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A NEW CONSTRUCT OF THE *CIS*-3*a*-ARYLOCTAHYDROINDOLE SKELETON *VIA* THE [4+2] CYCLOADDITION OF FURANYL CARBAMATES‡

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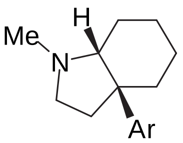
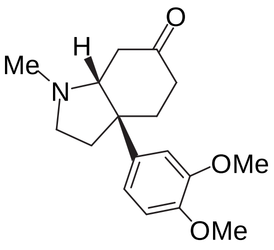
Abstract - Several 2-methylthio-5-amidofurans containing tethered unsaturation were prepared *via* the reaction of dimethyl(methylthio)-sulfonium tetrafluoroborate (DMTSF) with β-alkoxy-γ-dithiane amides. Thermolysis of these furans resulted in an intramolecular Diels-Alder reaction (IMDAF). The resulting oxa-bridged cycloadducts underwent a subsequent rearrangement to form bicyclic lactams. Model studies were directed toward mesembrine as well as the core skeleton of the 3,4-benzoerythrinane skeleton. Using this cascade sequence, a formal synthesis of the alkaloid erysotrine was accomplished.

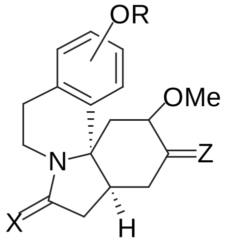
The *cis*-3*a*-arylhydroindole skeleton (**1**) is a basic structural element of the *Sceletium* alkaloids[1] and is also a key subunit of the *Erythrina* family of alkaloids.[2] These alkaloids constitute a large family of natural products that have attracted considerable attention over the years due to their diverse and interesting structures.[3] The *Sceletium* alkaloid mesembrine[4] (**2**) can be regarded as a structural prototype for the more complex members of this family. The vast majority of naturally occurring *Erythrina* alkaloids possess the tetracyclic framework and substitution pattern shown in structure (**3**).[5] The sterically congested quaternary carbon centers represent a particular challenge toward the synthesis of both these natural products. A number of creative strategies have emerged over the



1; *cis*-3*a*-arylocta-hydroindole ring system



2; mesembrine



3; erythrine series
X or Z = O; R = Me

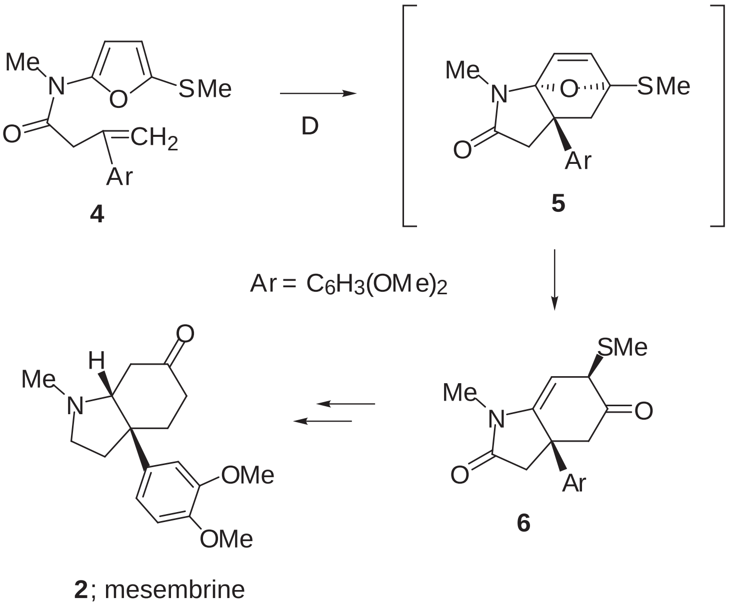
years to address this problem. Total syntheses of members of both classes of the above families have been reported by many different groups,[6,7] as have a number of important approaches to the characteristic core ring system.[8] Despite the availability of many synthetic methods, there still exists a need to develop procedures more efficient than those currently in existence.

Several years ago we began a synthetic program designed to provide general access to these alkaloids by [4+2] cycloaddition chemistry of furanyl carbamates.[9] The plan for assembling the requisite *cis*-3*a*-arylhydroindole skeleton was to take advantage of an intramolecular Diels-Alder[10] reaction of an alkenyl-substituted 2-amidofuran derivative (IMDAF), as had been outlined in earlier reports from these laboratories. Because initial studies into the cycloaddition chemistry of these furans were promising,[11] a more detailed investigation has been conducted. The results of these inquiries are reported herein.

Results and Discussion

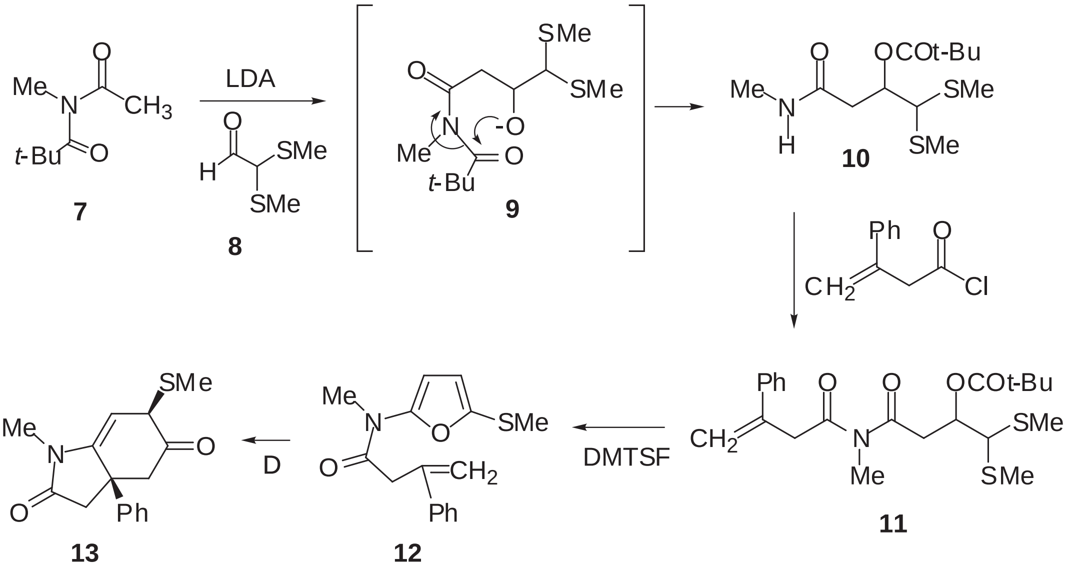
The convergency and stereochemical control associated with the IMDAF reaction sequence of furanyl carbamates make it particularly suited for the assembly of natural product scaffolds. Our preliminary studies were directed toward mesembrine (**2**) as well as the core skeleton of the erythrina family (*vide infra*). The key step in our plan for mesembrine involves the IMDAF reaction of furan (**4**) as outlined in Scheme 1. To pursue this approach, we decided to first evaluate the scope and generality of the cascade sequence by carrying out a model study using the simpler phenyl substituted system (**12**). The required furan (*i.e.*, **12**) necessary for the intramolecular [4+2] cycloaddition studies was prepared by a dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) induced cyclization of imido

