Asymmetric Construction of a Quaternary Carbon Center by Tandem [4 + 2]/[3 + 2] Cycloaddition of a Nitroalkene. The Total Synthesis of (−)-Mesembrine

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An efficient, total synthesis of the *Sceletium* alkaloid (−)-mesembrine is accomplished in seven steps and 19% yield from a functionalized nitroalkene (itself prepared in six steps and 34% yield from ethyl 3-bromopropionate). The construction of the octahydroindole framework of mesembrine features a tandem inter [4 + 2]/intra [3 + 2] cycloaddition of a 2,2-disubstituted 1-nitroalkene and a chiral vinyl ether derived from (1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexanol as the central strategic element. The two stereogenic centers of the natural product, which include a benzylic, quaternary center, were established in 26/1 selectivity in the tandem process.

Introduction

The tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes is emerging as an excellent method for the rapid construction of useful polycyclic, nitrogen-containing ring systems.[1] A number of inter- and intramolecular variants of the tandem sequence have been explored which provide access to structural frameworks contained within pyrrolidine,[2] pyrrolizidine,[3] Amaryllidaceae,[4] and *Sceletium*[5] alkaloids. Recent reports from these laboratories have described efficient total syntheses of several pyrrolizidine alkaloids including (−)-hastanecine,[6] (−)-rosmarinecine,[7] (−)-crotanecine,[8] and (−)-platynecine.[9] These syntheses have served to establish the viability of the tandem cycloaddition approach to pyrrolizidines by incorporating the requisite functional groups, and by demonstrating the ability to set all of the critical stereogenic centers.

One of the many structural and stereochemical challenges which can be addressed by the tandem cycloaddition is the ability to incorporate quaternary stereogenic centers at a carbon β to the nitrogen atom. This is a feature common to many octahydroindole-based alkaloids. Indeed, a large number of structurally complex and biologically interesting alkaloids possess this core nucleus, such as the Amaryllidaceae alkaloids crinine, pretazzettine, and amabiline as well as the *Sceletium* alkaloid A-4, Figure 1.

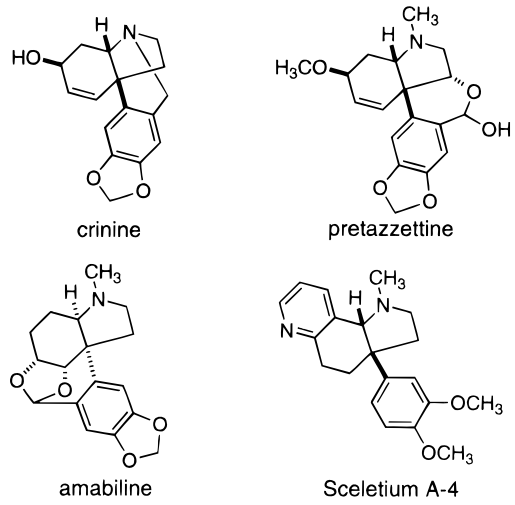
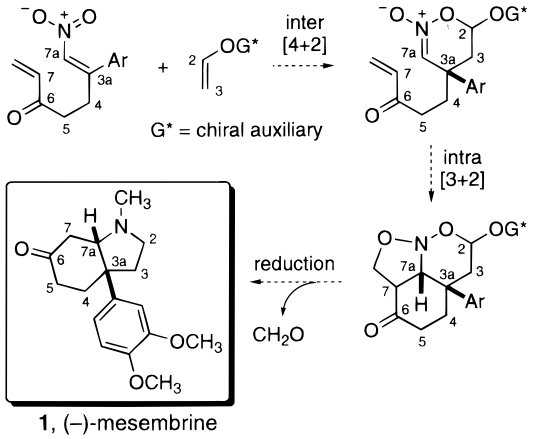


Figure 1. Several *cis*-3a-aryloctahydroindole-based natural products.

Scheme 1



As a vehicle to showcase the tandem method and also guide the development of variants, we selected the *Sceletium* alkaloid mesembrine (**1**) as a target for total synthesis, Scheme 1. We had envisioned that the *cis*-octahydroindole skeleton of mesembrine could be effectively constructed through a tandem inter [4 + 2]/intra [3 + 2] cycloaddition of an appropriately functionalized nitroalkene followed by a reduction of the resulting nitroso acetal and cleavage of the C(7) hydroxymethyl

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(3) (a) Leonard, N. J. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1960; Vol. 6, Chapter 3. (b) *Naturally Occurring Pyrrolizidine Alkaloids*; Rizk, A.-F. M., Ed.; CRC: Boston, 1991. (c) Robins, D. J. *Nat. Prod. Rep.* **1992**, *9*, 313 and references to earlier installments.
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(6) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672.
(7) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem.* **1996**, *118*, 8266.
(8) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125.
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residue. Previously, we had documented the construction of six-membered carbocycles by the use of a three-atom tether between the nitronate and the dipolarophile.[10] However, the synthesis of mesembrine would require the incorporation of a ketone or carbonyl equivalent in the tether. Additionally, the use of a nonracemic, chiral vinyl ether in the [4 + 2] cycloaddition allows for an asymmetric synthesis of natural mesembrine to be realized.

In the following report we detail our efforts to develop an asymmetric [4 + 2] cycloaddition of a 2,2-disubstituted 1-nitroalkene with various chiral vinyl ethers. This method has been effectively coupled to an intramolecular [3 + 2] cycloaddition to serve as the key step in a total synthesis of natural (−)-mesembrine.

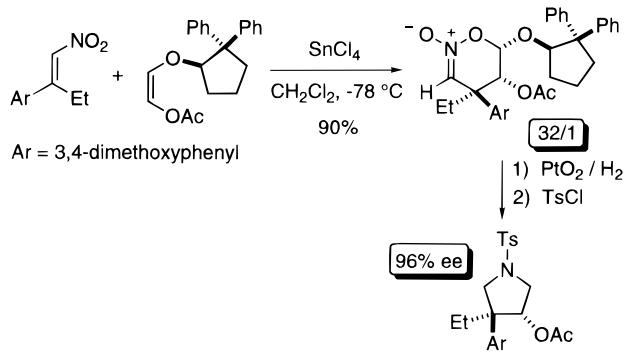
Background

3,3-Disubstituted Pyrrolidines. The creation of quaternary stereogenic centers in enantiomerically enriched form remains a serious challenge in organic synthesis, and methods to effectively accomplish this endeavor are still needed.[11] Accordingly, we envisioned the possibility of using 2,2-disubstituted 1-nitroalkenes as heterodiene components in asymmetric [4 + 2] cycloadditions with chiral vinyl ethers.[12] The resulting nitronates, containing a newly created quaternary carbon, would be useful intermediates for the synthesis of interesting heterocyclic compounds which incorporate this feature.

Toward this goal, we have previously developed a general method for the expedient synthesis of 2,2-disubstituted 1-nitroalkenes from readily available materials.[13] These hindered nitroalkenes were found to undergo Lewis acid-promoted [4 + 2] cycloadditions with *n*-butyl vinyl ether to afford the corresponding cyclic nitronates as anomeric mixtures in good yield.[14] Another report from these laboratories has described the use of 2,2-disubstituted 1-nitroalkenes as heterodiene components in the synthesis of 3-hydroxy 4,4-disubstituted pyrrolidines.[15] Significantly, this report contains an example of an effective asymmetric [4 + 2] cycloaddition of a 2,2-disubstituted 1-nitroalkene and a chiral, nonracemic 2-(acyloxy)vinyl ether, Scheme 2. The resulting nitronate was then reduced to afford the corresponding pyrrolidine in enantiomerically enriched form (96% ee). Thus, among the many challenges that we needed to address for the synthesis of (−)-mesembrine, one of the most critical was to demonstrate that the cycloaddition could tolerate functionalized precursors and deliver cycloadducts in high yield and selectivity.

History, Isolation, and Structure Determination of Mesembrine. The alkaloid mesembrine is an octahydroindole-based natural product that can be isolated in amounts of up to 1% (of the dried weight) from certain plants of the *Sceletium* genus, namely *S. namaquense*, *S. strictum*, and *S. tortuosum*.[5a] Structural investigations began in 1957, when it was revealed that mesembrine contains a ketone, a tertiary amine, and two methoxy substituents.[16] In 1960 the complete structure was elucidated by Popelak and co-workers through a combination of degradation and synthetic methods.[17]

Scheme 2



The absolute configuration of natural (−)-mesembrine remained unassigned until 1969, when Jeffs and co-workers proposed a (3a*S*,7a*S*) configuration through the comparison of circular dichroism spectra of mesembrine to closely related natural products.[18] In 1971, the first asymmetric synthesis of enantiomerically enriched mesembrine was accomplished.[19a] Unfortunately, the authors prepared (+)-(3a*R*,7a*R*) mesembrine which proved to be the unnatural antipode. Thus, Jeffs's original proposal of a (3a*S*,7a*S*) configuration was indeed correct.

Total Syntheses of Mesembrine. Although pure mesembrine was found to be void of interesting biological activity, it has received an enormous amount of attention from synthetic chemists for the past three decades. Primarily, it has provided a touchstone for the development of new synthetic methods and the application of existing technology. In all, 12 total syntheses of racemic mesembrine have been reported,[20] as well as three formal syntheses.[21] The first total synthesis was reported in 1965 and involved a synthetic sequence of 20 steps which afforded the racemic natural product in ~3% overall yield.[20a] Remarkably, racemic mesembrine can now be prepared in a minimum of three steps[20c,n] and as high as 40% overall yield from commercially available materials.[20j]

(10) Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *52*, 11579.

(11) (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Barta, N. S.; Brode, A.; Stille, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 6201.

(12) The use of chiral vinyl ethers in the cycloaddition of (*E*)-2-substituted and (*E*)-1,2-disubstituted 1-nitroalkenes is extrememly effective in providing enantiomerically enriched cycloadducts in good yield and with high diastereocontrol. For examples see footnotes 1 and 28 as well as: Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221.

(13) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3850.

(14) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3857.

(15) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576.

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(17) (a) Popelak, A.; Haack, E.; Lettenbaur, G.; Springer, H. *Naturwissenschaften* **1960**, *47*, 156. (b) Popelak, A.; Haack, E.; Lettenbaur, G.; Springer, H. *Naturwissenschaften* **1960**, *47*, 231.

(18) Jeffs, P. W.; Hawks, R. L.; Farrier, D. S. *J. Am. Chem. Soc.* **1969**, *91*, 3831.

(19) For total syntheses of (+)-mesembrine see: (a) Yamada, S.; Otani, G. *Tetrahedron Lett.* **1971**, *12*, 1133. (b) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron Asymmetry* **1993**, *4*, 1409. (c) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776.

(20) (a) Shamma, M.; Rodriquez, H. R. *Tetrahedron Lett.* **1965**, *6*, 4847. (b) Shamma, M.; Rodriquez, H. R. *Tetrahedron* **1968**, 24, 6583. (c) Curpney, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, *9*, 1441. (d) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. (e) Keely, S. L., Jr.; Tahk, F. C. *J. Am. Chem. Soc.* **1968**, *90*, 5584. (f) Oh-ishi, T.; Kugita, H. *Tetrahedron Lett.* **1968**, *9*, 5445. (g) Oh-ishi, T.; Kugita, H. *Chem. Pharm. Bull.* **1970**, *18*, 291. (h) Oh-ishi, T.; Kugita, H. *Chem. Pharm. Bull.* **1970**, *18*, 299. (i) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579. (j) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (k) Sanchez, I. H.; Tallabs, F. R. *Chem. Lett.* **1981**, 891. (l) Takano, S.; Imamura, Y.; Ogasawara, K. *Chem. Lett.* **1981**, 1385. (m) Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302. (n) Kochhar, K. S.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 4785. (o) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831.

(21) (a) Jeffs, P. W.; Redfearn, R.; Wolfrom, J. *J. Org. Chem.* **1983**, *48*, 3861. (b) Gramain, J.-C.; Remuson, R. *Tetrahedron Lett.* **1985**, *26*, 4083. (c) Hackett, S.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1629.

