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A Short Diastereoselective Synthesis of the Putative Alkaloid Jamtine, Using a Tandem Pummerer/Mannich Cyclization Sequence

Albert Padwa,* M. Diana Danca,† Kenneth I. Hardcastle,‡ and Michael S. McClure

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

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Treatment of 2-phenylhex-5-enal with benzylamine followed by sequential reaction with ethylthioacetyl chloride and sodium periodate oxidation afforded a *E*/*Z* mixture of α-sulfinylamides. As anticipated from a 4π-conrotatory mechanism, cyclization of each olefin afforded fused isoquinoline lactams as single diastereomers epimeric at the ethylthio position without any cross contamination. Some preliminary studies were directed toward the synthesis of mesembrine using a 3,4-dimethoxy aryl group. In this case, the *Z*-enamide prefers to undergo electrophilic aromatic substitution to give a substituted azepinone as the preferred product in 87% yield. In contrast, the *E*-enamide isomer provided the desired hydroindolone. The convergency and stereochemical control associated with the tandem Pummerer /Mannich cyclization make it particularly suited for the assembly of jamtine, a tetrahydroisoquinoline alkaloid reputed for its therapeutic properties. The key step in the synthesis involves a domino thionium/*N*-acyliminium ion cyclization to provide the tricyclic ring skeleton **27a** as the major diastereomer. Deprotonation of **27a** with NaH gave **28a**, which contains the fully assembled skeleton of jamtine. Completion of the synthesis entailed installation of the double bond and reduction of the lactam. Oxidation of a synthetic sample of jamtine with MCPBA afforded the corresponding *N*-oxide, which does not match the spectral data reported in the literature for this alkaloid. Our synthetic efforts raise the possibility of a revision of the earlier assignment.

Polyannular heterocyclic compounds have attracted much interest and a variety of synthetic methodologies have been developed over the years.[1−8] The elaboration of ring-fused heterocycles based upon cascade sequences such as cationic cyclization,[9] radical cyclization,[10] and tandem Heck processes[11] allows for the rapid and stereocontrolled synthesis of azapolycyclic skeletons. Domino reactions are among the most powerful strategic tools available to the synthetic organic chemist because they rapidly increase the complexity of a substrate while at the same time making economical use of available functional groups.[12−23] *N*-Acyliminium ion-mediated carbon−carbon bond-forming reactions have been utilized

† NIH Postdoctoral Fellow, grant GM20461-02.
‡ Emory University X-ray Crystallography Laboratory.

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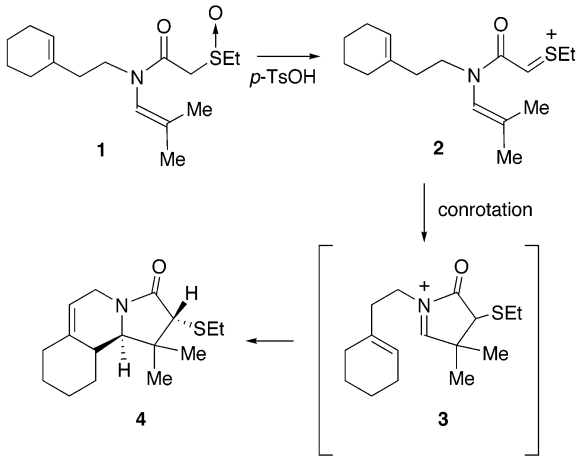
in an impressive number of synthetic applications.[23−25] In recent years, the Pummerer reaction followed by a π-cyclization has also been found to be a very effective and general method for the preparation of many diverse azapolycyclic skeletons.[26−28] The combination of a Pummerer/Mannich cyclization sequence offers unique opportunities for the assemblage of complex target molecules.[29,30]

A strategy that we have found particularly effective in the design of new processes for heterocyclic ring construction is to employ ene-amides such as **1** which contains a tethered sulfoxide.[31] The cascade reaction can be triggered by using a Pummerer promoter and, once the thionium ion (i.e., **2**) is generated, cyclization occurs

SCHEME 1



onto the proximal enamide π-bond to furnish *N*-acyliminium ion **3** (Scheme 1). Since a tethered nucleophile is present in the starting material, a subsequent cyclization takes place resulting in the formation of the octahydropyrrolo[2,1-*a*]-isoquinolinone **4**. To showcase the method, the above strategy was applied to the synthesis of jamtine,[32] a novel tetrahydroisoquinoline alkaloid that was isolated from a climbing shrub in Pakistan.[33] The present paper documents the results of our studies.[34]

Results and Discussion

The convergency and stereochemical control associated with the Pummerer/Mannich ion cyclization sequence make it particularly suited for the assembly of natural product scaffolds. With this in mind, some preliminary model studies were first directed toward the synthesis of the *cis*-3*a*-aryloctahydroindole nucleus which corresponds to a prominent substructural motif found in the *Amaryllidaceae* and *Sceletium* alkaloids.[35] This ring system (i.e., **8**) represents a considerable synthetic challenge as a result of the presence of a highly congested quaternary center at C_3a. In an earlier study we had demonstrated that treatment of the model *Z*-enamido sulfoxide **5** with *p*-TsOH afforded tosylate **6**, which was subsequently converted to the octahydro-indolone skeleton **7** (Scheme 2).[31]

The success we had with the cyclization of enamido sulfoxide **5** suggested that the method might be applicable for the synthesis of mesembrine.[36] Although mesembrine is devoid of significant biological activity, it has nevertheless attracted considerable interest over the years as a favorite target in alkaloid synthesis.[37] Beyond the issue of testing new methodologies, the preparation of this alkaloid provides access toward the more complex *Sceletium* alkaloids of pharmacological interest, such as tazettine, lycoramine, or galanthamine.[38] Initial feasibil-

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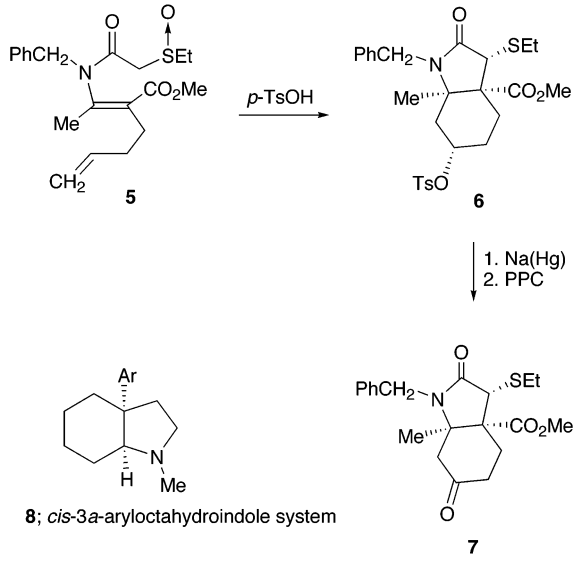
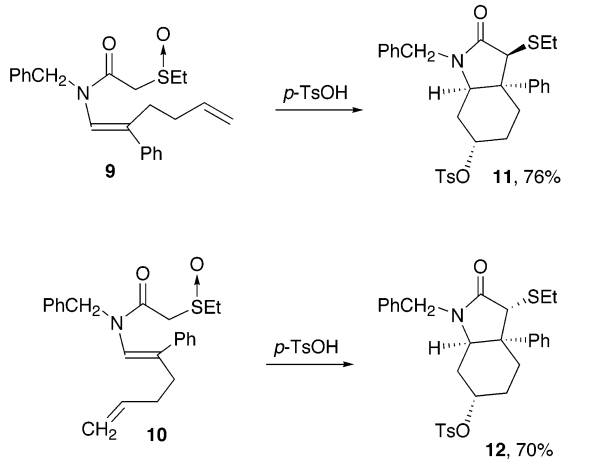
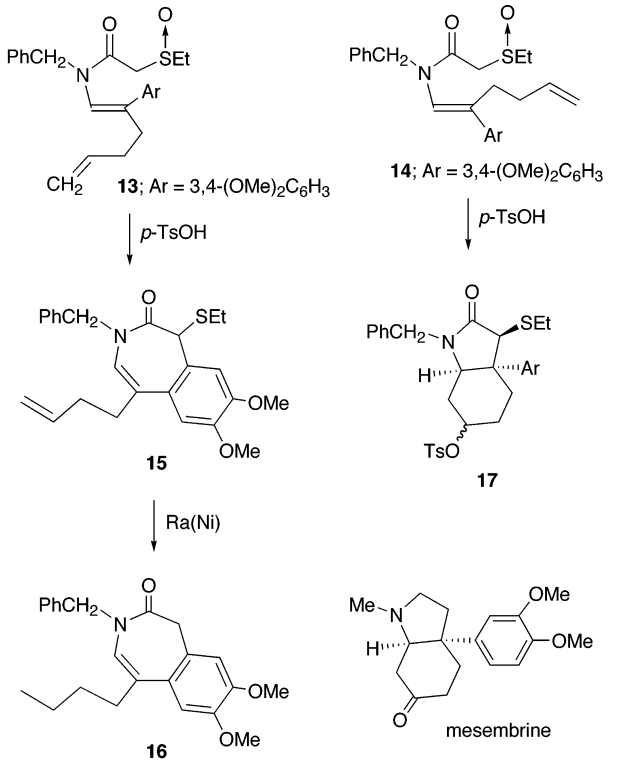
SCHEME 2



SCHEME 3



SCHEME 4



ity studies were conducted with the simple phenyl-substituted enamide **9**. Treatment of benzylamine with 2-phenylhex-5-enal followed by sequential reaction with ethylthioacetyl chloride and sodium periodate oxidation ultimately afforded a 2:1-mixture of the *E*- and *Z*-enamides **9** and **10** (Scheme 3). The olefin geometry was assigned on the basis of an NOE between the vinylic and allylic methylene hydrogens. Heating a sample of **9** with *p*-TsOH in benzene at 80 °C afforded tosylate **11** as the major diastereomer in 76% yield. As anticipated from a 4π-conrotatory mechanism,[31] cyclization of each olefin (i.e., **9** or **10**) afforded single diastereomers epimeric at the ethylthio position without any cross contamination.

A set of isomeric α-sulfinylenamides **13** and **14** containing the ubiquitous 3,4-dimethoxyphenyl moiety was also prepared by a related synthetic method. The dimethoxy-substituted aryl group was required for the synthesis of mesembrine. Surprisingly, when *Z*-enamide **13** was exposed to *p*-TsOH, the unexpected azepinone **15** was obtained in 78% isolated yield as the exclusive product (Scheme 4). Treatment of **15** with Raney-Ni resulted in reduction of the ethylthio group and gave rise to **16** in 87% yield. The presence of the dimethoxy substituents on the aromatic ring certainly enhances its electron density. This, coupled with its close proximity to the incipient thionium ion, allowed the electrophilic aromatic substitution process to become the preferred reaction path with this stereoisomer. In mark contrast, the reaction of α-sulfinyl enamide **14** with *p*-TsOH provided the desired hydroindolone **17**, but as a 3:1 mixture of tosylate isomers and in only 50% yield. Attempts to isomerize the *Z*-enamide **13** to the *E*-isomer **14** failed to provide us with sufficient quantities of the necessary stereoisomer and consequently we abandoned this approach toward mesembrine.