Scheme 1



dithioacetal (**11**) (*vide infra*).[12] This approach was devised by assuming that it should be possible to induce cyclization of the imide carbonyl group onto the resulting thionium ion formed from the DMTSF reaction of the dithioacetal. It is known that treatment of thioketals with DMTSF[13] causes the carbon-sulfur bond to become labile upon methylthiolation.[14] The resulting alkylthiosulfonium ion easily dissociates to produce a thionium ion and methyl disulfide.[15] Once the dihydrofuran ring has been forged, elimination of acetic acid (or its equivalent) should proceed readily to furnish the 2-alkylthio-amidofuran. We found that treating *N*-pivaloyl-*N*-methylacetamide (**7**) with LDA followed by reaction with *bis*(methylsulfanyl)- acetaldehyde[16] (**8**) furnished the cross-aldol intermediate (**9**), which underwent a rapid *N-O* acyl transfer reaction to provide the secondary amide (**10**) upon aqueous workup. Attempts to acylate this amide under basic conditions (*i.e.*, Et$_3$N, DMAP, *etc.*) resulted only in elimination of the pivolate. Using 4Å molecular sieves as a neutral acid scavenger,[17] however, resulted in the formation of imide (**11**) in good yield (Scheme 2). Treatment of **11** with DMTSF produced the desired 2-alkylthio-5-amidofuran (**12**) in 60%

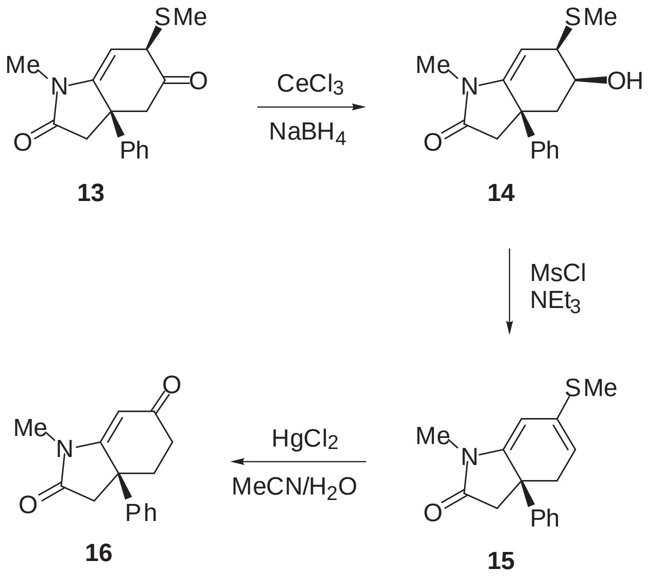
Scheme 2



yield. Heating a sample of **12** at 80 ^{o}C for 8 h afforded the rearranged lactam (**13**) as a single diastereomer in 61% yield. We then investigated the 1,2-carbonyl transposition of **13** so as to prepare the core skeleton of mesembrine. Ketone (**13**) was first reduced using Luche conditions[18] to the expected alcohol (**14**). Treatment of **14** with mesyl chloride and triethylamine furnished dienyl sulfide (**15**) which was easily hydrolyzed to ketone (**16**) using mercuric chloride in 3:1-acetonitrile/water[19] in 62% yield (Scheme 3). The facility of the *cycloaddition/carbonyl transposition sequence* using this model system provides a solid basis for applying the method to mesembrine (**2**). Studies along these lines are currently underway and will be reported in due course.

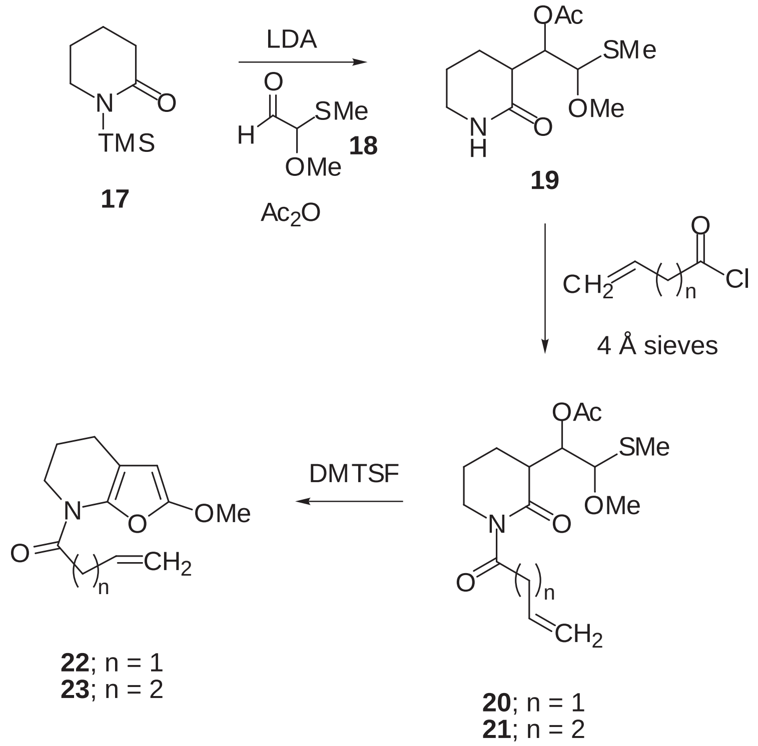
With a satisfactory method for the synthesis of the furan precursors in place, we became

Scheme 3



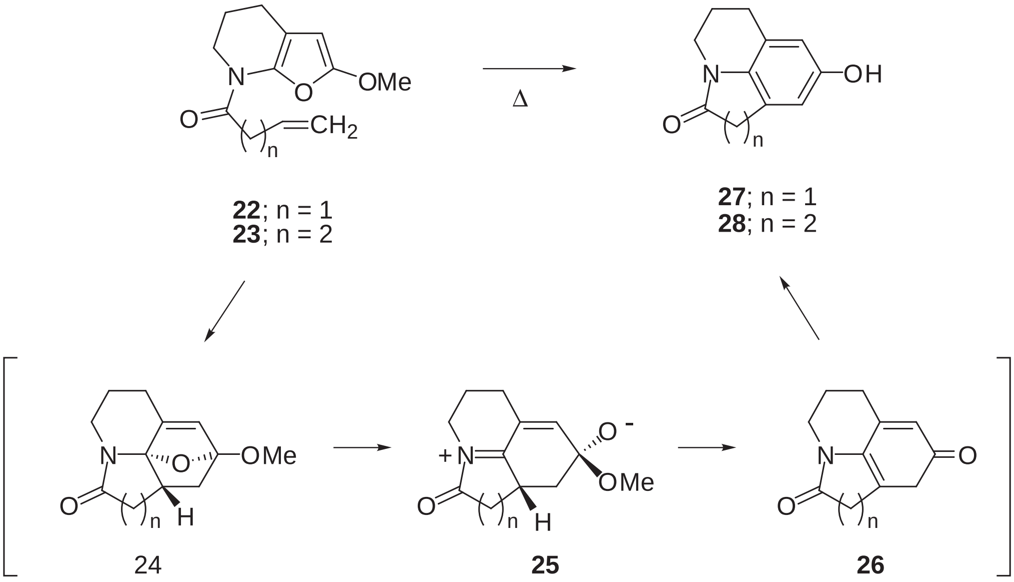
interested in evaluating the cycloaddition behavior of the closely related 2-methoxy-5-amidofuranyl system. Incorporation of an electron-donating group onto the 2-position of furan had been previously used as a means to enhance the reactivity of the 6π-heteroaromatic nucleus.[20] MO calculations show that the presence of a methoxy group in the 2-position of the furan ring increases its HOMO energy relative to that of the 2-thiomethyl substituted furan.[21] Consequently, one might expect that the 2-methoxy substituted system