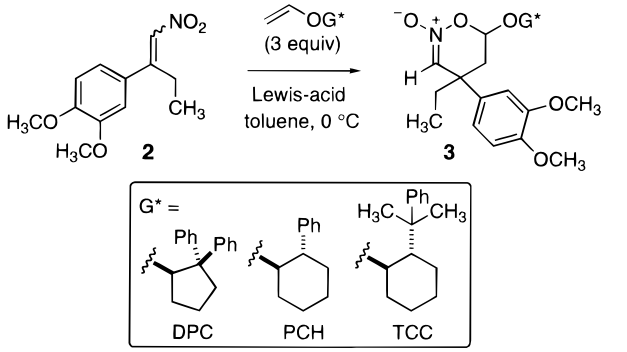
Seven total syntheses of enantiomerically enriched mesembrine have been accomplished.[19,22] These seven are supplemented with four formal syntheses in nonracemic form.[23] The most efficient asymmetric synthesis of mesembrine can be credited to Meyers and coworkers.[19c] These authors were able to prepare unnatural (+)-mesembrine (>99% ee) in nine steps and in 23% overall yield from (3,4-dimethoxyphenyl)acetic acid.

Results

Asymmetric [4 + 2] Cycloaddition of a Nitroalkene Model System. The veratryl-derived nitroalkene **2** was selected as a model diene to address the feasibility of creating a quaternary stereogenic center in an asymmetric [4 + 2] cycloaddition, Table 1.[24] This nitroalkene was chosen because it closely resembles the substitution pattern and electronic nature of the specific nitroalkene that would be suitable for the synthesis of mesembrine.

Cycloaddition results of the model nitroalkene with the chiral vinyl ethers derived from (*R*)-2,2-diphenylcyclopentanol (DPC),[25] (1*R*,2*S*)-2-phenylcyclohexanol (PCH),[26] and (1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexanol (TCC)[27] are summarized in Table 1. All of these chiral vinyl ethers have been found to be highly effective in asymmetric [4 + 2] cycloadditions involving (*E*)-2-substituted 1-nitroalkenes.[28] A survey of Lewis acids revealed that only methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[29] and methylaluminum bis(4-bromo-2,6-diphenylphenoxide) (MABr) were useful in promoting cycloadditions of the model substrate.[30] Cycloadditions of either the pure (*Z*)- or (*E*)-nitroalkenes with the chiral vinyl ether derived from DPC in the presence of 3 equiv of MAD unselectively afforded ternary mixtures of diastereomeric nitronates **3** in similar ratios, Table 1, entries 1 and 2. The use of MABr as the Lewis acid promoter provided no improvement in the diastereoselectivity of the reaction, entry 3. Cycloaddition of (*Z*)-**2** with the chiral vinyl ether derived from PCH afforded an equal mixture of two nitronate diastereomers in 86% yield, entry 4. When using the TCC-derived chiral vinyl ether, the (*E*)-nitroalkene, and MABr as the Lewis acid promoter, a 3.8/1.0 diastereomeric mixture of two nitronates was obtained, entry 5.

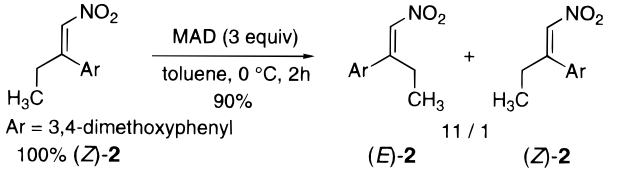
Table 1. Asymmetric [4 + 2] Cycloadditions of a Model Nitroalkene



entry	alkene geometry	Lewis acid [a]	G*	yield, %	diastereomeric ratio[b]
1	*Z*	MAD	DPC	73	1.5/1.0/1.9
2	*E*	MAD	DPC	48	1.9/1.0/1.4
3	*Z*	MABr	DPC	nd	1.7/1.7/1.0
4	*Z*	MAD	PCH	86	1/1
5	*E*	MABr	TCC	76	3.8/1.0
6	*Z*	MAD[c]	DPC	78	2.7/2.1/1.0
7	*Z*	MAD[c]	TCC	79	4/1

[a] The Lewis acid was introduced to a solution of nitroalkene and vinyl ether at 0 °C. [b] Determined by ^{1}H NMR integration.[c] The Lewis acid was added to a solution of the nitroalkene at 0 °C and allowed to stir for 15−60 min before introduction of the chiral vinyl ether.

Scheme 3



To obtain more stereochemical information about the asymmetric cycloaddition, a control experiment was performed in which a sample of pure (*Z*)-**2** was subjected to the reaction conditions and then reisolated, Scheme 3. Analysis of the recovered nitroalkene revealed that isomerization to an 11/1 (*E*/*Z*) mixture of isomers had occurred.[31] This interesting result prompted more cycloaddition experiments in which the nitroalkene was preequilibrated with the Lewis acid for 15−60 min prior to introduction of the chiral vinyl ether. Interestingly, when this modified protocol was employed, no significant change in diastereoselectivity was observed, Table 1, entries 6 and 7.

The stereostructures of the various diastereomers generated in the asymmetric cycloadditions could not be unambiguously assigned through routine spectroscopic methods. Thus, chemical transformation of the diastereomerically enriched nitronates **3** into an enantiomerically enriched 3,3-disubstituted pyrrolidine **4** was performed, Table 2. Reduction was accomplished with hydrogen and a catalytic amount of platinum oxide in the presence of 1 equiv of acetic acid according to the developed method.[14] Reaction of the crude hydrogenoly-

(22) For total syntheses of natural (−)-mesembrine see: (a) Strauss, H. F.; Weichers, A. *Tetrahedron Lett.* **1979**, *20*, 4495. (b) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479. (c) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239. (d) Yoshimitsu, T.; Ogasawara, K. *Heterocycles* **1996**, *42*, 135.

(23) (a) Bauermeister, S.; Gouws, I. D.; Strauss, H. F.; Venter, E. M. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 561. (b) Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1992**, *33*, 6999. (c) Nemoto, H.; Tanabe, T.; Fukumoto, K. *Tetrahedron Lett.* **1994**, *35*, 6499. (d) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785.

(24) For the preparation of nitroalkene **2** see reference 13.

(25) Denmark, S. E.; Marcin, L. R.; Schnute, M. E.; Thorarensen, A. *Org. Synth.* **1996**, *74*, 33.

(26) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1.

(27) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656.

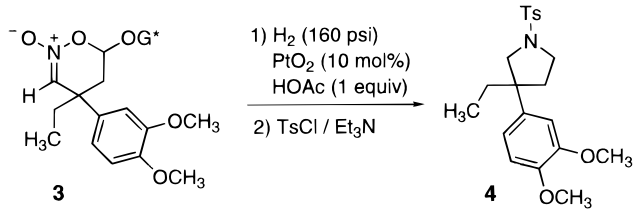
(28) (a) Denmark, S. E.; Senanayake, C. B. W.; Ho, G.-D. *Tetrahedron* **1990**, *46*, 4857. (b) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1991**, *56*, 6738. (c) Denmark, S. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1853. (d) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859. (e) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205. (f) Denmark, S. E.; Stolle, A.; Dixon, J. A.; Guagnano, V. *J. Am. Chem. Soc.* **1995**, *117*, 2100.

(29) (a) Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 5001. (b) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. (c) Maruoka, K.; Oishi, M.; Shiohara, K.; Yamamoto, H *Tetrahedron* **1994**, *50*, 8983.

(30) Other Lewis acids, including Ti(O*i*-Pr)$_2$Cl$_2$, SnCl$_4$, BF$_3$·OEt$_2$, EtAlCl$_2$, methylaluminum(bis-2,6-diisopropylphenoxide) (MAIPh), and methyl aluminum bis(2,6-diphenylphenoxide) (MAPh) were found to be ineffective in promoting the desired cycloaddition.

(31) Isomerization can also be achieved using DMAP in methylene chloride. Starting from either the pure (*Z*)- or (*E*)-nitroalkene, a mixture of nitroalkenes isomers was recovered in approximately a 5/1 (*E*/*Z*) ratio in 53% yield. The rest of the material consisted of a mixture of nitroalkenes in which the olefin had isomerized away from the nitro substituent.

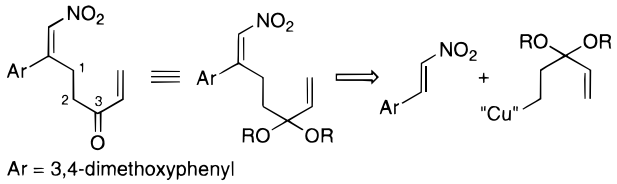
Table 2. Reduction of Diastereomeric Nitronate Mixtures



G*	diastereomeric ratio of **3**	yield of **4**, %	ee of **4**, %[a]
(*R*)-DPC	2.7/2.1/1.0	80	6
(1*R*,2*S*)-TCC	4/1	83	56

[a] Determined by chiral HPLC analysis (Diacel Chiralpak AD column).

Scheme 4



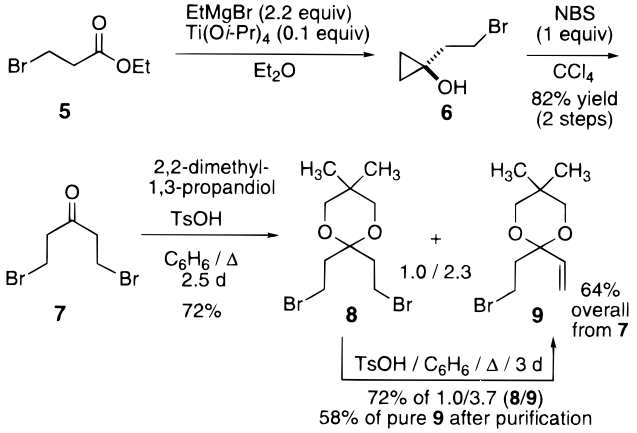
sis products with *p*-toluenesulfonyl chloride and triethylamine afforded the corresponding N-protected pyrrolidine **4**. In the reduction of a 2.7/2.1/1.0 diastereomeric mixture of DPC-derived nitronates, the protected pyrrolidine **4** was isolated in 80% yield and was found to be of 6% enantiomeric excess (ee) by chiral HPLC analysis. Reduction of a 4/1 mixture of TCC-derived nitronates afforded the same pyrrolidine in 83% yield and 56% ee.

Although the results from the model system were less than encouraging, we did learn that a TCC-based auxiliary in connection with MAD as the Lewis acid gave the highest yield and best selectivity in asymmetric [4 + 2] cycloadditions. We next moved forward to investigate cycloadditions of the actual nitroalkene that could be used for the total synthesis of mesembrine.

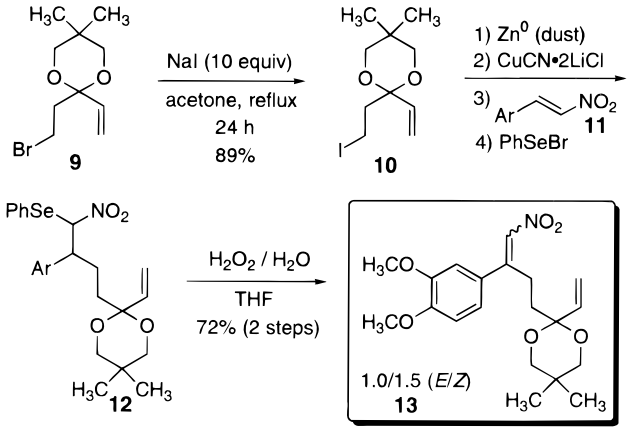
Synthesis of the Tandem Cycloaddition Precursor. A conjugated nitroalkene that would be suitable for the synthesis of mesembrine must possess a ketone or latent ketone functionality on the third carbon atom of the dipolarophile tether, Scheme 4. After suspecting that an unprotected enone might compromise the nitroalkene hetero-Diels−Alder reaction, we chose to pursue the preparation of a ketal-protected substrate. This was envisioned to be available from an (*E*)-2-substituted 1-nitroalkene and a functionalized alkyl cuprate.

