Synthesis of Indolizidine Alkaloids via the Intramolecular Imino Diels-Alder Reaction[1]

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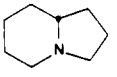
Abstract: An intramolecular imino Diels-Alder strategy has been developed for total synthesis of the indolizidine alkaloids δ-coniceine (**1**), tylophorine (**2**), elaeokanine A (**3**), and elaeokanine B (**4**). In all cases, an acyl imine dienophile was generated thermally in situ from a methylol acetate precursor. Diene-methylol acetate **8** has been cyclized via **10** to lactam **11**, which was converted to δ-coniceine. Similarly, intermediate methylol acetate **18** was transformed via **19** and **20** to pentacyclic lactam **21**, and then to tylophorine. In the syntheses of elaeokanine A and B, a masked diene precursor, in the form of a dihydrothiophene dioxide system, was prepared. Thus, compound **35** was cyclized via intermediate **23b** to afford bicyclic lactams **37** and **39** in a 5:4 ratio. These products were subsequently converted to **3** and **4**.

Alkaloids incorporating the indolizidine skeleton **1** comprise



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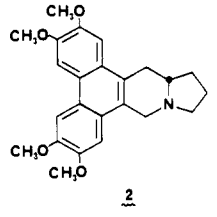
a rather large group of compounds isolated from diverse natural sources, and have an interesting range of biological activity.[3] Although syntheses of different members of this class of alkaloids abound, it seemed to us that this group is of sufficient importance to warrant further synthetic effort, particularly considering the lack of truly general strategies for preparation of indolizidines.[3]

The variation of the Diels-Alder reaction which utilizes an imine as the dienophilic component has been known for many years, but has only been sparsely applied to natural product total synthesis.[4] We recently used this sort of cycloaddition as one key step in a total synthesis of streptonigrin.[5] During that work it appeared to us that an imino Diels-Alder strategy could potentially provide attractive routes to various alkaloids, especially those possessing an indolizidine nucleus. One serious problem associated with this type of approach involves the possibility of forming mixtures of regioisomeric cycloaddition products when using unsymmetrical dienes. Although proper choice of substituents on diene and dienophile does often allow predictable regiochemical control in this reaction,[4b] it appeared to us that this potential difficulty could easily be avoided by making the cycloaddition intramolecular.

A literature search at the time we began this research program indicated that only a single example of an intramolecular imino Diels-Alder reaction existed. This one reported case was somewhat special, however, involving addition of a highly reactive quinone-methide diene to an oximino dienophile.[6] Thus, we set out to discover whether intramolecular Diels-Alder reactions of imines can be readily effected, and if so, to demonstrate the general utility of this strategy in indolizidine alkaloid synthesis.

These goals have been achieved and this paper describes in detail successful total syntheses of several structurally different indolizidine alkaloids, namely δ-coniceine (**1**), tylophorine (**2**), and the *Elaeocarpus* alkaloids elaeokanine A (**3**) and elaeokanine B (**4**).



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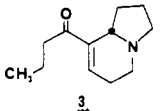

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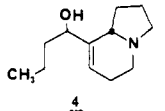

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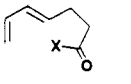
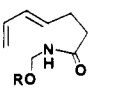
δ-Coniceine (**1**)[7] was chosen as our initial target since its almost trivial simplicity would allow us to easily test the basic principles of the approach. Thus, readily available diene ester **5**[8] was directly converted to amide **6** with dimethylaluminum amide in refluxing

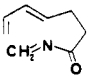


5 X = OCH_2CH_3
6 X = NH_2



7 R = H
8 R = $COCH_3$

9



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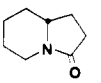

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benzene[9] in 69% yield. This amide was transformed to the methylol derivative **7** on treatment with 37% aqueous formaldehyde/sodium hydroxide in glyme, and **7** was immediately acetylated with acetic anhydride/pyridine, giving crystalline acetate **8** (83% from **6**).[10] We envisioned that **8** could be thermally converted to bicyclic lactam **9** via the unstable acyl imine **10**. This transformation could in practice be optimally effected by passing a dilute toluene solution of **8** through a column of glass helices heated at 370-390 °C, giving adduct **9** in 73% yield. Lactam **9** was then catalytically hydrogenated to **11**, which was reduced with BH_3/THF affording δ-coniceine (**1**), comparable to authentic material.[11]

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(1) Preliminary accounts of this research have appeared: (a) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073. (b) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372.

(2) Fellow of the A. P. Sloan Foundation, 1975-79; recipient of a Research Career Development Award from the National Heart, Lung and Blood Institute (HL-00541), 1975-80. Address correspondence to this author at The Pennsylvania State University.

(3) For extensive lead references to indolizidine alkaloids see: "The Alkaloids", Specialist Periodical Reports; The Chemical Society: London; Vol. 1-10.

(4) (a) Lora-Tomayo, M. In "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967; pp 127-142. (b) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949.

(5) Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.-T.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 3962.

(6) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1971**, *11*, 1031.

(7) For recent syntheses see: (a) Pizzorno, M. T.; Albonico, S. M. *J. Org. Chem.* **1977**, *42*, 909. (b) Stevens, R. V.; Luh, Y.; Sheu, J.-T. *Tetrahedron Lett.* **1976**, 3799. (c) McKee, R. S. Ph.D. Thesis, University of Pittsburgh, 1978. (d) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330.