Scheme 4



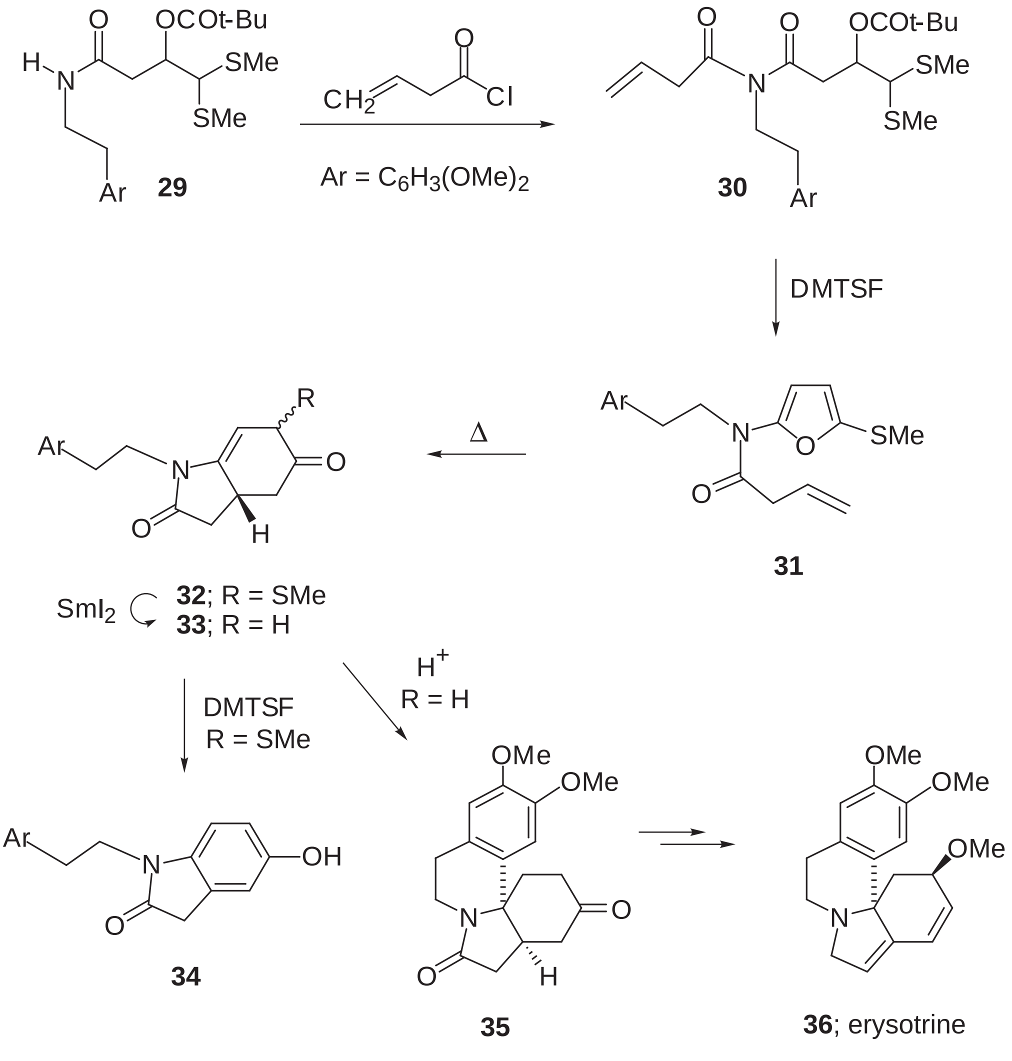
would exhibit higher reactivity in the IMDAF process, but would probably be less prone to undergo a subsequent 1,2-methoxy shift. Accordingly, cyclization precursors (**20**) and (**21**) were prepared by acylation of lactam (**19**) with the appropriate acid chlorides (Scheme 4). Reaction of these substrates with DMTSF afforded the desired furans (**22**) and (**23**) in 65% and 56% yield, respectively. Thermolysis of the furans furnished phenols (**27**) and (**28**) as the only isolable products. Interestingly, formation of the tricyclic phenol (**27**) (48%) required heating furan (**22**) at reflux in toluene, whereas the reaction of **23** to give **28** (30%) needed heating at 180 ºC in a sealed tube. Clearly, both furans react at a slower rate than the 2-thiomethyl substituted system (*i.e.*, **12**), thereby suggesting that factors other than simple MO considerations control the rate of cycloaddition. The higher temperature required for the IMDAF reaction of furan (**23**) (*vs.* **22**) is probably related to entropic factors which diminish its rate of cycloaddition. Formation of the tricyclic phenols can be rationalized in terms of an initial Diels-Alder cycloaddition that first produces an oxa-bridged cycloadduct (*i.e.*, **24**), which was not detected since it readily underwent nitrogen-assisted ring opening (Scheme 5). Methoxy group ejection followed by deprotonation most likely furnishes cyclohexadienone (**26**) as a transient species which rapidly tautomerizes to the observed products.

Scheme 5



The potential of further employing this methodology for the synthesis of other alkaloids prompted us to carry out a model study directed toward the 3,4-benzoerythrinane skeleton. Construction of furan (**31**) was accomplished in two steps from amide (**29**). Thus, treatment of **29** with butenoyl chloride followed by reaction with DMTSF provided the desired furan (**31**) in 66% yield (Scheme 6). Heating a toluene solution of **31** at reflux for 3 h furnished bicyclic lactam (**32**) in a respectable 63% yield. In this case, a 2:1-mixture of diastereomers was obtained, probably as a result of epimerization at the α-position upon silica gel chromatography. A prominent theme for elaborating the fully substituted carbon center at the BC ring fusion of the benzoerythrinane skeleton has been the trapping of a *N*-acyliminium ion intermediate with an adjacent electron rich aryl ring.[22] With this in mind, we treated bicyclic lactam (**32**) with DMTSF hoping that the thiomethylation reaction would transform the thiomethyl substituent into a good leaving group thereby generating the required *N*-acyliminium ion necessary for cyclization. Although the desired cationic intermediate was indeed formed, preferential deprotonation followed by tautomerization occurred to ultimately provide phenol (**34**) in 74% yield. To prevent aromatization, the thiomethyl substituent was first removed by treatment with samarium diiodide affording ketone (**33**) in 70% yield. Gratifyingly, the acid-catalyzed reaction of **33** furnished tetracycle (**35**) in 74% yield. The conversion of **35** into erysotrine (**36**), the most common alkaloid occurring in the *Erythrina* species, has already been reported by Haruna and Ito.[23]. Consequently, the sequence of reactions outlined in Scheme 6 constitutes a formal synthesis of this particular erythrinan alkaloid.

Scheme 6



In summary, a highly convergent synthesis of the *cis*-3*a*-arylhydroindole skeleton has been devised using an IMDAF cycloaddition reaction of 2-methylthio-5-amidofurans. Application of the methodology toward the construction of more complex alkaloids containing these skeletons is currently in progress and will be reported at a later date.

EXPERIMENTAL

Melting points are uncorrected. MS spectra were determined at an ionizing voltage of 70eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using a 5% ethyl acetate/hexane mixture as the eluent unless specified otherwise. All solids were recrystallized from 3% ethyl acetate/hexane for analytical data.

