for 15 h and then at 85 °C for 33 h at which point the NMR analysis of the reaction mixture indicated complete consumption of the diene. Evaporation of volatiles under high vacuum afforded 5.69 g (97%) of the cycloadduct **18** in good purity as a colorless oil.

Wittig Methylenation of Aldehyde 18. To a suspension of methyltriphenylphosphonium bromide (6.8 g, 19 mmol) in THF (40 mL) was added dropwise at 0 °C *n*-butyllithium in hexane (2.1 M, 8.0 mL, 17 mmol), and stirring was continued for additional 30 min. The resulting yellow ylide solution was cooled to −78 °C and treated with the aldehyde **18** (5.46 g, 14.3 mmol) in THF (30 mL). The resulting slurry was warmed to room temperature and diluted with ether (150 mL) and water (100 mL). The aqueous layer was back-extracted with ether (50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in a minimum amount of EtOAc and purified by flash column (20% EtOAc/hexanes) to afford 4.6 g (85%) of **19** as a colorless oil.

Representative Ring-Closing Metathesis of 19. To a degassed solution of **19** (130 mg, 0.34 mmol) in benzene (4.0 mL) under nitrogen atmosphere at 20 °C was added at Schrock's molybdenum catalyst in benzene (0.13 mL of 100 mg of the catalyst in 1.0 mL of benzene, 0.02 mmol, 5 mol %). The solution was heated to 60 °C for 1 h, at which point, TLC analysis indicated the reaction was complete.

(49) Racemic quebrachamine syntheses: (a) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872−2873. (b) Kuehne, M. E.; Bayha, C. *Tetrahedron Lett.* **1966**, 1311−1315. (c) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2342−2346. (d) Hoizey, M. J.; Olivier, L.; Levy, J.; Le Men, J. *Tetrahedron Lett.* **1971**, 1011−1014. (e) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 3022−3023. (f) Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 7084−7085. (g) Giri, V. S.; Ali, E.; Pakrashi, S. C. *J. Heterocycl. Chem.* **1980**, *17*, 1133−1134. (h) Takano, S.; Murakata, C.; Ogasawara, K. *Heterocycles* **1981**, *16*, 247−249. (i) Wenkert, E.; Halls, T. D. J.; Kwart, L. D.; Magnusson, G.; Showalter, H. D. H. *Tetrahedron* **1981**, *37*, 4017−4025. See also refs 39a and 48b,e,g,i,k,l. Asymmetric quebrachamine syntheses: (j) Takano, S.; Chiba, K.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1980**, 616−617. (k) Takano, S.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1153−1155. (l) Asaoka, M.; Takei, H. *Heterocycles* **1989**, *29*, 243−244. (m) Temme, O.; Taj, S.-A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 6007−6015. See also refs 10c, and 48r,s.

(50) (a) Ziegler, F. E.; Bennett, G. B. *Tetrahedron Lett.* **1970**, 2545−2547. (b) Wenkert, E.; Hagaman, E. W.; Wang, N.-Y.; Kunesch, N. *Heterocycles* **1979**, *12*, 1439−1443. See also refs 10b and 49d.

(51) The experimental procedures that lead to the target molecules are shown here. The remaining procedures, general experimental guidelines, and all spectral data and copies of actual spectra can be found in the Supporting Information.

Examination of the crude reaction product, after evaporation of the solvent, showed complete conversion to the product. Chromatographic purification (20% ether/hexanes) afforded 105 mg (88%) of **20** as a colorless oil.

(*o*-Nitrophenyl)phenyliodonium Iodide (38). Method A.[30] To a stirred solution of *o*-iodonitrobenzene (20.0 g, 80 mmol) in H_2SO_4 (450 mL) was added $K_2S_2O_8$ (24.0 g, 88 mmol) in small portions followed by benzene (100 mL) at room temperature, and the mixture was stirred vigorously for 3 h. The reaction mixture was poured over ice (total volume 1.6 L), and the insoluble material was removed by filtration. The filtrate was treated with aqueous KI (66 g/100 mL), causing an orange precipitate that was filtered and washed thoroughly with H_2O (~2 L) followed by acetone (**38** is slightly soluble in acetone). The collected solid was dried over P_2O_5 under reduced pressure to afford 27.8 g (76%) of the title compound as an orange powder.