(8) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020.

(9) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. (b) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Syn.* **1979**, *59*, 49.

(10) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.

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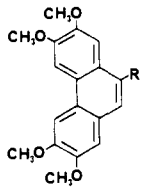
Having successfully tested the feasibility of the Diels–Alder process, we turned to more structurally complex indolizidine alkaloids, and specifically those which actually incorporate the double bond produced in the initial cycloadduct (cf. **9**).

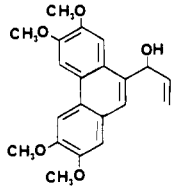
Tylophorine (**2**) is the most common member of a small class of phenanthroindolizidine alkaloids, some of which have potent antitumor activity.[12] Using an imino Diels–Alder strategy we have synthesized **2**[13] in eight steps from known ester **12**.[13a] Reduction of **12** with lithium aluminum hydride in THF gave alcohol



12 R = CO_2CH_3

13 R = CH_2OH

14 R = CHO



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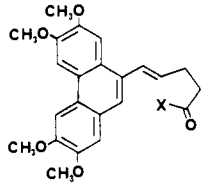
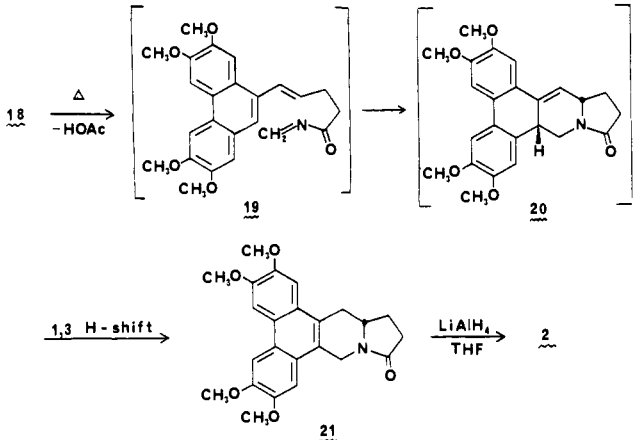


16 X = OCH_2CH_3

17 X = NH_2

18 X = $NHCH_2OCOCH_3$

13, which on oxidation with pyridinium chlorochromate afforded aldehyde **14** in good overall yield.[14] Allylic alcohol **15** was formed upon treatment of **14** with vinyllithium in THF (79% yield). Ortho ester Claisen rearrangement of **15** under standard conditions[15] led to ester **16** which was converted to amide **17** with dimethylaluminum amide in refluxing methylene chloride. As in the δ-coniceine synthesis this amide was transformed to the acyl imine precursor **18** by treatment with formaldehyde, followed by acetylation of the intermediate methylol with acetic anhydride/pyridine. After some experimentation, it was found that heating acetate **18** in bromobenzene at 219–220 °C for 5 h produced the known lactam **21**[13a] in 50% yield. This cycloaddition

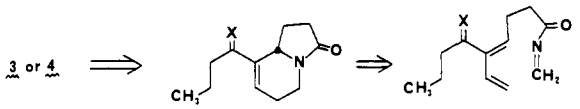


18 → (Δ, −HOAc) → **19** → **20**

21 → (1,3 H-shift; $LiAlH_4$, THF) → **2**

presumably goes via acyl imine **19**, and pentacyclic intermediate **20**, which rearomatizes to produce **21**. Examples of intermolecular [4 + 2] cycloadditions of imino dienophiles to styrenes are quite rare,[16] and it was thus gratifying to find that the vinyl phenanthrene function of **19** participates so well as a diene in the intramolecular process. Lactam **21** was identical with an authentic sample kindly provided by Drs. R. E. Summons and A. J. Liepa.[13a] Reduction of **21** with lithium aluminum hydride lead to racemic tylophorine (**2**) identical with natural material.[17]

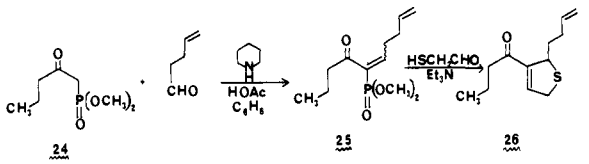
An even more challenging series of target molecules potentially amenable to our Diels–Alder strategy are the *Elaeocarpus* alkaloids,[18] exemplified by elaeokanine A (**3**) and elaeokanine B (**4**).[19–21] We anticipated that a bicyclic lactam precursor to **3** and **4** such as **22** could be generated via an intermediate such as **23**. The acyl imine function of **23** might be produced here, as



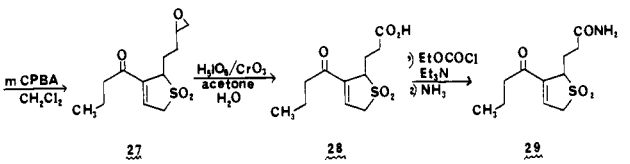
3 or **4** ⟹ **22a** X = O; **22b** X = H,OR ⟹ **23a** X = O; **23b** X = H,OR

in the δ-coniceine and tylophorine syntheses, by thermal elimination of a methylol acetate derivative. We were somewhat concerned, however, about the possible instability of the diene portion of **23**, and thus decided to construct this part of the molecule in "masked" form,[22] and to free it when needed for the pivotal cycloaddition.