According to the literature procedure,[32] ethylmagnesium bromide was added to a solution of ethyl 3-bromopropionate (**5**) in the presence of a catalytic amount of Ti(O*i*-Pr)$_4$ to afford the cyclopropanol **6**, Scheme 5. Treatment of the cyclopropanol with *N*-bromosuccinimide (NBS) provided 1,5-dibromopentan-3-one (**7**) in 82% overall yield. Ketalization of the dibromo ketone with 2,2-dimethyl-1,3-propanediol provided a mixture of the dibromide **8** and the vinyl dioxane **9**. The ratio of the products was observed to be dependent on the duration of heating. A larger amount of the desired vinyl derivative was produced when the reaction was maintained at reflux for longer periods of time. Thus, after heating for 2.5 days, a 1.0/2.3 mixture (**8**/**9**) could be obtained in a

Scheme 5



Scheme 6



73% combined yield. The mixture was separated by column chromatography on basic alumina (activity II), and the dibromide **8** was resubjected to the reaction conditions. After being heated to reflux for an additional 2.5 days, a 1.0/3.7 (**8**/**9**) mixture of products was afforded in 72% yield. From this mixture, the pure vinyl dioxane **9** was isolated in 58% yield after column chromatography. Thus, the desired vinyl ketal **9** could be obtained in 64% overall yield from 1,5-dibromopentan-3-one (**7**) through ketalization and one recycling step.

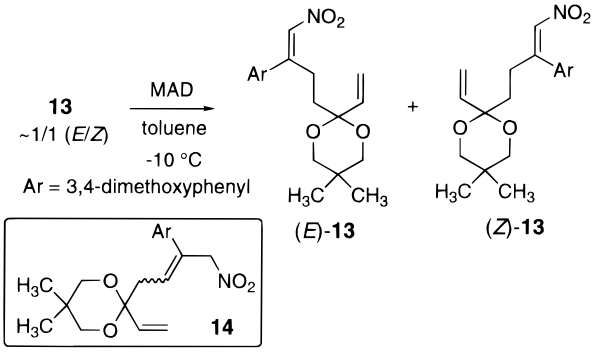
Reaction of the bromo ketal **9** with sodium iodide in refluxing acetone afforded the corresponding iodide **10** in 89% yield, Scheme 6. Treating the iodide with activated zinc, followed by transmetalation with copper cyanide in the presence of lithium chloride provided the intermediate organocopper species. This reagent added in a 1,4-conjugate fashion to (*E*)-2-(3,4-dimethoxyphenyl)-1-nitroethene (**11**)[33] to afford, after trapping with phenylselenenyl bromide, the corresponding nitro selenide **12**. Oxidation and elimination of the selenide was accomplished with aqueous hydrogen peroxide in THF at room temperature. The desired nitroalkene **13** was obtained in 72% overall yield (from **10**) as a 1.0/1.5 (*E*/*Z*) mixture of geometric isomers.

Synthesis of Mesembrine. Since we were concerned that the poor ratio of *E*/*Z*-isomers in **13** would presage a low diastereoselectivity in the [4 + 2] cycloaddition, a number of Lewis acid-assisted *E*/*Z*-isomerization experiments were conducted. As shown in Table 3, no change

(32) Sviridov, S. V.; Vasilevskii, D. A.; Kulinkovich, O. G. *Zh. Org. Khim.* **1991**, *27*, 1431.

(33) Sheth, J. P.; Bhattacharyya, S. C. *Indian J. Chem.* **1977**, *15B*, 595.

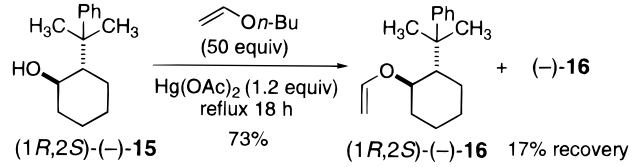
Table 3. Lewis Acid-Assisted Isomerization of Nitroalkene 13



entry	Lewis acid, equiv	time, min	recovery of **14**, %	ratio, E/Z^a
1	0.10	240	94	1/1.3
2	0.75	60	90	6.3/1.0
3	1.00	15	93	12/1.0
4	1.00	120	94	23/1.0

[a] Determined by ^{1}H NMR integration (400 MHz) of the vinylic proton α to the nitro group.

Scheme 7



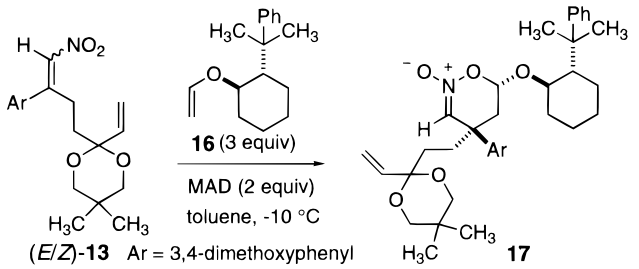
in the *E*/*Z* ratio was observed when a 1/1 mixture of nitroalkene isomers was stirred in toluene for 4 h in the presence of 10 mol % of MAD, entry 1. However, enrichment to a 6.3/1.0 (*E*/*Z*) ratio was observed after 1 h when 75 mol % of the Lewis acid was used, entry 2. Interestingly, when using 1 equiv of MAD, rapid equilibration to a 12/1.0 (*E*/*Z*) ratio occurred in 15 min, entry 3. Under these same conditions for 2 h, a 23/1 (*E*/*Z*) mixture of nitroalkene isomers was obtained. It should be noted that, in all of the isomerization experiments, except entry 1, the reisolated nitroalkene was contaminated with a small amount (<5%) of a common byproduct. ^{1}H NMR analysis suggested structure **14** in which the olefin has shifted out of conjugation with the nitro substituent.

Cycloadditions of the functionalized nitroalkene with the chiral vinyl ether derived from TCC were investigated. The choice of auxiliary was based on the observation that the TCC vinyl ether provided the highest levels of diastereoselectivity (~4/1) in [4 + 2] cycloadditions with the model nitroalkene. The chiral vinyl ether (−)-**16** was readily prepared in 73% yield from the corresponding alcohol (−)-**15** through a mercury-catalyzed transetherification in refluxing *n*-butyl vinyl ether, Scheme 7.[34]

Since the functionalized nitroalkene **13** undergoes rapid equilibration to the *E*-isomer in the presence of MAD, efforts were focused on developing an in-situ isomerization/[4 + 2] cycloaddition protocol. While several procedural variations were explored to optimize the yield and diastereoselectivity of this reaction, three

(34) (a) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1996**, *61*, 6727. (b) The TCC vinyl ether **16** has been found to undergo highly selective exo-mode [4 + 2] cycloadditions when using the aluminum-based Lewis acid MAPh.

Table 4. Optimization of the Asymmetric [4 + 2] Cycloaddition



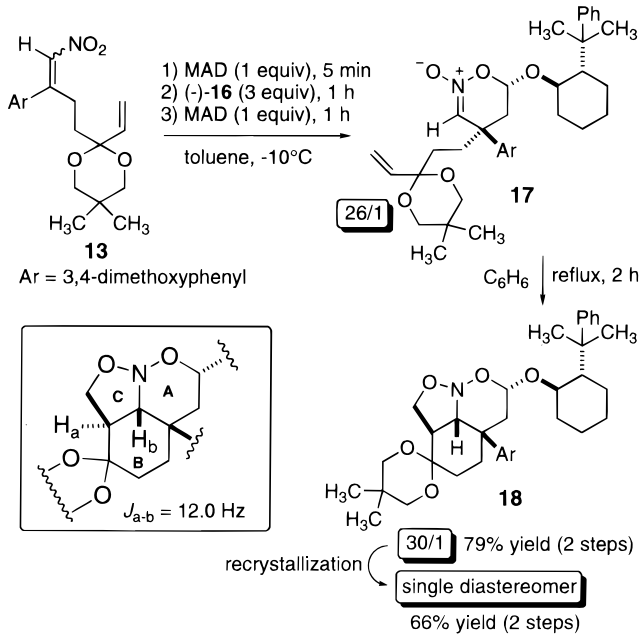
entry	E/Z ratio[a] of **13**	in-situ isomerization, time (procedure)[b]	yield of **17**, %	diastereomeric ratio[a] of **17**
1	~1/1	no (A)	91	7/1
2	~1/1	yes, 2 h (B)	76	13/1
3	~1/1	yes, 30 min (C)	78	15/1
4	26/1	no (D)	83	18/1
5	**~1/1**	**yes, 5 min (E)**	**84**	**26/1**

[a] Determined by ^{1}H NMR integrations (400 MHz). [b] Procedures: (A) Slow addition of MAD (2 equiv) over 1 h to vinyl ether and nitroalkene. (B) Addition of MAD (1 equiv) to nitroalkene, stir 2 h, and then add vinyl ether and more MAD (1 equiv). (C) Addition of MAD (2 equiv), stir 30 min, and then add vinyl ether. (D) Slow addition of MAD (2 equiv) over 2 h to vinyl ether and nitroalkene. (E) Addition of MAD (1 equiv) to nitroalkene, stir 5 min, introduce vinyl ether, stir 1 h, and then slowly added more MAD (1 equiv) over 1 h.

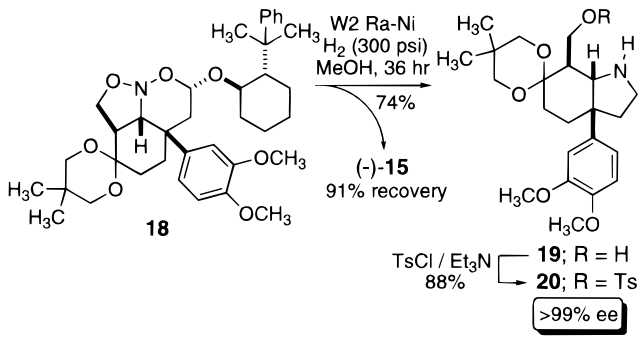
variables in all the experiments were held constant. First, 2 equiv of Lewis acid was deemed necessary for the reaction to reach completion. Second, the reactions proceeded at a reasonable rate (2 h) and afforded the best selectivity when conducted at −10 °C. Lastly, the use of 3 equiv of the chiral vinyl ether was required to achieve respectable yields. With these criteria fixed, manipulation of other experimental details were explored, Table 4. Simply adding the Lewis acid slowly over 1 h to a solution of the nitroalkene **13** and vinyl ether **16** provided a 7/1 mixture of diastereomeric nitronates **17** in 91% yield, entry 1. This selectivity is significantly better than that of the model nitroalkene (~4/1). Preequilibrating the nitroalkene with 1 equiv of MAD for 2 h and then adding the vinyl ether along with another 1 equiv of MAD afforded a 13/1 mixture of diastereomers in 76% yield, entry 2. The use of 2 equiv of the Lewis acid in a brief isomerization (30 min) provided the nitronate in 78% yield as a 15/1 mixture of diastereomers, entry 3. Interestingly, if nearly pure (*E*)-**13** was used with no in-situ isomerization, the [4 + 2]-cycloadduct could be obtained in good yield (83%) and high selectivity (18/1), entry 4. After extensive optimization, a satisfactory protocol that provided the highest yield and best diastereoselectivity was developed, entry 5. Thus, the (*E*/*Z*)-nitroalkene mixture was treated with 1 equiv of MAD and was allowed to stir for 5 min, and then the chiral vinyl ether was introduced. After 1 h, an additional 1 equiv of MAD was slowly added to drive the reaction to completion. This protocol *reproducibly* provided the desired [4 + 2]-cycloadduct in 82−86% yield and 25−29/1 diastereoselectivity.

The configurational assignments for the [4 + 2]-cycloadduct **17** could not be secured through routine methods, but are based on the results from analogous tandem cycloadditions from these laboratories.[7b,34] Ultimately, the absolute configuration of the quaternary center was unambiguously proven by conversion of the nitronate into natural (−)-mesembrine.