Method B. A mixture of CrO_3 (5.87 g, 59 mmol), AcOH (40 mL), and Ac_2O (20 mL) was stirred at room temperature for ~45 min. The resulting red brown solution was treated with 2-iodonitrobenzene (19.92 g, 80 mmol) followed by dropwise addition of concentrated H_2SO_4 (14 mL), while maintaining the temperature below 25 °C (water bath). After 15 min, benzene (14.2 mL, 160 mmol) was added dropwise, while continuing to keep the temperature below 25 °C. The resulting mixture was heated at ~55 °C for 1.5 h, cooled in an ice bath, and then poured into cold 30% MeOH in H_2O (200 mL). The resulting precipitate was removed by filtration, and the filtrate was treated with saturated aqueous $Na_2S_2O_3$ (3 mL) followed by aqueous KI (16.0 g, 96 mmol/45 mL of H_2O). After stirring for 1 h, the orange precipitate was filtered and washed with cold H_2O until the filtrate became colorless (~1 L), then with cold MeOH (~130 mL, **38** is slightly soluble in MeOH). The collected solid was dried over P_2O_5 in vacuo to afford **38** as an orange powder (24.3 g, 67%).

(*o*-Nitrophenyl)phenyliodonium Fluoride (NPIF, 39).[30] To a vigorously stirred solution of AgF (5.07 g, 40 mmol) in H_2O (80 mL) was added in small portions the iodonium iodide **38** (18.12 g, 40 mmol). The reaction was moderately exothermic. After the mixture was stirred for 3 h, the insoluble material was removed by filtration, and the filtrate was concentrated below 20 °C under reduced pressure (<1 Torr). The residue was suspended in MeCN (20 mL), to which was added ether (20 mL). The mixture was chilled to 0 °C, and the resulting crystalline product was filtered and washed with a small amount of MeCN followed by ether to give 10.45 g (76%) of NPIF as a brown solid. Impure NPIF gradually turns dark, but it can still be used for *o*-nitrophenylation.

***o*-Nitrophenylation of Enol Ether 20.** To a solution of silyl enol ether **20** (250 mg, 0.71 mmol) in 2.0 mL of 1:2 THF−DMSO solution was added in one portion the NPIF iodonium salt **39**[30] (287 mg, 0.83 mmol). The reaction mixture darkened and was stirred for 1.5 h at 20 °C, at which point TLC analysis revealed complete disappearance of starting material. The reaction mixture was diluted with water (50 mL) and extracted with ether (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (40% EtOAc/hexanes) to give **40** (236 mg, 94%) as a pale yellow solid.

Reductive Indolization of Nitrophenyl Ketone 40. To a solution of ammonium acetate (1.15 g, 15 mmol) in water (6.0 mL) was added 1.44 M $TiCl_3$ in water (3.7 mL, 5.3 mmol). The resulting dark purple solution was diluted with acetone (6.0 mL) and slowly treated with nitrophenyl ketone **40** (236 mg, 0.66 mmol) in acetone (6.0 mL). The reaction mixture was stirred for 15 min at 20 °C, diluted with water (100 mL), and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (33% EtOAc/hexanes) to give 182 mg (89%) of the desired tetracyclic carbamate **24** as a white foamy solid.

Cleavage of Carbamate 24. To a solution of the carbamate **24** (198 mg, 0.64 mmol) in CH_2Cl_2 (9 mL) was added under nitrogen atmosphere iodotrimethylsilane (0.21 mL, 1.45 mmol). The reaction mixture was heated to a gentle reflux for 1 h. Methanol (0.5 mL) was added, and the resulting solution concentrated. The residue was partitioned between 1.2 M aqueous HCl (20 mL) and ether (60 mL). The ethereal layer was washed with 1.2 M aqueous HCl (2 × 10 mL). The combined aqueous layers were neutralized at 0 °C with 30% aqueous NaOH. The resulting aqueous phase was reextracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated to afford 147 mg (91%) of **41** as a pale yellow solid.

Alkylation of Amine 41 with Bromoethanol. To a solution of **41** (30 mg, 0.12 mmol) in absolute ethanol (1.0 mL) were sequentially added freshly distilled bromoethanol (0.85 mL, 1.2 mmol) and anhydrous sodium carbonate (127 mg, 1.2 mmol). The resulting suspension was heated to reflux for 18 h, and the reaction was monitored by TLC. The reaction mixture was diluted with EtOAc, filtered, and concentrated, and the residue was purified by flash chromatography (10% MeOH/EtOAc) to afford 35 mg (100%) of the alkylated product **42** as a white solid.