Toward this end, keto phosphonate **24**, prepared from dimethyl methylphosphonate and ethyl butyrate,[23] was condensed with 4-pentenal[24] in the presence of piperidine/acetic acid in refluxing benzene[25b] affording the vinyl phosphonate **25** in 76% yield as a



24 → (HOAc, C_6H_6) → **25** → (HSCH₂CHO, Et_3N) → **26**



27 → (m-CPBA, CH_2Cl_2; H_5IO_6/CrO_3, acetone, H_2O) → **28** → (1) EtOCOCl, Et_3N 2) NH_3) → **29**

1:1 mixture of *E* and *Z* isomers. As in the elegant work of McIntosh et al.,[25] it was found that **25** reacts with mercaptoacetaldehyde (generated in situ from its commercially available dimer, *p*-dithane-2,5-diol), catalyzed by triethylamine, to afford dihydrothiophene **26** (56%). Oxidation of **26** with excess *m*-chloroperbenzoic acid gave epoxide–sulfone **27** in 92% yield.

It was our intention to next degrade this epoxide to the norcarboxylic acid **28**. A search of the literature indicated, to our surprise, that no one pot method for this particular transformation had been reported, although cleavage of epoxides to aldehydes was known.[26] Several years ago Perold and Pachler[27] found that

(11) We thank Professor S. Danishefsky for providing spectra of synthetic (±)-δ-coniceine.

(12) For a review see: Govindachari, T. R. *Heterocycles* **1978**, *11*, 587.

(13) For recent syntheses see: (a) Liepa, A. J.; Summons, R. E. *J. Chem. Soc., Chem. Commun.* **1977**, 826. (b) Chauncy, B.; Gellert, E. *Aust. J. Chem.* **1970**, *23*, 2503. (c) Herbert, R. B.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1970**, 121.

(14) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(15) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(16) Reference 4a, pp 132, 137.

(17) We are grateful to Dr. N. B. Mulchandani for a sample of natural tylophorine.

(18) Johns, S. R.; Lamberton, J. A. In "The Alkaloids"; Manske, R., Ed.; Academic Press: New York, 1973; Vol. 14, p 325.

(19) (a) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *J. Chem. Soc. D.* **1971**, 360. (b) *Aust. J. Chem.* **1972**, *25*, 817.

(20) For other syntheses of elaeokanine A see: (a) Tufariello, J. J.; Ali, Sk. A. *Tetrahedron Lett.* **1979**, 1339. (b) Howard, A. S.; Gerrans, G. C.; Meerholz, C. A. *Ibid.* **1980**, 1373.

(21) Other recent synthetic work in this area: (a) Tufariello, J. J.; Ali, Sk. A. *J. Am. Chem. Soc.* **1979**, *101*, 7116. (b) Watanabe, T.; Nakashita, Y.; Katayama, S.; Yamauchi, M. *Heterocycles* **1980**, *14*, 1433. (c) *Ibid.* **1981**, *16*, 39.

(22) Some nice examples now exist of the use of masked dienes in "all carbon" intramolecular Diels–Alder reactions: (a) Martin, S. F.; Desai, S. R.; Phillips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294. (b) Martin, S. F.; Tu, C.-Y.; Chou, T.-S. *Ibid.* **1980**, *102*, 5274. (c) Ichihara, A.; Kimura, R.; Yamada, S.; Sakamura, S. *Ibid.* **1980**, *102*, 6353.

(23) Dauben, W. G.; Beasly, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. *J. Am. Chem. Soc.* **1975**, *97*, 4973. Powell, J. Ph.D. Dissertation, Massachusetts Institute of Technology, 1970.

(24) Montgomery, L. K.; Matt. J. W. *J. Am. Chem. Soc.* **1967**, *89*, 6556.

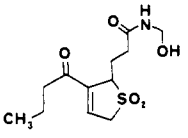
(25) (a) McIntosh, J. M.; Sieler, R. A. *J. Org. Chem.* **1978**, *43*, 8431. (b) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, *56*, 226. (c) McIntosh, J. M.; Masse, G. M. *J. Org. Chem.* **1975**, *40*, 1294. (d) McIntosh, J. M.; Goodbrand, H. B.; Masse, G. M. *Ibid.* **1974**, *39*, 2135. (e) McIntosh, J. M.; Goodbrand, H. B.; Masse, G. M. *Ibid.* **1974**, *39*, 202.

(26) Nagarkatti, J. P.; Ashley, K. R. *Tetrahedron Lett.* **1973**, 4599.

(27) Perold, G. W.; Pachler, K. G. R. *J. Chem. Soc. C* **1966**, 1918.

a vicinal diol could be cleaved to the dicarboxylic acid with a mixture of periodic acid/chromic acid. We have found that this same reagent combination serves to convert epoxide **27** to nor-acid **28** in excellent yield in a single step. This acid was then converted to amide **29** by standard means.

