1 h. After removal of the solvent, the reaction mixture was acidified with aqueous HBF_4, and the ethyl ether soluble products were removed. Addition of aqueous sodium hydroxide, extraction with methylene chloride, drying, and removal of the solvent yielded 2.15 g (75%) of **2b** as the $NaBF_4$ complex, after crystallization from benzene–ethyl ether: mp 84–85 °C; ^1H NMR ($CDCl_3$) δ 3.2–4.0 (m, 27 H), 2.45–2.85 (br t, 12 H), 1.05–1.70 (br s, 28 H), 0.90 (s, 3 H); mass spectrum, m/e 630 (M^+). Anal. Calcd for $C_{35}H_{70}N_2O_7NaBF_4$: C, 56.75; H, 9.53; N, 3.78. Found: C, 56.67; H, 9.34; N, 3.81.

Polymer-Supported 18-Crown-6 (9). (Chloromethyl)polystyrene (8), 1% cross-linked with *p*-divinylbenzene (1.04 mequiv of Cl/g; 3.0 g, 3.12 mmol, of organic chlorine) was added to a stirred solution of 1.96 g (4.7 mmol) of **1a**, as a KBF_4 complex, and 0.70 g (6.3 mmol) of potassium *tert*-butoxide in 40 mL of diglyme at 80 °C. The temperature and stirring were maintained for 6 h. The mixture was acidified with hydrochloric acid, filtered, and successively washed with water, methanol, methylene chloride, and ethyl ether to give 3.70 g of functionalized resin **9**. Spectrophotometric titration with excess potassium picrate[3c] gave a crown ether content of 0.73 mequiv/g, in agreement with the observed weight increase and corresponding to 88% functionalization.

Polymer-Supported [2.2.2]Cryptand (10). One percent cross-linked (chloromethyl)polystyrene (8; 1.04 mequiv of Cl/g; 3.0 g, 3.12 mmol, of organic chlorine) was condensed with **2a**, as a $NaBF_4$ complex (2.41 g, 4.7 mmol), under conditions similar to those described for resin **9** but with *N,N*-dimethylformamide (DMF, 40 mL) instead of diglyme. After repeated washing as described above as well as with aqueous lithium hydroxide, 4.15 g of functionalized resin **10** was obtained. Spectrophotometric titration with excess potassium picrate[3c] gave a cryptand content of 0.75 mequiv/g in agreement with the observed weight increase and corresponding to 100% functionalization.

Polymer-Supported Tributylammonium Salt 11. The tributylammonium salt was prepared by reaction of 1% cross-linked (chloromethyl)polystyrene (1.04 mequiv of Cl/g) with excess tributylamine as previously described.[5b] It had a Cl^- content of 0.56 mequiv/g (64% of the expected value). When the catalyst was recovered from the reaction mixture (see below) the halide ion content ($Cl^- + Br^-$) progressively decreased in agreement with the observed rate constants.

Kinetic Measurements. Kinetics were run, as previously described,[5b] in a flask thermostated at 25 ± 0.02 °C, with a mixture of benzyl methyl ketone (2.0 mmol), 1-bromobutane (2.4 mmol), and 50% aqueous NaOH (2.0 mL) and 0.02 mmol of catalyst (stirring speed 1300 ± 50 rpm; conditioning time 3 h at 25 °C without 1-bromobutane). The reactions were followed by GLC analysis (5% SE-30 on Varaport), and results were corrected by calibration with standard mixtures. The pseudo-first-order rate constants (k_{obsd}) were obtained by plotting ln [substrate] vs. time and determining the slope of the straight lines by the least-square method ($r \geq 0.995$). When catalysts were recovered for reuse or for halide ion content determination, higher amounts of resin were used, all other conditions remaining the same. Ethyl ether and water were added, and the catalyst was filtered and washed with ethyl ether, methanol, aqueous hydrochloric acid, and water until the disappearance of acidity and then with methanol and ethyl ether.

Complexation of Eu^{3+} and Pr^{3+} by 9 and 10. To a 0.2 M $CDCl_3$ solution of camphor or benzyl alcohol was added a 0.05 M $CDCl_3$ solution of $Eu(fod)_3$ or $Pr(fod)_3$ (0.25 molar equiv). ^1H NMR spectra, before and after the addition of the shift reagents, are reported in Figures 1 and 2 (spectra A and B). Further addition of 0.25–0.50 molar equiv of polymer-bound crown ether or cryptand afforded within a few seconds spectra C–E and spectra C and D of Figures 1 and 2, respectively. The poor resolution of these spectra was due to the presence of the insoluble resins in the analyzed mixtures. The resolution improved with time as a consequence of the separation of the resin; after filtration, the resolution of the spectra was identical with that of the starting compounds. A cholesterol solution was treated in the same way, giving similar NMR results. After addition of 4 molar equiv of polymer-supported crown ether **9** with respect to $Eu(fod)_3$, the resin was filtered and washed with methylene chloride. The collected organic solutions were evaporated to give the recovered cholesterol, mp 146 °C (original, mp 147 °C).

Registry No. **1a**·KBF_4, 80540-30-3; **1b**, 74339-04-1; **1c**, 74339-05-2; **1c**·KBF_4, 80533-25-1; **2a**·$NaBF_4$, 80540-32-5; **2b**·$NaBF_4$, 80533-27-3; **3**, 74338-98-0; **4a**, 74338-99-1; **4b**, 74339-01-8; **4c**, 80515-71-5; **5**, 74339-00-7; **6**, 23978-55-4; **7**, 74339-02-9; *tert*-butyl glycidyl ether, 7665-72-7; benzyl methyl ketone, 103-79-7; 1-bromobutane, 109-65-9; camphor, 76-22-2; benzyl alcohol, 100-51-6; cholesterol, 57-88-5.

Alkaloid Synthesis via Intramolecular Ene Reaction. 2. Application to *dl*-Mesembrine and *dl*-Dihydromaritidine

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The total syntheses of mesembrine (**2**) and dihydromaritidine (**3**), alkaloids of the genera *Sceletium* and *Amaryllis* (respectively), are described. The key strategy in each case involves the intramolecular ene cyclization of an appropriately constructed acylnitroso olefin, giving cyclic hydroxamic acid ("ene product") **12**. Reduction of the hydroxamic acid to the lactam **4** is followed by N-methylation and hydroxylation at position C-6 via bromohydrin **15**, introducing the oxygen functionality present in **2**. Removal of bromine, oxidation of the alcohol to the keto lactam **13**, and reductive removal of the lactam carbonyl gave racemic mesembrine. Removal of bromine from bromohydrin **20**, obtained from lactam **4**, followed by reduction with lithium aluminum hydride and Pictet–Spengler cyclization gave dihydromaritidine (**3**).

Introduction

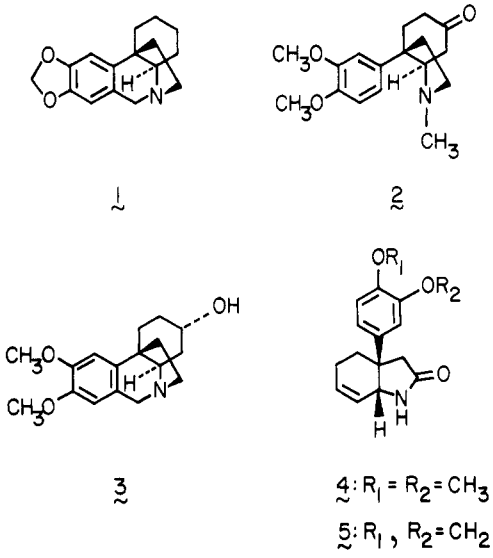
Previous investigations of electrocyclic reactions in which the acylnitroso moiety (RCONO) functions as a dienophile or an enophile have indicated the utility of such processes in the synthesis of a variety of nitrogen-containing materials. Intramolecular [4 + 2] cycloaddition utilizing an acylnitroso group as dienophile has been employed in construction of the pyrrolizidine alkaloids retronecine and heliotridine.[1] The perhydroindole skeletons characteristic of the *Amaryllis* and *Sceletium* alkaloids are easily con-

† Alfred P. Sloan Foundation Fellow, 1981–1983.

(1) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632.

0022-3263/82/1947-1302$01.25/0

Chart I



structed by an intramolecular ene reaction in which the acylnitroso moiety functions as enophile, as illustrated by a recent synthesis of (±)-crinane (1).[2] Presently we report the application of this methodology to the synthesis of two representative alkaloids of these genera: mesembrine (2),[3,4] genus Sceletium, and dihydromaritidine (3),[5,6] genus Amaryllidaceae.