To further elaborate the unique features exhibited by olefin geometry on the course of the cyclization reaction, we decided to examine the reactivity patterns of the related α-sulfinyl enamides **18** and **19**. Treatment of **18** with 2 equiv of *p*-TsOH in refluxing benzene afforded the rearranged lactam **21** in 62% yield (Scheme 5). In this

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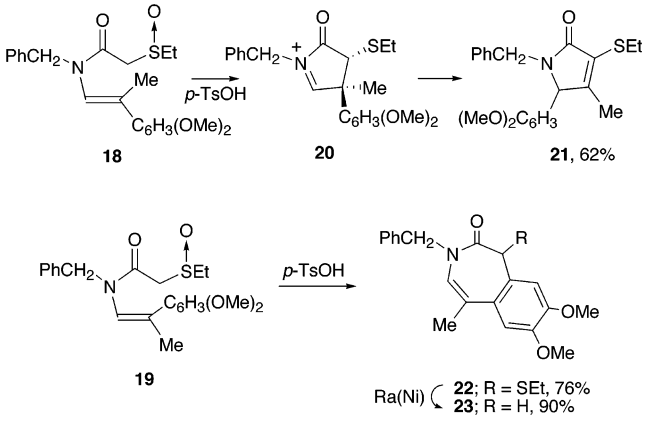
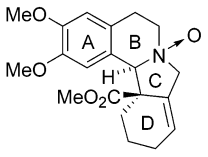
SCHEME 5



case, the initially formed thionium ion **20** undergoes a 1,2-aryl shift and is followed by deprotonation to furnish the observed product. Following the trend observed in the previous series, cyclization of the *Z*-enamide **19** provided azepinone **22** in 76% yield. Raney-Ni reduction of **22** smoothly removed the ethylthio group furnishing **23** in excellent yield. With the *Z*-stereoisomer **19**, attack by the activated aromatic ring onto the initially formed thionium ion is again much faster than the Nazarov-like electrocyclization that can only occur with the *E*-stereoisomer **18**.

Jamtine

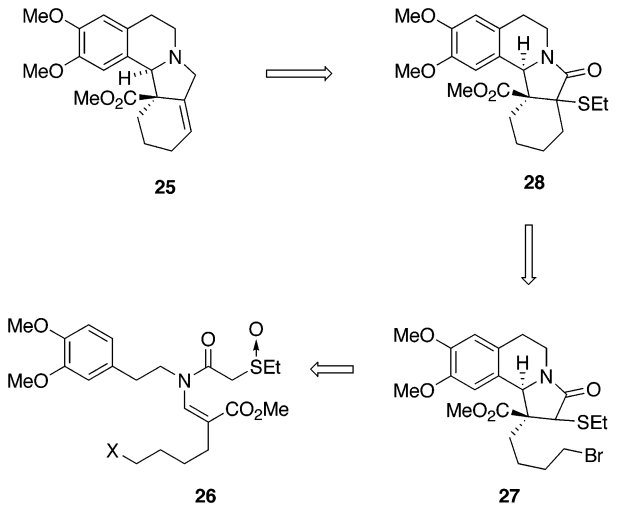
To properly highlight the potential of the linked thionium/*N*-acyliminium ion cascade, we opted to use the method for the synthesis of the alkaloid jamtine *N*-oxide (**24**). In 1987, Rahman and co-workers[32] reported the isolation of a novel *N*-oxide from the *Cocculus hirsutus*,[39] which is commonly found as a shrub in Pakistan. Its various parts are reputed to possess purgative, diuretic, abortificient, and antituberculotic properties and the shrub is used as a remedy for rheumatism and diarrhea.[40] The compound was named jamtine *N*-oxide and assigned the structure **24** on the basis of extensive NMR studies. This alkaloid contains a tetrahydroisoquinoline skeleton, a double bond in ring D, and two stereogenic centers in a relatively compact molecule.



24; (±)-jamtine *N*-oxide

It should be noted that reports of the isolation of alkaloid *N*-oxides have increased in number since 1970 and these compounds have become recognized as authentic natural products, not artifacts. Hypotheses have been

SCHEME 6



formulated about their role in plant metabolism.[41] In fact, more than 200 individual alkaloid *N*-oxides have been described in the literature, but it well may be that many other *N*-oxides have gone undetected.[41] Generally, the *N*-oxides of aliphatic tertiary amines are very polar substances not unlike the corresponding quaternary salts in terms of solubility and chromatographic behavior.[42] Alkaloid *N*-oxides such as **24** are easily obtained from the amine and likewise are easily deoxygenated.[43] Since the nonbasic, water-soluble *N*-oxide of jamtine is quite different from the corresponding amine in its properties, we opted to first synthesize jamtine (**25**) and then carry out a subsequent oxidation at the amino site. For our purposes, a synthesis of (±)-jamtine provided an opportunity to further develop the tandem Pummerer/Mannich sequence and its application to tetrahydroisoquinoline alkaloids.

Our retrosynthetic analysis of this structure is outlined in Scheme 6. The attractiveness of this strategem involves the efficient use of the ethylthio group in each of the critical stages of the synthesis. The first step in this highly convergent synthesis involves the domino ring closure of enamido sulfoxide **26** to provide the tricyclic ring skeleton **27**. Assembly of the D ring should proceed uneventfully by a base-induced cyclization and furnish the tetracyclic core of jamtine (**25**). Finally, standard functional group manipulations and selective reduction of the lactam would lead to the desired tetrahydroisoquinoline.

Our approach starts from commercially available ϵ-caprolactone which was transformed into the open chain hydroxymethyl ester under acidic conditions.[44] The primary alcohol was converted into a series of ethers (**29**–**31**)[45–47] as this would provide us with some flexibility in generating the alcohol at some later point in the syn-

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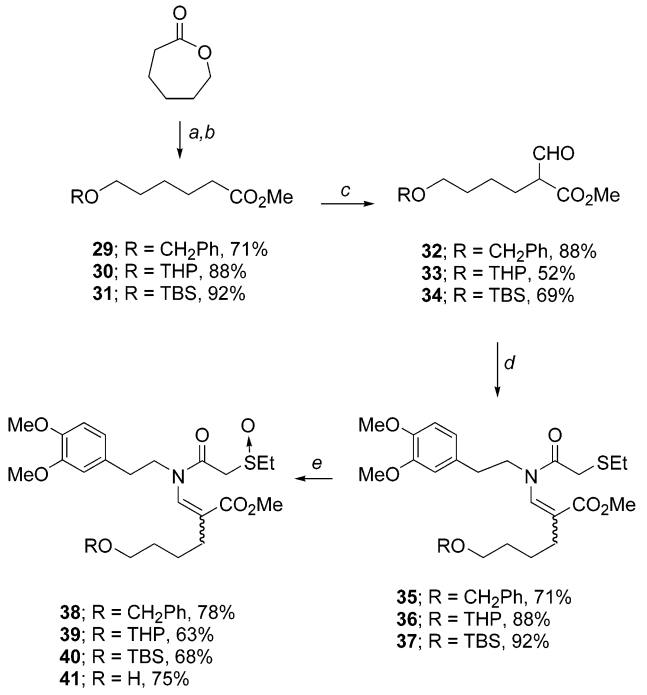
(47) Bookser, B. C.; Kasibhatla, S. R.; Applemann, J. R.; Erion, M. D. *J. Med. Chem.* **2000,** *43*, 1495.

SCHEME 7[a]

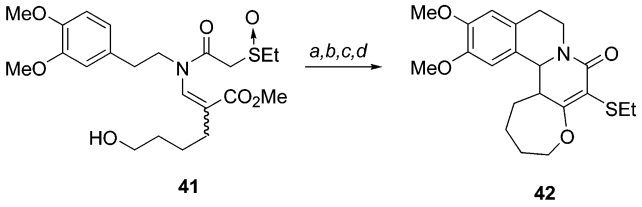


[a] Reagents: (a) H^+, MeOH; (b) see refs 45−47; (c) LDA, HCO_2Et; (d) 3,4-dimethoxyphenethylamine, $EtSCH_2COCl$; (e) $NaIO_4$, MeOH/H_2O.

thesis. Each carbomethoxy ether was formylated by treatment with LDA and ethyl formate to give the aldehydic esters **32**−**34** in good yield (Scheme 7). Condensation with 3,4-dimethoxyphenethylamine led to the expected enamines, which were in turn acylated with ethyl sulfenylacetyl chloride[48] to provide enamides **35**−**37** in high yield as *Z*/*E*-mixtures of isomers. Oxidation to the corresponding sulfoxides **38**−**40** was easily achieved by using $NaIO_4$ in aqueous methanol in good overall yield. In the case of **40**, the *tert*-butyldimethyl silyl group was removed under the oxidative conditions required for the formation of the sulfoxide, thereby allowing for an effortless purification of the highly polar alcohol **41**.

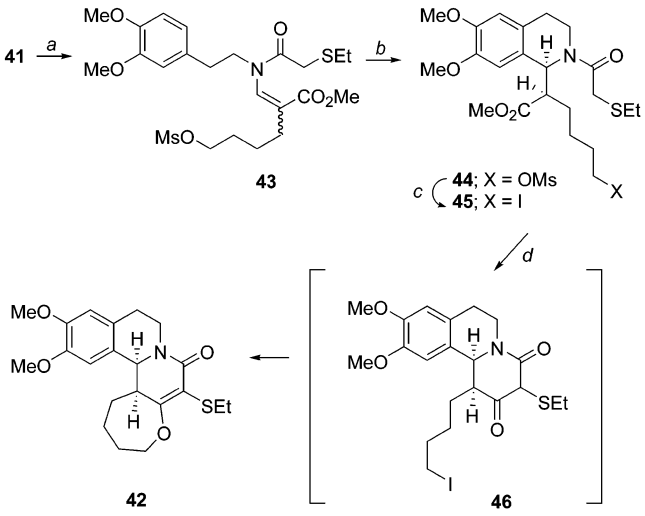
Studies dealing with the conversion of the hydroxyl functionality into an appropriate leaving group were carried out at this junction. Our intention was to first prepare an appropriate alcohol derivative that would be carried through the Pummerer/Pictet−Spengler cascade and then perform an anionic intramolecular cyclization (i.e., **27** → **28**) so as to install the D ring of jamtine. Most surprisingly, an intriguing and totally unexpected product was obtained when the following reaction sequence was executed (Scheme 8). Treatment of alcohol **41** with methanesulfonyl chloride and Et_3N was expected to furnish a mesylate, which we intended to subject to camphorsulfonic acid in refluxing benzene to induce the desired tandem thionium/*N*-acyliminium ion cascade (vide infra). Without isolation, the crude reaction mixture was treated with NaI in acetone so as to replace the mesylate with an iodo group, and this was followed by treatment with NaH. Surprisingly, the only product

SCHEME 8[a]



[a] Reagents: (a) MsCl, Et_3N; (b) CSA, benzene, reflux; (c) NaI, acetone; (d) NaH, THF, reflux.

SCHEME 9[a]



[a] Reagents: (a) MsCl, Et_3N, 68%; (b) CSA, benzene, reflux, 75%; NaI, acetone 93%; (d) NaH, THF, reflux, 72%.

isolated in 34% overall yield corresponded to the unusual cyclic enol ether **42**, whose structure was unequivocally established by an X-ray crystallographic study.

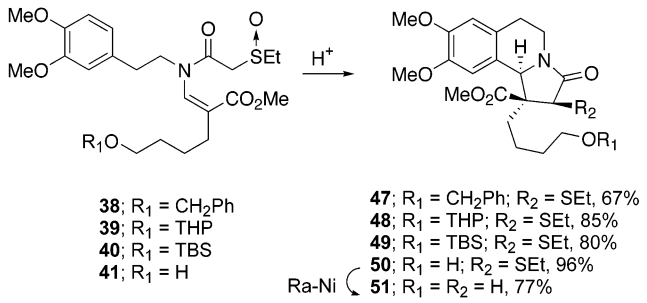
Scheme 9 outlines a working mechanistic hypothesis to rationalize the formation of **42**. Under the conditions used to convert the hydroxyl functionality to the corresponding mesylate, reduction of the sulfoxide to the corresponding sulfide **43** also occurred, an event not unprecedented in the literature.[49] In fact, we have been able to isolate sulfide **43** in 68% yield from this reaction. When treated with camphorsulfonic acid, **43** underwent Pictet−Spengler cyclization to give the tetrahydroisoquinoline substructure **44** in 75% yield. After conversion of **44** to iodide **45**, treatment with NaH resulted in a Dieckman condensation to first give **46** as a transient intermediate that underwent further *O*-alkylation under the basic conditions to furnish the observed product.