With a masked diene precursor (i.e., the dihydrothiophene dioxide **22ab**[28]) constructed, we attempted to establish the necessary functionality to produce the desired acyl imine (cf. **23**). Treatment of amide **29** with formaldehyde and various bases did not provide the desired methylol **30**, but instead gave several products resulting from mixed aldol condensations.



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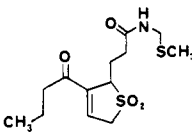

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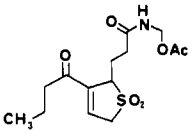
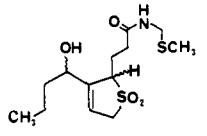


32

As an alternative, amide **29** was exposed to chloromethyl methyl sulfide in trifluoroacetic acid[29] giving thiomethyl derivative **31**. Interestingly, we found by carefully monitoring this reaction that the amide N-alkylation was, in fact, occurring during the evaporation of reagents and solvents in the workup procedure. It is quite possible that this conversion is an equilibrium process which requires efficient removal of HCl in order to go to completion, and thus is promoted by a slow evaporation under vacuum. It was also found to be important that this evaporation be conducted at 30–35 °C since at higher temperatures N,N-dialkylation of the amide occurred.

A number of unsuccessful attempts were made to thermally convert sulfide **31** (as well as its derived sulfoxide) to bicyclic lactam **22a** via diene–acyl imine **23a**. Since we could never be certain that we were actually generating the required acyl imine from these thiomethyl compounds, the acetate **32** was examined next in view of our previous successes with this system. This material could be prepared in excellent yield by treatment of sulfide **31** with 1 equiv of mercuric acetate in glacial acetic acid. Pyrolysis of **32** did, in fact, lead to some lactam **22a**, but unfortunately the yield was quite poor.

It was felt that perhaps this problem was due to the acyldiene moiety of **23a** being unstable to the Diels–Alder reaction conditions (Michael reactions?). Thus, the keto group of **31** was reduced to the corresponding alcohol ($NaBH_4/CeCl_3$),[30] giving **33** as an



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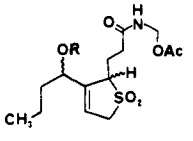
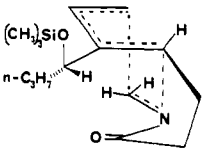


34 R=H
35 R=Si(CH$_3$)$_3$

inseparable mixture of diastereomers. The fact that a mixture of epimers is formed here is of no consequence since this relative stereochemistry is, of course, lost in going to the diene–acyl imine (e.g., **23b**). Thiomethyl compound **33** was next transformed to the desired methylol acetate **34** with mercuric acetate in glacial acetic acid. This allylic alcohol was silylated in high yield, giving **35**. Optimum conditions developed for pyrolysis of **35** involved using a heated tube of glass helices maintained at 370 °C, leading to a 68% yield of bicyclic lactams **37a/39a**. The ratio of stereoisomers here was 5:4, as determined by NMR analysis of the mixture. We are unable to establish specifically which isomer has which stereostructure at present. Hydrolysis of the mixture of silyl ethers with dilute HCl gave alcohols **37b/39b**, separable by MPLC.[31]

This cycloaddition presumably occurs via diene acyl imine intermediate **23b** (R = $SiMe_3$) having the double bond configuration shown.[28] Inspection of molecular models suggests that the two best transition states for this cycloaddition ("endo" carbonyls[32] and minimal side-chain eclipsing interactions[33]) are **36** and **38**,



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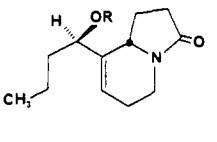
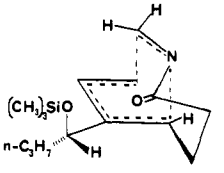
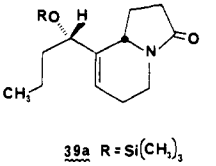


37a R = Si(CH$_3$)$_3$
37b R = H



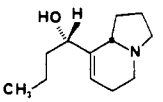
38



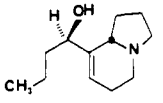
39a R = Si(CH$_3$)$_3$
39b R = H

leading to **37a** and **39a**, respectively. There appears to be very little difference in energy between **36** and **38**, thus explaining the nearly equal amounts of diastereomeric cycloaddition products. PCC oxidation of the mixture of alcohols **37b/39b** gave authentic keto lactam **22a**, which we had previously prepared in low yield by pyrolysis of intermediate **32**.

Reduction of the mixture lactams **37b** and **39b** with diisobutylaluminum hydride in THF gave a mixture of amino alcohols **40** and **41** in 91% yield. These compounds were separated, but only in with great difficulty, by preparative TLC on silica gel. Pure epimeric lactams **37b** and **39b** could also be similarly reduced individually to afford **40** and **41** as pure isomers. Based upon available data, we believe that natural elaeokanine B may be a mixture of diastereomers **40** and **41**.[19] A comparison of the



40



41

60-MHz ^1H NMR spectra of our pure synthetic compounds and mixture with that of the natural product[19,34] does tend to support such a possibility, but since an authentic sample of the alkaloid is not currently available, we unfortunately cannot definitively establish the stereochemical composition of elaeokanine B at this time.