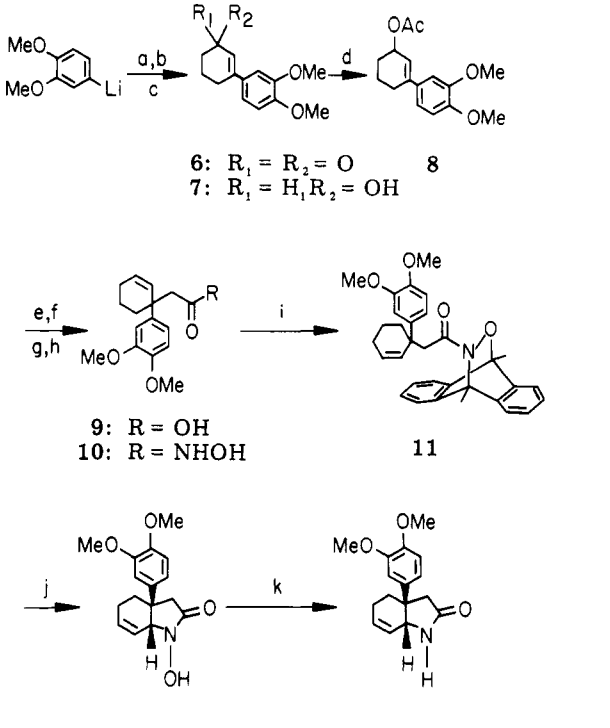
Results and Discussion

Crinane (1) and dihydromaritidine (3) differ primarily by the presence of an additional hydroxyl substituent at C-6 in 3. An additional trivial difference is found in the substitution of the aromatic nucleus, since dihydromaritidine incorporates the dimethoxyphenyl group rather than the methylenedioxy moiety characteristic of the bulk of the *Amaryllis* alkaloids. Mesembrine also incorporates the dimethoxyphenyl group and oxygenation at C-6. However, in this case the synthetic problem is simplified since the oxygen appears as a ketone and is therefore devoid of stereochemistry.

We anticipated that both mesembrine and dihydromaritidine could prove accessible from olefin 4, an intermediate precisely analogous to that previously employed (5) in our synthesis of crinane.[2] In the case of crinane, the unsaturation present in 5 was extraneous and was simply removed. However, a regio- and stereocontrolled hydroxylation of the unsaturation present in 4 should suffice to afford both mesembrine and dihydromaritidine. Hence our initial efforts concentrated on the development of a regiocontrolled hydroxylation of 4 which would serve to secure the synthesis of mesembrine (Chart I).

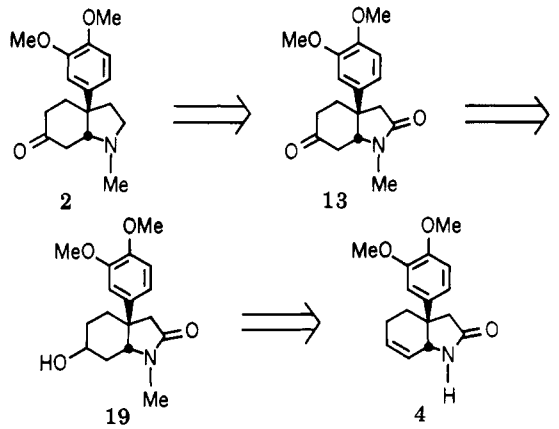
The requisite unsaturated lactam 4 was obtained via the following route which parallels that used previously in the synthesis of (±)-crinane.[2] Lithioveratrole (see Scheme I) was condensed with 3-methoxy-2-cyclohexen-1-one; workup with aqueous acid afforded the known enone 6.[7]

Scheme I[a]



[a] (a) 3-Methoxy-2-cyclohexen-1-one; (b) H_3^+O, (c) $NaBH_4$, EtOH, 0 °C; (d) Ac_2O, pyridine; (e) LICA, THF, HMPA, −78 °C; (f) *t*-BuMe$_2$SiCl, THF, then reflux; (g) $SOCl_2$, benzene, DMF, reflux; (h) $NH_2OH\cdot HCl$, Na_2CO_3, Et_2O-H_2O; (i) $(CH_3CH_2CH_2)_4NIO_4$, $CHCl_3$, DMF, 9,10-DMA; (j) toluene, reflux; (k) $TiCl_3$, H_2O, MeOH, Na_2CO_3.

Scheme II



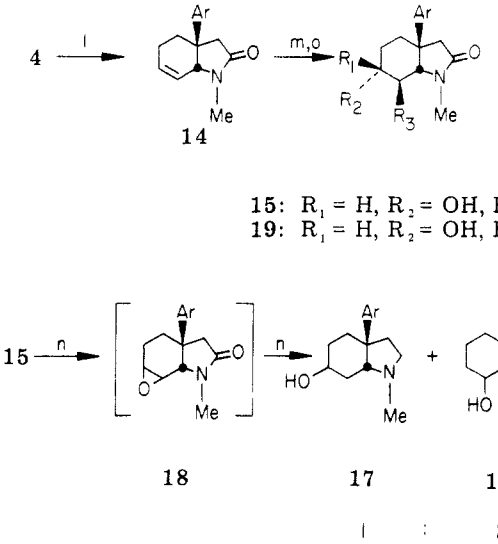
Sodium borohydride reduction produced alcohol 7 as a crystalline solid. Exposure of 7 to acetic anhydride in pyridine gave acetate 8 as an oil in 67% yield from 6. Claisen rearrangement of 8 via the method of Ireland[8] furnished the crystalline acid 9.

Treatment of 9 according to the method of Jones and Hurd[9] produced hydroxamic acid 10 as a crystalline solid in 78% yield. Oxidation of 10 in the presence of 9,10-dimethylanthracene (by the method described previously[2]) gave an 82.5% yield of Diels–Alder adduct 11 as a crystalline solid. This adduct was decomposed in refluxing toluene to afford, after rapid silica gel chromatography to remove 9,10-dimethylanthracene, a quantitative yield of "ene product" 12. This cyclic hydroxamic acid was con-

(2) Keck, G. E.; Webb, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3173.
(3) Popelak, A.; Lettenbauer, G. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 10, p 467.
(4) For recent syntheses of Mesembrine, note Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391 and references cited therein.
(5) Fuganti, C. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, Chapter 3.
(6) For recent syntheses of Maritidine, note Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579.
(7) Schwenker, G.; Metz, G. *Arch. Pharm. (Weinheim, Ger.)* **1968**, *301*, 592.
(8) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(9) Jones, L. W.; Hurd, C. D. *J. Am. Chem. Soc.* **1921**, *43*, 2422.

Scheme III[a]

Ar = dimethoxyphenyl



15: R_1 = H, R_2 = OH, R_3 = Br
19: R_1 = H, R_2 = OH, R_3 = H

[a] (l) NaH, CH_3I, THF; (m) NBS, 4:1 DME-H_2O, 0 °C; (n) LAH, THF, reflux; (o) AIBN, $(CH_3(CH_2)_2CH_2)_3SnH$, toluene, reflux.

verted to the corresponding lactam **4** by $TiCl_3$ reduction according to the procedure of Miller and Mattingly.[10]

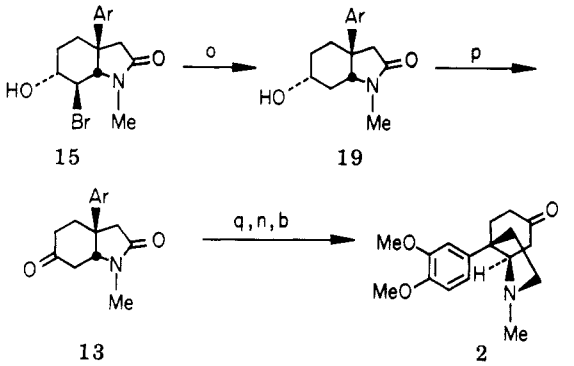
Having lactam **4** in hand, we addressed the problem of converting **4** into mesembrine (**2**). Conceptually this requires (only) N-methylation of **4** followed by regioselective hydroxylation and oxidation to yield the keto lactam **13**, followed by reductive removal of the lactam carbonyl. Actually, the synthesis of the known keto lactam **13** constitutes a total formal synthesis of mesembrine since the efficacy of protecting the ketone carbonyl as its ethylene ketal followed by lithium aluminum hydride reduction and deprotection to give the racemic alkaloid has been previously documented by two independent groups of researchers[6,11] (Scheme II).

The lactam **4** was easily N-methylated by exposure to an excess of oil-free NaH and iodomethane in dry THF, or by treatment with LDA/CH_3I at −78 °C in THF, yielding **14**. Unfortunately, **14** was found to be unreactive toward a host of organoboranes. Attempts to adjust reaction conditions to induce hydroxylation of this olefin by using organoboranes such as disiamylborane, dicyclohexylborane, 9-BBN, or thexylborane were uniformly unrewarding. Also disappointing were attempts to react **14** with $Hg(OAc)_2$ and $Hg(OCOCF_3)_2$, from which only unreacted starting material could be recovered. However, lactam **14** was found to react smoothly with 1 equiv of NBS in aqueous DME to give bromohydrin **15** as virtually the sole product detected (vide supra; Scheme III). The regiochemistry for this oxidative addition could be unambiguously established by ^1H NMR spectroscopy of **15** and its corresponding acetate. The stereochemical assignment, however, could not be made with confidence from NMR spectra. The stereochemistry shown for **15** was eventually established by correlation with an authentic sample of dihydromaritidine (vide supra).