1-Methyl-6-methylsulfanyl-3*a*-phenyl-1,3*a*,4,6-tetrahydro-3*H*-indole-2,5-dione (13). To a solution containing 1.0 g (3.3 mmol) of 2,2-dimethylpropionic acid 1-methylcarbamoylmethyl-2,2-*bis*-methylsulfanyl-ethyl ester (**10**)[24] in 16 mL of CH_2Cl_2 was added 0.8 g (4.7 mmol) of 3-phenylbut-3-enoyl chloride[25] followed by 3.3 g of powdered molecular sieves. After stirring at rt overnight, the suspension was filtered through a pad of silica gel and washed several times with ether. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was subjected to flash silica gel chromatography to give 1.1 g (88%) of 2,2-dimethylpropionic acid 1-(*bis*-(methylsulfanylmethyl)-3-[methyl-(3-phenylbut-3-enoyl)amino]-3-oxopropyl ester (**11**) as a yellow oil: IR (neat) 1729, 1696, 1146, and 1083 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 2.17 (s, 3H), 2.19 (s, 3H), 3.06 (dd, 1H, *J* = 17.2 and 7.2 Hz), 3.22 (s, 3H), 3.45 (dd, 1H, *J* = 17.2 and 5.4 Hz), 3.90 (d, 2H, *J* = 3.2 Hz), 3.94 (d, 1H, *J* = 4.4 Hz), 5.16 (s, 1H), 5.54-5.59 (m, 1H), 5.57 (s, 1H), and 7.27-7.42 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.4, 15.1, 27.3, 31.8, 39.0, 41.1, 44.9, 57.8, 71.5, 116.3, 125.9, 128.1, 128.7, 140.0, 141.4, 171.9, 172.9, and 173.9; HRMS Calcd for $C_{22}H_{31}NO_4S_2$: 437.1694. Found: 437.1693.

To a solution containing 2.7 g (6 mmol) of the above imide in 30 mL of MeCN was added 1.3 g (6.4 mmol) of DMTSF in one portion at -40 °C. The mixture was stirred for 1 h at -40 °C and then 4 mL (31 mmol) of triethylamine was added. The solution was diluted with ether, poured over a saturated aqueous $NaHCO_3$ solution, extracted with ether, and dried over K_2CO_3. The solvent was removed under reduced pressure and the crude residue was subjected to flash silica gel chromatography to give 1.1 g (64%) of 3-phenylbutenoic acid methyl-(5-methylsulfanylfuran-2-yl)amide (**12**) as a yellow oil: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.19 (s, 3H), 3.46 (s, 2H), 5.07 (s, 1H), 5.45 (s, 1H), 6.05 (d, 1H, *J* = 4.4 Hz), and 6.40 (d, 1H, J = 4.4 Hz). The furan was used for the next step without further purification.

A solution of 0.2 g (0.8 mmol) of the above furan in 10 mL of benzene was heated at reflux overnight. Upon cooling, the reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel chromatography to give 0.15 g (61%) of **13** as a white solid: mp 43-44 °C; IR (film) 1732, 1670, 1323, and 1117 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.84 (s, 2H), 2.94 (d, 1H, *J* = 12.8 Hz), 3.05 (s, 3H), 3.39 (d, 1H, *J* = 12.8 Hz), 3.48 (d, 1H, *J* = 2.8 Hz), 5.17 (d, 1H, *J* = 2.8 Hz), 7.13-7.21 (m, 3H), and 7.24-7.28 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.2, 26.6, 46.3, 47.5, 48.7, 49.2, 97.0, 125.8, 127.9, 129.3, 142.2, 147.2, 172.8, and 201.1; Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.88; H, 5.97; N, 4.88. Found: C, 66.72; H, 5.81; N, 4.65.

1-Methyl-3*a*-phenyl-3,3*a*,4,5-tetrahydro-1*H*-indole-2,6-dione (16). To a solution containing 0.6 g (2.1 mmol) of ketone (**13**) in 20 mL of MeOH at 0 ºC was added 0.8 g (2.3 mmol) of cerium chloride heptahydrate followed by 0.1 g (2.3 mmol) of sodium borohydride[18]. The mixture was stirred for 3 h and water was added. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc. The organic layers were combined and dried over $MgSO_4$. Silica gel chromatography of the crude reaction mixture afforded 0.4 g (65%) of 5-hydroxy-1-methyl-6-methylsulfanyl-3*a*-phenyl-1,3,3*a*,4,5,6-hexahydro-indol-2-one (**14**) as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.82-1.89 (m, 1H), 2.21 (s, 3H), 2.40 (dd, 1H, *J* = 16.2 and 4.2 Hz), 2.62-2.78 (m, 3H), 3.03 (s, 3H), 3.61-367 (m, 1H), 5.36 (d, 1H, *J* = 5.2 Hz), and 7.17-7.34 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.0, 2.64, 41.3, 46.8, 47.8, 51.1, 66.3, 100.2, 126.5, 127.3, 128.8, 144.6, 145.7, and 173.1. This alcohol was used for the next step without further purification.

To a solution containing 0.3 g (1.2 mmol) of the above alcohol in 12 mL of CH_2Cl_2 was added 0.2 mL (1.3 mmol) of triethylamine followed by 0.1 mL (1.3 mmol) of mesyl chloride. The reaction mixture was stirred at rt overnight. Water was added, and the reaction mixture was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was subjected to flash silica gel chromatography to give 0.3 g (88%) of 1-methyl-6-methylsulfanyl-3*a*-phenyl-1,3,3*a*,4-tetrahydroindol-2-one (**15**) as a yellow oil: IR (neat) 1721, 1649, 1321, and 1096 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.62 (d, 1H, *J* = 16.0 Hz), 2.66 (dd, 1H, *J* = 15.2 and 3.6 Hz), 2.83 (d, 1H, *J* = 16.4 Hz), 2.85 (d, 1H, *J* = 16.0 Hz), 3.11 (s, 3H), 5.56 (d, 1H, *J* = 6.0 Hz), 5.69 (dd, 1H, *J* = 5.8 and 2.6 Hz), 7.18-7.23 (m, 3H), and 7.24-7.29 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.0, 26.7, 42.7, 43.6, 47.5, 97.6, 116.3, 125.8, 127.4, 128.7, 130.2, 142.2, 143.9, and 174.1; HRMS Calcd for $C_{16}H_{17}NOS$: 271.1031. Found: 271.1028.

To a solution containing 0.4 g (1.6 mmol) of dienyl sulfide (**15**) in 20 mL of a 3:1 mixture of acetonitrile/water was added 0.9 g (3.2 mmol) of mercuric chloride. The reaction mixture was heated at reflux for 3 days. The orange suspension was filtered through Celite and washed with ether. The filtrate was washed with a saturated $NaHCO_3$ solution followed by brine, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography of the crude residue afforded 0.22 g (62%) of **16** as a yellow oil: IR (neat) 1726, 1680, 1321, and 1116 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.69-2.77 (m, 2H), 2.78-2.87 (m, 2H), 2.94 (dd, 1H, *J* = 18.6 and 5.8 Hz), 3.10 (s, 3H), 3.24 (d, 1H, *J* = 15.2 Hz), 5.19 (dd, 1H, *J* = 5.8 and 2.2 Hz), 7.18-7.24 (m, 3H), and 7.27-7.31 (m, 2H);

^{13}C-NMR (100 MHz, CDCl$_3$) δ 26.6, 37.9, 45.6, 46.8, 52.0, 94.3, 125.7, 127.8, 129.4, 142.1, 146.5, 173.1, and 207.8; Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.65; H, 6.27; N, 5.81. Found: C, 74.52; H, 6.09; N, 5.80.