Oxidation of the mixture of **40** and **41** with trifluoroacetic anhydride–Me_2SO[35] gave elaeokanine A (**3**) which had spectra identical with those of natural material.[19,34]

We believe that this work has amply demonstrated the versatility of the intramolecular imino Diels–Alder process in construction of indolizidine alkaloids of various types. Research is now in progress toward synthesis of some more complex indolizidine alkaloids, as well as other alkaloid systems.

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Experimental Section

Melting points were taken on a Thomas-Hoover "Uni-Melt" capillary melting point apparatus equipped with a calibrated thermometer. Boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 197 spectrophotometer. Ultraviolet (UV) spectra were recorded on a Cary 14 spectrophotometer using ethanol as the solvent. Proton magnetic resonance spectra (60 MHz) were recorded on either a Varian A60-A or an EM-360 NMR spectrometer. ^{1}H NMR spectra (100 MHz) were obtained on a JEOL PFT-100 Fourier transform NMR spectrometer and 200-MHz ^{1}H NMR on a Brücker WP 200 spectrometer. Chemical shifts are reported in delta (δ) units, using tetramethylsilane as an internal standard. Spin multiplicities are indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet), h (hextet), and m (multiplet). All spectra were taken in deuteriochloroform. Carbon-13 magnetic resonance (^{13}C NMR) spectra were obtained on a Varian CFT-20 NMR spectrometer equipped with a microprobe for sample sizes from 10 to 20 mg. Mass spectra (MS) were routinely recorded at 70 eV by electron impact (EI) on an Associated Electrical Industries, Ltd., MS-902 double-focusing mass spectrometer on which both low-resolution and high-resolution spectra were obtained. Compounds which did not yield molecular ions (M^+) by this instrument were analyzed by chemical ionization (CI) via a solid probe on a Finnigan 3200 quadrupole mass spectrometer using methane as a carrier gas. Values for CI-MS peaks are given in m/e − 1 units. Combustion analyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL. Gas chromatography (GC) was performed on a Varian Model 3700 instrument equipped with a thermal conductivity detector using a $^1/_8$ in. × 6 ft stainless steel column packed with 22% Carbowax 117 on Chromsorb G, 100/120 mesh. Analytical thin layer chromatography (TLC) was done on Silica Gel 60 PF-254 (E. M. Merck). Visualization was effected by basic aqueous permanganate spray. Liquid chromatography was carried out using 70–230 mesh Silica Gel 60 (E. M. Merck) as the stationary phase.

4,6-Heptadienamide (6). To a solution of 3.0 g (19.45 mmol) of ester **5**[8] in 50 mL of dry benzene at 0 °C was carefully added 1.5 equiv of dimethylaluminum amide in benzene.[9] The solution was stirred for 0.25 h at room temperature and was then refluxed for 1.5 h under an argon atmosphere. The reaction mixture was cooled and to it was carefully added 30 mL of cold water. The two-phase mixture was filtered, the organic phase was separated, and then the aqueous portion was extracted once with ethyl acetate. The organic phases were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give amide **6** (1.69 g, 69%) of sufficient purity for the next step. A sample recrystallized from ethyl acetate/hexane, had mp 94–95 °C: IR ($CHCl_3$) 3550, 3425, 3050, 3000, 1685, 1600 cm^{-1}; ^{1}H NMR δ 2.24–2.49 (m, 4 H), 4.98–5.18 (m, 2 H), 5.23–5.60 (br s, 2 H), 5.71 (t of d, J = 6.6 and 15 Hz, 1 H), 6.05–7.23 (m, 2 H); MS (EI, m/e rel intensity) 125 (M^+, 100), 96 (19), 82 (41), 81 (53), 67 (42), 59 (19). Exact mass: calcd for $C_7H_{11}NO$, 125.0840; found, 125.0839.

***N*-[(Acetyloxy)methyl]-4,6-heptadienamide (8).** A mixture of 219 mg (1.75 mmol) of amide **6**, 2 mL of glyme, 1.0 mL of 5% NaOH, and 0.3 mL of 37% aqueous formaldehyde was stirred at room temperature for 17 h.[10] Sodium bicarbonate (0.05 g) was added and the mixture was stirred for another 10 min. The solvent was evaporated in vacuo. The residue was dissolved in chloroform and dried over anhydrous $MgSO_4$; the solvent was evaporated to give a solid to which were added 2.0 mL of acetic anhydride and 2 drops of pyridine. The resulting mixture was stirred for 2 h at room temperature. The solvent was evaporated in vacuo and the oil obtained was dissolved in chloroform. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated to dryness. The resulting oil was chromatographed on a silica gel column using ethyl acetate/hexane (1:1) giving a colorless crystalline product (287 mg, 83%), mp 38–39 °C: IR ($CHCl_3$) 3450, 3050, 3000, 1740, 1695, 1600 cm^{-1}; ^{1}H NMR δ 2.01 (s, 3 H), 2.28–2.37 (m, 4 H), 4.93–5.11 (m, 2 H), 5.18 (d, J = 7 Hz, 2 H), 5.97–6.33 (m, 2 H), 6.63 (t of d, J = 6.5, 15 Hz, 1 H), 7.09 (br t, J = 7 Hz, 1 H); MS (EI, m/e rel intensity) 197 (M^+, 6), 138 (29), 137 (41), 136 (35), 123 (8), 110 (28), 109 (29), 96 (8), 84 (19), 82 (66), 81 (100), 80 (66), 78 (12), 68 (76). Exact mass: calcd for $C_{10}H_{15}O_3N$, 197.1051; found, 197.1080.