Removal of bromine from **15** before further transformation was found to be essential. For example, exposure of **15** to LAH in THF in the hopes of removing both the bromine and the lactam carbonyl gave an ca. 2:1 mixture (NMR) of amines **16** and **17**, respectively. These amines are presumably formed from conversion of **15** to an intermediate epoxide **18**, which is then further reduced (Scheme III). Removal of bromine via tin hydride reduction to give lactam alcohol **19** followed by oxidation with PCC in CH_2Cl_2 at 0 °C proceeded very smoothly to give the keto lactam **13** as essentially the sole product (vide supra) and further served to define the regiochemistry of bromohydrin formation (Scheme IV). The synthesis of mesembrine was completed from the known keto lactam **13** according to the previously reported procedure. Treatment with ethylene glycol in refluxing benzene containing a trace of *p*-toluenesulfonic acid gave a crude ethylene ketal[12] which was then reduced with LAH in THF. The crude amino ketal thus obtained was treated with dilute HCl to effect hydrolysis of the ketal. Normal extractive workup yielded racemic mesembrine as an oil whose 90-MHz proton NMR and thin-layer chromatographic behavior were identical with that of an authentic sample.[13]

Knowing that we could effectively control the regiochemistry of oxygenation at C-6 of the perhydroindole skeleton, we sought to apply the bromohydrin strategy to

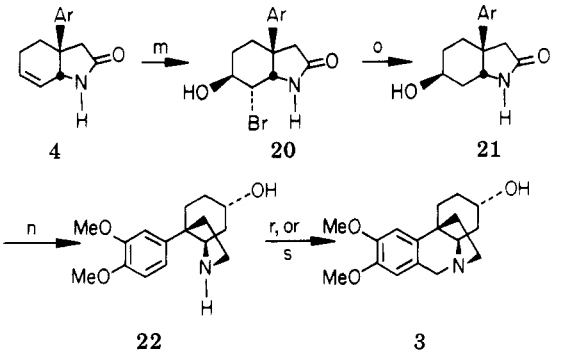
Scheme IV[a]



[a] (o) $(CH_3(CH_2)_2CH_2)_3SnH$, AIBN, toluene, reflux; (p) PCC, CH_2Cl_2, 0 °C; (q) $HOCH_2CH_2OH$, benzene, reflux, *p*-TsOH.

Scheme V[a]

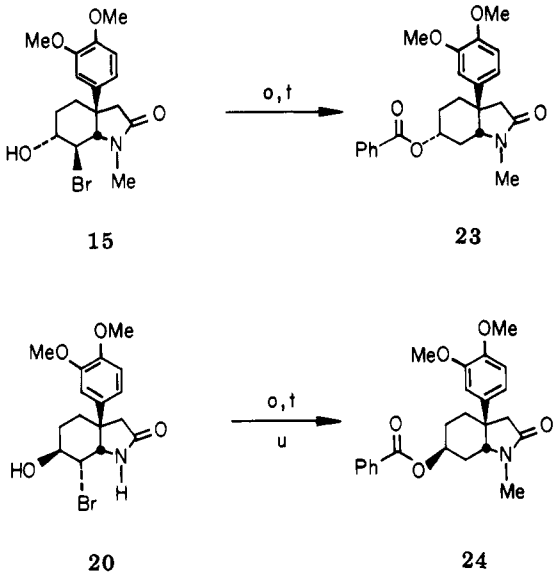
Ar = dimethoxyphenyl



[a] (r) 37% aqueous CH_2O, concentrated HCl; (s) $CH_2=N^+(CH_3)_2I^-$, THF, reflux.

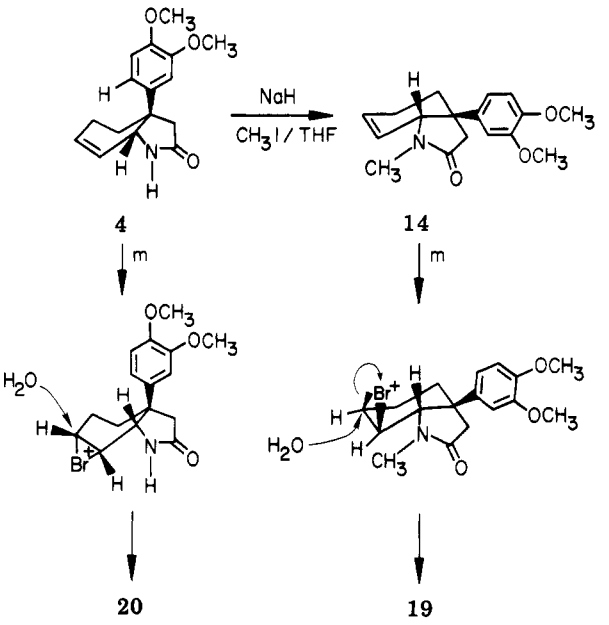
(10) Miller, P. G.; Mattingly, M. J. *J. Org. Chem.* **1980**, *45*, 410.
(11) Oh-ishi, T.; Kugita, H. *Chem. Pharm. Bull.* **1970**, *18*, 299.
(12) Note ref 6. These authors reported that the crude ethylene ketal was used in the reduction step without purification. Although we attempted to isolate the ketal to ensure our structural assignment, we note that the rather sensitive ethylene ketal suffers hydrolysis when exposed to silica gel chromatography.
(13) Kindly provided by Professor Steve Martin at the University of Texas at Austin.

Scheme VI[a]



[a] (t) PhCOCl, pyridine, room temperature; (u) LDA, MeI, THF, −78 °C.

Scheme VII[a]



the synthesis of dihydromaritidine. We assumed that on the basis of our results with the formation of the desired bromohydrin from *N*-methyl lactam **14**, we would obtain the same regiochemical result from the demethyl lactam **4**. At this point, we did not know the stereochemistry of bromohydrin formation. However, completion of the maritidine route would (vide supra) give us either of two epimers at C-6, both of which were known[6] and each of which could (in theory) be easily identified.[14]

Treatment of lactam **4** with 1 equiv[15] of *N*-bromosuccinimide in aqueous DME gave a sole crystalline bromohydrin **20** (Scheme V). Removal of the bromine by tin hydride reduction gave lactam alcohol **21**, which yielded the known amine **22** upon reduction with lithium aluminum hydride.[6] Pictet–Spengler cyclization of **22**[16] (or treatment with Eschenmoser's salt)[2,17] gave *d,l*-dihydromaritidine (**3**) whose melting point, 300-MHz proton NMR, and HPLC behavior were identical with those of an authentic sample.[18] This result unambiguously defined the stereochemistry of bromohydrin formation (Scheme V).

Finally, we wished to correlate the stereochemical results of bromohydrin formation from lactam **4** and *N*-methyl lactam **14**. Since conversion of **4** to dihydromaritidine demonstrated the stereochemistry of bromohydrin formation for lactam **4**, conversion of both **4** and **14** to a common intermediate should allow determination of the stereochemistry of hydroxylation of **14**.

Removal of bromine from **15** followed by treatment with benzoyl chloride gave benzoate **23** as a colorless oil. Similarly, removal of bromine from bromohydrin **20** followed by benzoylation and N-methylation (LDA, THF, −78 °C, CH_3I) gave benzoate **24** as a colorless oil which was shown to be *epimeric* with **23** (Scheme VI). Hence the structures of **15**, from reaction of *N*-methyl lactam **14** with NBS in aqueous DME, and **20**, from exposure of the demethyl lactam **4** to the same conditions, must be as shown (Scheme VI).

This surprising result reveals a reversal of stereochemistry for bromohydrin formation on going from the parent lactam **4** to its *N*-methyl analogue **14**. Although the reasons for such a stereochemical reversal are far from clear, this observation may reflect different reacting conformations for **4** and **14**. In the case of **4**, the results are easily rationalized, assuming that the aryl group occupies a pseudoaxial position, in which case the aromatic ortho hydrogens may significantly shield the β face of the olefin. Formation of a bromonium ion from the α face and trans opening by water would yield **20**[21] (Scheme VII).[21,22] In the case of **14**, however, a pseudoaxial orientation for the aryl group results in a significant nonbonded interaction between the *N*-methyl group and the proximate vinyl proton at C-7. Hence **14** may adopt a conformation in which the aryl group assumes a pseudoequatorial disposition, from which it may no longer shield approach to the β face of the olefin. In both cases, the observed regiochemistry could be anticipated simply on the basis of electronic effects, since one end of the olefin is attached to the rather electron-deficient amide moiety, thus discouraging the development of positive charge at C-7 relative to C-6 (Scheme VII).

(14) Oxidation of either epimer to the ketone followed by reduction with sodium borohydride is known to give a 3:1 mixture of dihydromaritidine and its epimer, respectively.

(15) It was found that an excess of NBS resulted in bromination of the aromatic ring; however, it was also discovered that this could be remedied by the use of excess trialkyltin hydride to remove both aliphatic and aromatic bromides (see Experimental Section).

(16) This transformation was effected via the procedure used for Elwesine; note Stevens, R. V., DuPree, L. E., Loewenstein, P. L. *J. Org. Chem.* **1972**, *37*, 977. It was found, however, that exclusion of oxygen in this step was necessary to preclude formation of large amounts of contaminating byproduct believed to arise from formaldehyde.

(17) Eschenmoser, A.; Schreiber, J.; Maag, H.; Hashimoto, N. *Angew. Chem., Int. Ed. Engl.* **1971**, *8*, 171.

(18) Kindly provided by Professor Speckamp at the University of Amsterdam, The Netherlands.

(19) Mawdsley, E. A.; Berlin, K. D. *Org. Prep. Proc. Int.* **1974**, *6*, 169.

(20) Originally, the melting point reported for this compound was 230–233 °C. (Note ref 8.) However, the sample that Professor Speckamp provided us with had a melting point of 237–240 °C. Professor Speckamp also noted this fact in a personal communication to us.

(21) In each case, formation of the stereoisomeric bromohydrins amounted to ca. 2% of the observed products as determined by HPLC.