Because the attempted thionium ion cascade of alcohol **41** failed due to the ease with which the sulfoxide group was reduced, we decided to proceed in a stepwise manner. Subjection of enamides **38**−**41** to camphorsulfonic acid gave rise to the expected fused isoquinoline lactams **47**−**50** in high yield but as a mixture of diastereomers. In all cases the major diastereomer (ca. 60%) was derived from a Nazarov type 4π-electrocyclic reaction followed by π-cyclization onto the least hindered side of the *N*-acyliminium ion (Scheme 10). The *tert*-butyldimethylsilyl protecting group present in lactam **49** was easily hydro-

(48) Mooradian, A.; Cavallito, C. J.; Bergman, A. J.; Lawson, E. J.; Suter, C. M. *J. Am. Chem. Soc.* **1949**, *71*, 3372.

(49) Madesclaire, M. *Tetrahedron* **1988**, *44*, 6537.

SCHEME 10



lyzed to afford the corresponding alcohol **50** in excellent yield. Surprisingly, conversion of the hydroxyl group present in **50** to a suitably activated derivative (i.e., bromo, iodo, mesylate, tosylate, triflate, etc.) only proceeded in low yield (<20%). Either the starting alcohol was recovered unchanged or decomposition occurred at the elevated temperatures employed. This lack of reactivity at the hydroxylic functionality was unanticipated since the primary alcohol seemed devoid of any steric hindrance. Removal of the ethylthio group from **50** was easily accomplished using Raney-Ni but our efforts to replace the OH group in **50** with an appropriate leaving group for eventual SN_2 displacement were also unsuccessful.

To gain some insight into the resilience of the C(4′) hydroxyl toward functionalization, we performed a simple conformational search of lactam **50** using the Monte−Carlo Multiple Minimum (MCMM) protocol.[50−52] Low-energy conformations, a representative example of which appears in Figure 1, were identified with the MM2* force field and $CHCl_3$ GB/SA solvation model.[53] Based upon the examination of several low-energy conformations, it would appear that a combination of the aromatic ring and the thioethyl and carbomethoxy groups shields the C(4′) hydroxyl from potential electrophiles. Although conformations which allow free access to the C(4′) hydroxyl were identified, the higher temperatures required to sufficiently populate these conformations led to extensive decomposition.

Our Pummerer/Mannich ion approach toward jamtine was reduced to practice in the following manner. The hydroxyl present in the acyclic enamide **41** was first converted to the corresponding bromide,[54] which also resulted in the simultaneous reduction of the sulfoxide functionality. Subsequent reoxidation with $NaIO_4$ delivered the required bromo-enamide **52** as a 4:1 (*Z*/*E*) mixture of isomers in high yield. Heating a sample of **52** with camphorsulfonic acid afforded the expected tetrahydroisoquinoline **27** in excellent yield (88%) but as a 5:2:1:1 mixture of diastereomers (Scheme 11). The major

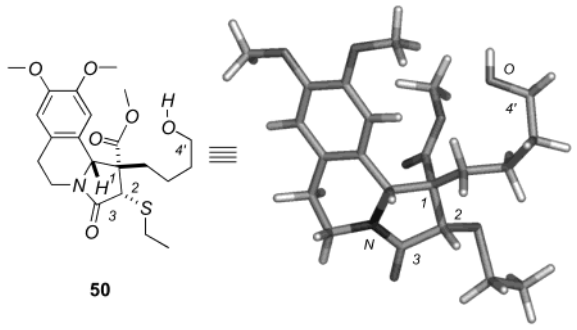
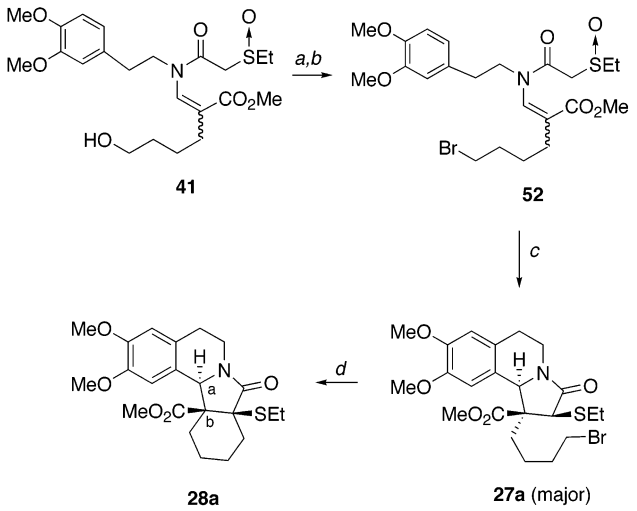


FIGURE 1. A representative low-energy conformer of **50**.

SCHEME 11[a]



[a] Reagents: (a) CBr_4, PPh_3, 83%; (b) $NaIO_4$, MeOH/H_2O, 99%; (c) CSA, toluene, reflux, 88%; (d) NaH, THF, reflux, 99%.

product obtained corresponded to the desired diastereomer **27a**. The preferential formation of **27a** is consistent with our earlier stereochemical observations,[31] suggesting that a 4π-Nazarov-type electrocyclization[55] controls the direction of closure from the α-acylthionium ion intermediate. The subsequent Pictet−Spengler step involves attack of the proximal aromatic ring from the less hindered side of the iminium ion. Deprotonation of **27a** with NaH resulted in quantitative cyclization to give **28a**, which contains the fully assembled skeleton of jamtine and whose structure was verified by X-ray analysis. It should be noted that treating the crude mixture of diastereomers **27** obtained from **52** with NaH not only afforded **28a** (67%) but also gave some of the corresponding *cis*-(*a*,*b*)-isomer **28b** (25%).

Completion of the synthesis entailed installation of the double bond and reduction of the lactam. This was accomplished by oxidation of the sulfide to the sulfoxide followed by thermal elimination to furnish the unsaturated lactam **53** in 89% overall yield (Scheme 12). Conversion of **53** to thioamide **54** with Lawesson's reagent was followed by reduction to jamtine (**25**) with Meerwein's salt and $NaBH_4$[56] in a respectable 61% yield.

(50) MCMM as implemented by MacroModel v.7.0. See: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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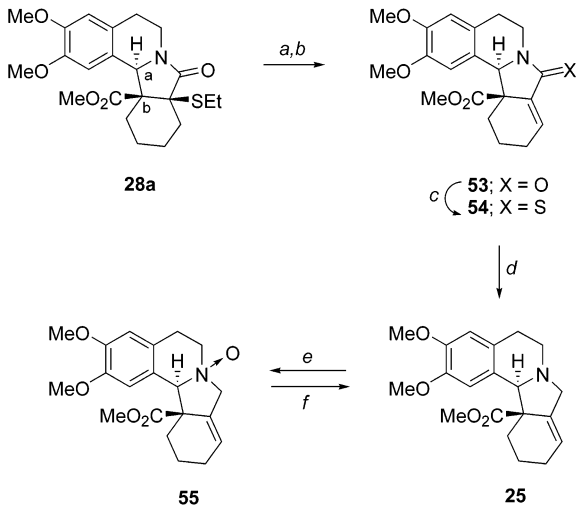
SCHEME 12[a]



[a] Reagents: (a) NaIO4, MeOH/H_2O; (b) heat, 90%; (c) Lawesson's reagent, 99%; (d) Meerwein's salt, $NaBH_4$, MeOH, 61%; (e) MCPBA, CH_2Cl_2, 95%; (f) PCl_3, CH_2Cl_2, 78%.

The structure of **25** was unequivocally verified by X-ray analysis. Oxidation of **25** with MCPBA led to the corresponding *N*-oxide **55** as a single isomer in 95% yield. We were surprised to find, however, that the ^1H and ^{13}C NMR data of synthetic *N*-oxide **55** did not match the corresponding data reported by Rahman for jamtine *N*-oxide (**24**).[32] *N*-Oxide **55** was subsequently reduced with PCl_3 to give **25** in 78% yield thereby establishing that a structural reorganization did not occur during the oxidation step. The nonplanarity of the N→O group potentially gives rise to the issue of stereoisomerism. In most cases, a single *N*-oxide isomer is generally isolated from natural sources, though only in a few instances has the stereochemistry actually been determined.[41] Chemical oxidation of the corresponding tertiary base often produces a mixture of stereoisomers. In our case, however, only a single diastereomer was formed from the MCPBA oxidation. Thus, one explanation to account for the fact that synthetic *N*-oxide **55** does not correspond to the isolated alkaloid is that we have simply prepared the other diastereomer.[57] Of course, an alternate possibility is that a structure reassignment is in order for the natural product isolated from the *Cocculus hirsutus* shrub. Further work is necessary to sort out these possibilities.

In conclusion, we have accomplished the total synthesis of the putative alkaloid jamtine (**25**) and our synthetic efforts raise the possibility of a revision of the earlier assignment. This approach to jamtine demonstrates the utility of the domino Pummerer/Mannich ion cyclization for preparing stereochemically complex azapolycyclic ring systems. Further studies on the synthesis of related alkaloids using this methodology are in progress and will be reported in due course.

(57) **Note Added in Proof:** Recent work by Professor Nigel S. Simpkins and C. D. Gill has resulted in an independent synthesis of jamtine **25**. These workers have also concluded that the original structure assignment[32] of jamtine *N*-oxide (**24**) is incorrect. The spectral data obtained by us for compound **24** are virtually identical with those forwarded to us by Professor Simpkins (private communication).

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column with an ethyl acetate−hexane mixture as the eluent unless specified otherwise.

***N*-Benzyl-2-ethylsulfanyl-*N*-(2-phenylhexa-1,5-dienyl)-acetamide.** To a stirred solution containing 3.5 g (20 mmol) of 2-phenyl-hex-5-enal[58] in 150 mL of benzene was added 2.2 g (20 mmol) of benzylamine and the resulting mixture was heated at reflux for 16 h in a flask equipped with a Dean−Stark trap. The solvent was removed under reduced pressure and the crude imine was taken up in 150 mL of CH_2Cl_2 and to this solution was added 4.7 g (60 mmol) of pyridine followed by 2.8 g (20 mmol) of ethylthioacetyl chloride. The mixture was stirred for 2 h at 25 °C, washed with a saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by silica gel chromatography afforded 4.2 g (58%) of *N*-benzyl-2-ethylsulfanyl-*N*-(2-phenylhexa-1,5-dienyl)acetamide as a yellow oil that consisted of a 2:1 mixture of stereomers that could be separated by silica gel chromatography. The major *E*-isomer showed the following properties: IR (neat) 1656, 1405, and 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, 3H, J = 7.2 Hz), 1.86 (dt, 2H, J = 8.4 and 6.6 Hz), 2.44−2.49 (m, 2H), 2.69 (q, 2H, J = 7.2 Hz), 3.35 (s, 2H), 4.76 (s, 2H), 4.85−4.95 (m, 2H), 5.64 (ddt, 1H, J = 17.1, 10.5, and 6.6 Hz), 6.29 (s, 1H), and 7.24−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.7, 26.5, 28.8, 31.4, 33.8, 56.7, 115.5, 126.2, 127.0, 127.6, 128.2, 128.6, 128.7, 128.8, 137.0, 137.5, 138.5, 143.8, and 169.7. Anal. Calcd for $C_{23}H_{27}NOS$: C, 75.58; H, 7.45; N, 3.83. Found: C, 75.42; H, 7.48; N, 3.76.

The minor *Z*-isomer exhibited the following spectral properties: IR (neat) 1657, 1631, 1491, and 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H, J = 7.6 Hz), 2.02 (dt, 2H, J = 7.6 and 6.8 Hz), 2.42−2.46 (m, 2H), 2.62 (q, 2H, J = 7.6 Hz), 3.27 (s, 2H), 4.32 (s, 2H), 4.89−4.96 (m, 2H), 5.69 (ddt, 1H, J = 16.8, 10.4, and 6.4 Hz), 6.24 (s, 1H), 7.11−7.15 (m, 4H), and 7.21−7.34 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 26.3, 32.2, 33.7, 35.2, 50.2, 115.7, 124.9, 127.4, 127.6, 128.2, 128.3, 128.6, 129.0, 137.4, 137.5, 137.6, 139.2, and 169.5. Anal. Calcd for $C_{23}H_{27}NOS$: C, 75.58; H, 7.45; N, 3.83. Found: C, 75.55; H, 7.41; N, 3.67.