8-Hydroxy-5,6-dihydro-1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (27). To a solution containing 6.5 mL (46 mmol) of diisopropylamine in 150 mL of THF was added 30 mL (45 mmol) of a 1.6 M solution of *n*-butyllithium in hexane at -40 °C. After stirring for 1 h, the reaction was cooled to -75 °C and 7.4 g (43 mmol) of 1-trimethylsilyl-2-piperidone[26] in 25 mL of THF was added. The temperature was raised to -40 °C, and the reaction mixture was stirred for 30 min. The temperature was lowered to -75 °C and 8.2 g (45 mmol) of methoxy(phenylsulfanyl)acetaldehyde[27] (**18**) in 40 mL of THF was added dropwise over 45 min. Following addition, the reaction mixture was stirred for an additional 30 min, and then 4.5 mL (48 mmol) of acetic anhydride was added. The solution was slowly warmed to rt overnight and poured into a saturated aqueous NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. The solvent was removed under reduced pressure and the crude residue was subjected to flash silica gel chromatography to give 8.1 g (58%) of acetic acid 2-methoxy-2-methylsulfanyl-1-(2-oxo-piperidin-3-yl)ethyl ester (**19**) as a yellow oil which consisted of a complex mixture of diastereomers which was used in the next step without further purification. For analytical purposes, the major two diastereomers were separated by HPLC: IR (neat) 1747, 1660, 1491, 1372, and 1229 cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$) (major diastereomer) δ 1.64-1.93 (m, 4H), 2.06 (s, 3H), 3.22-3.28 (m, 3H), 3.47 (s, 3H), 5.20 (dd, 1H, J = 10.8 and 3.6 Hz), 5.54 (d, 1H, J = 10.8 Hz), 5.92 (br s, 1H), 7.27-7.33 (m, 3H), and 7.46-7.56 (m, 2H); (minor diastereomer) δ 1.64-1.93 (m, 4H), 2.08 (s, 3H), 2.93 (ddd, 1H, J = 14.7, 7.8 and 2.8 Hz), 3.22-3.28 (m, 2H), 3.53 (s, 3H), 5.15-5.19 (m, 1H), 5.43 (d, 1H, J = 12.0 Hz), 5.82 (br s, 1H), 7.27-7.33 (m, 3H), and 7.46-7.56 (m, 2H); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 21.2, 21.4, 22.2, 22.3, 25.4, 42.0, 42.3, 45.1, 56.9, 74.6, 75.7, 91.1, 91.7, 127.7, 127.9, 128.9, 129.2, 132.9, 133.2, 133.4 133.7, 170.5, 170.8, 171.1, and 171.2; HRMS Calcd for $C_{16}H_{21}NO_4S$: 323.1191. Found: 323.1190.

To a solution containing 0.6 g (1.8 mmol) of the above lactam in 9 mL of CH$_2$Cl$_2$ was added 0.3 g (3.1 mmol) of 3-butenoyl chloride followed by 1.9 g of powdered molecular sieves. After stirring at rt overnight, the suspension was filtered through a pad of silica and washed several times with ether. The filtrate was washed with a saturated aqueous NaHCO$_3$ solution, dried over MgSO$_4$, and concentrated under reduced pressure. The crude reaction mixture was subjected to flash silica gel chromatography to give 0.7 g (94%) of acetic acid 1-(1-but-3-enoyl-2-oxo-piperidin-3-yl)-2-methoxy-2-methylsulfanylethyl ester (**20**) as a yellow oil which contained a complex mixture of diastereomers and was used in the next step without further purification. For analytical purposes, the major two diastereomers were separated by HPLC: IR (neat) 1747, 1690, 1475, 1291, 1224, and 1163 cm^{-1}; ^{1}H-NMR (400 MHz, CDCl$_3$) (major diastereomer) δ 1.56-1.61 (m, 1H), 1.73-1.80 (m, 1H), 1.84-1.90 (m, 2H), 2.05 (s, 3H), 3.32-3.37 (m, 1H), 3.51 (s, 3H), 3.62-3.65 (m, 2H), 3.67-3.73 (m, 2H), 5.11-

5.17 (m, 2H), 5.26 (d, 1H, *J* = 7.2 Hz), 5.32 (dd, 1H, *J* = 7.2 and 3.6 Hz), 5.95-6.04 (m, 1H), 7.29-7.34 (m, 3H), and 7.50-7.52 (m, 2H); (minor diastereomer) δ 1.68-1.79 (m, 2H), 1.87-1.93 (m, 1H), 2.01-2.08 (m, 1H), 2.07 (s, 3H), 3.02-3.07 (m, 1H), 3.47 (s, 3H), 3.62-3.68 (m, 2H), 3.74-3.79 (m, 2H), 4.88 (d, 1H, *J* = 6.8 Hz), 5.09-5.15 (m, 2H), 5.61 (dd, 1H, *J* = 6.8 and 3.4 Hz), 5.95-6.04 (m, 1H), 7.28-7.34 (m, 3H), and 7.48-7.53 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) (major diastereomer) δ 21.1, 21.7, 24.3, 43.7, 44.2, 45.3, 56.9, 75.0, 91.3, 118.3, 128.2, 129.3, 131.5, 132.8, 133.5, 170.5, 173.1, and 174.9; (minor diastereomer) δ 21.2, 21.8, 22.1, 43.7, 44.2, 45.6, 56.9, 73.4, 92.3, 118.3, 128.1, 129.3, 131.5, 132.5, 133.3, 133.6, 169.9, 173.6, and 175.0; HRMS Calcd for $C_{20}H_{25}NO_5S$: 391.1453. Found: 391.1452.

To a solution containing 0.5 g (1.4 mmol) of lactam (**20**) in 7 mL of CH_2Cl_2 was added 0.3 g (1.4 mmol) of DMTSF in one portion at -40 °C. The temperature was allowed to warm slowly to 15 °C over 2 h and then 1 mL (6.8 mmol) of triethylamine was added. The reaction mixture was diluted with ether, poured over a saturated aqueous $NaHCO_3$ solution, extracted with ether, and dried over K_2CO_3. The solvent was removed under reduced pressure and the crude mixture was subjected to flash silica gel chromatography to give 0.2 g (65%) of 1-(2-methoxy-5,6-dihydro-4*H*-furo[2,3-*b*]pyridin-7-yl)but-3-en-1-one (**22**) as a yellow oil: IR (neat) 1752, 1670, 1603, and 1378 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.86-1.94 (m, 2H), 2.43 (t, 2H, *J* = 8.6 Hz), 3.46 (d, 2H, *J* = 8.6 Hz), 3.77-3.82 (m, 2H), 3.83 (s, 3H), 5.08 (s, 1H), 5.13-5.18 (m, 2H), and 5.94-6.06 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.0, 23.7, 40.6, 43.2, 58.3, 81.6, 92.3, 118.1, 131.5, 133.6, 157.3, and 174.9; HRMS Calcd for $C_{12}H_{15}NO_3$: 221.1052. Found: 221.1054.

A solution containing 0.04 g (0.2 mmol) of furan (**22**) in 5 mL of toluene was heated at reflux for 30 min. At the end of this time, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 0.02 g (48%) of **27** as a white solid: mp 200-201 °C (hexane/ether); IR (film) 1654, 1629, 1480, and 1280 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 1.92-1.98 (m, 2H), 2.67 (t, 2H, *J* = 6.0 Hz), 3.42 (s, 2H), 3.61-3.64 (m, 2H), 6.48 (br s, 1H), and 6.59 (br s, 1H); ^{13}C-NMR (100 MHz, CD_3OD) δ 22.7, 25.4, 37.7, 40.2, 111.4, 114.0, 122.7, 125.9, 134.5, 154.8, and 176.2; Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.81; H, 5.86; N, 7.41. Found: C, 69.72; H, 5.69; N, 7.31.