(22) (a) Molecular models of lactams **4** and **14** reveal that these materials are conformationally ill-defined, due to the presence of four sp^2 centers in these hydroindoles. The drawings to Scheme VII are intended to depict only what appears to be two extreme orientational possibilities for the aryl substituent with respect to the six-membered ring. (b) An alternative explanation for the observed results could involve initial bromination of **4** at nitrogen. Ionization would then situate the bromine atom in a position to form the bromonium ion (note Scheme VII), leading to **20**. No experimental evidence relevant to this possibility is available.

In summary, a novel intramolecular ene cyclization of an acylnitroso olefin has been used successfully in the syntheses of perhydroindole alkaloids mesembrine (2) and dihydromaritidine (3). This strategy essentially entails annulation of a five-membered nitrogen-containing ring onto a six-membered carbocycle. Further application of this "ene strategy" to other nitrogen-containing materials with different skeletal structures should prove possible by varying the number of carbons in either the carbocycle or heterocycle (or both) and control of the mode of ene cyclization through construction of the appropriate olefin precursor.[23] Further studies toward application of this strategy to other biologically important nitrogenous compounds is in progress in these laboratories and will be reported in due course.

Experimental Section

Melting points were obtained on an Electrothermal melting-point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 298 infrared spectrophotometer using polystyrene as external reference; values reported are in reciprocal centimeters. NMR spectra were obtained on a Varian EM390 spectrometer for protons at 90 MHz and a Varian SC-300 spectrometer for protons at 300 MHz and carbon at 75 MHz; chemical shifts are reported in parts per million downfield from internal Me_4Si. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet, m, multiplet, dd, doublet of doublets, etc. Mass spectra were obtained on a Varian MAT-112 GC–mass spectrometer, in the indicated mode. Yields reported are for material judged homogeneous by NMR, TLC, and GLC (for liquids) and melting point (for solids). Thin-layer chromatography was performed on Merck 0.25-mm glass silica gel plates; visualization of developed plates was by fluorescence quenching and staining was with phosphomolybdic acid or with ferric chloride solution (for hydroxamic acids). Column chromatography was performed with Merck silica gel 60 (60–240 mesh). MPLC refers to medium-pressure liquid chromatography over Merck silica gel 60 (230–400 mesh), using an FMI lab pump operated at 60–100 psi, Altex columns, UV detector, and fraction collector. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN; values reported were within 0.3% of those calculated for the particular compound. Exact mass values were obtained on a Varian Mat 731 mass spectrometer using a direct probe/inlet system.

Solvents used were purified as follows. THF by distillation from Na–benzophenone under argon; toluene, benzene, diisopropylamine, isopropylcyclohexylamine, hexane, iodomethane, dimethylformamide, and pentane by distillation from CaH_2; chloroform by passage through Alumina (Woelm basic activity, chromatographic grade); dichloromethane by distillation from P_2O_5; ethanol and methanol by distillation from Mg; pyridine by stirring with KOH, followed by distillation from BaO; sulfolane by distillation from KOH and then from CaH_2; Eschenmoser's salt (Aldrich) was recrystallized from sulfolane. The following reagents were employed as received: Fisher acetic anhydride, Mallinckrodt anhydrous ether, Baker acetonitrile (HPLC grade), Eastman benzoyl chloride and 1,2-dimethoxyethane, Alfa tri-*n*-butyltin hydride, and Petrarch *tert*-butyldimethylchlorosilane.

4-Bromo-1,2-dimethoxybenzene (bromoveratrole) was prepared according to the method of Mawdsley and Berlin.[19] To a solution of veratrole (Aldrich; 43.2 mL, 0.336 mol) in 600 mL of Spectrograde CCl_4 were added 60.0 g (0.337 mol) of *N*-bromosuccinimide and 1.63 g (6.72 mmol) benzoyl peroxide. The resulting suspension was heated at reflux for 16 h and then cooled, filtered, and concentrated under reduced pressure. The dark brown oil which remained was distilled, yielding 48.1 g (66%) of light yellow oil: bp 92–94 °C (0.05 mm) [lit.[19] bp 83–85 °C (0.02 mm)]; NMR (CCl_4) δ 6.96 (m, 2 H), 6.70 (m, 1 H), 3.75 (s, 6 H); IR (CCl_4) 3060 (w), 2995, 2823, 1575, 1430, 1220–1245 (br), 1015 (s); mass spectrum (EI, probe), 219.1, 218.1, 216.0, 203.0, 201.0, 172.0, 94.1 (P), 85.1, 79.1.

3-[3,4-(Dimethoxy)phenyl]-2-cyclohexen-1-one (6). 4-Bromo-1,2-dimethoxybenzene (17.7 g, 0.092 mol) was metalated with *n*-butyllithium (Alfa; 2.3 M in hexane, 44.0 mL, 0.101 mol) at −78 °C in diethyl ether (400 mL) and treated with 3-methoxy-2-cyclohexen-1-one (13.9 g, 0.110 mol). Warming to room temperature followed by acid hydrolysis and standard extractive workup yielded 17.0 g of yellow solid material. Recrystallization from ether gave 15.4 g (72%) as colorless crystals: mp 116–118 °C (lit.[7] mp 117–118.5 °C); NMR ($CDCl_3$) δ 7.03 (nm, 2 H), 6.81 (nm, 1 H), 6.28 (s, 1 H), 3.83 (s, 6 H), 2.7 (t, J = 6 Hz, 2 H), 2.4 (t, J = 6 Hz, 2 H), 2.1 (qt, J = 6 Hz, 2 H); IR ($CHCl_3$) 3400 (w), 3050 (w), 2970 (s), 2850, 1660 (vs), 1610 (s), 1590, 1475, 1373, 1200–1244 (br), 1040 cm^{-1}; UV (EtOH) λ_{max} 236 (ϵ 8926), 323 (ϵ 1140); mass spectrum (CI, isobutane), 234.2 (M^+), 233.2 (P), 232.2; ^{13}C NMR ($CDCl_3$) δ 199.9, 159.6, 149.5, 131.5, 124.2, 119.8, 111.3, 109.3, 56.3, 56.1, 37.3, 28.1, 27.9, 22.8. Anal. ($C_{14}H_{16}O_3$) C, H.

3-[3,4-(Dimethoxy)phenyl]-2-cyclohexen-1-ol (7). A suspension of enone 6 (12 g, 0.051 mol) in 100 mL of EtOH was cooled to −20 °C and treated with $NaBH_4$ (2.54 g, 0.067 mol). The resulting suspension was stirred under argon for 12 h at −20 °C (cold room). Acetone (10 mL) was then added to destroy the excess hydride, and the resulting clear solution was allowed to warm to room temperature and was partitioned between water and ethyl acetate. The phases were separated, and the aqueous phase was extracted 6 times with 20-mL portions of ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated in vacuo to a colorless oil which crystallized on standing to yield 10.8 g (89%) of colorless fanlike crystals: mp 95–97 °C (lit.[7] mp 97–98 °C); NMR ($CDCl_3$) δ 6.8 (m, complex, 3 H), 6.1 (nm, 1 H), 4.3 (br s, 1 H), 3.83 (s, 6 H), 2.35 (m, 2 H), 1.77 (m, complex, 5 H); IR ($CHCl_3$) 3250–3400 (br), 2910 (s), 2840, 1610, 1580, 1470 (s), 1371, 1200–1250 (br), 1150, 1040 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 149.1, 148.9, 139.2, 134.7, 128.6, 126.1, 118.1, 111.3, 109.2, 66.3, 55.9, 31.7, 27.5, 19.7; mass spectrum (CI, isobutane), 235.2 (M^+), 219.2, 218.2, 217.2 (P, M − H_2O).

3-[3,4-(Dimethoxy)phenyl]-2-cyclohexen-1-yl Acetate (8). A solution of alcohol 7 (6.0 g, 0.028 mol) in 15 mL of pyridine was exposed to acetic anhydride (4.2 mL, 0.041 mol) and the resulting mixture stirred for 18 h at room temperature. Thin-layer chromatographic analysis revealed the absence of the starting alcohol (R_f 0.38, 35% EtOAc–pentane) and the presence of a faster UV spot (R_f 0.48). The solvent was then removed in vacuo with toluene azeotrope, and the yellow oil remaining chromatographed on a 2 × 195 cm silica gel column (MPLC), eluting with 35% EtOAc–pentane; sixty 20-mL fractions were collected. Fractions 10–22 were combined and concentrated in vacuo to yield 5.9 g (76%) of a colorless, viscous syrup which could not be crystallized: NMR ($CDCl_3$) δ 6.95 (nm, complex, 2 H), 6.78 (m, 1 H), 6.02 (nm, complex, 1 H), 5.48 (m, complex, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 2.36 (br m, 2 H), 2.08 (s, 3 H), 1.84 (m, complex, 4 H); IR ($CHCl_3$) 3050 (w), 3011, 2970 (s), 2935, 1725 (vs), 1640 (w), 1590, 1520 (s), 1470, 1380 (s), 1260, 1180, 1040, 921 cm^{-1}; mass spectrum (EI), 277.1, 276.1 (M^+), 234.1 (M − CH_3CO), 217.2 (P, M − OAc), 151.1; ^{13}C NMR ($CDCl_3$) δ 170.1, 148.7, 148.6, 141.1, 133.5, 120.4, 117.5, 110.7, 108.5, 68.4, 55.2, 27.5, 26.7, 20.5, 18.8. Anal. ($C_{16}H_{20}O_4$) C, H.