(*E*)-*N*-Benzyl-2-ethylsulfinyl-*N*-(2-phenylhexa-1,5-dienyl)acetamide (9). To a stirred solution containing 0.8 g (3.8 mmol) of sodium periodate in 15 mL of H_2O was added 0.6 g (1.5 mmol) of the above *E*-isomer in 15 mL of methanol. The resulting mixture was stirred for 3 h at 25 °C, extracted with chloroform, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography to give 0.49 g (86%) of α-sulfinyl enamide **9** as a yellow oil: IR (neat) 1656, 1399, and 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, 3H, J = 7.5 Hz), 1.79 (dt, 2H, J = 8.1 and 6.9 Hz), 2.38−2.43 (m, 2H), 2.79−2.91 (m, 1H), 3.03−3.15 (m, 1H), 3.78 (d, 1H, J = 14.1 Hz), 3.91 (d, 1H, J = 13.8 Hz), 4.71 (d, 1H, J = 14.1 Hz), 4.79 (d, 1H, J = 14.1 Hz), 4.82−4.94 (m, 2H), 5.58 (ddt, 1H, J = 17.1, 10.2, and 6.6 Hz), 6.20 (s, 1H), and 7.22−7.36 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.8, 28.8, 31.2, 46.7, 51.7, 55.8, 115.7, 125.1, 126.8, 127.9, 128.5, 128.7, 129.0, 136.1, 137.1, 137.7, 145.6, and 164.7. Anal. Calcd for $C_{23}H_{27}NO_2S$: C, 72.41; H, 7.14; N, 3.67. Found: C, 72.33; H, 7.08; N, 3.56.

(*Z*)-*N*-Benzyl-2-ethylsulfinyl-*N*-(2-phenylhexa-1,5-dienyl)acetamide (10). To a stirred solution containing 0.6 g (2.8 mmol) of sodium periodate in 15 mL of H_2O was added 0.4 g (1.1 mmol) of the above *Z*-isomer in 15 mL of methanol. The resulting mixture was stirred for 3 h at 25 °C, extracted with chloroform, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography to give 0.38 g (91%) of

α-sulfinyl enamide **10** as a yellow oil: IR (neat) 1636, 1439, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, 3H, J = 7.5 Hz), 2.01−2.08 (m, 2H), 2.42−2.56 (m, 2H), 2.59−2.71 (m, 1H), 2.85−2.97 (m, 1H), 3.47 (d, 1H, J = 14.1 Hz), 3.75 (d, 1H, J = 14.1 Hz), 4.49 (s, 2H), 4.91−5.01 (m, 2H), 5.71 (ddt, 1H, J = 17.1, 10.2, and 6.6 Hz), 6.11 (s, 1H), 6.99−7.02 (m, 4H), and 7.23−7.36 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.7, 32.1, 35.4, 46.5, 51.2, 55.9, 115.9, 124.0, 127.4, 127.9, 128.4, 128.7, 128.8, 129.1, 136.0, 136.9, 137.2, 141.4, and 164.3. Anal. Calcd for $C_{23}H_{27}NO_2S$: C, 72.41; H, 7.14; N, 3.67. Found: C, 72.16; H, 6.95; N, 3.44.

***p*-Toluene-4-sulfonic Acid 1-Benzyl-3-ethylsulfanyl-2-oxo-3*a*-phenyloctahydroindol-6-yl Ester (11).** To a solution containing 0.7 g (3.9 mmol) of *p*-TsOH in 50 mL of benzene at 80 °C was added 0.5 g (1.3 mmol) of *E*-enamide **9** in 2 mL of benzene. After being heated at reflux for 20 min, the reaction mixture was cooled to room temperature, washed with a saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by silica gel chromatography afforded 0.52 g (76%) of the title compound as a 5:1 mixture of diastereomers. The major diastereomer exhibited the following spectral data, mp 181−183 °C: IR (neat) 1691, 1362, and 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, 3H, J = 7.6 Hz), 1.45−1.66 (m, 3H), 1.75−1.79 (m, 1H), 2.32−2.55 (m, 4H), 2.47 (s, 3H), 3.51 (s, 1H), 3.76 (d, 1H, J = 15.2 Hz), 4.04 (s, 1H), 4.28−4.36 (m, 1H), 5.28 (d, 1H, J = 14.8 Hz), 7.20−7.43 (m, 12H), and 7.77 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7, 21.9, 27.2, 27.4, 28.2, 29.6, 29.9, 44.4, 46.5, 59.7, 61.7, 126.7, 127.7, 128.0, 128.1, 128.3, 129.1, 129.2, 130.2, 134.1, 135.9, 139.5, 145.2, 172.8. Anal. Calcd for $C_{30}H_{33}NO_4S_2$: C, 67.27; H, 6.21; N, 2.62. Found: C, 67.21; H, 6.25; N, 2.57.

***p*-Toluene-4-sulfonic Acid 1-Benzyl-3-ethylsulfanyl-2-oxo-3*a*-phenyloctahydroindol-6-yl Ester (12).** To a solution containing 0.5 g (2.5 mmol) of *p*-TsOH in 50 mL of benzene at 80 °C was added 0.4 g (0.8 mmol) of *Z*-enamide **10** in 2 mL of benzene. After being heated at reflux for 20 min, the reaction mixture was cooled to room temperature, washed with a saturated $NaHCO_3$ solution, washed with brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by silica gel chromatography afforded 0.3 g (70%) of the title compound as a white solid, mp 124−125 °C: IR (neat) 1688, 1592, 1354, and 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, 3H, J = 7.5 Hz), 1.56−1.67 (m, 2H), 1.82−1.94 (m, 2H), 2.17−2.28 (m, 2H), 2.46 (s, 3H), 2.57−2.81 (m, 2H), 3.47 (s, 1H), 3.99 (d, 1H, J = 15.6 Hz), 4.23 (d, 1H, J = 3.3 Hz), 4.81 (s, 1H), 5.38 (d, 1H, J = 15.6 Hz), 7.14 (m, 12H), and 7.83 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 22.0, 25.2, 26.6, 27.3, 29.3, 43.3, 47.7, 53.0, 54.6, 76.4, 127.3, 127.4, 127.5, 127.7, 127.9, 128.5, 128.8, 130.1, 134.2, 135.8, 138.5, 145.0, and 172.2. Anal. Calcd for $C_{30}H_{33}NO_4S_2$: C, 67.27; H, 6.21; N, 2.62. Found: C, 67.04; H, 6.15; N, 2.66.

2-(3,4-Dimethoxyphenyl)hex-5-enal. To a stirred solution containing 2.7 g (12 mmol) of 2-(3,4-dimethoxyphenyl)hex-5-ene nitrile in 110 mL of dry toluene at 0 °C was added 18 mL of a 1.0 M solution of diisobutylalumminum hydride in toluene and the resulting mixture was stirred at 25 °C for 1.5 h. To this solution was added 65 mL of a 1.0 M solution of tartaric acid in ether and the reaction mixture was diluted with 300 mL of ether. The mixture was washed with 10% Rochelle's salt, the two layers were separated, and the aqueous layer was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 2.0 g (72%) of the titled aldehyde as a colorless oil: IR (neat) 1727, 1517, and 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75−1.84 (m, 1H), 1.98−2.20 (m, 3H), 3.47−3.51 (m, 1H), 3.88 (s, 6H), 4.99−5.03 (m, 2H), 5.73−5.83 (m, 1H), 6.67 (d, 1H, J = 2.0 Hz), 6.75 (dd, 1H, J = 8.0 and 2.0 Hz), 6.88 (d, 1H, J = 8.0 Hz), and 9.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.8, 31.1, 56.0, 57.9, 111.7, 111.8, 115.7, 121.3, 137.8, 148.7, 149.6, and 200.8. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.76; H, 7.75. Found: C, 71.59; H, 7.78.

***N*-Benzyl-*N*-[2-(3,4-dimethoxyphenyl)hexa-1,5-dienyl]-2-ethylsulfanylacetamide.** To a stirred solution containing 2.0 g (8.6 mmol) of 2-(3,4-dimethoxyphenyl)hex-5-enal in 60 mL of benzene was added 0.9 g (8.6 mmol) of benzylamine and the resulting mixture was heated at reflux for 16 h in a flask equipped with a Dean−Stark trap. The solvent was removed under reduced pressure and the crude imine was taken up in 60 mL of CH_2Cl_2 and to this solution was added 2.0 g (26 mmol) of pyridine followed by 1.2 g (8.6 mmol) of ethylthioacetyl chloride. The mixture was stirred for 2 h at 25 °C, washed with a saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by silica gel chromatography afforded 0.8 g (37%) of *N*-benzyl *N*-[2-(3,4-methoxyphenyl)hexa-1,5-dienyl]-2-ethylsulfanylacetamide as a yellow oil. Silica gel chromatography of the 1.4:1 mixture of stereoisomers afforded the *Z*-isomer as a clear oil: IR (neat) 1652, 1510, 1254, and 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.3 Hz), 2.09 (q, 2H, J = 7.0 Hz), 2.47 (t, 2H, J = 7.0 Hz), 2.66 (q, 2H, J = 7.3 Hz), 3.30 (s, 2H), 3.80 (s, 3H), 3.91 (s, 3H), 4.39 (s, 2*H*), 4.98 (m, 2H), 5.75 (ddt, 1H, J = 17.0, 10.3, and 6.6 Hz), 6.24 (s, 1H), 6.75 (m, 2H), 6.85 (d, 1H, J = 7.9 Hz), 7.19 (m, 2H), and 7.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 26.2, 32.1, 33.3, 35.0, 49.9, 55.8, 55.9, 110.6, 111.2, 115.5, 119.9, 124.1, 127.2, 128.1, 128.3, 129.6, 137.3, 137.4, 138.0, 148.7, 149.0, and 169.5; Anal. Calcd for $C_{25}H_{31}NO_3S$: C, 70.55; H, 7.35; N, 3.29. Found: C, 70.46; H, 7.35; N, 3.21.

The minor *E*-stereoisomer exhibited the following spectral properties: IR (neat) 1652, 1510, 1410, 1254, and 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.3 Hz), 1.87 (q, 2H, J = 7.0 Hz), 2.43 (m, 2H), 2.67 (q, 2H, J = 7.5 Hz), 3.32 (s, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.74 (s, 2H), 4.90 (m, 2H), 5.64 (ddt, 1H, J = 17.0, 10.3, and 6.6 Hz), 6.22 (s, 1H), 6.70 (d, 1H, J = 1.8 Hz), 6.82 (m, 2H), and 7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 26.1, 28.5, 31.2, 33.4, 51.4, 55.8 (2), 109.9, 111.0, 115.3, 119.3, 125.1, 127.4, 128.4, 128.6, 131.0, 136.9, 137.4, 143.2, 148.8, 149.0, and 169.7. Anal. Calcd for $C_{23}H_{27}NOS$: C, 70.55; H, 7.35; N, 3.29. Found: C, 75.40; H, 7.28; N, 3.15.

(*Z*)-*N*-Benzyl-*N*-[2-(3,4-dimethoxyphenyl)hexa-1,5-dienyl]-2-ethylsulfinylacetamide (13). To a solution containing 0.7 g (3.1 mmol) of $NaIO_4$ in 20 mL of water was added 0.7 g (1.6 mmol) of the above *Z*-sulfide in 20 mL of methanol. The reaction mixture was stirred at 25 °C for 2.5 h and then poured into water and extracted with $CHCl_3$. The combined extracts were dried over anhydrous $MgSO_4$. Silica gel chromatography provided 0.64 g (93%) of the title compound as a colorless oil: IR (neat) 1631, 1510, 1254, and 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.3 Hz), 2.01 (m, 2H), 2.46 (m, 2H), 2.65 (m, 1H), 2.88 (m, 1H), 3.42 (d, 1H, J = 14.3 Hz), 3.66 (s, 3H), 3.72 (d, 1H, J = 14.3 Hz), 3.85 (s, 3H), 4.42 (d, 1H, J = 14.3 Hz), 4.54 (d, 1H, J = 14.3 Hz), 4.93 (dd, 1H, J = 15.6 and 1.6 Hz), 4.98 (d, 1H, J = 9.2 Hz), 5.71 (ddt, 1H, J = 16.8, 10.3, and 6.6 Hz), 6.07 (s, 1H), 6.53 (d, 1H, J = 1.8 Hz), 6.63 (dd, 1H, J = 8.2 and 1.8 Hz), 6.80 (d, 1H, J = 8.2 Hz), and 7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.2, 31.9, 34.9, 46.1, 50.9, 55.5, 55.6, 55.7, 110.1, 111.3, 115.6, 119.7, 123.3, 127.6, 128.5, 128.7, 128.8, 135.9, 137.1, 139.9, 148.8, 149.0, and 164.3. Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 68.00; H, 7.08; N, 3.17. Found: C, 67.79; H, 7.02; N, 3.11.