1,5,6,8a-Tetrahydro-3(2*H*)-indolizinone (9). A solution of 106 mg (0.536 mmol) of methylol acetate **8** in 70 mL of toluene was passed through a hot tube (15 cm, packed with $^1/_{16}$ in. i.d. glass helices, maintained with an electric heating tape at 370–390 °C) over 2.75 h. The toluene was evaporated in vacuo to give virtually pure **9** (53.7 mg, 73%): IR ($CHCl_3$) 3050, 3000, 1680 cm^{-1}; ^{1}H NMR δ 1.53–2.49 (m, 6 H), 2.84 (d of t, J = 5.2 and 12 Hz, 1 H), 4.14–4.24 (m, 2 H), 5.63–5.77 (m, 2 H); MS (EI, m/e rel intensity) 137 (M^+, 100), 136 (89), 134 (23), 132 (20), 109 (8), 108 (17), 97 (25), 91 (25), 82 (15), 81 (31), 80 (29), 79 (15), 67 (29). Exact mass: calcd, for $C_8H_{11}NO$, 137.0840; found, 137.0847.

Hexahydro-3(2*H*)-indolizinone (11). A mixture of 53.8 mg (0.393 mmol) of lactam **9** in 15 mL of ethyl acetate containing 11 mg of 5% Pd–C was hydrogenated at atmospheric pressure and room temperature for 2.5 h. The mixture was filtered through a Celite pad and the solvent was evaporated to give **11** as an oil homogeneous by TLC (52 mg, 95%): IR ($CHCl_3$) 3000, 2950, 1675 cm^{-1}; ^{1}H NMR δ 1.16–2.39 (m, 10 H), 2.54–2.68 (m, 1 H), 3.33–3.47 (m, 1 H), 4.10 (t of d, J = 2.2 and 13.60 Hz, 1 H); MS (EI, m/e rel intensity) 139 (M^+, 82), 138 (100), 111 (18), 110 (11), 98 (22), 96 (11), 86 (22), 84 (31), 83 (44), 69 (9), 68 (11). Exact mass: calcd for $C_8H_{13}NO$, 139.0997; found, 139.0991.

(±)-δ-Coniceine (1). To a solution of 52 mg of indolizinone **11** in 5 mL of THF was added 1 mL of 1 M borane–THF and the solution was refluxed under nitrogen for 2.0 h. The solution was cooled and the THF was evaporated. To the residue was added 3 mL of 10% H_2SO_4 and the mixture was heated at 88–92 °C for 0.5 h. After cooling, the mixture was made slightly basic by addition of Na_2CO_3 in small portions and the aqueous layer was extracted with ether. The ther layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated to give 23.8 mg (51%) of essentially pure racemic δ-coniceine (**1**) (picrate mp 227–231 °C; lit. mp 233–234 °C,[7c] 224–228 °C[7d]).

2,3,6,7-Tetramethoxy-9-phenanthrenemethanol (13). To a suspension of 1.56 g (41.0 mmol) of lithium aluminum hydride in 50 mL of dry THF at ice bath temperature was added in small portions a suspension of 9-carbomethoxy-2,3,6,7-tetramethoxyphenanthrene (**12**, 4.90 g, 13.7 mmol) in 150 mL of dry THF. After the reaction mixture was stirred at room temperature under a dry nitrogen atmosphere for 2.0 h, the mixture was cooled, and to it was added carefully 2.0 mL of water dropwise, followed by 2.0 mL of 15% NaOH and 6.0 mL of water. The precipitated inorganic salts were removed by filtration, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$; the solvent was evaporated. The crude product obtained was recrystallized from ethyl acetate, affording 3.63 g (80%) of alcohol **13**. An analytical sample recrystallized from benzene had mp 186–187 °C (lit. mp 183–184 °C,[13b] 185 °C[36]): IR ($CHCl_3$) 3600, 3050, 3010, 1620 cm^{-1}; ^{1}H NMR δ 1.73 (br s, 1 H), 4.00 (s, 3 H), 4.05 (s, 3 H), 4.11 (s, 3 H), 4.12 (s, 3 H), 5.10 (s, 2 H), 7.16 (s, 1 H), 7.52 (s, 1 H), 7.55 (s, 1 H), 7.73 (s, 1 H), 7.79 (s, 1 H); MS (EI, m/e rel intensity) 328 (M^+, 11), 327 (32), 326 (13), 325 (59), 312 (19), 311 (81), 298 (11), 281 (11), 215 (13), 207 (27), 205 (13), 203 (18), 202 (26), 201 (70), 200 (100), 199 (70), 195 (27), 185 (50), 178 (15), 176 (9), 170 (18), 168 (27), 165 (27), 152 (59), 121 (26), 119 (39), 117 (32), 107 (9), 91 (13).