Preparation of Chloroethyl Tetracycle 44. To a CH_2Cl_2 (10 mL) solution of amino alcohol **42** (72 mg, 0.24 mmol) and triethylamine (51 mg, 70 μL, 0.50 mmol) was added methanesulfonyl chloride (34 mg, 23 μL, 0.30 mmol) at −20 °C. The reaction mixture was allowed to reach room temperature and stirred for an additional 30 min. Saturated aqueous solution of $NaHCO_3$ was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the crude product (50% ether/hexanes) yielded 68 mg (90%) of **44** as a white solid, which slowly decomposes at room temperature.

Preparation of Didehydroaspidospermidine (43). To a solution of chloramine **44** (60 mg, 0.19 mmol) in THF (6.0 mL) was added dropwise a 0.4 M solution of *t*-BuOK in THF (0.71 mL, 0.28 mmol), causing the formation of a white precipitate. The reaction mixture was stirred for 16 h at 20 °C. Excess base was quenched by addition of small amounts of water (0.10 mL). The resulting mixture was diluted with ether (40 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was redissolved in CH_2Cl_2 (7 mL), dried further with anhydrous Na_2SO_4, and filtered. Concentration under vacuum gave 46 mg (87%) of **43** as a yellow foamy solid which was used directly in the next step. Further purification of **43** was accomplished using preparative TLC ($CHCl_3$/MeOH/Et_3N, 300:9:4). The complete structural assignment was established by COSY, HMQC, and NOESY experiments. See Supporting Information.

(±)-Tabersonine (*rac*-1). A solution of LDA was prepared by addition of *n*-BuLi (2.5 M solution in hexane, 80 μL, 0.20 mmol) to diisopropylamine (65 μL, 0.50 mmol) in THF (0.8 mL) at −70 °C. The resulting clear solution was stirred for 20 min at −70 °C and slowly treated with a solution of imine **43** (28 mg, 0.10 mmol) in THF (0.7 mL). The reaction mixture was allowed to warm to −20 °C over a 1.0-h period and then cooled to −70 °C, and methyl cyanoformate (20 μL, 0.25 mmol) was added in one portion. The reaction mixture was diluted with ether (6 mL) and 1.2 M aqueous solution of HCl (3 mL). The aqueous phase was separated and carefully neutralized by addition of saturated aqueous $NaHCO_3$ solution. The product was extracted into CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated to give 27 mg (80%) of tabersonine as a pale yellow solid that was clean by NMR. ^1H and ^{13}C NMR spectra for this sample were in good agreement with those described in the literature.

Catalytic Asymmetric Diels−Alder Reaction. To a chilled (−40 °C), stirred mixture of catalyst **45b** (50 mg, 0.05 mmol) and oven-dried, powdered 4-Å molecular sieves (0.8 g) in CH_2Cl_2 (1.0 mL) were added ethacrolein (196 mL, 2.0 mmol) and diene **16** (296 mg, 1.0 mmol). The stirred mixture was kept at −40 °C for 2 days. The molecular sieves were removed by filtration through Celite and washed

with CH_2Cl_2. The filtrate was concentrated in vacuo and the residue purified by flash column chromatography (5% EtOAc/hexane containing 1% Et_3N) to give 346 mg (91%) of cycloadduct *ent*-**18** as a colorless oil. The ee of *ent*-**18** was determined to be 96% by the Mosher ester analysis of the corresponding alcohol (see Supporting Information). The absolute stereochemistry of *ent*-**18** was determined to be 6*R* by comparison of chemical shifts of the Mosher ester in ^1H NMR with the reported value.[1b,e,i]

Multigram-Scale Catalytic Asymmetric Diels−Alder Reaction. The reaction was carried out as above but using 1.0 g of catalyst **45b** (83% purity, 1.0 mmol), 16 g of oven-dried powdered 4-Å sieves, 20 mL of CH_2Cl_2, 2.35 mL of ethacrolein (24 mmol), and 6.00 g of crude diene **16** dissolved in 5 mL of CH_2Cl_2. Chromatographic purification afforded 6.43 g (84%) of *ent*-**18** as a yellow oil in two steps from ketone **15**. The ee of *ent*-**18** was determined, as described above, to be 95%.