Scheme 8



Scheme 9

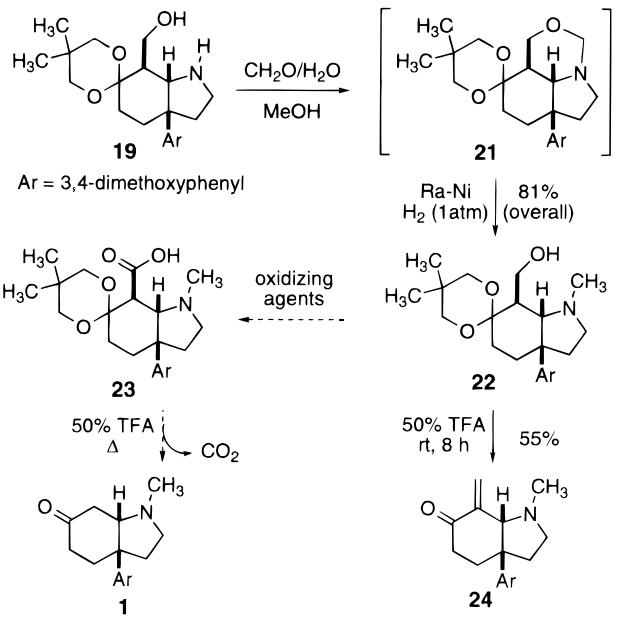


Tandem, intramolecular [3 + 2]-dipolar cycloaddition of the nitronate **17** proceeded smoothly in refluxing benzene to afford the crystalline tricyclic nitroso acetal **18**, as a 30/1 mixture of diastereomers, in 79% overall yield (from **13**), Scheme 8. Recrystallization provided an analytically pure sample of **18** as a single diastereomer in 66% yield. The trans assignment for the B−C ring fusion was based on a large ^{1}H NMR coupling constant (J_{a-b} = 12.0 Hz) between the ring protons H_a and H_b. The cis assignment for the A−B ring fusion is based on geometrical constraints that only permit the intramolecularly tethered dipolarophile to approach the same face of the nitronate dipole to which the tether is connected. Additionally, these stereochemical assignment are in agreement with previous tandem cycloaddition results from these laboratories involving three-methylene tethered unactivated dipolarophiles.[10]

Reduction of the nitroso acetal **18** to the corresponding amine **19** was accomplished in 74% yield using W2 Raney-nickel catalyst under 300 psi of hydrogen, Scheme 9. The chiral auxiliary (−)-**15** was recovered in 91% yield. A small portion of the amino alcohol **19** was transformed into its *N*-*p*-toluenesulfonamide **20** in 88% yield. Chiral HPLC analysis of the sulfonamide showed the product to be enantiomerically enriched to the extent of >99% ee.[35]

Reaction of the amino alcohol **19** with formaldehyde produced an intermediate that was subsequently reduced with hydrogen (1 atm) over Raney-nickel to afford the N-methylated amino alcohol **22** in 81% yield, Scheme 10. The intermediate could be isolated and purified using silica gel column chromatography and was assigned to be the corresponding tricyclic aminal **21**.

Scheme 10



The removal of the unnecessary hydroxymethyl group in **22** by oxidation to the corresponding amino acid **23** proved impossible. Unsuccessful methods included Jones reagent (CrO_3/H_2SO_4/acetone),[36a] chromic acid (CrO_3/H_2SO_4/HOAc),[36b] pyridinium dichromate (PDC) in dimethylformamide (DMF),[36c] ruthenium trichloride with sodium periodate,[36d] purple benzene ($KMnO_4$/*n*-Bu_4NBr/C_6H_6),[36e] and platinum oxide with oxygen.[36f] In most cases an impure mixture of starting material and intermediate aldehyde was reisolated, but this typically accounted for less than 50% of the mass balance. A reversed approach, involving initial deprotection of the ketal followed by oxidation of the alcohol also failed. Reaction of the *N*-methylamino alcohol **22** with 50% TFA, at room temperature for 8 h, provided the undesired enone **24** in modest yield (55%).

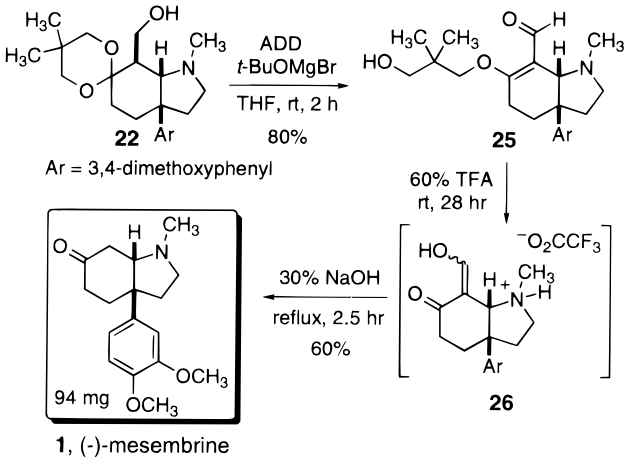
We next assayed the possibility of removing the vestigial carbon at the aldehyde oxidation state by deformylation reactions. Thus, oxidation of the *N*-methylamino alcohol **22** with pyridinium chlorochromate (PCC)[37] in methylene chloride provided a compound in 70−75% yield that was tentatively assigned to be the corresponding aldehyde. Isolation of the pure product, free from all chromium species, proved to be very difficult. Many alternative methods to accomplish the same oxidation were examined without success, resulting in the isolation of varying mixtures of starting material and product aldehyde in poor yields.[38]

(35) A racemic sample of the N-protected amine (±)-**20** that was needed to establish chiral HPLC conditions was prepared from racemic vinyl ether (±)-**16** using a parallel sequence of reactions.

(36) (a) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548. (b) Newman, M. S.; Arkell, A.; Fukunaga, T. *J. Am. Chem Soc.* **1960**, *82*, 2498. (c) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. (d) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (e) Herriot, A. W.; Picker, D. *Tetrahderon Lett.* **1974**, 1511. (f) Marino, J. P.; Pradilla, R. F.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.

(37) Herscovici, J.; Egron, M.-J.; Antonakis, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1967.

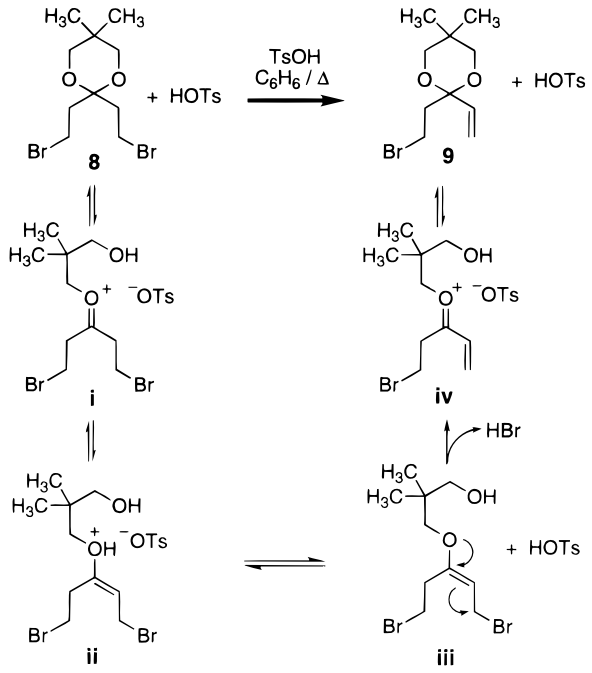
Scheme 11



Ultimately, it was found that an aldehyde, identical to that from the PCC oxidation, could be obtained in 80% yield by employing the oxidation method developed by Mukaiyama (1,1′-(azodicarbonyl)dipiperidine (ADD) and *tert*-butoxymagnesium bromide),[39] Scheme 11. Subsequently it was discovered that the initial structural assignment was incorrect. Collective spectroscopic data are more consistent with an isomeric enal structure **25**, in which the dioxane ring had opened.

Despite the unanticipated result, the enal **25** proved to be a suitable intermediate for conversion into mesembrine. Reaction of the enal with 60% trifluoroacetic acid, for 28 h at room temperature, provided a compound that was presumed to be the enolic β-keto aldehyde **26**.[40] Following a traditional procedure,[41] the alkoxymethylene group in the unpurified enol intermediate **26** was cleaved under basic conditions to afford, after chromatography, 94 mg (60%, two steps) of a pure product that was determined to be identical with a sample of natural mesembrine.[42] An analytically pure sample of the synthetic material was obtained after bulb-to-bulb distillation under reduced pressure (0.01 Torr/160 °C). The optical rotation of the synthetic product, $[\alpha]_D = -63.3°$ (MeOH, $c = 1.13$), was in close agreement with values reported in the literature for natural mesembrine, $[\alpha]_D = -55.4°, -59°$ (MeOH).[17,43] Spectral data, including ^{1}H NMR, ^{13}C NMR, and IR, were collected for both the natural and synthetic samples and found to be in full agreement.[44]

Scheme 12



Discussion

Nitroalkene Preparation. The ketalization of 1,5-dibromopentan-3-one (**7**) with 2,2-dimethylpropanediol provided an interesting result that is worthy of discussion. The reaction was expected to afford the corresponding dibromoketal **8**; however, a mixture of the dibromoketal and the vinyl dioxane **9** was obtained. This result was propitious, since it ultimately eliminated a step in the synthesis of the desired nitroalkene. Formation of the vinyl derivative **9** may result from an irreversible elimination of the dibromide **8**. A plausible mechanism to explain this conversion is presented in Scheme 12.

This proposal is supported by the following observations: (1) the vinyl compound **9** could be obtained by resubjecting the purified dibromide **8** to the reaction conditions, (2) the evolution of acidic vapors from the reaction was detected using litmus paper, and (3) attempted ketalization of 5-bromo-1-penten-3-one under the same reaction conditions did not provide any of the vinyl dioxane **9**. Regardless, it is curious as to why the elimination does not proceed further and eliminate both bromides to afford the corresponding divinyl ketal.

Nitroalkene Isomerization. The ability to equilibrate the *E*/*Z*-mixture of nitroalkene isomers **13** to predominantly the *E*-isomer was critical to the success of the asymmetric [4 + 2] cycloaddition. Furthermore, the development of an effective in-situ isomerization was highly advantageous. In fact, the Lewis acid-promoted isomerization of a 2,2-disubstituted 1-nitroalkene has precedent. In related investigations, the isomerization of pure (*Z*)-2-(3,4-dimethoxyphenyl)-1-nitrobutene (**2**) to a 17/1 (*E*/*Z*) isomeric mixture using $SnCl_4$ for 30 min at −78 °C was documented.[15] This result was rationalized by invoking a reversible conjugate addition of chloride ion to the nitroalkene−Lewis acid complex. In the current work, MAD was used to promote the isomerization of both the model nitroalkene **2** as well as the functionalized nitroalkene **13**. When using MAD as the Lewis acid, it is again possible to postulate that the isomerization could be occurring through a reversible 1,4-

(38) Other methods that were explored included (a) tetrapropylammonium perruthenate (TPAP): Griffith, W. P. *Aldrichim. Acta* **1990**, *23*, 13. (b) Swern oxidation (oxalyl chloride, DMSO, triethylamine): Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148. (c) Phenyl dichlorophosphate with DMSO and triethylamine: Liu, H.-J.; Nyangulu, J. M. *Tetrahedron Lett.* **1988**, *29*, 3167. (d) PDC in dichloromethane.[38c] (e) Dess−Martin periodinane: Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(39) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773.

(40) This reaction was optimized using NMR scale experiments (CF_3CO_2D/D_2O) that followed the conversion of the starting aldehyde into a single product.

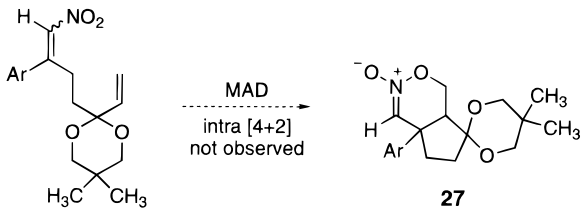
(41) The alkoxymethylene group has been commonly used as a blocking group for alkylations of unsymmetrical ketones. Johnson, W. S.; Posvic, H. *J. Am. Chem. Soc.* **1947**, *69*, 1361.

(42) A sample of the hydrochloride salt of natural mesembrine (~7 mg) was kindly provided by Professor Steven A. Martin (University of Texas). Conversion of the hydrochloride salt back to the free amine was accomplished by passing a chloroform solution of the sample through a short plug of basic alumina (activity I).

(43) Nieuwenhuis, J. J. M. Sc. Thesis, University of Pretoria, 1971.

(44) A comparison of the ^{1}H and ^{13}C NMR spectra of natural and synthetic mesembrine is included in the Supporting Information.