[β-[3,4-(Dimethoxy)phenyl]cyclohex-2-enyl]acetic Acid (9). The Claisen rearrangement of acetate 8 was effected by using Ireland's modification.[8] Thus, a solution of the acetate (11.26 g, 0.040 mol) in anhydrous THF (20 mL) was added slowly dropwise, via syringe, to a solution of 1.2 equiv of lithium isopropylcyclohexylamide containing 5% HMPA under argon at −78 °C. After the addition was complete, the solution was stirred for 5 min and then treated in one batch with *tert*-butyldimethylchlorosilane (7.8 g, 0.052 mol) dissolved in THF (20 mL). The bath was then removed, and the solution was heated at reflux for 3 h. The solution was cooled and 30 mL of a 3:1:1 mixture of MeOH–H_2O–acetic acid was added to effect hydrolysis of the silyl ester, and after the mixture had stirred for 3 h, it was basified with saturated aqueous potassium carbonate, and the phases were separated. The organic phase was washed with three portions of H_2O, and the combined aqueous phases were washed twice with ether, acidified (pH 3) with concentrated HCl, and extracted exhaustively with dichloromethane. The combined CH_2Cl_2 layers were washed with brine, dried, and concentrated in vacuo to give a white solid which was recrystallized from dichloromethane–

(23) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* 1981, *37*, 4007.

pentane to yield 8.0 g (71%) as colorless plates: mp 110 °C; NMR ($CDCl_3$) δ 11.7 (s, 1 H), 7.05 (nm, complex, 3 H), 6.22 (AB q, J = 12, 2 H), 3.95 (s, 6 H), 2.83 (s, 2 H), 2.0 (m, complex, 4 H), 1.55 (m, complex, 2 H); IR ($CHCl_3$) 2750–3550 (br s), 1720 (vs), 1600 (s), 1476 (s), 1387, 1200–1240 (br m), 1070 cm^{-1}; mass spectrum (EI, probe), 276.2 (M^+), 218.1, 217.1 (P, M – CH_2CO_2H); mass spectrum (CI, isobutane), 278.2, 277.2 (M^+), 259.3, 219.2, 139.0 (P, Ar^+); ^{13}C NMR ($CDCl_3$) δ 177.8, 148.8, 147.6, 139.6, 132.2, 129.0, 119.4, 111.0, 110.8, 56.0, 55.9, 46.8, 41.6, 37.3, 25.1, 18.7. Anal. ($C_{16}H_{20}O_4$) C, H.

[β-[3,4-(Dimethoxy)phenyl]cyclohex-2-enyl]acetohydroxamic acid (10) was prepared from acid **9** via the method of Jones and Hurd.[9] To a solution of the acid (**9**; 6.02 g, 0.020 mol) in benzene (80 mL) containing 10 drops of DMF was added $SOCl_2$ (1.80 mL, 0.025 mol). The resulting mixture was heated at reflux for 2 h, cooled to 0 °C, and diluted with diethyl ether (50 mL); solid NH_2OH·HCl (1.75 g, 0.025 mol) and anhydrous Na_2CO_3 (6.14 g, 0.050 mol) were then added. The suspension was cooled to 0 °C and treated with 10 mL of H_2O followed by 10 mL 5 min later. The mixture was allowed to warm to room temperature over 12 h and then acidified to pH 2 with concentrated HCl, and the layers were separated. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried, and concentrated in vacuo to yield 5.0 g (78%) of the acid as a white solid: mp 150–152 °C; NMR ($CDCl_3$) δ 8.32 (br s, 2 H), 7.08 (nm, 3 H), 6.28 (s, 2 H), 3.98 (s, 6 H), 2.64 (s, 2 H), 2.08 (nm, 4 H), 1.57 (m, 2 H); IR ($CHCl_3$) 3100–3350 (br m), 2961 (s), 1672 (s), 1510, 1465, 1200–1245 (br m), 1150, 1040 (s), 913 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 169.7, 149.0, 147.7, 139.7, 132.2, 129.5, 119.5, 111.3, 111.0, 56.1, 55.9, 46.1, 41.9, 36.5, 25.1, 18.7. Anal. ($C_{16}H_{21}NO_4$) C, H.

12-[[1-(3,4-(Dimethoxy)phenyl)cyclohex-2-enyl]acetyl]-9,10-dihydro-9,10-dimethyl-10,9-(epoxyimino)anthracene (11). A suspension of 9,10-dimethylanthracene (1.62 g, 9.85 mmol) and tetrapropylammonium periodate (4.1 g, 11.00 mmol) in 10 mL of $CHCl_3$ and 2 mL of DMF (under argon) was treated via syringe (syringe pump) with 2.3 g (7.60 mmol) of hydroxamic acid **10** dissolved in 5 mL of $CHCl_3$ and 1 mL of DMF (syringe pump adjusted to deliver 1 drop every 8–10 s). After addition was complete (3 h) the dark brown solution was diluted with dichloromethane and poured into dichloromethane overlaid with saturated aqueous sodium thiosulfate solution, and the phases were separated. The organic layer was washed with saturated aqueous sodium thiosulfate, water, and brine, the resulting combined aqueous layers were back-extracted 5 times with 20 mL of dichloromethane, and the combined organic layers were dried over Na_2SO_4. Removal of the solvent and chromatography of the crude product (2 × 200 cm column of silica gel, slurry packed in 35% THF–hexanes, eluting with the same) gave the desired adduct as a colorless solid. One cold recrystallization from dichloromethane–pentane (to prevent decomposition) yielded 3.1 g (82.5%) of colorless plates: mp 127–130 °C dec; ^1H NMR ($CDCl_3$) δ 7.4 (m, complex, 4 H), 7.2 (m, complex, 4 H), 6.72 (d, J = 4, 1 H), 6.6 (d, J = 9 Hz, 1 H), 6.52 (dd, J = 4, 9 Hz, 1 H), 5.86 (d, J = 12 Hz, 1 H), 5.69 (dt, J = 5, 12 Hz, 1 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 2.67 (AB q, J = 18 Hz, 2 H), 2.61 (s, 3 H), 2.23 (s, 3 H), 1.80 (br s, 2 H), 1.22 (m, complex, 1 H), 1.55 (td, J = 5, 12, 1 H), 1.31 (m, complex, 2 H); ^{13}C NMR ($CDCl_3$) δ 176.6, 148.5, 146.9, 141.7, 141.5, 141.1, 133.5, 127.7, 127.3, 121.7, 121.6, 120.8, 120.6, 118.7, 110.7, 110.5, 79.8, 63.8, 55.8, 46.8, 41.9, 37.5, 24.9, 18.7, 16.9, 15.1; IR ($CHCl_3$) 3002 (w), 2940 (s), 2842, 1663 (s), 1591, 1460 (s), 1200–1240 (br), 1152, 1026 cm^{-1}. Anal. ($C_{32}H_{33}NO_4$) C, H.

***N*-Hydroxy-2-oxo-3a-[3,4-(dimethoxy)phenyl]-2,3,3a,4,5,7a-hexahydroindole (12).** Diels–Alder adduct **11** (3.1 g, 6.26 mmol) dissolved in 500 mL of dry toluene was pyrolyzed at reflux. After 20 min, thin-layer chromatographic analysis revealed the absence of the starting adduct and the presence of 9,10-dimethylanthracene and a very polar weakly UV active spot (R_f 0.02, 35% EtOAc–pentane). The solution was then cooled, and the toluene was removed under reduced pressure. The yellow solid material that remained was chromatographed on a 2 × 50 cm column of silica gel, eluting with 50% EtOAc–pentane; thirty 20-mL fractions were collected. Fractions 16–20 were combined and concentrated in vacuo to yield a peach-colored solid material. One recrystallization from dichloromethane–pentane yielded 1.76 g (100%) of colorless plates: mp 67–70 °C; ^1H NMR ($CDCl_3$) δ 7.5 (br s, 1 H), 6.7 (m, complex, 3 H), 6.15 (m, 2 H), 4.4 (s, 1 H), 3.89 (s, 6 H), 2.67 (s, 2 H), 1.85 (m, complex, 4 H); IR ($CHCl_3$) 3100–3250 (br), 3050 (w), 2960 (s), 1710 (vs), 1460, 1370, 1250 (s), 1030 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 176.4, 149.2, 148.0, 137.8, 133.2, 124.8, 118.4, 111.3, 110.0, 56.09, 56.02, 55.8, 46.3, 44.5, 32.6, 22.0. Anal. ($C_{16}H_{19}NO_4$) C, H.