Gram-Scale Synthesis of *o*-Nitrophenylated Ketone *ent*-40. (1) Wittig Reaction. To a suspension of methyltriphenylphosphonium bromide (7.79 g, 21.8 mmol) in THF (42 mL) cooled at 0 °C was added dropwise a 2.47 M solution of *n*-butyllithium in hexane (8.2 mL, 20.3 mmol). The yellow ylide solution was stirred for 1 h at 0 °C, cooled to −78 °C, and treated dropwise over 15 min with *ent*-**18** (6.40 g, 16.8 mmol) in THF (34 mL). The cold bath was removed, and the mixture was allowed to warm to room temperature. After dilution with ether (180 mL), the organic phase was washed with water (120 mL). The aqueous phase was back-extracted with ether (60 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was suspended in hexanes (150 mL), and the precipitated triphenylphosphine oxide was removed by filtration. Concentration of the filtrate in vacuo afforded 6.47 g of crude *ent*-**19** as an orange oil, which was used without purification.

(2) Ring-Closing Metathesis of *ent*-19. To a solution of crude diene *ent*-**19** (6.47 g, 16.8 mmol) in CH_2Cl_2 (340 mL) under N_2 was added Grubbs's catalyst (1.00 g, 1.22 mmol, 7.2 mol %). The resulting solution was heated at gentle reflux for 44 h. The reaction mixture was concentrated in vacuo to afford 7.04 g of crude bicycle *ent*-**20**, which was used in the next step without purification.

(3) *o*-Nitrophenylation. To a stirred solution of *ent*-**20** (7.04 g, crude material obtained above, assumed to be 16.8 mmol) in DMSO−THF (34 mL−17 mL) was added iodonium fluoride **39** (5.80 g, 16.8 mmol) at once with partial cooling (ice bath). The reaction was exothermic. After stirring at room temperature for 3.5 h, the reaction mixture was poured into water (680 mL) and extracted with ether (3 × 400 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane, 1:4−1:2) to give 3.54 g (59% in three steps from *ent*-**18**) of *ent*-**40** as a yellow oil.

Gram-Scale (+)-Tabersonine (*ent*-1). (1) Indole Formation. To a stirred solution of ammonium acetate (16.96 g, 220 mmol) in H_2O (85 mL) was added a purple solution of 1.32 M $TlCl_3$ in H_2O (58 mL, 76.6 mmol) followed by acetone (85 mL). The resultant dark brown mixture was stirred vigorously and treated dropwise over 15 min with a solution of *ent*-**40** (3.45 g, 9.63 mmol) in acetone (85 mL). After 30 min, the reaction mixture was concentrated to about half of the original volume and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 200 mL), dried over Na_2SO_4, and concentrated in vacuo to give 3.03 g of crude indole *ent*-**24** as a yellowish-green foam, which was used without purification in the next step.

(2) Cleavage of the Carbamate Group of *ent*-24. Trimethylsilyl iodide (3.2 mL, 22.8 mmol) was added to a stirred solution of crude *ent*-**24** (3.03 g, assumed to be 9.63 mmol) in CH_2Cl_2 (135 mL). The reaction mixture was heated at gentle reflux for 1 h, cooled to room temperature, and then treated with methanol (7.5 mL). The resulting solution was washed with 1% aqueous NaOH (100 mL) and brine (70 mL), dried over Na_2SO_4, and concentrated in vacuo to afford 2.63 g of crude amine *ent*-**41** as a greenish brown solid, which was used in the next step without purification.

(3) Alkylation of *ent*-41. A solution of crude *ent*-**41** (2.63 g, assumed to be 9.63 mmol) in absolute ethanol (96 mL) was treated with bromoethanol (2.73 mL, 38.5 mmol) followed by anhydrous sodium carbonate (4.08 g, 38.5 mmol). The resulting suspension was heated at reflux for 15 h. After cooling, the reaction mixture was concentrated under reduced pressure, and the residue was suspended in ether (50 mL) and water (50 mL). The ether layer was separated, and the aqueous layer was back-extracted with ether (50 mL). The combined ether extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to afford 3.37 g of crude alcohol *ent*-**42** as a dark brown gum, which was used without purification in the next step.