Scheme 13



13 Ar = 3,4-dimethoxyphenyl **27**

conjugate addition, since in the presence of trace amounts of oxygen, BHT forms radicals that have been shown to add conjugatively nitroalkenes.[45]

Periselectivity. While an *intramolecular* [4 + 2] cycloaddition of nitroalkene **13** to afford the bicyclic nitronate **27** might be expected to compete with an *intermolecular* reaction involving a bulky chiral vinyl ether, none of the cycloadduct **27** was ever detected, Scheme 13. This was still the observation when the nitroalkene was stirred with the Lewis acid, MAD, in the absence of the vinyl ether for extended periods of time (~2 h). Apparently, the tethered olefin is not sufficiently activated (electron-rich) to participate in an inverse electron demand [4 + 2] cycloaddition under the reaction conditions (MAD, toluene, −10 °C). These results are consistent with previous investigations involving tandem cycloadditions of nitroalkenes bearing three-methylene tethered, unactivated olefins.[10] In those experiments exclusive intermolecular [4 + 2] cycloaddition with *n*-butyl vinyl ether was observed when $Ti(Oi\text{-}Pr)_2Cl_2$ was used as the Lewis acid promoter.

Origin of Diastereoselectivity in the Cycloaddition. The stereochemical course of an asymmetric nitroalkene [4 + 2] cycloaddition is governed by two principle criteria: (1) the orientation of the vinyl ether in its approach to the nitroalkene (exo or endo) and (2) the stereodifferentiation for one π-face of the nitroalkene by the chiral vinyl ether.[28e] We have previously shown that the vinyl ether derived from TCC has a strong preference to undergo exo-mode [4 + 2] cycloadditions with *E*-2-substituted nitroalkenes when using MAPh as the Lewis acid promoter.[7b,34] This phenomenon has been attributed to a minimization of steric interactions between the bulky aluminum-based Lewis acid and the significantly large chiral auxiliary on the vinyl ether.

Facial selectivity in the [4 + 2] cycloaddition is dictated by the shape of the chiral auxiliary as well as the reactive conformation of its vinyl ether, s-cis or s-trans. Molecular mechanics (MM2) calculations on vinyl ether **16** revealed two significantly different ground state conformations, nearly equal in energy, Figure 2.[46,47] In the slightly lower energy conformation (**a**), the vinyl ether exists in a pseudo s-trans geometry, Φ = 141.09° (the C=C−O−C dihedral angle is defined as Φ), with the phenyl substituent providing moderate *re*-face shielding of the vinyl group.[48] In the slightly higher energy conformation (**b**), the vinyl ether is maintained in a near perfect s-cis geometry (Φ = −3.48°); however, no significant π-facial shielding is apparent. Given the high diastereoselectivity

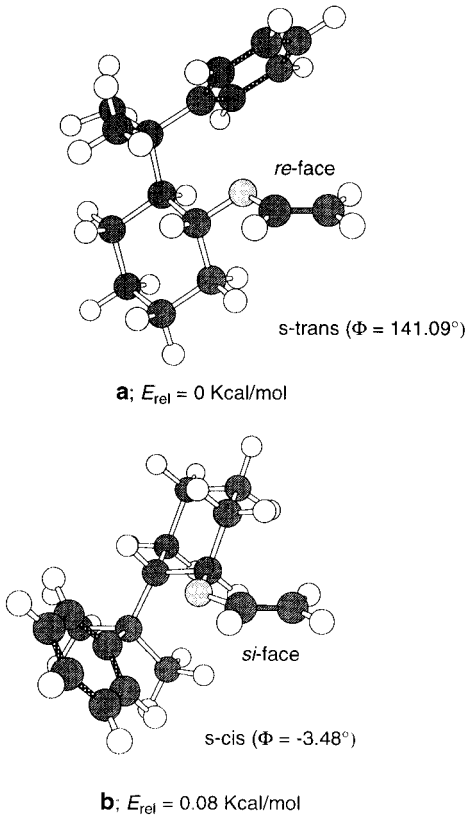


Figure 2. Minimized conformations of vinyl ether **16**.

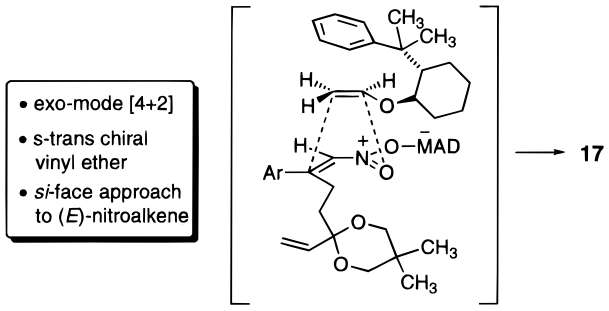


Figure 3. Proposed model of the asymmetric [4 + 2] cycloaddition.

that is observed in the asymmetric [4 + 2] cycloaddition, it is highly unlikely that the s-cis conformation (**b**) can be considered as a reactive species. Moreover, the *re*-face shielding in the s-trans conformation (**a**) is consistent with the observed stereochemical course of the reaction.

A model to rationalize the asymmetric cycloaddition is shown in Figure 3. In this model, it is proposed that the nitroalkene reacts through the more abundant *E*-isomer in an exo-mode [4 + 2] cycloaddition. Since complete isomerization of the starting nitroalkene to the *E*-isomer does not occur, it suspected that the *Z*-isomer is considerably less reactive. The chiral vinyl ether is depicted in a low energy pseudo s-trans conformation and approaches the *si*-face of the nitroalkene.[49]

Intramolecular [3 + 2] Cycloaddition. Intramolecular [3 + 2] cycloadditions of cyclic nitronates bearing unactivated three-methylene tethered dipolarophiles have been studied in detail.[10] Nitronate **17**, lacking a C(3) substituent, undergoes a rather facile intramolecular [3

(45) Middleton, D. S. Unpublished results, University of Illinois, Urbana.

(46) The program Macromodel version 3.5a, Columbia University, was employed for these caculations.

(47) The third lowest energy conformation (s-trans, E_{rel} = 0.55 kcal/mol) exhibited very little π-facial shielding.

(48) The *si*- and *re*-faces of the enol ether are defined with respect to the C(1) alkoxy-bearing carbon atom.

(49) The *re*- and *si*-faces of the nitroalkene are defined at the β-carbon atom of the nitroalkene.

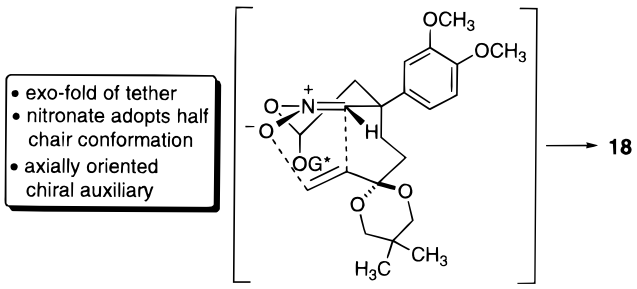


Figure 4. Proposed model of the intramolecular [3 + 2] cycloaddition of **17**.

+ 2] cycloaddition as expected. The stereochemical outcome of this cycloaddition is consistent with an exclusive preference for an exo-fold of the side chain as illustrated in Figure 4. The nitronate is depicted in a half chair conformation and the chiral auxiliary is axially oriented in order to maintain favorable anomeric stabilization.

Summary of Synthesis. The total synthesis of enantiomerically pure (−)-mesembrine (94 mg) was accomplished in seven steps and 19% yield from the 2,2-disubstituted 1-nitroalkene **13**, which was prepared in six steps and 34% yield from commercially available ethyl 3-bromopropionate (**5**). The benzylic stereogenic center (C(3a)) in the natural product was established in 26/1 selectivity through an auxiliary-controlled asymmetric [4 + 2] cycloaddition. Exclusive selectivity in the formation of C(7a) was achieved through an intramolecular [3 + 2] cycloaddition.

Conclusion

The asymmetric, total synthesis of the *Sceletium* alkaloid (−)-mesembrine was accomplished using an asymmetric, tandem inter [4 + 2]/intra [3 + 2] cycloaddition sequence as the key strategic transformation. Moreover, this work demonstrates the effective use of a 2,2-disubstituted 1-nitroalkene in an asymmetric [4 + 2] cycloaddition with a chiral vinyl ether to establish the quaternary stereogenic center with high diastereocontrol. This advance should provide the groundwork for future applications of tandem cycloadditions to the total synthesis of more complex alkaloids containing similar *cis*-3a-aryloctahydroindole skeleta.

Experimental Section

General. See Supporting Information for details.

Materials. 2-(3,4-Dimethoxyphenyl)-1-nitrobutene (**2**),[13] 1,5-dibromopetan-3-one (**7**),[32] (*E*)-1-(3′,4′-dimethoxyphenyl)-2-nitroethene (**11**),[33] and (1*R*,2*S*)-(1-methyl-1-phenethyl)cyclohexanol (**15**)[27] were prepared by the literature methods.

2,2-Bis(2-bromoethyl)-5,5-dimethyl-1,3-dioxane (8) and 2-(2-Bromoethyl)-5,5-dimethyl-2-ethenyl-1,3-dioxane (9). To a round bottom flask, fitted with a Dean−Stark trap and a reflux condenser, were added 1,5-dibromo-3-pentanone (**7**) (4.16 g, 17.1 mmol), 2,2-dimethyl-1,3-propanediol (1.95 g, 18.8 mmol, 1.1 equiv), TsOH·H_2O (81 mg, 0.43 mmol, 2.5 mol %), and benzene (170 mL). The resulting mixture was heated to reflux under nitrogen for 2.5 days (the evolution of acidic vapor was detected using litmus paper). During this time, the Dean−Stark trap (5 mL) was drained approximately every 4−6 h, and fresh benzene was added to maintain the reaction at a constant volume. After cooling to room temperature, the mixture was poured into a saturated, aqueous $NaHCO_3$ solution (100 mL) and extracted with TBME (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4/$MgSO_4$, 1/1), filtered, and concentrated. The crude concentrate was purified by column chromatography on basic alumina (activity II) (hexane/TBME, 30/1) to provide 1.05 g of **8** and 2.59 g of a 7/1 mixture (by ^{1}H NMR integration) of **9** and **8**. The 7/1 mixture was separated by column chromatography on basic alumina (activity II) (hexane/TBME, 30/1) to provide, after bulb-to-bulb distillation, 2.14 g (50%) of **9** as a clear colorless oil and 0.350 g of **8.** An analytical sample of **9** was obtained after further purification using silica gel column chromatography (hexane/CH_2Cl_2, 10/1) and bulb-to-bulb distillation. The two samples of **8** were combined and further purified by chromatography on basic alumina (activity II) (hexane/TBME, 30/1) to afford 1.25 g (22%) of **8** as a white solid. A portion of **8** was recrystallized (hexane) to provide an analytically pure sample as white needles. Data for **8**: mp 49−50 °C (hexane); ^{1}H NMR (400 MHz) 3.48 (s, 4 H), 3.44 (AA′XX′, $J_{AA'} = -10$, $J_{XX'} = -7$, $J_{AX} = 13$, $J_{AX'} = 6$, 4 H), 2.29 (AA′XX′, $J_{AA'} = -10$, $J_{XX'} = -7$, $J_{AX} = 13$, $J_{AX'} = 6$, 4 H), 0.94 (s, 6 H); ^{13}C NMR (100.6 MHz) 99.01, 70.20, 38.19, 29.51, 26.58, 22.56; IR (CCl_4) 1365 (m), 1223 (m), 1112 (s), 1102 (s), 1038 (m); MS (CI, CH_4) 329 ($M^+ + 1$, 4); TLC R_f 0.31 (hexane/EtOAc, 20/1). Anal. Calcd for $C_{10}H_{18}Br_2O_2$ (327.97): C, 36.39; H, 5.50; Br, 48.42. Found: C, 36.37; H, 5.38; Br, 48.45. Data for **9**: bp 95 °C (0.3 Torr) (air bath temperature); ^{1}H NMR (400 MHz) 5.67 (dd, J = 17.8, 11.0, 1 H), 5.43 (dd, J = 11.0, 1.5, 1 H), 5.39 (dd, J = 17.6, 1.6, 1 H), 3.59 (d, J = 11.2, 2 H), 3.53 (AA′XX′, $J_{AA'} = -10$, $J_{XX'} = -7$, $J_{AX} = 13$, $J_{AX'} = 6$, 2 H), 3.31 (dt, $J_d = 11.2$, $J_t = 1.4$, 2 H), 2.20 (AA′XX′, $J_{AA'} = -10$, $J_{XX'} = -7$, $J_{AX} = 13$, $J_{AX'} = 6$, 2 H), 1.14 (s, 3 H), 0.68 (s, 3 H); ^{13}C NMR (100.6 MHz) 136.83, 119.88, 99.73, 71.33, 45.23, 30.06, 29.51, 26.95, 22.83, 21.94; IR (CCl_4) 2956 (s), 2872 (s), 1172 (s); MS (CI, CH_4) 249 ($M^+ + 1$, 31); TLC R_f 0.37 (hexane/EtOAc, 20/1). Anal. Calcd for $C_{10}H_{17}BrO_2$ (248.04): C, 48.21; H, 6.88; Br, 32.07. Found: C, 48.47; H, 6.99; Br, 31.75.