2-Oxo-3a-[3,4-(dimethoxy)phenyl]-2,3,3a,4,5,7a-hexahydroindole (4). A solution of ene product **12** (400 mg, 1.38 mmol) in 5 mL of H_2O and 5 mL of methanol was treated with Na_2CO_3 (337 mg, 2.76 mmol) and $TiCl_3$ (Alfa; 839 mg, 5.52 mmol) and the resulting purple mixture was stirred for 18 h under argon at room temperature. The white suspension was then extracted exhaustively with EtOAc, and the combined EtOAc layers were dried and concentrated in vacuo to yield 294 mg (78%) of lactam **4** as colorless plates: mp 168–170 °C (dichloromethane–pentane); ^1H NMR ($CDCl_3$) δ 7.7 (s, 1 H), 6.84 (d, J = 10 Hz, 1 H), 6.75 (m, complex, 2 H), 4.27 (d, J = 4 Hz, 1 H), 3.86 (s, 6 H), 2.72 (AB q, J = 16 Hz, 2 H), 1.96 (m, complex, 2 H), 1.67 (m, complex, 2 H); IR ($CHCl_3$) 3090 (w), 2918 (s), 2831, 1680 (vs), 1578 (w), 1500, 1460, 1350, 1190–1250 (br m), 1150, 1041 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 176.4, 149.2, 148.0, 137.8, 133.2, 124.8, 118.6, 118.4, 111.4, 111.3, 110.0, 56.09, 56.02, 55.8, 46.3, 44.5, 32.6, 22.0; mass spectrum (EI), 274.1 (M^+), 273.1 (M – 1), 135.1 (P, M – veratryl). Anal. ($C_{16}H_{19}NO_3$) C, H.

***N*-Methyl-2-oxo-3a-[3,4-(dimethoxy)phenyl]-2,3,3a,4,5,7a-hexahydroindole (14).** A flame-dried, three-necked, 100-mL, round-bottomed flask was flushed with argon and charged with 120 mg of NaH (50% dispersion in oil). NaH was washed with pentane under a stream of argon, suspended in 10 mL of dry THF, and treated with 0.3 mL (3.50 mmol) of iodomethane. The flask was then cooled to 0 °C and treated (via syringe) with lactam **4** (400 mg, 1.46 mmol), and the resulting mixture allowed to warm to room temperature and then stirred for 12 h under argon. The flask was again cooled to 0 °C and treated in portions with MeOH (3 mL) followed by H_2O (3 mL). Standard extractive workup and chromatography over silica gel (MPLC, 1 × 100 cm column, 20:10:1 toluene–dioxane–acetic acid as eluent) yielded 377 mg (90%) of the *N*-methyl lactam as a white solid: mp 87–90 °C; NMR ($CDCl_3$) 6.76 (d, J = 10 Hz, 1 H), 6.68 (dd, J = 4, 10 Hz, 2 H), 6.12 (dd, J = 5, 11 Hz, 1 H), 6.00 (d, J = 11 Hz, 1 H), 4.02 (d, J = 5 Hz, 1 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 2.8 (s, 3 H), 2.63 (narrow AB q, J = 16 Hz, 2 H), 1.93 (m, complex, 1 H), 1.74 (m, complex, 1 H), 1.60 (m, complex, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.1, 149.2, 148.1, 137.7, 135.0, 123.0, 118.4, 111.3, 109.9, 60.2, 56.1, 56.0, 46.1, 42.2, 30.4, 29.7, 27.1; IR ($CHCl_3$) 3640 (w, sharp), 2946 (s), 1703 (vs), 1594, 1471 (s), 1455, 1200–1255 (broad s), 1160, 1066, 1045, 984 cm^{-1}; mass spectrum (EI), 288.3, 287.3 (M^+), 149.2 (P, M – veratryl), 148.2, 77.1. Anal. ($C_{17}H_{21}NO_3$) C, H.

***N*-Methyl-2-oxo-3a-[3,4-(dimethoxy)phenyl]-6-hydroxy-7-bromo-2,3,3a,4,5,6,7,7a-octahydroindole (15).** A solution of lactam **14** (100 mg, 0.347 mmol) in 10 mL of DME–H_2O (4:1) was cooled to −18 °C and treated with *N*-bromosuccinimide (MCB, 62 mg, 0.347 mmol) and the resulting suspension stirred at −18 °C. After 5 h, thin-layer chromatographic examination of the reaction mixture revealed the absence of the starting material (R_f 0.38 vs. 0.20 for **15**). The mixture was then diluted with saturated aqueous sodium thiosulfate and extracted exhaustively with EtOAc. The combined EtOAc layers were washed with brine, dried, and concentrated in vacuo to a yellow oil. Chromatography over silica gel (MPLC) with 20:10:1 toluene–dioxane–acetic acid as eluent gave 118 mg (88%) of the bromohydrin as rhomboid plates ($CHCl_3$): mp 173–175 °C; ^1H NMR ($CDCl_3$) δ 6.84 (nm, complex, 3 H), 4.04 (m, complex, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.76 (m, complex, 2 H), 3.51 (br s, 1 H, simplifies w/D_2O), 3.04 (s, 3 H), 2.86 (AB q, J = 16 Hz, 2 H), 2.18 (dd, J = 4, 14 Hz, 1 H), 2.00 (dt, J = 4, 14 Hz, 1 H), 1.94 (td, J = 4, 14 Hz, 1 H), 1.69 (qd, J = 4, 14 Hz, 1 H); IR ($CHCl_3$) 3560 (m), 3100–3465 (br m), 2940 (s), 2868 (w), 1688 (vs), 1606 (m), 1596 (m), 1455 (br s), 1200–1245 (br s), 1140, 1080, 912 cm^{-1} (s, sharp); mass spectrum (EI), 386.2 (M + 2), 385.2, 384.2 (M^+), 383.2, 234.2, 166.2, 165.2 (P), 148.2, 91.1, 84.1; ^{13}C NMR ($CDCl_3$) δ 173.5, 149.1, 148.2, 137.8, 125.4, 117.5, 111.3, 109.4, 73.3, 72.1, 64.8, 56.1, 55.9, 48.4, 39.2, 32.3, 29.0. Anal. ($C_{17}H_{22}NO_4Br$) C, H.

***N*-Methyl-2-oxo-3a-[3,4-(dimethoxy)phenyl]-6-hydroxy-2,3,3a,4,5,6,7,7a-octahydroindole (19).** A solution of bromohydrin **15** (165 mg, 0.430 mmol) in 20 mL of dry benzene was

degassed with argon for 20 min and then treated with 25 mg of solid α,α′-azobis(isobutyronitrile) (VAZO) and tributyltin hydride (Alfa; 0.17 mL, 0.644 mmol) via syringe, and the resulting suspension was degassed for an additional 20 min. The mixture was then heated at reflux for 2.5 h at which time TLC indicated the absence of the starting bromohydrin and the presence of a slower UV active spot (R_f 0.12 vs. 0.22 for **15** in 20:10:1 toluene–dioxane–acetic acid). The mixture was then cooled, the benzene removed in vacuo, and the material chromatographed over silica gel, giving 118 mg (90%) of the lactam alcohol as a colorless oil: NMR ($CDCl_3$) δ 7.03 (nm, 3 H), 4.02 (m, partially overlapped by methoxyl, 2 H), 3.98 (s, 3 H), 3.96 (s, 3 H), 2.98 (s, 3 H), 2.67 (nm, 3 H, OH overlapped with $CH_2C{=}O$), 1.71–2.20 (m, complex, 6 H); IR ($CHCl_3$) 3640, 3250–3520 (br m), 2940 (s), 2868, 1680 (vs), 1605, 1593, 1470, 1195–1243 (br), 1150, 910 cm^{-1}; mass spectrum (CI, methane), 307.1 (M + 1), 306.1 (M^+), 305.1 (P), 247.1, 234.0, 233.0, 167.1, 149.1. Anal. ($C_{17}H_{23}NO_4$) C, H.

***N*-Methyl-2-oxo-3a-[3,4-(dimethoxy)phenyl]-6-acetoxy-2,3,3a,4,5,6,7,7a-octahydroindole.** A solution of keto alcohol **19** (20 mg, 0.065 mmol) in 5 mL of pyridine was exposed to acetic anhydride (0.014 mL, 0.130 mmol). After the mixture was stirred for 1 h, the solvent was removed in vacuo with toluene azeotrope to give 22 mg (97%) of the acetate as a yellow oil: ^1H NMR ($CDCl_3$) δ 6.9 (nm, 3 H), 5.05 (m, 1 H), 4.05 (t, J = 4.5 Hz, 1 H), 3.91 (s, 3 H), 3.80 (s, 3 H), 2.90 (s, 3 H), 2.65 (AB q, J = 16 Hz, 2 H), 2.14 (m, 2 H), 1.98 (s, 3 H), 1.91 (m, complex, 2 H), 1.72 (m, complex, 2 H); IR ($CHCl_3$) 2940, 1728 (s), 1680 (vs), 1185–1255 cm^{-1} (br m); ^{13}C NMR ($CDCl_3$) δ 173.9, 171.0, 149.6, 148.4, 136.9, 118.4, 111.4, 110.1, 68.2, 61.4, 56.2, 56.0, 46.4, 42.7, 29.8, 29.2, 27.6, 26.1, 21.3.