2,3,6,7-Tetramethoxy-9-phenanthrenecarboxaldehyde (14). To a suspension of 3.58 g (16.6 mmol) of pyridinium chlorochromate in 30 mL of dry methylene chloride, was added in one portion a solution of 3.63 g (11.0 mmol) of 2,3,6,7-tetramethoxy-9-phenanthrenemethanol (**13**) dissolved in 75 mL of dry methylene chloride. The reaction mixture was stirred under nitrogen at room temperature for 3.0 h. Anhydrous ether (150 mL) was added and the mixture was stirred for 10 min, allowed to settle for 0.25 h, and filtered through a sintered glass funnel. The filtrate was evaporated to dryness to give a dark brown solid, which was filtered through a column of Florisil (100–200 mesh) using chloroform as eluant to give a greenish-yellow solid. This material was recrystallized from chloroform/hexane to give 3.53 g (98%) of yellow crystalline aldehyde **14**. An analytical sample recrystallized from ethyl acetate had mp 218–219 °C (lit.[37] mp 210 °C): IR ($CHCl_3$) 3050, 1680 and 1620 cm^{-1}; ^{1}H NMR δ 4.06 (s, 3 H), 4.10 (s, 3 H), 4.13 (s, 3 H), 4.16 (s, 3 H) 7.32 (s, 1 H), 7.75 (s, 1 H), 7.77 (s, 1 H), 8.04 (s, 1 H), 8.96 (s, 1 H), 10.25 (s, 1 H); MS (EI, m/e rel intensity) 326 (M^+, 100), 313 (7), 312 (25), 298 (12), 283 (12), 281 (10), 279 (6), 209 (9), 207 (41), 166 (16), 163 (10), 150 (9), 149 (48), 142 (8).

α-Ethenyl-2,3,6,7-tetramethoxy-9-phenanthrenemethanol (15). To an ice-cold solution of 8.5 mL of vinyllithium (1.19 M in THF) was added a suspension of 3.518 g (10.8 mmol) of aldehyde **14** in 200 mL of dry THF; the resulting light brown solution was stirred at room temperature under a dry nitrogen atmosphere for 1.0 h. Excess vinyllithium was destroyed by dropwise addition of 25 mL of saturated ammonium chloride solution. The mixture was stirred for 5 min and filtered to remove inorganic salts. The filtrate was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of solvent, the residue was chromatographed on a silica gel column using chloroform as eluant. The material obtained was recrystallized from ethyl acetate/hexane to afford 3.027 g (79%) of **15** as a colorless solid, mp 149–150 °C. An analytical sample recrystallized from ethyl acetate/hexane had mp 151–152 °C: IR ($CHCl_3$) 3600, 3050, 1620 cm^{-1}; ^{1}H NMR δ 2.19 (br s, 1 H, exchangeable), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.11 (s, 3 H), 4.12 (s, 3 H),

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5.35 (d of d, J = 9.19, 1.37 Hz, 1 H), 5.53 (d of d, J = 17.28, 1.37 Hz, 1 H), 5.82 (d, J = 3.12 Hz, 1 H), 6.23–6.39 (m, 1 H), 7.19 (s, 1 H), 7.65 (s, 2 H), 7.73 (s, 1 H), 7.80 (s, 1 H); MS (EI, m/e rel intensity) 354 (M^+, 3), 353 (12), 352 (50), 350 (29), 337 (29), 336 (100), 334 (20), 322 (9), 321 (9), 311 (5), 310 (7), 306 (10), 292 (7), 280 (12), 278 (5), 209 (12), 208 (17), 207 (82), 191 (11), 176 (7), 149 (15), 133 (9), 96 (12). Exact mass: calcd for $C_{21}H_{22}O_5$, 354.1466; found, 354.1489.

Ethyl 5-(2,3,6,7-Tetramethoxy-9-phenanthrenyl)-4-pentenate (16). A solution containing 2.92 g (8.24 mmol) of allylic alcohol **15**, 70 mL of triethyl orthoacetate (dried over anhydrous K_2CO_3), and 4 drops of propionic acid was heated with stirring at 135–136 °C for 2.0 h. The solution was cooled and to it was added 50 mL of ether. The mixture was washed with 5% $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo and the residual crude oil was chromatographed on a silica gel column using chloroform as eluant giving 1.88 g (54%) of ester **16**, which when recrystallized from ethyl acetate/hexane had mp 97–98 °C: IR ($CHCl_3$) 3050, 3010, 1730, 1620 cm^{-1}; ^1H NMR δ 1.27 (t, J = 7 Hz, 3 H), 2.56–2.70 (m, 4 H), 4.02 (s, 3 H), 4.06 (s, 3 H), 4.11 (s, 6 H), 4.17 (q, J = 7 Hz, 2 H), 6.24 (t of d, J = 6, 15 Hz, 1 H), 7.08 (d, J = 15 Hz, 1 H), 7.20 (s, 1 H), 7.43 (s, 1 H), 7.59 (s, 1 H), 7.75 (s, 1 H), 7.80 (s, 1 H); MS (EI, m/e rel intensity) 424 (M^+, 100), 410 (2), 379 (5), 337 (7), 321 (5), 306 (8), 291 (2), 275 (2), 189 (4), 175 (6), 168 (4.0).

Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.63; H, 6.76.