Conversion of 8 into 9. To a round bottom flask, fitted with a Dean−Stark trap and a reflux condenser, were added the dibromide **8** (1.5 g, 4.5 mmol), TsOH·H_2O (43 mg, 0.23 mmol, 5 mol %), and benzene (180 mL). The resulting mixture was heated to reflux for 2.5 days. During this time, the Dean−Stark trap (5 mL) was drained approximately every 4−6 h, and fresh benzene was added to maintain the reaction at a constant volume. After cooling to room temperature, the mixture was poured into a saturated, aqueous $NaHCO_3$ solution (50 mL) and extracted with TBME (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4/$MgSO_4$, 1/1), filtered, and concentrated. The crude concentrate was purified by column chromatography on basic alumina (activity II) (hexane/TBME, 30/1) to afford 0.922 g (77%) of a 3.7/1.0 mixture (by ^{1}H NMR integration) of **9** and **8**. The mixture was separated by column chromatography on a basic alumina (activity II) (pentane/TBME, 1/0, 30/1, 10/1) to provide 0.206 g (14%) of **8** as a white solid and 0.644 g (58%) of pure **9** as a clear, colorless oil.

5,5-Dimethyl-2-ethenyl-2-(2-iodoethyl)-1,3-dioxane (10). A solution of **9** (6.50 g, 26.1 mmol) dissolved in dry acetone (20 mL) was added to a round bottom flask charged with a mixture of sodium iodide (39.1 g, 0.261 mol, 10 equiv) and acetone (241 mL). The flask and reflux condenser were enclosed in aluminum foil (to eliminate exposure to light), and the mixture was heated to reflux for 26 h. After cooling to room temperature, the reaction mixture was poured into a saturated, aqueous $NaHCO_3$ solution (20 mL) and water (230 mL) and extracted with TBME (3 × 100 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The crude concentrate was purified by column chromatography on basic alumina (activity II) (pentane/TBME, 1/0, 30/1) to provide 6.80 g (89%) of **10** as a clear, colorless oil: bp 95 °C (0.3 Torr) (air bath temperature); ^{1}H NMR (400 MHz) 5.64 (dd, J = 17.6, 11.0, 1 H), 5.43 (dd, J = 11.0, 1.4, 1 H), 5.37 (dd, J = 17.7, 1.4, 1 H), 3.58 (d, J = 11.0, 2 H), 3.30 (dt, $J_d = 11.2$, $J_t = 1.3$, 2 H), 3.27 (AA′XX′, $J_{AA'} = -10$, $J_{XX'} = -7$, $J_{AX} = 13$, $J_{AX'} = 6$, 2 H), 2.22 (AA′XX′, $J_{AA'} = -10$, $J_{XX'} = -7$, $J_{AX} = 13$, $J_{AX'} = 6$, 2 H), 1.14 (s, 3 H), 0.67 (s, 3 H); ^{13}C NMR (100.6 MHz) 136.75, 119.88, 100.28, 71.32, 46.73, 30.06, 22.81, 21.93, 21.83; IR (neat) 2955 (s), 1471

(m), 1170 (s), 1076 (s); MS (CI, CH_4) 297 ($M^+ + 1$, 36); TLC: R_f 0.34 (hexane/EtOAc, 20/1).

2-[4-[2-(3,4-Dimethoxyphenyl)-1-nitro-1-butenyl]]-2-ethenyl-5,5-dimethyl-1,3-dioxane (13). A suspension of zinc dust (1.42 g, 21.3 mmol, 1.7 equiv) in THF (3.2 mL) was sonicated for 30 min at room temperature in an ultrasonic cleaning bath. The ultrasonic bath was removed and replaced with a magnetic stirring apparatus. Dibromoethane (70.0 μL, 0.813 mmol, 6 mol %) was added and the stirred suspension heated at 63−65 °C (internal temperature) for 2 min. After cooling to room temperature, chlorotrimethylsilane (83.0 μL, 0.652 mmol, 5 mol %) was added, and the mixture was stirred for 10 min before introducing a solution of the iodide **10** (6.00 g, 20.3 mmol, 1.6 equiv) in THF (13 mL). The resulting suspension was stirred for 12 h at 35−37 °C (some unreacted zinc remained) and was subsequently cooled to −10 °C, and a solution of copper(I) cyanide (1.60 g, 17.9 mmol, 1.4 equiv) and lithium chloride (1.52 g, 35.8 mmol, 2.8 equiv) in THF (18 mL) was added. The resulting brown mixture was stirred for 10 min at 0 °C and cooled to −30 °C. A solution of nitroalkene **11** (2.67 g, 12.8 mmol, 1 equiv) in THF (48 mL) was added to the prepared organometallic reagent at −30 °C. The mixture was allowed to warm to 0 °C, stirred for 3 h, and then quenched with a solution of PhSeBr (4.29 g, 17.9 mmol, 1.4 equiv) in THF (13 mL). After an additional 1 h at 0 °C, the reaction mixture was poured into water (150 mL) and extracted with TBME (4 × 150 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The concentrate was purified by silica gel column chromatography (hexane/EtOAc, 3/1) to afford 5.79 g of the intermediate selenide **12** as a viscous yellow oil. The selenide **12** was dissolved in THF (110 mL) and treated with a 30% aqueous solution of H_2O_2 (22 mL) at room temperature. After 2.5 h, the yellow reaction mixture was poured into a saturated, aqueous $NaHCO_3$ solution (10 mL) and water (90 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude concentrate was purified by silica gel column chromatography (hexanes/EtOAc, 4/1) to afford 3.49 g (72%) of **13** as a bright yellow oil. The product was determined to be a 1.0/1.5 (*E*/*Z*) mixture of isomers by ^{1}H NMR integration. A small portion of **13** was further purified by chromatography (CH_2Cl_2/TBME, 9/1) to provide an analytically pure sample that was a 1.9/1.0 (*E*/*Z*) mixture of isomers. Data for (*E*/*Z*)-**13**: ^{1}H NMR (400 MHz) *Z*-isomer: 7.03 (t, J = 1.2, 1 H), 6.86 (d, J = 8.3, 1 H), 6.76 (dd, J = 8.3, 2.0, 1 H), 6.68 (d, J = 2.0, 1 H), 5.62 (dd, J = 17.8, 11.0, 1 H), 5.41 (dd, J = 11.0, 1.5, 1 H), 5.33 (dd, J = 17.6, 1.5, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.59 (d, J = 10.7, 2 H), 3.30 (d, J = 11.2, 2 H), 2.66 (m, 2 H), 1.66 (m, 2 H), 1.15 (s, 3 H), 0.66 (s, 3 H); *E*-isomer: 7.31 (s, 1 H), 7.13 (dd, J = 8.5, 2.4, 1 H), 7.07 (d, J = 2.2, 1 H), 6.89 (d, J = 8.5, 1 H), 5.71 (dd, J = 17.6, 11.0, 1 H), 5.44 (dd, J = 11.0, 1.5, 1 H), 5.39 (dd, J = 17.6, 1.6, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.62 (d, J = 10.7, 2 H), 3.34 (d, J = 11.2, 2 H), 3.26 (m, 2 H), 1.86 (m, 2 H), 1.16 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR (100.6 MHz) *Z*-isomer: 152.12, 149.33, 148.64, 136.97, 133.96, 128.08, 119.73, 119.47, 110.82, 110.13, 99.28, 71.31, 55.83, 55.71, 39.13, 30.94, 30.01, 22.81, 21.84; *E*-isomer: 153.66, 150.94, 149.04, 137.00, 134.81, 129.01, 120.21, 119.53, 111.03, 109.94, 99.58, 71.34, 55.88, 55.83, 39.34, 30.08, 24.64, 22.85, 21.93; IR (CCl_4) 2957 (s), 1523 (s), 1519 (s), 1515 (s), 1464 (s), 1334 (s), 1268 (s), 1176 (s), 1089 (s), 1030 (s); MS (EI, 70 eV) 377 (M^+, 13); TLC R_f 0.26 (hexane/EtOAc, 3/1). Anal. Calcd for $C_{20}H_{27}NO_6$ (377.44): C, 63.65; H, 7.21; N, 3.71. Found: C, 63.62; H, 6.98; N, 3.68.

(−)-(1*R*,2*S*)-[[2-(1-Methyl-1-phenylethyl)cyclohexyl]oxy]-ethene ((−)-16). A mixture of mercuric acetate (4.82 g, 15.1 mmol, 0.6 equiv), chiral alcohol (−)-**15** (5.51 g, 25.2 mmol), and *n*-butyl vinyl ether (350 mL) were heated to reflux for 24 h. The mixture was subsequently cooled to room temperature, and a second portion of mercuric acetate (4.82 g, 15.1 mmol, 0.6 equiv) was added. After heating to reflux for an additional 24 h, the reaction was cooled to room temperature and poured into a mixture of aqueous K_2CO_3 solution (100 mL) and TBME (100 mL). The separated organic layer was washed with a second portion of K_2CO_3 solution (100 mL), and the aqueous layers were back-extracted with TBME (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The crude concentrate was purified by column chromatography using basic alumina (activity II) (pentane/TBME, 1/0, 1/1) to provide (−)-**16** as a clear oil and a sample of recovered (−)-**15**. The vinyl ether (−)-**16** was further purified by column chromatography using basic alumina (activity II) to afford after bulb-to-bulb distillation 4.51 g (73%) of analytically pure (−)-**16**. The recovered alcohol was repurified by silica gel column chromatography (hexane/EtOAc, 10/1) to provide 0.940 g (17% recovery) of (−)-**15** as a clear viscous oil. Data for (−)-**16**: bp 150 °C (0.2 Torr) (air bath temperature); ^{1}H NMR (400 MHz) 7.25 (m, 4 H), 7.11 (m, 1 H), 6.12 (dd, J = 14.2, 6.6, 1 H), 4.12 (dd, J = 14.2, 1.5, 1 H), 3.90 (dd, J = 6.6, 1.5, 1 H), 3.50 (td, J_t = 10.3, J_d = 6.1, 1 H), 2.00 (m, 1 H), 1.82 (ddd, J = 12.2, 10.1, 3.7, 1 H), 1.64 (m, 1 H), 1.50 (m, 1 H), 1.38 (m, 1 H), 1.36 (s, 3 H), 1.28 (s, 3 H), 1.23 (m, 1 H), 1.12−1.01 (m, 2 H), 0.83 (qd, J_q = 12.9, J_d = 3.4, 1 H); ^{13}C NMR (100.6 MHz) 150.54, 150.16, 127.70, 125.89, 125.03, 87.66, 81.10, 51.94, 40.52, 32.90, 29.02, 27.43, 25.93, 24.95, 24.68; IR (neat) 2996 (s), 2963 (s), 2931 (s), 2877 (s), 1630 (s), 1191 (s), 1088 (s); MS (EI, 70 eV) 377 (M^+, 13); TLC R_f 0.16 (hexane); Optical rotation $[\alpha]^{23}_D = -25.1°$ (c = 3.41, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O$ (244.38): C, 83.55; H, 9.90. Found: C, 83.60; H, 9.79.