9-Hydroxy-1,2,6,7-tetrahydro-5*H*-pyrido[3,2,1-*ij*]quinolin-3-one (28). To a solution containing 0.9 g (2.9 mmol) of amide (**19**) in 15 mL of CH_2Cl_2 was added 0.6 g (4.6 mmol) of pent-4-enoyl chloride followed by 3.0 g of powdered molecular sieves. After stirring at rt overnight, the suspension was filtered through a pad of silica gel and washed several times with ether. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The crude reaction mixture was subjected to flash silica gel chromatography to give 0.9 g (76%) of acetic 2-methoxy-2-methylsulfanyl-1-(2-oxo-1-pent-4-enoyl-piperidin-3-yl)ethyl ester (**21**) as a yellow oil which contained a complex mixture of diastereomers and was used in the next step without further purification; IR (neat) 1752, 1696, 1373, 1224, and 1158 cm^{-1}; ^{1}H-NMR

(400 MHz, $CDCl_3$) (major diastereomer) δ 1.53-1.63 (m, 1H), 1.68-1.79 (m, 1H), 1.82-1.92 (m, 2H), 2.04 (s, 3H), 2.36-2.43 (m, 2H), 2.89-2.99 (m, 2H), 3.31-3.37 (m, 1H), 3.51 (s, 3H), 3.63-3.73 (m, 2H), 4.97-5.08 (m, 2H), 5.27 (d, 1H, *J* = 7.6 Hz), 5.32 (dd, 1H, *J* = 7.2 and 3.6 Hz), 5.79-5.89 (m, 1H), 7.27-7.34 (m, 3H), and 7.49-7.52 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) (major diastereomer) δ 21.1, 21.8, 24.4, 29.1, 38.8, 43.6, 45.3, 56.9, 75.1, 91.3, 115.4, 128.2, 129.3, 132.8, 133.4, 137.6, 170.5, 173.0, and 176.2; HRMS Calcd for $C_{21}H_{27}NO_5S$: 405.1610. Found: 404.1608.

To a solution containing 0.1 g (0.3 mmol) of amide (**21**) in 2 mL of MeCN was added 0.1 g (0.3 mmol) of DMTSF in one portion at -40 °C. The mixture was stirred for 1 h at -40 °C and then 0.2 mL (1.5 mmol) of triethylamine was added. The reaction mixture was diluted with ether, poured over a saturated aqueous $NaHCO_3$ solution, extracted with ether, and dried over K_2CO_3. The solvent was removed under reduced pressure and the crude residue was subjected to flash silica gel chromatography to give 0.04 g (56%) of 1-(2-methoxy-5,6-dihydro-4*H*-furo[2,3-*b*]pyridin-7-yl)pent-4-en-1-one (**23**) as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.86-1.92 (m, 2H), 2.40-2.45 (m, 4H), 2.76 (t, 2H, *J* = 7.4 Hz), 3.77-3.81 (m, 2H), 3.82 (s, 3H), 4.96-5.08 (m, 2H), 5.07 (s, 1H), and 5.83-5.93 (m, 1H); HRMS Calcd for $C_{13}H_{17}NO_3$: 235.1208. Found: 235.1213. The furan was used in the next step without further purification.

A solution of 0.19 g (0.8 mmol) of furan (**23**) dissolved in toluene (5 mL) was heated in a sealed tube at 180 ^{o}C for 12 h. The solution was cooled to rt at which point a brown solid precipitated from solution. The solid was collected by filtration and purified by recrystallization from MeOH to provide 0.05 g (30%) of **28** as a white solid, mp 220-221 ^{o}C; IR (film) 1727, 1632, 1393, 1180, and 1154 cm^{-1}; ^{1}H-NMR (CD_3OD, 400 MHz) δ 1.82-1.85 (m, 2H), 2.50-2.54 (m, 2H), 2.67-2.70 (m, 2H), 2.73-2.77 (m, 2H), 3.75-3.77 (m, 2H), and 6.42-6.44 (m, 2H); ^{13}C-NMR (CD_3OD, 100 MHz) δ 22.9, 26.2, 28.3, 32.5, 42.2, 114.1, 114.9, 128.4, 128.6, 129.2, 154.4, and 171.5; Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.90; H, 6.45; N, 6.89. Found: C, 70.82; H, 6.26; N, 6.80.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-6-methylsulfanyl-1,3*a*,4,6-tetrahydro-3*H*-indole-2,5-dione (32). To a solution containing 13 g (60 mmol) of *N*-(3,4-dimethoxy-benzyl)acetamide in 300 mL of CH_2Cl_2 was added 13 mL (106 mmol) of pivalyl chloride followed by 59 g of powdered molecular sieves. After stirring at rt overnight, the suspension was filtered through a pad of silica and washed several times with ether. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 17 g (93%) of *N*-acetyl-*N*-[2-(3,4-dimethoxy-phenyl)ethyl]-2,2-dimethylpropionamide as a yellow oil: IR (neat) 1685, 1516, 1265, and 1029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 2.17 (s, 3H), 2.79-2.83 (m, 2H), 3.76-3.80 (m, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.72-6.74 (m, 2H), and 6.79-6.81 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$)

δ 24.5, 28.5, 35.5, 43.1, 47.6, 56.1, 111.5, 112.4, 120.9, 130.9, 148.0, 149.2, 173.2, and 187.1; HRMS Calcd for $C_{17}H_{25}NO_4$: 307.1783. Found: 307.1782.

To a solution containing 3.4 mL (24 mmol) of diisopropylamine in 78 mL of THF was added 16 mL (23 mmol) of 1.4 M solution of *n*-butyllithium in hexane at 0°C. After stirring for 1 h, the reaction mixture was cooled to -40 °C and 6.8 g (22 mmol) of the above imide in 12 mL of THF was added and the solution was stirred for 1 h. The temperature was lowered to -75 °C and 3.1 g (23 mmol) of 2,2-*bis*(methylsulfanyl)acetaldehyde[16] in 23 mL of THF was added dropwise over 3 h. Following the addition, the mixture was stirred for an additional 30 min and was quenched by the addition of a saturated aqueous NH_4Cl solution. The mixture was slowly warmed to rt and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Silica gel column chromatography of the crude residue afforded 5.6 g (57%) of 2,2-dimethylpropionic acid 1-{[2-(3,4-dimethoxyphenyl)ethylcarbamoyl]methyl}-2,2-bismethylsulfanylethyl ester (**29**) as a yellow oil; IR (film) 1726, 1644, 1460, 1158, and 1024 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 2.16 (s, 3H), 2.18 (s, 3H), 2.55 (dd, 1H, *J* = 14.8 and 7.2 Hz), 2.74 (t, 2H, *J* = 7.2 Hz), 2.82 (dd, 1H, *J* = 14.8 and 5.8 Hz), 3.44-3.52 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 3.95 (d, 1H, *J* = 4.8 Hz), 5.41-5.45 (m, 1H), 5.66 (brt, 1H, *J* = 5.2 Hz), 6.71-6.73 (m, 2H), and 6.79-6.81 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.5, 15.1, 27.3, 35.4, 38.7, 39.1, 40.9, 56.0, 56.1, 57.6, 72.1, 111.6, 112.0, 120.8, 131.3, 147.9, 149.3, 169.2, and 177.7; HRMS Calcd for $C_{21}H_{33}NO_5S_2$: 443.1800. Found: 443.1798.