(*E*)-*N*-Benzyl-*N*-[2-(3,4-dimethoxyphenyl)hexa-1,5-dienyl]-2-ethylsulfinylacetamide (14). To a solution containing 0.9 g (4.2 mmol) of $NaIO_4$ in 25 mL of water was added 0.9 g (2.1 mmol) of the above *E*-sulfide in 25 mL of methanol. The reaction mixture was stirred at 25 °C for 2.5 h and then poured into water and extracted with $CHCl_3$. The combined extracts were dried over anhydrous $MgSO_4$. Silica gel chromatography provided 0.55 g (60%) of the title compound as a colorless oil: IR (neat) 1652, 1510, 1247, and 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.5 Hz), 1.76 (m,

2H), 2.31 (t, 2H, J = 7.7 Hz), 2.78 (m, 1H), 3.04 (m, 1H), 3.70 (d, 1H, J = 14.1 Hz), 3.79 (s, 3H), 3.81 (s, 3H), 3.84 (d, 1H, J = 14.1 Hz), 4.62 (d, 1H, J = 13.9 Hz), 4.70 (d, 1H, J = 13.9 Hz), 4.79 (dd, 1H, J = 17.0 and 1.6 Hz), 4.85 (dd, 1H, J = 10.3 and 1.5 Hz), 5.53 (ddt, 1 H, J = 16.8, 10.3, and 6.6 Hz), 6.07 (s, 1H), 6.63 (d, 1H, J = 1.8 Hz), 6.73 (dd, 1H, J = 8.2 and 1.8 Hz), 6.76 (d, 1H, J = 8.2 Hz), and 7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.4, 28.5, 31.0, 46.4, 51.4, 55.5, 55.8, 55.9, 109.8, 111.0, 115.5, 119.3, 124.0, 127.7, 128.6, 128.9, 130.2, 136.0, 137.1, 145.1, 148.8, 149.2, and 164.7. Anal. Calcd for $C_{25}H_{31}NO_4S$: C, 68.00; H, 7.08; N, 3.17. Found: C, 68.14; H, 6.83; N, 3.06.

3-Benzyl-5-but-3-enyl-1-ethylsulfanyl-7,8-dimethoxy-1,3-dihydrobenzo[*d*]azepin-2-one (15). To a refluxing solution containing 0.8 g (4.3 mmol) of *p*-TsOH in 45 mL of benzene was added dropwise 0.6 g (1.4 mmol) of *Z*-sulfoxide **13** dissolved in 30 mL of benzene. After the addition was complete, the reaction mixture was stirred for an additional 1 h before cooling to rt and pouring into a saturated solution of $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and further purified by silica gel chromatography to give 0.48 g (78%) of the title compound as a mixture of atropoisomers: IR (neat) 1652, 1510, 1446, 1261, and 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, 3H, J = 7.5 Hz), 2.16 (m, 2H), 2.42 (m, 2H), 2.63 (dt, 1H, J = 14.7 and 7.3 Hz), 2.89 (m, 1H), 3.85 (s, 3H), 3.91 (s, 3H), 4.37 (s, 1H), 4.56−5.00 (m, 4H), 5.60 (ddt, 1H, J = 17.2, 10.0, and 6.0 Hz), 6.11 (s, 1H), 6.80 (s, 1H), 6.96 (m, 2H), 7.24 (m, 3H), and 7.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 24.8, 33.1, 33.9, 50.2, 52.3, 55.8, 56.0, 107.5, 108.1, 115.5, 125.1, 125.5, 127.1, 127.2, 127.4, 128.4, 128.5, 137.4, 138.1, 148.0, 150.3, 166.4. Anal. Calcd for $C_{25}H_{29}NO_3S$: C, 70.89; H, 6.91; N, 3.31. Found: C, 70.74; H, 7.04; N, 3.15.

3-Benzyl-5-butyl-7,8-dimethoxy-1,3-dihydrobenzo[*d*]-azepin-2-one (16). To a solution containing 0.07 g (0.2 mmol) of azepinone **15** in 30 mL of a 1:1-THF/EtOH mixture was added an excess of Raney nickel. The reaction mixture was stirred at 25 °C for 30 min and then filtered through Celite. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give 0.05 g (87%) of the title compound as a colorless oil: IR (neat) 1659, 1510, 1261, and 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, 3H, J = 7.1 Hz), 1.17−1.40 (m, 4H), 2.20−2.82 (m, 2H), 3.48 (s, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 4.70 (s, 2H), 6.12 (s, 1H), 6.85 (s, 1H), 6.86 (s, 1H), 7.07 (m, 2H), and 7.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.3, 31.5, 34.5, 42.9, 50.0, 55.9, 56.1, 107.9, 110.8, 125.1, 126.5, 127.1, 127.2, 127.3, 128.4, 130.5, 136.9, 147.8, 149.6, and 168.6. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.58; H, 7.45; N, 3.83. Found: C, 75.41; H, 7.26; N, 3.50.

***p*-Toluene-4-sulfonic Acid 1-Benzyl-3*a*-(3,4-dimethoxyphenyl)-3-ethylsulfanyl-2-oxooctahydroindol-6-yl Ester (17).** To a refluxing solution containing 0.7 g (3.6 mmol) of *p*-TsOH in 35 mL of benzene was added dropwise a solution containing 0.5 g (1.2 mmol) of *E*-enamido sulfoxide **14** in 25 mL of benzene. After the addition was complete, the reaction mixture was heated for 1 h at reflux before being cooled to room temperature. The mixture was poured into a saturated solution of $NaHCO_3$. The organic phase was separated, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography to give 0.3 g (50%) of the title compound as a 3:1 mixture of diastereomers. The major diastereomer was a crystalline solid, mp 183−184 °C: IR (neat) 1695, 1510, 1168, and 934 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, 3H, J = 7.3 Hz), 1.41−1.50 (m, 1H), 1.57−1.75 (m, 3H), 2.30−2.44 (m, 2H), 2.46 (s, 3H), 2.35−2.62 (m, 2H), 3.44 (s, 1H), 3.77 (d, 1H, J = 15.0 Hz), 3.84 (s, 3H), 3.85 (s, 3H), 3.99 (br s, 1H), 4.29 (m, 1H), 5.23 (d, 1H, J = 15.0 Hz), 6.77 (d, 1H, J = 8.6 Hz), 6.84 (dd, 1H, J = 8.6 and 2.4 Hz), 7.10 (d, 1H, J = 2.2 Hz), 7.19 (d, 1H, J = 2.2 Hz), 7.35 (m, 5H), and 7.75 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz) δ 14.5, 21.6, 27.3, 27.7, 27.8, 29.3, 44.2, 45.8, 55.8, 56.0, 59.1, 61.2, 77.2, 110.2, 110.8, 118.6, 127.7, 127.8, 128.0, 128.9, 129.9, 131.9, 133.8, 135.6, 144.9, 148.2, 148.9, 172.7. Anal. Calcd for $C_{32}H_{37}NO_6S_2$: C, 64.51; H, 6.26; N, 2.35. Found: C, 64.65; H, 6.17; N, 2.33.

2-(3,4-Dimethoxyphenyl)propionaldehyde. To a stirred solution containing 2.5 g (13 mmol) of 2-(3,4-dimethoxyphenyl)-propionitrile in 100 mL of dry toluene at 0 °C was added 20 mL (20 mmol) of a 1.0 M solution of diisobutylalumminum hydride in toluene and the resulting mixture was stirred for 1.5 h. To this mixture was added 60 mL of a 1.0 M tartaric acid solution in ether and the mixture was diluted with 300 mL of ether. The solution was washed with a 10% solution of Rochelle's salt, the two layers were separated, and the aqueous layer was extracted with ether. The organic portion was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography to give 2.4 g (95%) of the titled aldehyde as a colorless oil: IR (neat) 1723 and 1506 cm^{-1}; ^{1}H NMR ($CDCl_3$, 40.0 MHz) δ 1.41 (d, 3H, J = 6.8 Hz), 3.55−3.60 (s, 6H), 6.68 (d, 1H, J = 2.0 Hz), 6.76 (dd, 1H, J = 8.0 and 2.0 Hz), 6.87 (d, 1H, J = 8.4 Hz), and 9.62 (s, 1H); ^{13}C NMR $CDCl_3$, 100 MHz) δ 14.8, 52.7, 56.1, 111.4, 111.7, 120.6, 130.1, 148.6, 149.5, and 201.2. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.01; H, 7.27. Found: C, 68.12; H, 7.09.

***N*-Benzyl-*N*-[2-(3,4-dimethoxyphenyl)propenyl-2-ethylsulfanylacetamide.** To a stirred solution containing 2.4 g (12 mmol) of 2-(3,4-dimethoxyphenyl)propionaldehyde in 90 mL of benzene was added 1.3 g (12 mmol) of benzylamine and the resulting mixture was heated at reflux for 24 h in a flask equipped with a Dean-Stark trap. The solvent was removed under reduced pressure and the crude imine was taken up in 90 mL of CH_2Cl_2 and to this solution was added 2.9 g (37 mmol) of pyridine followed by 1.7 g (12 mmol) of ethylthioacetyl chloride. The mixture was stirred for 2 h at 25 °C, washed with a saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by silica gel chromatography afforded 2.0 g (42%) of *N*-benzyl-*N*-[2-(3,4-dimethoxyphenyl)propenyl]-2-ethylsulfinylacetamide as a yellow oil, which contained a 1:1 mixture of *E*/*Z* isomers. The *E*-isomer exhibited the following spectral properties: IR (neat) 1652, 1517, and 1138 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H, J = 7.4 Hz), 1.86 (d, 3H, J = 1.2 Hz), 2.69 (q, 2H, J = 7.4 Hz), 3.29 (s, 2H), 3.87 (s, 1H), 3.88 (s, 1H), 4.72 (s, 2H), 6.35 (d, 1H, J = 1.2 Hz), 6.82 (s, 1H), 6.83 (d, 1H, J = 8.0 Hz), 6.90 (dd, 1H, J = 8.4 and 2.0 Hz), and 7.27−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 16.0, 26.5, 33.8, 51.2, 56.1, 109.5, 111.2, 118.9, 124.8, 127.6, 128.6, 129.0, 132.5, 137.1, 138.6, 149.0, 149.4, and 170.0. Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.64. Found: C, 68.43; H, 7.02; N, 3.44.

The *Z*-isomer exhibited the following spectral properties: IR (neat) 1655, 1509, and 1262 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H, J = 7.2 Hz), 2.04 (d, 3H, J = 1.2 Hz), 2.64 (q, 2H, J = 7.2 Hz), 3.25 (s, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 4.46 (s, 2H), 6.23 (d, 1H, J = 1.2 Hz), 6.84 (br s, 3H), and 7.20−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 22.1, 26.4, 33.6, 50.3, 56.0, 56.1, 110.3, 111.3, 119.9, 123.7, 127.5, 128.4, 128.6, 129.0, 131.0, 134.1, 137.5, 149.0, and 169.8. Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.64. Found: C, 68.66; H, 7.15; N, 3.58.