(4*S*,6*S*)-4-[5-[3,3-(2,2-Dimethylpropylenedioxy)-1-pentenyl]]-4-(3,4-dimethoxyphenyl)-6-[[(1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexyl]oxy]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (17). Trimethylaluminum (2.0 M in toluene, 2.12 mL, 4.24 mmol, 2 equiv) was added dropwise to a solution of 2,6-di-*tert*-butyl-4-methylphenol (1.91 g, 8.69 mmol, 4 equiv) in CH_2Cl_2 (12.0 mL) at room temperature. Gas evolution (CH_4) was observed as the solution was stirred at room temperature for 30 min. Half of the resulting solution of MAD (8.0 mL) was added over 2 min to a solution the nitroalkene **13** dissolved in toluene (3 mL) which was maintained between −15 and −10 °C (internal temperature). The resulting dark red mixture was stirred at −15 °C for 7 min, and then a solution of the chiral vinyl ether (−)-**16** dissolved in toluene (5 mL) was added. After stirring for 1 h at −15 °C, the remainder of the MAD solution (8 mL) was added over 1 h. After complete addition, the reaction mixture was left to stir an additional 90 min at −15 °C. The cold reaction contents were added to CH_2Cl_2 (250 mL) and washed with water (3 × 250 mL). The aqueous layers were back-extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated (never warming above 27 °C). The crude material was purified by silica gel column chromatography (pentane/TBME, 2/1 (500 mL); 1/1 (500 mL); 2/3 (1000 mL)) to afford 1.14 g (∼86%) of **17** as a white crusty foam. The product was determined by ^{1}H NMR integration to be a 26/1 mixture of nitronate diastereomers **17** contaminated with ∼5% of the tandem cycloadduct **18**. Data for **17**: ^{1}H NMR (400 MHz) 7.26−7.09 (m, 5 H), 6.80 (d, J = 8.3, 1 H), 6.67 (dd, J = 8.3, 2.2, 1 H), 6.64 (d, J = 2.2, 1 H), 6.46 (s, 1 H), 5.58 (dd, J = 17.7, 11.0, 1 H), 5.39 (dd, J = 11.0, 1.7, 1 H), 5.30 (dd, J = 17.7, 1.7, 1 H), 4.89 (dd, J = 5.3, 3.8, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.57 (m, 2 H), 3.42 (td, J_t = 10.0, J_d = 4.3, 1 H), 3.27 (m, 2 H), 3.15 (ddd, J = 13.9, 12.2, 4.5, 1 H), 2.29 (m, 1 H), 1.98−1.87 (m, 2 H), 1.83 (dd, J = 13.9, 3.7, 1 H), 1.64 (m, 3 H), 1.44−1.26 (m, 8 H), 1.19−0.99 (m, 8 H), 0.68 (s, 3 H); ^{13}C NMR (100.6 MHz) 151.33, 149.07, 147.85, 137.32, 135.97, 127.91, 125.40, 124.90, 119.31, 118.58, 117.82, 111.01, 109.10, 103.60, 99.67, 82.81, 71.33, 71.31, 55.93, 55.84, 51.95, 41.85, 40.00, 38.78, 36.03, 34.97, 33.31, 30.12, 28.76, 27.02, 26.10, 25.69, 24.55, 23.02, 21.94; IR (CCl_4) 2957 (s), 2935 (s), 1257 (s), 1241 (s), 1085 (s), 1032 (s); TLC R_f 0.19 (TBME/pentane, 3/2).

(+)-(5*S*,6a*S*,9a*R*,9b*S*)-9,9-(2,2-Dimethylpropylenedioxy)-6a-(3,4-dimethoxyphenyl)-5-[[(1*R*,2*S*)-2-(1-methyl-1-phenylethyl)cyclohexyl]oxy]hexahydro-1*H*-isooxazolo-[2,3,3-*h*] [2,1]benzoxazine (18). The 26/1 mixture of nitronate diastereomers **17** was dissolved in benzene (50 mL) and heated at reflux for 1 h. After cooling to room temperature, the reaction mixture was concentrated to afford a slightly yellow,

viscous oil. The crude material was purified by silica gel column chromatography (hexane/EtOAc, 4/1) to afford 1.04 g (79%, based on nitroalkene) of **18** as a white crusty foam. The product was determined by ^{1}H NMR integration to be a 30/1 mixture of nitroso acetal diastereomers. The entire sample was recrystallized (EtOH/MeOH, 1/1) to provide 0.833 g of a single nitroso acetal diastereomer **18** as white prisms. The mother liquor was concentrated and repurified by silica gel chromatography (hexane/EtOAc, 4/1) to provide 78 mg of **18** as a white, solid foam. The material was recrystallized (EtOH/MeOH, 1/1) to afford an additional 37 mg of **18**, for a total combined mass of 0.870 g (66% over two steps) of **18** as a single diastereomer: mp 133−135 °C (EtOH/MeOH); ^{1}H NMR (400 MHz) 7.17−7.03 (m, 7 H), 6.88 (d, J = 8.5, 1 H), 4.42 (m, 2 H), 4.19 (dd, J = 10.3, 6.3, 1 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.71 (d, J = 11.5, 1 H), 3.68 (d, J = 12.0, 1 H), 3.50 (d, J = 11.5, 1 H), 3.34−3.21 (m, 4 H), 2.65 (m, 1 H), 2.29 (m, 1 H), 2.01 (m, 1 H), 1.92 (dd, J = 13.1, 9.9, 1 H), 1.78 (m, 1 H), 1.61−1.45 (m, 4 H), 1.36−1.25 (m, 6 H), 1.12 (s, 6 H), 1.02, (m, 2 H), 0.77 (m, 1 H), 0.71 (s, 3 H); ^{13}C NMR (100.6 MHz) 151.08, 148.50, 147.41, 139.51, 127.70, 125.53, 124.84, 118.94, 110.77, 110.13, 99.84, 98.32, 83.71, 70.70, 70.20, 69.87, 56.00, 55.86, 51.95, 45.14, 40.35, 39.91, 36.04, 35.64, 35.38, 30.01, 28.78, 27.57, 25.90, 25.87, 25.08, 24.86, 22.88, 21.98; IR ($CHCl_3$) 2961 (s), 2936 (s),1520 (s), 1252 (s), 1161 (s), 1148 (s), 1126 (s), 1095 (s), 1027 (s); MS (FAB) 622 (M^+ + 1, 53); TLC R_f 0.35 (hexane/EtOAc, 2/1); Optical rotation $[\alpha]^{23}_D$ = 12.3° (c = 1.09, $CHCl_3$). Anal. Calcd for $C_{37}H_{51}NO_7$ (621.81): C, 71.47; H, 8.27; N, 2.25. Found: C, 71.36; H, 8.37; N, 2.31.

(+)-[(3a*S*,7*R*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-6,6-(2,2-dimethylpropylenedioxy)octahydroindol-7-yl]methanol (19). Two small spatulas of W-2 Raney nickel catalyst, which had been prewashed with methanol (5 × 10 mL), were added to a solution of nitroso acetal **18** (0.500 g, 0.804 mmol) dissolved in warm methanol (∼150 mL). The flask was placed in a steel autoclave which was then purged and filled with hydrogen to a pressure of 300 psi. After stirring (magnetically) for 48 h at rt, the vessel was slowly depressurized and subsequently flushed with nitrogen. The resulting supernatant was passed through a short (4 cm) plug of Celite, using nitrogen as the pressure source. The residual nickel in the reaction vessel was thoroughly washed with fresh methanol (4 × 20 mL) under an atmosphere of nitrogen. The clear filtrate was concentrated and the resulting oil purified by silica gel column chromatography (chloroform/methanol, 95/5, 85/15) to provide 0.268 g (85%) of slightly impure amino alcohol **19** and 180 mg of recovered chiral alcohol (−)-**15**. The amino alcohol was further purified using silica gel column chromatography (chloroform/methanol, 80/10) to afford 0.233 g (74%) of pure **19** as a white foam. The recovered chiral alcohol was also repurified using silica gel column chromatography (hexane/EtOAc, 12/1) to afford 0.160 g (91%) of pure (−)-**15** as a clear oil. Data for **19**: ^{1}H NMR (400 MHz) 6.88 (m, 2 H), 6.77 (m, 1 H), 4.24 (dd, J = 10.4, 3.6, 1 H), 3.88 (dd, J = 10.3, 8.5, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.72 (d, J = 11.5, 1 H), 3.57 (d, J = 10.7, 1 H), 3.55 (d, J = 11.2, 1 H), 3.32 (dd, J = 11.2, 2.4, 1 H), 3.31 (dd, J = 11.2, 2.4, 1 H), 3.05 (ddd, J = 12.5, 9.5, 3.4, 1 H), 2.89 (dt, J_d = 12.0, J_t = 8.5, 1 H), 2.58 (dt, J_d = 14.6, J_t = 3.9, 1 H), 2.25−2.12 (m, 2 H), 1.89−1.76 (m, 3 H), 1.38 (ddd, J = 14.2, 12.2, 5.7, 1 H), 1.13 (s, 3 H), 0.69 (s, 3 H); ^{13}C NMR (100.6 MHz) 148.74, 147.37, 139.70, 117.80, 110.66, 109.74, 98.93, 69.82, 69.51, 67.69, 62.74, 55.82, 55.70, 50.37, 46.29, 42.60, 31.84, 31.78, 29.74, 22.95, 22.88, 22.01; IR ($CHCl_3$) 3200 (br, w), 2960 (s), 1519 (s), 1465 (s), 1262 (s), 1249 (s), 1159 (s), 1146 (s), 1105 (s), 1027 (s); MS (FAB) 392 (M^+ + 1, 100); TLC R_f 0.21 ($CHCl_3$/EtOH, 8/1); Optical rotation $[\alpha]^{23}_D$ = 16.0° (c = 0.50, $CHCl_3$).

(+)-[(3a*S*,7*R*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-6,6-(2,2-dimethylpropylenedioxy)-1-[(4-methylphenyl)sulfonyl]-octahydroindol-7-yl]methanol (20). A small portion of the free amino alcohol **19** (20 mg, 0.051 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C, and triethylamine (17.8 μL, 0.128 mmol, 2.5 equiv) was added, followed by TsCl (19.4 mg, 0.102 mmol, 2.0 equiv). The mixture was allowed to stir for 1 h at 0 °C and then was poured into water (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude concentrate was purified by silica gel column chromatography (hexane/EtOAc, 1/1, 2/3) to afford 0.025 mg (89%) of **20** as white solid that was determined to be >99% ee by chiral HPLC analysis. An analytical sample of **20** was obtained after recrytallization (EtOAc/hexane): mp 193−194 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.16 (d, J = 8.3, 2 H), 6.87 (d, J = 8.0, 2 H), 6.64 (dd, J = 8.3, 2.2, 1 H), 6.50 (d, J = 8.5, 1 H), 6.43 (d, J = 2.2, 1 H), 4.35−4.21 (m, 3 H), 3.83 (s, 3 H), 3.79 (d, J = 11.2, 1 H), 3.71 (s, 3 H), 3.65 (dd, J = 8.8, 4.1, 1 H), 3.60 (d, J = 11.0, 1 H), 3.56−3.43 (m, 3 H), 3.24 (td, J_t = 10.3, J_d = 7.8, 1 H), 2.62 (ddd, J = 14.4, 4.4, 2.7, 1 H), 2.44 (dt, J_d = 14.2, J_t = 9.8, 1 H), 2.31 (s, 3 H), 2.26 (td, J_t = 13.9, J_d = 7.6, 1 H), 1.86 (ddd, J = 9.3, 6.8, 2.4, 1 H), 1.76 (td, J_t = 14.2, J_d = 4.4, 1 H), 1.64 (m, 1 H), 1.36 (td, J_t = 14.2, J_d = 4.4, 1 H), 1.32 (s, 3 H), 0.77 (s, 3 H); ^{13}C NMR (100.6 MHz) 148.54, 147.72, 142.31, 138.04, 134.63, 128.65, 127.07, 118.06, 110.43, 108.94, 100.67, 70.17, 69.66, 67.18, 59.28, 55.56, 55.35, 51.42, 48.93, 44.67, 33.93, 30.19, 30.03, 23.16, 23.13, 22.16, 21.32; IR ($CHCl_3$) 3528 (br, w), 2961 (s), 1520 (s), 1338 (s), 1266 (s), 1251 (s), 1163 (s), 1151 (s), 1107 (s), 1089 (s), 1028 (s); MS (FAB) 546 (M^+ + 1, 27); TLC R_f 0.17 (EtOAc/Hex, 3/2); Optical rotation $[\alpha]^{23}_D$ = 42.2° (c = 0.55, $CHCl_3$); chiral HPLC (column: DIACEL Chiralpak AD (EtOH/hexane, 65/35), 1.0 mL/min) t_R (3a*S*,7*R*,7a*S*)-**20** 5.24 min (99.6%); t_R (3a*R*,7*S*,7a*R*)-**20** 13.3 min (0.4%), >99% ee. Anal. Calcd for $C_{29}H_{39}NSO_7$ (545.70): C, 63.83; H, 7.20; N, 2.57. Found: C, 63.86; H, 7.27; N, 2.48.