(4) Cyclization of *ent*-42. A stirred solution of crude alcohol *ent*-**42** (3.06 g, assumed to be 8.75 mmol) and Et_3N (1.83 mL, 13.1 mmol) in CH_2Cl_2 (44 mL) was cooled at −15 °C (ice−NaCl) and treated dropwise with methanesulfonyl chloride (0.81 mL, 10.5 mmol). After 30 min, a solution of 1 M potassium *tert*-butoxide in THF (21.9 mL, 21.9 mmol) was added over 5 min, and the resulting mixture was allowed to reach room temperature. After 45 min, the reaction mixture was poured into brine (110 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to afford 2.75 g of crude *ent*-**43**, a dark brown oil that was used for the next step without purification.

(5) Introduction of Ester Group. To a solution of LDA (17.5 mmol) in THF (53 mL) cooled at −70 °C was added dropwise a solution of the crude imine *ent*-**43** (2.75 g, assumed to be 8.75 mmol) in THF (20 mL) over 25 min. After 40 min, methyl cyanoformate (1.74 mL, 21.9 mmol) was added over 5 min. The resulting mixture was stirred at −70 °C for 20 min and then poured into brine (150 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 40 mL). The combined extracts were washed with brine (70 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (1/10 hexanes/??????) to give 1.14 g (39% in five steps from *ent*-**40**) of (+)-tabersonine (*ent*-**1**) as a pale yellow gum: The ^1H NMR and ^{13}C NMR spectra of this sample were in full agreement with those of (±)-tabersonine synthesized above.[46]

(*p*-Methoxy-*o*-nitrophenyl)-*p*-methoxyphenyliodonium Iodide (48). A mixture of CrO_3 (2.20 g, 22.0 mmol), AcOH (15 mL), and Ac_2O (7 mL) was stirred at room temperature for ∼45 min. To the resulting reddish brown solution was added 2-iodo-5-methoxynitrobenzene (8.37 g, 30 mmol) in one portion. The resulting mixture was treated dropwise with H_2SO_4 (5 mL), while keeping the temperature below 25 °C (water bath). After 15 min, anisole (3.59 mL, 33 mmol) was added dropwise. The mixture was stirred for 30 min at room temperature, cooled to 0 °C, and poured into cold 30% MeOH in H_2O (70 mL). The solids were removed by filtration, and the filtrate was treated with saturated aqueous $Na_2S_2O_3$ (1.0 mL) followed by aqueous KI (6.0 g, 36 mmol/20 mL of H_2O). After stirring for 1 h, the orange precipitate that had formed was isolated by suction filtration and washed with cold H_2O (∼200 mL, until the filtrate was colorless) followed by cold MeOH (∼10 mL; **48** is slightly soluble in MeOH). The collected solid was dried over P_2O_5 in vacuo to give 10.90 g (71%) of **48**.

(*p*-Methoxy-*o*-nitrophenyl)-*p*-methoxyphenyliodonium Fluoride (46). To a vigorously stirred solution of AgF (5.07 g, 40 mmol) in H_2O (80 mL) was added the iodonium iodide **48** (20.52 g, 40 mmol; exothermic), and the mixture was stirred for 3 h. After removal of insoluble material by filtration, the solution was concentrated below 20 °C under reduced pressure (<1 Torr). To the residue was added 20 mL of MeCN, casuing a precipitate to form. Ether (20 mL) was added to the suspension, and the resulting mixture was cooled at −0 °C. The precipitate was filtered, washed with 1:1 MeCN/ether followed by ether to give 12.43 g (77%) of the title compound as a brown solid. Some samples of this compound darkened with time, presumably due to the presence of Ag residues.

***p*-Methoxy-*o*-nitrophenylated Ketone (*ent*-47).** *ent*-**47** was prepared following the procedures used for the preparation of *ent*-**40**. **(1) Wittig Reaction.** A total of 6.25 g of crude *ent*-**19** was obtained as an orange oil from methyltriphenylphosphonium bromide (7.57 g, 21 mmol) and aldehyde *ent*-**18** (6.20 g, 16.2 mmol).

(2) Ring-Closing Metathesis of *ent*-19. A total of 6.69 g of crude bicycle *ent*-**20** was obtained from 6.25 g of crude *ent*-**19** (assumed to be 16.2 mmol) using 0.99 g (1.2 mmol, 7.5 mol %) of Grubbs's catalyst.