(*E*)-*N*-Benzyl-*N*-[2-(3,4-dimethoxyphenyl)propenyl-2-ethylsulfinylacetamide (18). To a stirred solution containing 0.4 g (2.0 mmol) of sodium periodate in 7 mL of H_2O was added 0.4 g (0.1 mmol) of the above *E*-sulfide in 7 mL of methanol. The resulting mixture was stirred for 2 h at 25 °C, extracted with chloroform, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography to give 0.3 g (74%) of α-sulfinyl enamide **18** as a yellow oil: IR (neat) 1514 and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, 3H, J = 7.5 Hz), 1.82 (br s, 3H), 2.78−2.90 (m, 1H), 3.01−3.13 (m, 1H), 3.76 (d, 1H, J = 13.8 Hz), 3.87 (s, 6H), 3.88 (d, 1H, J = 13.8 Hz), 4.68 (d, 1H, J = 13.8 Hz), 4.76 (d, 1H, J = 14.1 Hz), 6.93 (d, 1H, J

= 1.2 Hz), 6.82 (s, 1H), 6.83 (d, 1H, J = 8.4 Hz), and 6.91 (dd, 1H, J = 8.4 and 1.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.7, 16.0, 46.5, 51.2, 55.6, 56.0, 109.2, 110.0, 118.7, 123.4, 127.7, 128.5, 128.9, 131.5, 135.9, 140.2, 148.7, 149.4, and 164.5. Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49. Found: C, 65.77; H, 6.53; N, 3.59.

(*Z*)-*N*-Benzyl-*N*-[2-(3,4-dimethoxyphenyl)propenyl-2-ethylsulfinyl-acetamide (19). To a stirred solution containing 0.24 g (1.1 mmol) of sodium periodate in 7 mL of H_2O was added 0.18 g (0.5 mmol) of the above *Z*-sulfide in 7 mL of methanol. The resulting mixture was stirred for 4 h at room temperature, extracted with chloroform, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography to give 0.16 g (92%) of α-sulfinyl enamide **19** as a yellow oil: IR (neat) 1642, 1509, 1414, and 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, 3H, J = 7.4 Hz), 2.04 (d, 3H, J = 1.2 Hz), 2.57−2.65 (m, 1H), 2.84−2.93 (m, 1H), 3.40 (d, 1H, J = 13.6 Hz), 3.66 (s, 3H), 3.70 (d, 1H, J = 14.4 Hz), 3.84 (s, 3H), 4.49 (d, 1H, J = 14.4 Hz), 4.57 (d, 1H, J = 14.0 Hz), 6.06 (d, 1H, J = 0.8 Hz), 6.62 (d, 1H, J = 1.6 Hz), 6.71 (dd, 1H, J = 8.0 and 2.0 Hz), 6.79 (d, 1H, J = 8.0 Hz). and 7.23−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.6, 22.3, 46.6, 51.2, 56.0, 56.1, 109.9, 111.4, 119.7, 122.8, 127.9, 128.8, 128.9, 130.3, 136.0, 136.1, 149.1, and 164.6. Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49. Found: C, 65.64; H, 6.82; N, 3.61.

1-Benzyl-5-(3,4-dimethoxyphenyl)-3-ethylsulfanyl-4-methyl-1,5-dihydropyrrol-2-one (21). To a solution containing 0.4 g (2.0 mmol) of *p*-TsOH in 35 mL of benzene at 80 °C was added 0.3 g (0.67 mmol) of *E*-enamide in 1 mL of benzene. After being heated at reflux for 20 min, the reaction mixture was cooled to room temperature, washed with a saturated $NaHCO_3$ solution, washed with brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by silica gel chromatography afforded 0.16 g (62%) of lactam **21** as a clear oil: IR (neat) 1680, 1512, 1396, and 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, 3H, J = 7.2 Hz), 1.82 (s, 1H), 2.96−3.05 (m, 1H), 3.11−3.20 (m, 1H), 3.64 (d, 1H, J = 14.8 Hz), 3.79 (s, 3H), 3.91 (s, 3H), 4.55 (s, 1H), 5.16 (d, 1H, J = 14.8 Hz), 6.40 (d, 1H, J = 2.4 Hz), 6.66 (dd, 1H, J = 10.8 and 2.8 Hz), 6.87 (d, 1H, J = 10.8 Hz), 7.12−7.15 (m, 2H), and 7.27−7.35 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 15.8, 26.5, 44.4, 56.1, 67.4, 111.4, 121.0, 125.7, 127.2, 127.6, 128.5, 128.7, 129.5, 137.5, 149.4, 149.8, 158.8, and 169.4. Anal. Calcd for $C_{22}H_{25}NO_3S$: C, 68.90; H, 6.58; N, 3.65. Found: C, 68.83; H, 6.62; N, 3.49.

3-Benzyl-1-ethylsulfanyl-7,8-dimethoxy-5-methyl-1,3-dihydrobenzo[*d*]azepin-2-one (22). To a solution containing 0.23 g (1.2 mmol) of *p*-TsOH in 40 mL of benzene at 80 °C was added 0.17 g (0.4 mmol) of enamide **19** in 1 mL of benzene. After being heated at reflux for 20 min, the reaction mixture was cooled to room temperature, washed with a saturated $NaHCO_3$ solution, then with brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by silica gel chromatography afforded 0.12 g (76%) of the title compound as a colorless oil as a mixture of atropoisomers. IR (neat) 1648, 1512, 1400, and 1258 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 2.17 (d, 3H, J = 1.6 Hz), 2.52 (dt, 2H, J = 7.6 and 7.2 Hz), 3.90 (s, 3H), 3.92 (s, 3H), 4.62 (d, 1H, J = 15.2 Hz), 4.70 (s, 1H), 4.89 (d, 1H, J = 15.2 Hz), 6.05 (s, 1H), 6.78 (s, 1H), 6.87 (s, 1H), 7.16−7.18 (m, 2H), and 7.22−7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 21.4, 25.3, 28.3, 51.2, 56.2, 56.3, 107.8, 111.5, 125.4, 125.5, 127.4, 127.5, 127.7, 128.7, 128.8, 137.0, 148.9, 149.6, and 168.9. Anal. Calcd for $C_{22}H_{25}NO_3S$: C, 68.90; H, 6.58; N, 3.65. Found: C, 68.75; H, 6.50; N, 3.58.

3-Benzyl-7,8-dimethoxy-5-methyl-1,3-dihydrobenzo[*d*]-azepin-2-one (23). To a solution containing 0.05 g (0.12 mmol) of **22** in 20 mL of a 1:1 mixture of THF/EtOH was added an excess of Raney Nickel. The reaction mixture was stirred at 25 °C for 30 min and then filtered through Celite. The solvent was removed under reduced pressure to give 0.04 g (90%) of **23** as a clear oil: IR (neat) 1659, 1510, 1356, 1261, and 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.14 (d, 2H, J = 1.2 Hz), 3.50 (s, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 4.70 (s, 2H), 6.12 (d, 1H, J = 1.2 Hz), 6.83 (s, 1H), 6.86 (s, 1H), 7.06−7.09 (m, 2H), and 7.21−7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 42.9, 50.0, 55.9, 56.0, 108.0, 110.9, 125.2, 125.5, 125.8, 127.2, 127.3, 128.5, 128.7, 137.0, 147.9, 149.8, and 168.7. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.27; H, 6.55; N, 4.33. Found: C, 74.20; H, 6.43; N, 4.22.

2-[4-(*tert*-Butyldimethylsilanyloxy)butyl]-3-hydroxy-acrylic Acid Methyl Ester (34). A solution containing 9.6 g (37 mmol) of 6-(*tert*-butyldimethylsilanoxy)hexanoic acid methyl ester[59] in 30 mL of THF was added dropwise to a solution of LDA prepared from 19 mL (48 mmol) of 2.5 M *n*-BuLi in hexane and 6.2 mL (44 mmol) of diisopropylamine in 130 mL of THF at −78 °C. The reaction mixture was stirred for 1 h then treated with 3.9 mL (48 mmol) of ethyl formate. The solution was stirred for an additional 2 h while warming to room temperature, quenched with H_2O, and extracted with hexane to remove any impurities. The aqueous layer was acidified with 10% HCl and extracted with CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to afford 10.1 g (95% yield) of aldehydic ester **34** as a pale yellow oil: IR (neat) 1723, 1670, 1444, and 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.01 (s, 6H), 0.09 (s, 6H, enol), 0.85 (s, 9H), 0.9 (s, 9H, enol), 1.33−1.55 (m, 4H), 1.84−1.88 (m, 2H, enol), 2.04−2.06 (t, 2H, J = 7.5 Hz), 2.39−2.41 (m, 1H, enol), 3.23−3.27 (td, 1H, J = 7.6 and 2.4 Hz, enol), 3.57−3.59 (t, 2H, J = 7.5 Hz), 3.66 (s, 3H, enol), 3.74 (s, 3H), 6.95−6.98 (d, 1H, J = 12.6 Hz, enol), 9.66 (s, 1H), 11.33−11.36 (d, 1H, J = 12.6 Hz, enol); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.0, 18.6, 26.2, 26.3, 27.4, 32.5, 51.5, 63.1, 104.7, 160.9, and 172.8; HRMS calcd for $C_{14}H_{28}O_4Si$ 288.1757, found 288.1757.

2-[4-(*tert*-Butyldimethysilanyloxy)butyl]-3-[[2-(3,4-dimethoxyphenyl)ethyl](2-ethylsulfanylacetyl)amino]-acrylic Acid Methyl Ester (37). A solution of 8.9 g (31 mmol) of aldehyde **34** and 6.2 g (34 mmol) of 3,4-dimethoxyphenethylamine in 125 mL of benzene was heated at reflux overnight using a Dean−Stark water trap. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude enamine was taken up in 100 mL of CH_2Cl_2 and treated with 3.2 g (40 mmol) of pyridine. To the resulting solution was added 40 mmol of ethylsulfanyl acetyl chloride[48] in 25 mL of CH_2Cl_2 and the solution was stirred at room temperature for an additional 2 h. The reaction mixture was quenched with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layer was washed with NH_4Cl and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 15.9 g (92% yield) of **37** as a 1:4 *E*/*Z* mixture of isomers: IR (film) 1716, 1669, 1511, and 1255 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) *E*-isomer δ 0.03 (s, 6H), 0.87 (s, 9H), 1.21 (t, 3H, J = 7.4 Hz), 1.45−1.49 (m, 4H), 2.25−2.28 (t, 2H, J = 6.8 Hz), 2.55−2.60 (q, 2H, J = 7.4 Hz), 2.73−2.76 (t, 2H, J = 7.5 Hz), 3.25 (s, 2H), 3.57−3.60 (t, 2H, J = 6.0 Hz), 3.64−3.68 (t, 2H, J = 7.5 Hz), 3.70 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 6.36 (s, 1H), and 6.69−6.77 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *E*-isomer, δ −5.0, 14.5, 18.5, 25.2, 26.1, 26.3, 32.0, 32.4, 33.7, 50.3, 52.2, 56.0, 62.8, 111.3, 112.1, 120.9, 131.5, 134.1, 147.7, 149.0, 160.0, and 169.3; ^{1}H NMR ($CDCl_3$, 400 MHz) *Z*-diastereomer, δ 0.01 (s, 6H), 0.85 (s, 9H), 1.22−1.26 (m, 5H), 1.48−1.49 (m, 4H), 2.27−2.30 (t, 2H, J = 7.0 Hz), 2.55−2.61 (q, 2H, J = 7.4 Hz), 2.76−2.80 (t, 2H, J = 7.6 Hz), 3.21 (s, 2H), 3.54−3.57 (t, 2H, J = 5.6 Hz), 3.76 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 6.71−6.78 (m, 3H), and 7.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *Z*-isomer, δ −5.1, 14.4, 14.8, 18.4, 21.0, 24.7,

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25.7, 26.3, 26.6, 33.0, 33.8, 34.2, 44.9, 52.2, 52.3, 56.0, 62.4, 62.7, 71.8, 111.3, 112.1, 120.7, 120.9, 131.3, 137.7, 145.4, 149.0, 165.4, and 171.0. Anal. Calcd for $C_{28}H_{47}NO_6SSi$: C, 60.73; H, 8.56; N, 2.53. Found: C, 60.59; H, 8.41; N, 2.54.