(+)-(3a*R*,6a*S*,6b*S*)-6a-(3,4-Dimethoxyphenyl)-4,4-(2,2-dimethylpropylenedioxy)perhydropyrrolo[3,2,1-*i*,*j*]-benzoxazine (21). An aqueous solution of formaldehyde (35.7%, 77.0 μL, 0.965 mmol, 2.5 equiv) was added to a solution of amino alcohol **19** (0.151 g, 0.386 mmol) dissolved in methanol (10 mL) at room temperature. After stirring for 1 h, the mixture was concentrated to afford an opaque residue. The residue was dissolved in CH_2Cl_2 and purified by silica gel column chromatography (hexane/EtOAc, 1/1) to afford 109 mg (70%) of **21** as a white foam: ^{1}H NMR (400 MHz) 6.98 (m, 2 H), 6.80 (d, J = 8.5, 1 H), 4.52, 4.45 (ABq, J = 10.7, 2 H), 4.37 (dd, J = 10.5, 3.2, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.71 (d, J = 11.0, 1 H), 3.68 (t, J = 10.6, 1 H), 3.60 (d, J = 11.0, 1 H), 3.52 (d, J = 11.2, 1 H), 3.36−3.27 (m, 3 H), 2.98 (dt, J_d = 9.0, J_t = 5.9, 1 H), 2.36−2.20 (m, 3 H), 2.14 (td, J_t = 10.0, J_d = 3.4, 1 H), 1.90−1.75 (m, 2 H), 1.59 (ddd, J = 14.2, 11.0, 4.9, 1 H), 1.12 (s, 3 H), 0.70 (s, 3 H); ^{13}C NMR (100.6 MHz) 148.57, 147.01, 141.47, 117.66, 110.63, 109.98, 97.85, 80.28, 69.92, 65.98, 64.95, 55.78, 55.69, 48.19, 45.09, 40.11, 34.35, 32.73, 29.92, 25.01, 22.69, 21.94; IR (CCl_4) 2955 (s), 1519 (s), 1263 (s), 1250 (s), 1182 (s), 1152 (s), 1142 (s), 1094 (s), 1033 (s), 1016 (s); MS (FAB) 404 (M^+ + 1, 100); TLC R_f 0.28 (hexane/EtOAc, 1/1); Optical rotation $[\alpha]^{23}_D$ = 4.71° (c = 0.595, $CHCl_3$).

(+)-(3a*S*,7*R*,7a*S*)-[3a-(3,4-Dimethoxyphenyl)-6,6-(2,2-dimethylpropylenedioxy)-1-methyloctahydroindol-7-yl]-methanol (22). An aqueous solution of formaldehyde (35.7%, 254 μL, 3.18 mmol, 2.5 equiv) was added to a solution of amino alcohol **19** (0.498 g, 1.27 mmol) dissolved in methanol (25 mL) at room temperature. After stirring for 10 min, the mixture was transferred to a flask charged with one spatula of W-2 Raney nickel catalyst, which had been prewashed with methanol (5 × 6 mL). The flask was stirred under one atmosphere of hydrogen for 48 h. The nickel catalyst was removed by filtration through a small plug of Celite (4 cm). The reaction vessel and Celite were washed with fresh methanol (4 × 15 mL). The clear filtrate was concentrated and the residue purified by silica gel column chromatography (chloroform/methanol, 99/1, 85/15) to afford 0.75 mg (15%) of intermediate aminal **21** and 0.376 g (73%) of pure *N*-methylamino alcohol **22** as a white foam. An analytical sample of **22** was obtained after heating the entire sample at 100 °C under vacuum (0.2 Torr) for 24 h. The recovered aminal **21** (75 mg) was resubjected to the reaction conditions for 48 h to provide, after purification, an additional 40 mg (8%) of **22** as a white foam, for a total combined mass of 0.416 g (81%) of **22**: ^{1}H NMR (400 MHz) 6.99 (dd, J = 8.2, 2.3, 1 H), 6.97 (d, J = 2.2, 1 H),

6.81 (d, J = 8.3, 1 H), 4.22 (dd, J = 10.5, 3.9, 1 H), 4.01 (dd, J = 10.5, 6.3, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.73 (d, J = 11.2, 1 H), 3.54 (d, J = 11.2, 1 H), 3.48 (d, J = 10.7, 1 H), 3.36 (dd, J = 11.5, 2.7, 1 H), 3.33 (dd, J = 11.6, 2.7, 1 H), 3.18 (ddd, J = 9.8, 7.6, 2.2, 1 H), 2.41 (td, J_t = 10.0, J_d = 6.6, 1 H), 2.35−2.23 (m, 3 H), 2.20 (s, 3 H), 1.86−1.68 (m, 4 H), 1.5 (ddd, J = 14.2, 11.7, 4.4, 1 H), 1.20 (s, 3 H), 0.72 (s, 3 H); ^{13}C NMR (100.6 MHz) 148.54, 147.18, 140.63, 118.39, 110.52, 110.25, 99.98, 72.18, 69.84, 69.68, 61.85, 55.90, 55.70, 52.78, 50.16, 49.27, 45.42, 34.32, 34.28, 29.88, 23.59, 22.99, 22.09; IR ($CHCl_3$) 3515 (br, w), 2960 (s), 1519 (s), 1249 (s), 1027 (s). MS (FAB) 406 (M^+ + 1, 100); TLC R_f 0.29 ($CHCl_3$/EtOH, 85/15); Optical rotation $[\alpha]^{23}_D$ = 19.2° (c = 0.50, $CHCl_3$). Anal. Calcd for $C_{23}H_{35}NO_5$ (405.54): C, 68.12; H, 8.70; N, 3.45. Found: C, 68.30; H, 8.78; N, 3.45.

(+)-(3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)-1-methyl-6-[(2,2-dimethyl-3-hydroxypropyl)oxy]-7-formyl-2,3,3a,4,5,-7a-hexahydro-6*H*-indole (25). *tert*-Butyl alcohol (0.176 mL, 1.85 mmol, 3 equiv) was added to a stirred mixture of ethylmagnesium bromide (3.0 M/Et_2O, 0.616 mL, 1.85 mmol, 3.0 equiv) and THF (5 mL) at room temperature. After 10 min, a solution of amino alcohol **22** (250 mg, 0.616 mmol) dissolved in THF (7 mL) was introduced, and the resulting mixture was stirred for an additional 10 min. A solution of 1,1′-(azodicarbonyl)dipiperidine (0.651g, 1.85 mmol, 3 equiv) dissolved in THF (7 mL) was added, and the dark red reaction mixture was stirred at room temperature for 2.5 h. The mixture was poured into CH_2Cl_2 (75 mL) and washed with water (2 × 50 mL). The aqueous layers were back-extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified twice by silica gel column chromatography (chloroform/methanol, 99/5, 85/15) to afford 200 mg (80%) of **25** as a slightly brown foam. A small portion of **25** was further purified by recrystallization (EtOAc/hexane) to provide a tan powder-like solid: mp 173−175 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 10.31 (s, 1 H), 6.77 (d, J = 8.0, 1 H), 6.57 (d, J = 1.9, 1 H), 6.55 (dd, J = 8.3, 2.4, 1 H), 4.59 (s, 1 H), 4.35 (d, J = 10.0, 1 H), 4.00 (dt, J_d = 11.7, J_t = 8.5, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.72 (br s, 1 H), 3.56 (dd, J = 10.5, 4.6, 1 H), 3.55 (d, J = 10.0, 1 H), 3.23 (dd, J = 10.5, 2.4, 1 H), 3.11 (dd, J = 18.8, 4.8, 1 H), 2.95 (td, J_t = 11.2, J_d = 4.2, 1 H), 2.84 (m, 4 H), 2.41−2.22 (m, 2 H), 2.10 (dd, J = 14.5, 6.5, 1 H), 1.92 (ddd, J = 18.3, 11.0, 6.6, 1 H), 0.97 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (100.6 MHz) 188.67, 177.82, 148.67, 147.52, 135.84, 117.72, 111.57, 110.83, 109.01, 73.13, 67.16, 63.57, 55.75, 55.73, 53.13, 45.72, 41.40, 38.10, 37.05, 31.78, 24.62, 21.60, 21.31; IR ($CHCl_3$) 2962 (s), 1648 (s), 1601 (s), 1519 (s), 1250 (s), 1236 (s), 1185 (s), 1146 (s), 1028 (s); MS (FAB) 404 (M^+ + 1, 100); TLC R_f 0.16 ($CHCl_3$/MeOH, 85/15); Optical rotation $[\alpha]^{23}_D$ = 208.2° (c = 0.83, $CHCl_3$); HRMS (FAB) Calcd for $C_{23}H_{34}NO_5$, 404.2437. Found, 404.2439.

(−)-(3a*S*,7a*S*)-3a-(3,4-Dimethoxyphenyl)octahydro-1-methyl-6*H*-indol-6-one (1). (−)-Mesembrine. Amino aldehyde **25** (220 mg, 0.545 mmol) was dissolved in an aqueous solution of trifluoroacetic acid (65%, 10 mL) and allowed to stir at room temperature for 28 h. The reaction mixture was cooled to 0 °C and made basic by the addition of an aqueous solution of NaOH (30%, 22.4 mL). The resulting mixture was heated to reflux for 2.5 h. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (5 × 75 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to afford a brown oil. The crude concentrate was purified twice by silica gel column chromatography (chloroform/acetone, 8/1) to provide a clear colorless oil. The oil was passed through a small plug of basic alumina (activity I) (chloroform/acetone, 8/1) to afford 94 mg (60%) of pure **1**. An analytical sample of **1** was obtained after bulb-to-bulb distillation and found to be identical with a sample of natural (−)-mesembrine.[42,44] Data for synthetic **1**: bp 160 °C (0.01 Torr) (air bath temperature); ^{1}H NMR (500 MHz) 6.92 (dd, J = 8.4, 2.3, 1 H), 6.89 (d, J = 2.2, 1 H), 6.83 (d, J = 8.3, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.13 (ddd, J = 9.6, 7.9, 2.8, 1 H), 2.94 (t, J = 3.5, 1 H), 2.59 (m, 2 H), 2.42, (m, 1 H), 2.32 (m, 1 H), 2.31 (s, 3 H), 2.25−2.05 (m, 5 H); ^{13}C NMR (100.6 MHz) 211.45, 148.93, 147.42, 140.15, 117.85, 110.89, 109.86, 70.34, 55.95, 55.35, 54.82, 47.46, 40.53, 40.05, 38.79, 36.20, 35.24; IR (CCl_4) 2952 (s), 2935 (s), 1723 (s), 1520 (s), 1464 (s), 1454 (s), 1256 (s), 1233 (s), 1149 (s), 1032 (s); MS (FAB) 290 (M^+ + 1, 100); TLC R_f 0.16 ($CHCl_3$/acetone, 6/1); Optical rotation $[\alpha]^{24}_D$ = −63.3° (c = 1.13, MeOH). Anal. Calcd for $C_{17}H_{23}NO_3$ (289.38): C, 70.56; H, 8.01; N, 4.84. Found: C, 70.49; H, 8.13; N, 4.84.

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Supporting Information Available: Complete ^{1}H and ^{13}C NMR assignments, IR and MS data for all characterized compounds, along with ^{1}H and ^{13}C NMR spectra of natural and synthetic (−)-mesembrine (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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