(3) *p*-Methoxy-*o*-nitrophenylation. The reaction of crude enol ether *ent*-**20** (5.68 g, assumed to be 14.0 mmol) with iodonium fluoride **46** (5.76 g, 14.0 mmol), carried out as described above, yielded after chromatography 0.929 g (28% in three steps from *ent*-**18**) of hydrolyzed ketone *ent*-**23** as the less polar product and 1.743 g (32% in three steps from *ent*-**18**) of *ent*-**47** as the more polar product.

(+)-16-Methoxytabersonine (*ent*-7). *ent*-**7** was synthesized following the procedures used for the preparation of (+)-tabersonine (*ent*-**1**). **(1) Indole Formation.** Crude indole *ent*-**49** (1.84 g) was obtained as a greenish brown foam from ketone *ent*-**47** (2.02 g, 5.2 mmol) and 1.32 M $TiCl_3$ in H_2O (32 mL, 42 mmol).

(2) Cleavage of the Carbamate Group of *ent*-49. Amine *ent*-**50** (2.54 g, crude) was obtained as a dark brown foam from *ent*-**49** (2.91 g, crude material obtained from two batches, assumed to be 8.19 mmol) and trimethylsilyl iodide (2.68 mL, 18.8 mmol).

(3) Alkylation of *ent*-50. Alcohol *ent*-**51** (2.91 g, crude) was obtained as a dark brown gum from *ent*-**50** (2.54 g, crude, assumed to be 8.19 mmol) and bromoethanol (2.32 mL, 32.7 mmol).

(4) Cyclization of *ent*-51. The cyclization of crude alcohol *ent*-**51** (2.91 g, assumed to be 8.19 mmol) yielded pentacyclic imine *ent*-**52** (3.01 g, crude), which was used without purification.

(5) Introduction of Ester Group. The acylation of crude imine *ent*-**52** (3.01 g, assumed to be 8.19 mmol) and methyl cyanoformate (1.62 mL, 20.4 mmol), as described for (+)-tabersonine (*ent*-**1**), afforded (+)-16-methoxytabersonine (*ent*-**7**, 1.11 g, 37% in five steps from *ent*-**47**) as a light yellow gum. The ^{1}H NMR and ^{13}C NMR spectra of this sample were in agreement with those reported in the literature.[46]

Synthesis of (+)-Aspidospermidine (53). To a solution of the pentacyclic intermediate *ent*-**43** (43.3 mg, 0.156 mmol) in EtOH (1.5 mL) was added $NaBH_4$ (17.7 mg, 0.468 mmol) at 0 °C. After stirring for 30 min at 0 °C followed by 1 h at room temperature, the reaction mixture was diluted with ether, washed twice with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in EtOH (1.5 mL) treated with Pt_2O (3.5 mg, 0.016 mmol) and placed under a hydrogen atmosphere (balloon) at room temperature for 15 h. The reaction mixture was diluted with ether, washed twice with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (1/2 ether/hexane) to give 32 mg (73%) of (+)-aspidospermidine (**53**) as a light yellow gum. The ^{1}H NMR and ^{13}C NMR spectra of this sample were in agreement with those reported in the literature.[48o,p]

Synthesis of (−)-Quebrachamine (54). A solution of the pentacyclic intermediate *ent*-**43** (32 mg, 0.115 mmol) in AcOH (1.5 mL) was treated with Pt_2O (2.6 mg, 0.012 mmol) placed under a hydrogen balloon at room temperature for 2 h. The reaction mixture was diluted with ether, washed with 1 N NaOH aqueous solution, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (1/2 ether/hexane) to give 22.3 mg (69%) of (−)-quebrachamine (**54**) as a light yellow gum. The ^{1}H NMR and ^{13}C NMR spectra of this sample were in agreement with those reported in the literature.[49m]

Synthesis of (−)-Dehydroquebrachamine (55). To a solution of the pentacyclic intermediate *ent*-**43** (29.3 mg, 0.105 mmol) in AcOH (1.5 mL) at room temperature was added $NaBH_3CN$ (19.8 mg, 0.315 mmol) in one portion. After 1 h, the reaction mixture was diluted with ether, washed with 1 N aqueous NaOH solution, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (ether/hexane, 1/10) to give 20 mg (68%) of (−)-dehydroquebrachamine (**55**) as a light yellow gum. The ^{1}H NMR and ^{13}C NMR spectra of this sample were in agreement with those reported in the literature.[10b,50b]

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Supporting Information Available: Additional information as noted in text (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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