To a solution containing 13 g (29 mmol) of the above amide in 140 mL of CH_2Cl_2 was added 5.1 g (48 mmol) of 3-butenoyl chloride followed by 28 g of powdered molecular sieves. After stirring at rt overnight, the suspension was filtered through a pad of silica and washed several times with ether. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 11.9 g (81%) of 2,2-dimethylpropionic acid 1-(*bis*-methylsulfanylmethyl)-3-{but-3-enoyl-[2-(3,4-dimethoxy-phenyl)ethyl]amino}3-oxopropyl ester (**30**) as a pale yellow oil: IR (neat) 1726, 1705, 1378, and 1029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 2.11 (s, 3H), 2.12 (s, 3H), 2.74 (t, 2H, *J* = 7.2 Hz), 2.97 (dd, 1H, *J* = 16.8 and 8.0 Hz), 3.22-3.25 (m, 2H), 3.26 (dd, 1H, *J* = 16.8 and 4.8 Hz), 3.75-3.78 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 3.87 (d, 1H, *J* = 4.8 Hz), 4.99 (dd, 1H, *J* = 17.2 and 1.2 Hz), 5.09 (dd, 1H, *J* = 10.2 and 1.2 Hz), 5.49-5.53 (m, 1H), 5.78-5.89 (m, 1H), 6.65-6.67 (m, 2H), and 6.73-6.75 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.1, 14.8, 27.0, 31.5, 34.7, 38.7, 40.4, 42.4, 46.2, 55.8, 57.5, 71.2, 111.3, 112.0, 118.6, 120.8, 130.5, 130.6, 147.8, 149.0, 172.5, 174.1, and 177.3; Anal. Calcd for $C_{25}H_{37}NO_6S_2$: C, 58.68; H, 7.29; N, 2.74. Found: C, 58.54; H, 7.08; N, 2.63.

To a solution containing 8.8 g (17 mmol) of the above amide in 80 mL of MeCN was added 3.6 g (18 mmol) of DMTSF in one portion at -40 °C. The mixture was stirred for 1 h at -40 °C and 12 mL (86 mmol) of triethyl amine was added. The mixture was diluted with ether, poured over a saturated aqueous $NaHCO_3$ solution, extracted with ether, and dried over K_2CO_3. The solvent was removed under reduced pressure and the crude residue was subjected to flash silica gel chromatography to give 4.2 g (66%) of but-3-enoic acid [2-(3,4-dimethoxy-phenyl)ethyl]-(5-methyl-sulfanyl-furan-2-yl)-amide (**31**) as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.81 (t, 2H, *J* = 7.8 Hz), 3.78-3.82 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 3.84-3.86 (m, 2H), 4.97-5.08 (m, 2H), 5.81-5.91 (m, 1H), 5.87 (d, 1H, *J* = 3.2 Hz), and 6.38 (d, 1H, *J* = 3.2 Hz); HRMS Calcd for $C_{19}H_{23}NO_4S$: 361.1348. Found: 361.1341. The furan was used for the next step without further purification.

A solution of 0.1 g (0.2 mmol) of furan (**31**) in 2 mL of toluene was heated at reflux for 3 h. Upon cooling, the reaction mixture was concentrated under reduced pressure and the residue was subjected to silica gel chromatography to give 0.06 g (63%) of **32** as a pale yellow oil which contained a 2:1-mixture of diastereomers: IR (neat) 1716, 1669, 1321, and 1029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) (major diastereomer) δ 2.10 (s, 3H), 2.16-2.23 (m, 2H), 2.73 (dd, 1H, *J* = 17.4 and 9.8 Hz), 2.80 (t, 2H, *J* = 7.8 Hz), 3.03 (dd, 1H, *J* = 11.6 and 6.4 Hz), 3.52-3.57 (m, 2H), 3.63 (d, 1H, *J* = 6.8 Hz), 3.74-3.83 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 5.04 (dd, 1H, *J* = 6.8 and 2.4 Hz), 6.70-6.74 (m, 2H), and 6.77 (s, 1H); (minor diastereomer) δ 2.13 (s, 3H), 2.24-2.32 (m, 2H), 2.56-2.69 (m, 1H), 2.77-2.82 (m, 2H), 3.05-3.07 (m, 1H), 3.50-3.60 (m, 3H), 3.73-3.83 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 4.87 (t, 1H, *J* = 2.6 Hz), 6.70-6.74 (m, 2H), and 6.79 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.1, 16.4, 30.0, 32.4, 32.6, 35.4, 36.2, 36.4, 39.1, 41.5, 41.6, 41.7, 49.0, 49.9, 56.0, 56.1, 91.6, 94.4, 111.4, 112.0, 120.9, 130.4, 130.5, 144.4, 147.9, 148.1, 149.1, 173.8, 174.3, 200.8, and 202.0; HRMS Calcd for $C_{19}H_{23}NO_4S$: 361.1348. Found: 361.1346.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-1,3*a*,4,6-tetrahydro-3*H*-indole-2,5-dione (33). To a solution containing 2.5 mL (0.3 mmol) of a 0.1 M solution of SmI_2 in THF was added dropwise 0.04 g (0.1 mmol) of sulfide (**32**) in a 3:1 THF/MeOH mixture at -78 °C. The temperature was allowed to rise to 0 °C and the reaction mixture was stirred for an additional 10 min. The mixture was poured into a saturated K_2CO_3 solution, extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was subjected to silica gel chromatography to give 0.03 g (70%) of **33** as a yellow oil: IR (neat) 1721, 1675, 1408, and 1019 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.26 (dd, 1H, *J* = 17.2 and 8.8 Hz), 2.35 (dd, 1H, *J* = 15.4 and 12.6 Hz), 2.71-2.84 (m, 4H), 2.99-3.01 (m, 2H), 3.06-3.16 (m, 1H), 3.53-3.61 (m, 1H), 3.77-3.86 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 4.93-4.96 (m, 1H), and 6.73-6.80 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 32.0, 32.7, 36.4, 38.3, 41.6, 44.4, 56.0, 56.1, 92.2, 111.4, 112.1, 120.9, 130.8, 143.1, 147.9, 149.1, 174.0, and 208.5; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.54; H, 6.72; N, 4.44. Found: C, 68.37; H, 6.69; N, 4.28.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-hydroxy-1,3-dihydro-indol-2-one (34). To a solution containing 0.3 g (0.9 mmol) of **32** in 5 mL of MeCN was added 0.2 g (0.9 mmol) of DMTSF in one portion at -40 °C. The mixture was stirred for 10 min at -40 °C and then 0.6 mL (4.3 mmol) of triethylamine was added. The mixture was diluted with ether, poured over a saturated aqueous $NaHCO_3$ solution, extracted with ether, and dried over K_2CO_3. The solvent was removed under reduced pressure and the crude residue was subjected to flash silica gel chromatography to give 0.2 g (74%) of **34** as a pale yellow oil; IR (neat) 1675, 1516, 1260, and 1019 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 2.87-2.92 (m, 2H), 3.47 (s, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.86-3.90 (m, 2H), 5.33 (br s, 1H), 6.63 (d, 1H, J = 8.0 Hz), and 6.72-6.82 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 33.5, 36.3, 42.0, 56.0, 56.1, 108.9, 111.5, 112.2, 113.1, 114.1, 120.9, 126.2, 130.9, 138.0, 147.9, 149.2, 151.8, and 174.8; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.98; H, 6.12; N, 4.47. Found: C, 68.83; H, 6.09; N, 4.33.

11,12-Dimethoxy-1,2,4*a*,5,8,9-hexahydro-4*H*-indolo[1*a*,7*a*]isoquinoline-3,6-dione (35). To 0.3 g (1 mmol) of lactam (**33**) in 10 mL of toluene was added a catalytic amount of camphorsulfonic acid, and the reaction mixture was stirred overnight at rt. The solution was poured over a saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography to give 0.25 g (74%) of **35** as a white solid: mp 165-166 °C (hexane/ether); IR (film) 1716, 1680, 1419, and 1260 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 2.09-2.15 (m, 1H), 2.23-2.44 (m, 4H), 2.58-2.75 (m, 3H), 2.93-3.12 (m, 4H), 3.85 (s, 3H), 3.87 (s, 3H), 4.34-4.39 (m, 1H), 6.56 (s, 1H), and 6.67 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.7, 33.7, 34.9, 35.4, 37.6, 37.9, 43.4, 56.1, 56.5, 62.6, 107.4, 111.9, 125.7, 134.5, 148.4, 148.6, 172.3, and 210.3; Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.44; H, 6.67; N, 4.39.