***N*-Methyl-3a-[3,4-(dimethoxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2,6-dione (13).** A solution of keto alcohol **19** (70 mg, 0.220 mmol) in 10 mL of dry dichloromethane was cooled to 4 °C and treated with pyridinium chlorochromate (Aldrich; 75 mg, 0.330 mmol) and the resulting suspension stirred for 1.5 h at 4 °C and then warmed to room temperature and filtered through a small Florisil pad. The pad was washed with several portions of dichloromethane, and the solvent was removed in vacuo. Chromatography of the crude product over silica gel yielded 56 mg (85%) of keto lactam **13** as a colorless oil: ^1H NMR ($CDCl_3$) δ 6.94 (nm), 3 H), 4.33 (t, J = 4.5 Hz, 1 H), 4.05 (s, 3 H), 3.98 (s, 3 H), 2.92 (s, 3 H), 2.89 (nm, 6 H), 2.58 (nm, complex, 4 H); IR ($CHCl_3$) 2944, 2855 (w), 1722 (s), 1686 (vs), 1596, 1510, 1468, 1195–1255 (br m), 1145 cm^{-1}; mass spectrum (CI, methane), 305.1 (MH^+ + 1), 304.1 (MH^+), 303.1 (P, M^+), 246.1 (MH^+ – CH_3COCH_3), 138.0 (Ar^+); ^{13}C NMR ($CDCl_3$) δ 183.0, 173.2, 148.6, 148.4, 136.9, 118.2, 110.6, 110.1, 68.2, 65.0, 56.2, 42.7, 29.8, 29.1, 27.5, 22.2, 21.5; exact mass calcd for $C_{17}H_{21}NO_4$ 303.1470, found 303.1477.

***dl*-Mesembrine (2).** A solution of keto lactam **13** (120 mg, 0.400 mmol) in dry benzene (20 mL) containing ethylene glycol (2 mL) and *p*-toluenesulfonic acid monohydrate (5 mg) was heated at reflux in a 100-mL, round-bottomed flask fitted with a reflux condenser and a Dean–Stark trap for 4 days. The mixture was then cooled and diluted with 5 mL of pyridine. After being stirred for 10 min, the mixture was poured into 100 mL of toluene, and the solution was concentrated in vacuo. The crude ketal was dissolved in saturated aqueous potassium carbonate and extracted with EtOAc. The combined organic layers were dried and concentrated to yield the crude ketal as a colorless oil, which was used in the next step without purification: IR ($CHCl_3$) 2940, 1680 (s), 1460, 1200–1260 cm^{-1}; mass spectrum (CI, isobutane), 350.1 (3.0), 349.1 (21.2), 348.1 (100), 347.1 (14.2); exact mass calcd for $C_{19}H_{25}NO_5$ 347.1732, found 347.1732. The crude ketal was then dissolved in 10 mL of dry THF and the solution added to a suspension of 40 mg of $LiAlH_4$ in 10 mL of THF. The solution was heated at reflux for 1 h at which time TLC analysis of an aliquot revealed the absence of the starting ketal. The mixture was cooled and quenched by the addition of a 1 :1 mixture of $Na_2SO_4{\cdot}10H_2O$–Celite. The gelatinous mixture was then diluted with 20 mL of a 6:1 mixture of THF–NEt_3 and filtered through a Celite pad. The filtrate was diluted with 1 volume of toluene and concentrated in vacuo. IR of the crude material indicated the absence of the lactam carbonyl (1680 cm^{-1}). The crude amino ketal was then dissolved in 20 mL of 10% aqueous hydrochloric acid and stirred for 12 h at room temperature. The mixture was then washed with two small portions of diethyl ether, and the ether layers were discarded. The aqueous phase was then basified to pH 9 with concentrated NH_4OH and extracted with chloroform. The combined chloroform layers were dried over anhydrous potassium carbonate and concentrated in vacuo to give 87 mg (75%) of *dl*-mesembrine as a colorless oil, identical in all respects to an authentic sample:[13] exact mass calcd for $C_{17}H_{23}NO_3$ 289.1677, found 289.1679.

2-Oxo-3a-[3,4-(dimethoxy)phenyl]-6-hydroxy-7-bromo-2,3,3a,4,5,6,7,7a-octahydroindole (20). A solution of lactam **4** (193 mg, 0.700 mmol) in 6 mL of DME–H_2O (4:1) was cooled to 0 °C and treated with *N*-bromosuccinimide (126 mg, 0.700 mmol) and the resulting suspension stirred for 12 h at 0 °C. Thin-layer chromatographic analysis of the mixture revealed the absence of the starting material (R_f 0.26 vs. 0.15 for **20** in 20:10:1 toluene–dioxane–acetic acid). The solution was then diluted with saturated aqueous sodium thiosulfate solution, poured into EtOAc, and extracted exhaustively with EtOAc. The combined organic layers were dried and concentrated in vacuo to a yellow oil which was recrystallized from $CHCl_3$–hexanes, yielding 220 mg (87%) of the bromohydrin as colorless rhomboid plates: mp 219–220 °C; ^1H NMR (Me_2SO-d_6) δ 8.27 (s, 1 H), 7.08 (nm, 1 H), 7.01 (nm, 2 H), 5.3 (d, J = 4.5 Hz, 1 H), 3.96 (m, complex, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.37 (s, 1 H), 3.00 (B part, AB q, J = 17 Hz, 1 H), 2.40 (A part AB q, J = 17 Hz, 1 H), 1.87 (m, complex, 4 H) [when the signal at 3.96 ppm was irradiated, the resonance at 5.3 ppm simplified to a singlet; when the 5.3-ppm signal was irradiated, the multiplet at 3.96 ppm simplified to a broad singlet]; IR ($CHCl_3$) 3460 (m), 3230–3440 (br), 2940, 1683 (s), 1190–1240 cm^{-1} (br); ^{13}C NMR ($CDCl_3$) δ 173.5, 149.1, 148.2, 137.8, 125.4, 117.5, 111.3, 109.4, 73.3, 72.1, 64.8, 56.1, 55.9, 48.4, 39.2, 32.3, 29.0; mass spectrum (EI), 372.0 (4.0), 371.0 (22.1), 370.0 (5.0), 369.0 (24.1), 152.1 (P), 151.1 (69.7), 134.0 (26.0). Anal. ($C_{16}H_{20}NO_4Br$) C, H.

2-Oxo-3a-[3,4-(dimethoxy)phenyl]-6-hydroxy-2,3,3a,4,5,6,7,7a-octahydroindole (21). A solution of bromohydrin **20** (200 mg, 0.500 mmol) in dry degassed toluene (20 mL) was treated with tri-*n*-butyltin hydride (0.28 mL, 1.00 mmol) and α,α′-azobis(isobutyronitrile) (VAZO, 20 mg) and the mixture degassed an additional 20 min. The suspension was then heated at reflux for 1 h, the toluene removed in vacuo, and the crude material remaining partitioned between CH_3CN and pentane. The CH_3CN was removed in vacuo to give the crude alcohol **21** as a colorless solid. Recrystallization from $CHCl_3$–pentane gave 113 mg (76%) of the lactam alcohol as a colorless crystalline solid: mp 138–140 °C; NMR ($CDCl_3$) δ 7.3 (s, 1 H), 7.05 (nm, 3 H), 4.40 (m, 1 H), 4.33 (m, 1 H), 4.0 (s, 3 H), 3.98 (s, 3 H), 3.22 (br m, 2 H, simplifies with D_2O), 2.55 (br s, 2 H), 2.15 (m, 3 H), 2.0 (m, 1 H), 1.75 (m, 2 H); IR ($CHCl_3$) 3420, 3150–3400 (br), 2932, 1689 (s); mass spectrum (CI, isobutane), 294.3 (3.4), 293.3 (15.6), 292.2 (100), 291.2 (43.5), 274.2 (24.1, M – OH); exact mass calcd for $C_{16}H_{21}NO_4$ 291.1470, found 291.1477.

2-Oxo-3a-[3,4-(dimethoxy)phenyl]-6-acetoxy-7-bromo-2,3,3a,4,5,6,7,7a-octahydroindole. A solution of bromohydrin **20** (500 mg, 1.350 mmol) in pyridine (10 mL) was treated with acetic anhydride (0.20 mL, 2.020 mmol) and the resulting solution stirred for 2 h and then diluted with 12 volumes of toluene and concentrated in vacuo. The oil that remained was recrystallized from benzene–hexanes, yielding 545 mg (98%) of the acetylated bromohydrin as colorless rosettes: mp 203 °C; ^1H NMR (CD_3CN) δ 7.0 (d, J = 4 Hz, 1 H), 6.95 (dd, J = 4, 9 Hz, 1 H), 6.88 (d, J = 9 Hz, 1 H), 6.68 (s, 1 H), 5.16 (m, complex (6 lines), 1 H), 4.15 (d, J = 7.5 Hz, 1 H), 3.82 (s, 3 H), 3.80 (m, 1 H), 3.78 (s, 3 H), 2.04 (s, 3 H), 2.02 (m, complex, 2 H), 1.99 (m, complex, 1 H), 1.72 (m, complex, 1 H) [when the signal at 5.16 ppm was irradiated, the resonance at 4.15 ppm simplified to a singlet; when the 4.15-ppm signal was irradiated, the 5.16 signal became a doublet of doublets, J = 5, 12]; IR ($CHCl_3$) 3420 (m), 2940, 1720 (s), 1702 (vs), 1145–1255 (br); mass spectrum (EI), 414.1 (4.2), 413.1 (20.5), 412.1 (4.5), 411.1 (21.2, M^+), 272.1 (25.7), 151.1 (22.9), 135.1 (17.4), 134.1 (p, Ar^+). Anal. ($C_{18}H_{22}NO_5Br$) C, H.