2-[4-(*tert*-Butyldimethylsilanyloxy)butyl]-3-[[2-(3,4-dimethoxyphenyl)ethyl](2-ethanesulfinylacetyl)amino]-acrylic Acid Methyl Ester (40). To a solution of 6.7 g (12 mmol) of **37** in 100 mL of a 4:1 mixture of MeOH/H_2O was added 3.9 g (18 mmol) of $NaIO_4$ and the resulting solution was stirred at room temperature for 2 h. A white precipitate appeared after 30 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash silica gel chromatography afforded 4.8 g (68% yield) of a 1:3 mixture of *E*/*Z* isomers of sulfoxide **40** as a colorless oil: IR (film) 1716, 1664, 1511, and 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ −0.05 (s, 6H, minor isomer), −0.02 (s, 6H, major isomer), 0.79 (s, 9H, minor isomer), 0.82 (s, 9H, major isomer), 1.26−1.30 (t, 2H, J = 7.6 Hz), 1.41−1.48 (m, 5H), 2.22−2.27 (m, 2H), 2.68−2.76 (m, 4H), 2.85−2.96 (m, 1H), 3.51−3.78 (m, 7H), 3.66 (s, 3H), 3.70 (s, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 6.20 (s, 1H, major isomer), 6.64−6.74 (m, 3H), and 7.13 (s, 1H, minor isomer); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.1, 6.7, 18.5, 24.7, 25.2, 26.1, 27.1, 31.9, 32.4, 33.1, 33.5, 33.7, 46.5, 49.6, 50.1, 52.4, 55.7, 55.8, 56.0, 62.6, 62.7, 111.3, 112.0, 120.9, 130.5, 131.0, 132.1, 133.5, 134.4, 136.8, 147.8, 147.9, 149.1, 164.4, 166.5, and 167.1; HRMS calcd for $C_{28}H_{47}NO_7SSi$ 569.2843, found 569.2849.

3-[[2-(3,4-Dimethoxyphenyl)ethyl](2-ethanesulfinylacetyl)amino]-2-(4-hydroxybutyl)acrylic Acid Methyl Ester (41). To a solution of 30.1 g (54 mmol) of **37** in 1 L of MeOH was added 58.2 g (272 mmol) of $NaIO_4$ in 200 mL of H_2O. The resulting mixture was stirred at room temperature for 16 h and then diluted with H_2O. The mixture was extracted with CH_2Cl_2 and the organic layers were combined and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by silica gel flash chromatography afforded 18.7 g (75% yield) of the 1:4 mixture *E*/*Z*-sulfoxide **41** as a pale-yellow oil: IR (film) 3411, 1716, 1654, 1623, 1516, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27−1.31 (t, 3H, J = 7.2 Hz), 1.49−1.50 (m, 5H), 2.36−2.45 (m, 2H), 2.74−2.78 (t, 2H, J = 7.6 Hz), 2.82−3.00 (m, 1H), 3.53−3.56 (m, 2H), 3.64−3.77 (m, 4H), 3.72 (s, 3H), 3.77 (s, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 6.26 (s, 1H), and 6.68−6.78 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 26.8, 32.5, 33.6, 46.4, 49.7, 52.5, 53.6, 55.6, 56.0, 61.9, 111.4, 112.0, 120.9, 130.5, 132.3, 136.9, 148.0, 149.1, 164.4, and 167.1. Anal. Calcd for $C_{22}H_{33}NO_7S$: C, 58.00; H, 7.31; N, 3.08. Found: C, 57.91; H, 7.23; N, 2.84.

2-(4-Bromobutyl)-3-[[2-(3,4-dimethoxyphenyl)ethyl](2-ethylsulfanylacetyl)amino]acrylic Acid Methyl Ester. To a solution of 1.8 g (4.0 mmol) of alcohol **41** in CH_2Cl_2 at room temperature was added 4.0 g (12 mmol) of carbon tetrabromide. The resulting solution was stirred at room temperature for 10 min followed by the addition of 3.1 g (12 mmol) of triphenyl phosphine in several portions. The resulting mixture was stirred at room temperature for 1 h followed by quenching with water and extraction with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography to provide 1.6 g (83% yield) of the titled compound as a 1:4 mixture of E/Z isomers: IR (neat) 1706, 1655, 1629, 1511, 1440, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.27 (t, 3H, J = 7.3 Hz), 1.55−1.62 (m, 2H), 1.79−1.85 (m, 2H), 2.26−2.30 (m, 2H), 2.56−2.61 (q, 2H, J = 7.3 Hz), 2.77−2.81 (t, 2H, J = 7.4 Hz), 3.21 (br s, 2H), 3.34−3.40 (m, 3H), 3.76 (s, 3H), 3.77−3.79 (m, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 6.70−6.78 (m, 3H), and 7.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 26.3, 26.4, 26.8, 32.6, 32.8, 33.3, 33.6, 33.8, 43.8, 52.4, 56.1, 111.5, 112.1, 120.9, 127.6, 130.8, 138.2, 147.9, 149.2, 167.7, and 169.4; HRMS calcd for $C_{22}H_{32}BrNO_5S$ 501.1185, found 501.1184.

2-(4-Bromobutyl)-3-[[2-(3,4-dimethoxyphenyl)ethyl](2-ethanesulfinylacetyl)amino]acrylic Acid Methyl Ester (52). To a solution of 1.4 g of the above sulfide in 50 mL of a 4:1 mixture of MeOH/H_2O was added 0.9 g of $NaIO_4$ and the resulting solution was stirred at room temperature for 16 h. A white precipitate appeared after several hours. The mixture was stirred for an additional 14 h to ensure full consumption of the starting material. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash silica gel chromatography afforded 1.2 g (88%) of bromosulfoxide **52** as a 1:4 mixture of *E*/*Z*-isomers as a light-yellow oil: IR (neat) 1711, 1660, 1629, 1511, 1261, and 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32−1.36 (t, 3H, J = 7.4 Hz), 1.53−1.61 (m, 4H), 1.82−1.89 (m, 2H), 2.28−2.32 (m, 2H), 2.74−2.83 (m, 3H), 2.93−3.00 (m, 1H), 3.39−3.42 (t, 2H, J = 6.6 Hz), 3.68 (s, 2H), 3.73 (s, 3H), 3.79 (s, 3H, minor isomer) 3.84 (s, 3H), 3.85 (s, 3H), 6.27 (s, 1H), 6.70−6.79 (m, 3H), and 7.22 (s, 1H, minor isomer); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.7, 26.4, 26.7, 27.4, 31.2, 31.3, 32.3, 32.7, 33.3, 33.6, 33.8, 46.6, 49.7, 50.4, 52.5, 55.7, 56.1, 111.4, 112.1, 120.9, 130.5, 131.1, 133.1, 134.5, 137.4, 147.9, 149.2, and 164.5. Anal. Calcd for $C_{22}H_{32}BrNO_6S$: C, 51.05; H, 6.24; N, 2.71. Found: C, 50.92; H, 6.09; N, 2.55.

1-(4-Bromobutyl)-2-ethylsulfanyl-8,9-dimethoxy-3-oxo-1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinoline-1-carboxylic Acid Methyl Ester (27). To a refluxing solution containing 3.1 g (13 mmol) of camphorsulfonic acid in 100 mL of benzene was added 1.7 g (3.3 mmol) of sulfoxide **52** in 30 mL of benzene. The reaction mixture was heated at reflux for 30 min, cooled to room temperature, and quenched with a saturated $NaHCO_3$ solution. The aqueous solution was extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed under reduced pressure followed by silica gel chromatography to give the tricyclic ring system as a 5:2:1:1 mixture of four diastereomers. One of the minor diastereomers (**27b**) was obtained (0.1 g, 8% yield) as a pale-yellow solid: mp 111−114 °C; IR (film) 1726, 1690, 1516, and 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95−1.07 (m, 2H), 0.87−1.22 (m, 1H), 1.22−1.26 (t, 3H, J = 7.4 Hz), 1.33−1.48 (m, 3H), 1.53−1.60 (m, 1H), 2.59−2.63 (m, 1H), 2.73−2.85 (m, 3H), 3.05−3.10 (m, 2H), 3.26 (s, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 4.34−4.38 (m, 1H), 5.47 (s, 1H), 6.55 (s, 1H), and 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 23.3, 26.7, 28.9, 33.0, 33.1, 33.3, 37.3, 52.5, 53.1, 56.0, 56.1, 59.2, 59.4, 110.8, 111.9, 123.6, 127.6, 147.9, 148.3, 169.7, and 172.7. Anal. Calcd for $C_{22}H_{30}BrNO_5S$: C, 52.80; H, 6.04; N, 2.80. Found: C, 52.60; H, 6.07; N, 2.75.

Diastereomers **27d** and **27c** (0.4 g, 22% yield) could not be fully separated and the 2:1 mixture showed the following spectral properties: IR (film) 2934, 2858, 1716, 1705, 1511, and 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18−1.22 (t, 3H, J = 7.6 Hz), 1.23−1.27 (t, 3H, J = 7.2 Hz), 1.28−1.35 (m, 2H), 1.53−2.03 (m, 6H), 2.27−2.41 (m, 1H), 2.45−2.54 (m, 1H), 2.55−2.80 (m, 4H), 2.86−2.95 (m, 2H), 3.00−3.07 (m, 1H), 3.15 (s, 3H), 3.34−3.38 (t, 2H, J = 6.8 Hz), 3.53 (s, 1H), 3.73 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.22 (s, 1H), 4.25−4.29 (m, 1H), 4.34−4.36 (m, 1H), 4.73 (s, 1H), 5.09 (s, 1H), 6.46 (s, 1H), 6.49 (s, 1H), 6.53 (s, 1H), and 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 14.9, 22.5, 24.1, 25.6, 27.6, 27.9, 28.6, 28.8, 31.1, 33.3, 33.4, 33.5, 37.5, 37.8, 48.9, 52.1, 53.2, 55.3, 55.9, 56.0, 56.3, 59.6, 60.9, 64.0, 108.7, 110.2, 111.8, 112.2, 123.0, 123.2, 126.9, 127.9, 147.6, 147.8, 148.3, 148.4, 169.6, 171.5, 172.5, and 175.3.

The major diastereomer **27a** was isolated (0.8 g, 58% yield) as a white solid, mp 49−51 °C; IR (film) 1713, 1695, 1512, and 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23−1.27 (t, 3H, J = 7.4 Hz), 1.67−1.71 (m, 1H), 1.84−2.06 (m, 3H), 2.17−2.22 (m, 2H), 2.48−2.52 (m, 1H), 2.67−2.85 (m, 4H), 3.14 (s, 3H), 3.48−3.53 (m, 2H), 3.54 (s, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.36−4.04 (dd, 1H, J = 13 and 4.0 Hz), 4.77 (s, 1H), 6.51 (s, 1H), and 6.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2, 23.1, 28.2,

28.7, 32.1, 32.8, 33.6, 38.1, 51.3, 53.0, 55.9, 56.3, 59.8, 60.0, 108.8, 111.8, 123.9, 127.8, 128.6, 128.7, 132.1, 132.3, 147.7, 148.2, 170.7, and 170.8. Anal. Calcd for $C_{22}H_{30}BrNO_5S$: C, 52.80; H, 6.04; N, 2.80. Found: C, 52.82; H, 6.09; N, 2.74.