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REFERENCES AND NOTES

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1. P. W. Jeffs, 'The Alkaloids' Vol. 19, ed. by R. G. A. Rodrigo, Academic Press, New York, 1981, pp. 1-80.
2. S. F. Dyke and S. N. Quessy, 'The Alkaloids' Vol. 18, ed. by R. G. A. Rodrigo, Academic Press, New York, 1981, pp. 1. A. H. Jackson, 'The Chemistry and Biology of Isoquinoline Alkaloids' ed. by J. D. Phillipson, M. F. Roberts, and M. H. Zenk, Springer, Berlin, 1985, p. 62.
3. O. Hoshino, 'The Alkaloids' Vol. 51, ed. by G. A. Cordell, Academic Press, New York, 1987, p. 323.
4. For some recent syntheses, see: J. H. Rigby and W. Dong, *Org. Lett.*, 2000, **2**, 1673; P. I. Dalko, V. Brun, and Y. Langlois, *Tetrahedron Lett.*, *199*8, **39**, 8979; M. Mori, S. Kuroda, C. S. Zhang, and Y. Sato, *J. Org. Chem.*, *199*7, **62**, 3263; S. E. Denmark and L. R. Marcin, *J. Org. Chem.*, *199*7, **62**, 1675.
5. A. S. Chawla and A. H. Jackson, *Nat. Prod. Rep.*, 1984, 371; A. S. Chawla and A. H. Jackson, *Nat. Prod. Rep.*, 1986, 355; A. S. Chawla and A. H. Jackson, *Nat. Prod. Rep.*,

1989, 55, A. S. Chawla and A. H. Jackson, *Nat. Prod. Rep.*, 1990, 565; K. W. Bentley, *Nat. Prod. Rep.*, 1991, 339; K. W. Bentley, *Nat. Prod. Rep.*, 1992, 365; K. W. Bentley, *Nat. Prod. Rep.*, 1993, 449; K. W. Bentley, *Nat. Prod. Rep.*, 1994, 555; K. W. Bentley, *Nat. Prod. Rep.*, 1995, 419.

6. For some leading references, see: J. H. Rigby, A. Cavezza, and M. J. Heeg, *J. Am. Chem. Soc.*, *199*8, **120**, 3664.
7. A. Mondon and H. J. Nestler, *Angew. Chem.*, *Int. Ed. Engl.,* 1964, **3**, 588; T. Sano, J. Toda, N. Kashiwaba, T. Oshima, and Y. Tsuda, *Chem. Pharm. Bull.*, 1987, **35**, 479; T. Sano, *J. Org. Chem.*, 1985, **50**, 5667; R. Ahmad-Schofiel and P. S. Mariano, *J. Org. Chem.*, 1987, **52**, 1478; H. Ishibashi, T. Sato, M. Takahashi, M. Hayashi, and M. Ikeda, *Heterocycles*, 1988, **27**, 2787.
8. H. Ishibashi, N. Uemura, H. Nakatani, M. Okazaki, T. Sato, N. Nakamura, and M. Ikeda, *J. Org. Chem.*, 1993, **58**, 2360; S. W. Baldwin, J. Auge and A. T. McPhail, *J. Org. Chem.*, 1991, **56**, 6546; T. Nishimata and M. Mori, *J. Org. Chem.*, 1998, **63**, 7586.
9. A. Padwa, M. Dimitroff, A. G. Waterson, and T. Wu, *J. Org. Chem*., 1998, **63**, 3986; A. Padwa, M. A. Brodney, and M. Dimitroff, *J. Org. Chem*., 1998, **63**, 5304; A. Padwa, M. A. Brodney, B. Liu, K. Satake, and T. Wu, *J. Org. Chem.*, 1999, **64**, 3595; A. Padwa, M. A. Brodney, M. Dimitroff, B. Liu, and T. Wu, *J. Org. Chem.*, 2001, **66**, 3119; A. Padwa, M. A. Brodney and S. M. Lynch, *J. Org. Chem.*, 2001, **66**, 1716.
10. C. O. Kappe, S. S. Murphree, and A. Padwa, *Tetrahedron*, 1997, **53**, 14179.
11. A. Padwa, R. Henning, C. O. Kappe, and T. S. Reger, *J. Org. Chem.*, 1998, **63**, 1144.
12. A. Padwa, J. D. Ginn, and M. S. McClure, *Org. Lett.*, 1999, **1**, 1559.
13. B. M. Trost and E. Murayama, *J. Am. Chem. Soc.*, 1981, **103**, 6529; B. M. Trost and T. Sato, *J. Am. Chem. Soc.*, 1985, **107**, 719. Commercially available from Aldrich Chemical Co.
14. J. L. Kice and N. A. Favstritsky, *J. Am. Chem. Soc.*, 1969, **91**, 1751; S. H. Smallcombe and M. C. Caserio, *J. Am. Chem. Soc.*, 1971, **93**, 5826; J. K. Kim, J. K. Pau, and M. C. Caserio, *J. Org. Chem.*, 1979, **44**, 1544.
15. T. F. Braish, J. C. Saddler, and P. L. Fuchs, *J. Org. Chem.*, 1988, **53**, 3648; J. Grácia, N. Casamitjana, J. Bonjoch, and J. Bosch, *J. Org. Chem.*, 1994, **59**, 3939.
16. M. Nakane and C. Hutchinson, *J. Org. Chem.,* 1978, **43**, 3922; M. Barbero, S. Cadamuro, I. Degani, S. Dughera, and R. Fochi, *J. Org. Chem.*, 1995, **60**, 6017.
17. L. M. Weinstock, S. Karady, F. E. Roberts, A. M. Hoinowski, G. S. Brenner, T. B. K. Lee, W. C. Lumma, and M. Sletzinger, *Tetrahedron Lett.*, 1975, **16**, 3979.
18. A. Gemal and J. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
19. E. J. Corey and J. I. Shulman, *J. Org. Chem.*, 1970, **35**, 777.
20. K. T. Potts and E. B. Walsh, *J. Org. Chem.*, 1988, **53**, 1199.
21. FMO Calculations were determined with MOPAC 6.0 using the PM3 Hamiltonian. J. J. P. Stewart, *J. Comput. Aided Mol. Des.*, 1990, **4**, 1.

22. Y. Tsuda and T. Sano, 'Studies in Natural Products Chemistry,' Vol. 3, ed. by A. U. Rahman, Elsevier, Amsterdam, 1989, Part B, p. 455.
23. M. Haruna and K. Ito, *J. Chem. Soc.*, *Chem. Commun.*, 1976, 345.
24. A. Padwa, C. K. Eidell, J. D. Ginn, and M. S. McClure, *J. Org. Chem.*, 2002, **67**, 1595.
25. G. F. Luteri and W. T. Ford, *J. Org. Chem.*, 1977, **42**, 820.
26. Y. Yamamoto and H. Kimura, *Chem. Pharm. Bull.*, 1976, **24**, 1236.
27. V. H. Rawal, M. Akiba, and M. P. Cava, *Synth. Commun.*, 1984, **14**, 1129.