2-Oxo-3a-[3,4-(dimethoxy)phenyl]-6-acetoxy-2,3,3a,4,5,6,7,7a-octahydroindole. A suspension of 2-oxo-3a-[3,4-(dimethoxy)phenyl]-6-acetoxy-7-bromo-2,3,3a,4,5,6,7,7a-octahydroindole (760 mg, 1.840 mmol) in dry, degassed benzene (20 mL) was treated with α,α′-azobis(isobutyronitrile) (VAZO, 50 mg) and tri-*n*-butyltin hydride (Alfa; 0.63 mL, 2.400 mmol)

and the resulting mixture degassed with argon for an additional 20 min. The mixture was then heated at reflux for 1 h at which time TLC of the crude mixture revealed the absence of the starting material and the presence of a UV active product spot (R_f 0.16 vs. 0.23 for starting material in 20:10:1 toluene–dioxane–acetic acid). The benzene was then removed under reduced pressure and the residue that remained was partitioned between CH_3CN and pentane. Removal of the CH_3CN in vacuo and recrystallization of the crude white solid from acetone–hexanes yielded 472 mg (77%) of the debrominated material as a white solid: mp 200–203 °C; ^1H NMR ($CDCl_3$) δ 7.48 (s, 1 H), 6.88 (nm, 3 H), 5.02 (nm, 1 H), 4.24 (t, J = 4 Hz, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.56 (AB q, J = 21, 2 H), 2.20 (m, complex, 2 H), 2.1 (m, complex, 2 H), 2.06 (br s, 3 H), 1.74 (m, 1 H), 1.59 (m, 1 H); IR ($CHCl_3$) 3425 (w), 2940, 1722 (s), 1694 (vs), 1145–1254 (br); mass spectrum (EI), 335.1 (3.1), 334.1 (19.3), 333.1 (P) 219.1 (16.2), 164.1 (17.9), 135.0 (54.2), 43.1 (66.9). Anal. ($C_{18}H_{23}NO_5$) C, H.

3a-[3,4-(Dimethoxy)phenyl]-6-hydroxy-2,3,3a,4,5,6,7,7a-octahydroindole (22). A solution of lactam alcohol **21** (120 mg, 0.412 mmol) in dry DME was treated with $LiAlH_4$ (Alfa; 228 mg, 0.600 mmol) and the resulting suspension refluxed for 1 h. The mixture was then cooled with an ice bath, quenched by the addition of a 1:1 mixture of ground $Na_2SO_4 \cdot 10H_2O$–Celite, and filtered. The filter pad was washed with several small portions of THF–NEt_3 (6:1), and the filtrate was concentrated in vacuo with toluene, giving 95 mg (83%) of the amine as a white crystalline solid: mp 106–108 °C; ^1H NMR ($CDCl_3$) δ 6.92 (nm, 2 H), 6.84 (d, J = 8 Hz, 1 H), 4.04 (m, complex 3 H; simplifies to a simple multiplet with D_2O), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.4 (m, 1 H), 3.2 (q, J = 10 Hz, 1 H), 3.03 (td, J = 4, 10 Hz, 1 H), 2.32 (m, 2 H), 2.1 (m, 2 H), 1.91 (m, 2 H), 1.79 (m, 2 H); IR ($CHCl_3$) 3638. 3100–3400 (br), 2920, 1603, 1595, 1470, 1195–1243 cm^{-1} (br); mass spectrum (CI, isobutane), 280.3 (2.4), 279.2 (17.1), 278.2 (100), 276.2 (28), 107.1 (20); exact mass calcd for $C_{16}H_{23}NO_3$ 277.1677, found 277.1679.

***dl*-Dihydromaritidine (3).** A solution of amine **22** (60 mg, 0.216 mmol) in MeOH (2 mL) was treated with 3 mL of 37% aqueous formaldehyde. After being stirred for 15 min *under argon*,[16] the mixture was treated with 4 mL of 8 N HCl and the resulting solution allowed to stand for 12 h at room temperature. Washing with ether followed by basification with concentrated NH_4OH, extraction with $CHCl_3$, drying, and removal of the solvent gave 32.5 mg (52%) of the alkaloid as a crude white solid. Recrystallization from EtOAc–MeOH or $CHCl_3$ gave essentially pure dihydromaritidine as colorless crystals, mp 237–240 °C (lit.[20] mp 230–233 °C), whose NMR spectrum was identical with that of an authentic sample.[18] Treatment of a THF solution of amine **22** with a stoichiometric amount of Eschenmoser's salt[17] (*N,N*-dimethylmethyleneammonium iodide), heating to 40 °C for 12 h followed by normal extractive workup gave *dl*-dihydromaritidine, identical with that prepared by Pictet–Spengler cyclization: exact mass calcd for $C_{17}H_{23}NO_3$ 289.1677, found 289.1677.

***N*-Methyl-2-oxo-3a-[3,4-(dimethoxy)phenyl]-6-(benzoyloxy)-2,3,3a,4,5,6,7,7a-octahydroindole (23).** A solution of keto alcohol **19** (15 mg, 0.050 mmol) in 1 mL of pyridine was treated with excess benzoyl chloride (0.2 mL) and the solution stirred for 1 h at room temperature. Evaporation of the solvent with toluene and chromatography over silica gel (MPLC, eluting with 5% MeOH–CH_2Cl_2) gave 19 mg (95%) of the benzoate as colorless crystals: mp 167–170 °C; NMR ($CDCl_3$) δ 8.02 (d, J = 8 Hz, 2 H), 7.62 (td, J = 2, 8 Hz, 1 H), 7.50 (td, J = 2, 8 Hz, 1 H), 7.32 (nm, 2 H), 6.92 (nm, 1 H), 5.4 (m, complex (5 lines), 1 H), 4.29 (t, J = 4, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.17 (d, J = 17 Hz, 1 H), 2.86 (d, J = 4 Hz, 1 H), 2.83 (s, 3 H), 2.58 (m, complex, 1 H), 2.51 (t, J = 4 Hz, 2 H), 2.15 (m, complex, 1 H), 1.83 (m, 2 H); IR ($CHCl_3$) 2930, 1710 (s), 1680 (vs), 1600, 1200–1270 cm^{-1} (br m); mass spectrum (CI, isobutane), 412.3 (3.5), 411.3 (24.0), 410.3 (100.0), 409.3 (22.5), 288.3 (19.5); exact mass calcd for $C_{24}H_{27}NO_5$ 409.1889, found 409.1889.

2-Oxo-3a-[3,4-(dimethoxy)phenyl]-6-(benzoyloxy)-2,3,3a,4,5,6,7,7a-octahydroindole. A solution of keto alcohol **21** (55 mg, 0.188 mmol) in dry pyridine (1 mL) was treated with benzoyl chloride (0.025 mL, 0.188 mmol) and the resulting mixture stirred for 20 min at room temperature, and then the solvent was removed in vacuo with toluene and the material chromatographed (MPLC, eluting with 5% MeOH–CH_2Cl_2), giving 65 mg (93%) of the benzoate as a colorless oil: NMR ($CDCl_3$) δ 8.33 (dd, J = 3, 8 Hz, 2 H), 7.7 (nm, 3 H), 7.0 (nm, 3 H), 6.5 (s, 1 H), 5.5 (m, complex, 1 H), 4.45 (t, J = 5 Hz, 1 H), 4.0 (s, 3 H), 3.97 (s, 3 H), 2.6 (br s, 2 H), 2.3 (m, 2 H), 1.6–2.1 (4 H); IR ($CHCl_3$) 3422, 2930, 1698 (s), 1190–1260 cm^{-1}(br); mass spectrum (CI, isobutane), 398.3 (3.56), 397.3 (26.9), 396.3 (100.0), 395.3 (17.0), 274.2 (24.4).

***N*-Methyl-2-oxo-3a-[3,4-(dimethoxy)phenyl]-6-(benzoyloxy)-2,3,3a,4,5,6,7,7a-octahydroindole (24).** A solution of diisopropylamine (0.03 mL, 0.216 mmol) in dry THF was treated with *n*-butyllithium (Alfa; 0.08 mL, 0.200 mmol) and the resulting mixture cooled to −78 °C and treated with a solution of 2-oxo-3a-[3,4-(dimethoxy)phenyl]-6-(benzoyloxy)-2,3,3a,4,5,6,7,7a-octahydroindole (40 mg, 0.100 mmol) in 1 mL of dry THF. After the mixture was stirred for 20 min, iodomethane (0.13 mL, 2.000 mmol) was added neat, and the solution was allowed to warm to room temperature over 1 h and stirred for an additonal hour. Normal extractive workup yielded 29 mg (78%) of the *N*-methyl lactam, *isomeric* with the compound derived from the mesembrine route, as a colorless oil: NMR ($CDCl_3$) δ 8.02 (d, J = 2, 8 Hz, 2 H), 7.62 (td, J = 2, 8 Hz, 1 H), 7.50 (td, J = 2, 8 Hz, 2 H), 6.91 (nm, complex, 3 H), 5.34 (m, complex (5 lines), 1 H), 4.06 (t, J = 6 Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 2.82 (s, 3 H), 2.62 (narrow AB q, J = 19 Hz, 2 H), 2.52 (td, J = small, 6 Hz, 1 H), 2.25 (m, complex 3 H), 1.91 (m, 1 H), 1.78 (m, 1 H); IR ($CHCl_3$) 2930, 1710 (s), 1680 (vs), 1600, 1590, 1450, 1200–1260 cm^{-1} (br m); mass spectrum (CI, isobutane), 412.3 (3.56), 411.3 (26.2), 410.3 (100.0), 409.3 (23.5), 288.3 (19.0), 149.2 (12.9), 105.1 (12.9); exact mass calcd for $C_{24}H_{27}NO_5$ 409.1889, found 409.1889.

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