8*a*-Ethylsulfanyl-2,3-dimethoxy-8-oxo-5,8,8*a*,9,10,11,12,12*b*-octahydro-6*H*-isoindolo[1,2-*a*]isoquinoline-12*a*-carboxylic Acid Methyl Ester (28a). To a solution of 0.63 g (1.3 mmol) of bromide **27a** in 40 mL of THF was added 0.13 g (3.1 mmol) of NaH (60% in oil) and the resulting mixture was heated at reflux for 4 h. The mixture was cooled to room temperature and quenched with water. The aqueous layer was extracted with CH_2Cl_2 and dried over $MgSO_4$. Flash silica gel chromatography provided 0.5 g (99% yield) of the titled compound as a white solid: mp 153−156 °C; IR (film) 1726, 1705, 1516, 1429, and 1296 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.25 (t, 3H, J = 7.6 Hz), 1.66−1.68 (m, 3H), 1.75−1.79 (m, 2H), 1.95−1.98 (m, 1H), 2.21−2.30 (m, 2H), 2.54−2.57 (m, 1H), 2.81−2.88 (m, 3H), 3.06−3.11 (dd, 1H, J = 11 and 7.6 Hz), 3.22 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.39−4.41 (m, 1H), 5.02 (s, 1H), and 6.58 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 19.9, 21.9, 22.8, 26.0, 28.3, 32.1, 37.5, 51.3, 56.0, 56.3, 56.5, 56.9, 58.7, 108.8, 111.9, 124.4, 128.4, 147.7, 148.1, 171.7, and 175.6. Anal. Calcd for $C_{22}H_{29}NO_5S$: C, 62.98; H, 6.97; N, 3.34. Found: C, 62.81; H, 6.73; N, 3.27.

8*a*-Ethylsulfanyl-2,3-dimethoxy-8-oxo-5,8,8*a*,9,10,11,12,12*b*-octahydro-6*H*-isoindolo[1,2-*a*]isoquinoline-12*a*-carboxylic Acid Methyl Ester (28b). A solution of 0.1 g (0.2 mmol) of bromide **27d** in 2 mL of anhydrous THF was treated with 0.02 g (0.4 mmol) of NaH (60% in oil). The resulting mixture was heated at reflux for 2 h, cooled to room temperature, and quenched with water. The aqueous layer was extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash silica gel chromatography of the residue afforded 0.02 g (21% yield) of the titled compound as a white solid: mp 144−146 °C; IR (film) 1726, 1690, 1516, 1424, and 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.77−0.85 (td, 1H, J = 14 and 5.0 Hz), 1.06−1.11 (m, 1H), 1.13−1.18 (t, 3H, J = 7.6 Hz), 1.23−1.25 (m, 1H), 1.34−1.37 (m, 1H), 1.64−1.75 (m, 2H), 1.76−1.84 (td, 1H, J = 14 and 5.0 Hz), 2.46−2.49 (m, 1H), 2.63−2.66 (m, 1H), 2.67−2.73 (q, 2H, J = 7.6 Hz), 2.78−2.85 (td, 1H, J = 12 and 4.5 Hz), 2.89−2.96 (td, 1H, J = 12 and 4.5 Hz), 3.79 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.39−4.44 (dd, 1H, J = 14 and 4 Hz), 5.54 (s, 1H), 6.56 (s, 1H), and 7.13 (s, 1H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 21.1, 23.0, 23.3, 29.2, 29.9, 37.3, 52.3, 55.6, 55.9, 56.0, 57.1, 59.3, 110.4, 111.6, 124.1, 128.0, 147.9, 169.4, and 173.4. Anal. Calcd for $C_{22}H_{29}NO_5S$: C, 62.98; H, 6.97; N, 3.34. Found: C, 62.67; H, 6.84; N, 3.24.

8*a*-Ethanesulfinyl-2,3-dimethoxy-8-oxo-5,8,8*a*,9,10,11,12,12*b*-octahydro-6*H*-isoindolo[1,2-*a*]isoquinoline-12*a*-carboxylic Acid Methyl Ester. A solution containing 0.7 g (1.7 mmol) of sulfide **28a** in 25 mL of a 4:1 mixture of MeOH/H_2O was treated with 1.1 g (5.0 mmol) of $NaIO_4$ at room temperature. The mixture was stirred at 25 °C for 16 h, diluted with H_2O, and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.65 g (90% yield) of the titled compound as a white solid: mp 131−132 °C; IR (film) 1720, 1691, 1513, 1453, 1296, and 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42−1.46 (t, 3H, J = 7.6 Hz), 1.68−1.72 (m, 2H), 1.85−1.90 (m, 2H), 1.99−2.10 (m, 1H), 2.40−2.44 (m, 2H), 2.52−2.55 (m, 1H), 2.77−2.84 (m, 3H), 3.01−3.06 (dd, 1H, J = 13 and 7.6 Hz), 3.22 (s, 3H), 3.29−3.35 (dd, 1H, J = 13 and 7.6 Hz), 3.84 (s, 3H), 3.86 (s, 3H), 4.32−4.34 (m, 1H), 5.08 (s, 1H), 6.58 (s, 1H), and 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6, 20.6, 21.2, 26.6, 28.4, 28.5, 37.7, 43.9, 51.7, 56.0, 56.4, 57.9, 58.4, 66.1, 109.4, 111.9, 123.3, 128.5, 147.8, 148.5, 171.3, and 171.6. Anal. Calcd for $C_{22}H_{29}NO_6S$: C, 60.67; H, 6.71; N, 3.22. Found: C, 60.64; H, 6.52; N, 3.12.

2,3-Dimethoxy-8-oxo-5,8,10,11,12,12*b*-hexahydro-6*H*-isoindolo[1,2-*a*]isoquinoline-12*a*-carboxylic Acid Methyl Ester (53). A solution of 1.2 g (2.8 mmol) of the above sulfoxide in 100 mL of toluene was heated at reflux for 16 h and then cooled to room temperature. The solvent was removed under reduced pressure and the crude product was purified by flash silica gel chromatography to give 1.0 g (98% yield) of **53** as a white solid: mp 155−157 °C; IR (film) 1731, 1685, 1516, 1429, and 1224 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.52−1.69 (m, 2H), 1.87−1.92 (m, 1H), 2.13−2.29 (m, 2H), 2.55−2.59 (m, 1H), 2.72−2.80 (m, 1H), 2.83−2.89 (m, 2H), 3.13 (s, 3H), 3.79 (s, 3H), 3.82 (3H), 4.41−4.45 (dd, 1H, J = 12 and 4.4 Hz), 4.58 (s, 1H), 6.54 (s, 1H), 6.57 (s, 1H), and 6.59−6.61 (t, 1H, J = 3.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5, 24.4, 28.3, 30.1, 37.2, 51.6, 53.9, 55.9, 56.1, 65.1, 109.2, 111.5, 123.7, 127.4, 130.5, 134.6, 147.7, 148.2, 167.0, and 171.1; HRMS calcd for $C_{20}H_{23}NO_5$ 357.1576, found 357.1578. Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.08; H, 6.50; N, 3.84.

2,3-Dimethoxy-8-thioxo-5,8,10,11,12,12*b*-hexahydro-6*H*-isoindolo[1,2-*a*]isoquinoline-12*a*-carboxylic Acid Methyl Ester (54). To a solution of 0.4 g of lactam **53** in 4 mL of THF was added 1.0 g of Lawesson's reagent at room temperature and the resulting yellow solution was stirred at 25 °C for 18 h. The solution was taken up in ether resulting in the formation of yellow precipitate, which was subsequently filtered. Concentration of the filtrate under reduced pressure followed by flash silica gel chromatography provided 0.2 g (61% yield) of thiolactam **54** as a yellow solid: mp 185−186 °C; IR (film) 1726, 1669, 1603, 1511, 1465, and 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57−1.65 (m, 1H), 1.66−1.75 (m, 1H), 1.93−1.98 (m, 1H), 2.18−2.27 (m, 1H), 2.28−2.38 (m, 1H), 2.69−2.74 (m, 1H), 2.85−2.96 (m, 2H), 3.14−3.21 (m, 1H), 3.17 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.80 (s, 1H), 5.23−5.28 (ddd, 1H, J = 13.0, 4.4, and 1.6 Hz), 6.60−6.61 (d, 2H, J = 2.8 Hz), and 6.98−6.99 (t, 1H, J = 3.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 24.9, 28.0, 30.2, 42.6, 51.8, 55.6, 56.0, 56.2, 71.2, 108.9, 111.4, 122.1, 127.1, 134.2, 141.3, 148.0, 148.6, 170.6, and 192.7. Anal. Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.23; H, 6.14; N, 3.82.

(±)-Jamtine (25). A solution containing 0.2 g (0.4 mmol) of thiolactam **54** in 2 mL of THF was treated with 0.1 g (0.4 mmol) of Meerwein's salt at 0 °C. The resulting yellow-orange solution was stirred at 0 °C for 5 min and then at room temperature for an additional 1 h. The solvent was removed under reduced pressure and the residue was taken up in MeOH and cooled to 0 °C. To this solution was added 0.04 g (1.2 mmol) of $NaBH_4$ and the resulting mixture was warmed to room temperature over a 2-h period. The solution was quenched with 10% HCl, stirred for 5 min at room temperature, and then neutralized with a 10% NaOH solution. The crude mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. Silica gel chromatography afforded 0.1 g (61% yield) of (±)-jamtine **25** as a pale yellow solid: mp 102−104 °C; IR (film) 1726, 1613, 1521, and 1260; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.51−1.54 (m, 2H), 1.83−1.85 (m, 1H), 2.09−2.10 (m, 2H), 2.47−2.49 (dt, 1H, J = 15.6 and 3.2 Hz), 2.51−2.53 (t, 1H, J = 3.2 Hz), 2.69−2.91 (m, 2H), 3.06−3.11 (m, 1H), 3.27 (s, 3H), 3.38−3.41 (dd, 1H, J = 12 and 1.8 Hz), 3.82 (s, 3H), 3.83 (s, 1H), 3.85 (s, 3H), 3.95−3.98 (dd, 1H, J = 12 and 1.8 Hz), 5.69 (br s, 1H), 6.55 (s, 1H), and 6.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 24.5, 27.4, 32.1, 48.0, 51.6, 55.9, 56.1, 57.0, 57.2, 71.4, 110.2, 111.2, 121.3, 127.1, 128.6, 138.0, 146.8, 147.5, and 173.6. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.76; H, 7.22; N, 3.97.

(±)-Jamtine-*N*-oxide (55). To a solution containing 0.1 g (0.3 mol) of jamtine (**25**) in 1.5 mL of CH_2Cl_2 at 0 °C was added 0.06 g (0.4 mmol) of MCPBA. The reaction mixture was stirred at room temperature for 2 h and then quenched with water. The organic layer was extracted with $CHCl_3$ and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Silica gel chromatography afforded 0.09 g (95% yield) of **55** as a pale yellow oil: IR (film) 1726, 1234, and 1122 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49−1.54 (m, 1H), 1.77−1.84 (t, 1H, J = 14 Hz), 1.91−1.94 (m, 1H), 2.15−2.24 (m, 2H), 2.76−2.85 (m,

2H), 3.20−3.25 (m, 1H), 3.28 (s, 3H), 3.80−3.81 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.43−4.46 (d, 1H, J = 13.6 Hz), 4.82 (s, 1H), 4.88−4.91 (d, 1H, J = 13.6 Hz), 6.00 (s, 1H), 6.59 (s, 1H), and 6.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5, 24.3, 25.8, 33.0, 52.2, 56.2, 56.3, 58.0, 64.1, 76.5, 90.3, 110.2, 111.6, 121.9, 125.1, 127.7, 131.1, 148.0, 148.7, and 172.1. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.72; H, 6.94; N, 3.87.

To a solution containing 0.03 g (0.09 mmol) of **55** in 8 mL of CH_2Cl_2 was added 1.6 mL (18 mmol) of PCl_3. The resulting yellow reaction mixture was heated at reflux for 15 min, cooled to 0 °C, and quenched with a dilute NH_4OH solution. The organic layer was extracted with $CHCl_3$ and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Silica gel chromatography afforded 0.03 g (78% yield) of pure jamtine (**25**).

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Supporting Information Available: Spectroscopic and experimental procedures for compounds **30**, **32**, **33**, **35**, **36**, **38**, **39**, **42**−**45**, **47**, **48**, **50**, and **51** and ^{1}H and ^{13}C NMR spectra for new compounds lacking elemental analyses together with ORTEP drawings for structures **25**, **28a**, **28b**, **42**, and **54**. This material is available free of charge via the Internet at http://pubs.acs.org. The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre.

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