5-(2,3,6,7-Tetramethoxy-9-phenanthrenyl)-4-pentenamide (17). To a solution of 850 mg (2.00 mmol) of ester **16** in 75 mL of dry methylene chloride was added 5.0 mL (7 mmol) of dimethylaluminum amide in methylene chloride. The solution was refluxed under a dry nitrogen atmosphere for 19.0 h. The reaction mixture was cooled, and 30 mL of water was added dropwise. The precipitated salts were removed by filtration. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product was chromatographed on a silica gel column using 25% hexane/ethyl acetate followed by 3% methanol/ethyl acetate. After evaporation of solvent, 633 mg (80%) of amide **17** suitable for the next step was obtained. An analytical sample was recrystallized from chloroform/hexane giving a colorless crystalline product, mp 213–214 °C: IR ($CHCl_3$) 3550, 3425, 3050, 3010, 1680, 1620 cm^{-1}; ^1H NMR δ 2.50 (t, J = 7 Hz, 2 H), 2.72 (q, J = 7 Hz, 2 H), 4.03 (s, 3 H), 4.06 (s, 3 H), 4.12 (s, 6 H), 5.46–5.53 (br s, 2 H), 6.26 (t of d, J = 7, 15.2 Hz, 1 H), 7.18 (d, J = 15.6 Hz, 1 H), 7.20 (s, 1 H), 7.42 (s, 1 H), 7.61 (s, 1 H), 7.75 (s, 1 H), 7.81 (s, 1 H); MS (EI, m/e rel intensity), 395 (M^+, 100), 378 (50), 377 (78), 337 (47), 338 (13), 321 (13), 307 (20), 306 (65), 305 (36), 291 (16), 279 (15), 275 (16), 202 (8), 189 (16). Exact mass: calcd for $C_{23}H_{25}NO_5$, 395.1731; found, 395.1727.

***N*-[(Acetoxy)methyl]-5-(2,3,6,7-tetramethoxy-9-phenanthrenyl)-4-pentenamide (18).** A solution of 132 mg (0.334 mmol) of amide **17** in 2.0 mL of glyme containing 2.0 mL of 5% NaOH and 0.25 mL of 37% aqueous formaldehyde was stirred at room temperature for 14 h. Sodium bicarbonate was added and the mixture was stirred for 10 min. The solvent was evaporated in vacuo, and the residue was dissolved in chloroform (75 mL), dried over $MgSO_4$, and evaporated to give the methylol as a low-melting solid which was evacuated under vacuum for 10 min. To this material was added 2.0 mL of acetic anhydride and 2 drops of pyridine, and the mixture was stirred at room temperature for 22.5 h. The solvent was evaporated in vacuo and the residue was dissolved in chloroform (75 mL), washed with water (25 mL) and brine (25 mL), and dried over $MgSO_4$. The chloroform was evaporated and the residue was chromatographed on a silica gel column using 3% methanol/ethyl acetate affording 93 mg (60%) of **18**. An analytical sample was recrystallized from ethyl acetate giving colorless crystalline acetate **18**, mp 155–156 °C: IR ($CHCl_3$) 3450, 3050, 3000, 1740, 1695, 1620 cm^{-1}; ^1H NMR δ 1.92 (s, 3 H), 2.48 (t, J = 7 Hz, 2 H), 2.71 (q, J = 7 Hz, 2 H), 4.03 (s, 3 H), 4.08 (s, 3 H), 4.12 (s, 6 H), 5.26 (d, J = 7 Hz, 2 H), 6.22 (t of d, J = 7, 15 Hz, 1 H), 6.70 (br t, J = 7 Hz, 1 H), 7.10 (d, J = 15 Hz, 1 H), 7.21 (s, 1 H), 7.42 (s, 1 H), 7.60 (s, 1 H), 7.75 (s, 1 H), 7.81 (s, 1 H); MS (EI, m/e rel intensity) 467 (M^+, 17), 409 (43), 408 (51), 407 (100), 395 (27), 392 (16), 379 (22), 378 (41), 377 (83), 350 (19), 337 (37), 326 (40), 324 (92), 312 (23), 311 (67), 306 (44), 305 (19), 291 (13), 281 (11), 276 (13), 207 (40), 189 (13). Exact mass: calcd for $C_{26}H_{29}O_7N$, 467.19441; found, 467.1964.

12,13,13a,14-Tetrahydro-2,3,6,7-tetramethoxydibenzo[*f*,*h*]pyrrolo-[1,2-*b*]isoquinolin-11(9*H*)-one (21). A solution of 41.6 mg (0.089 mmol) of methylol acetate **18** in 5 mL of redistilled bromobenzene was heated at 219–220 °C in a sealed tube for 5.0 h. The solvent was evaporated in vacuo. The crude product was purified by passing through a short column of silica gel (~1 g) using ethyl acetate/hexane (1:1), followed by methanol/ethyl acetate (1:9) affording 18 mg (50%) of pure lactam **21** which had IR, NMR, mass spectrum, TLC, and UV identical with an authentic sample (mp 263 °C; lit.[13a] mp 273 °C): IR ($CHCl_3$) 3000, 1680, 1620 cm^{-1}; ^1H NMR δ 1.20–1.27 (m, 2 H), 2.47–2.70 (m, 4 H), 3.43–3.53 (m, 1 H), 4.04 (s, 3 H), 4.06 (s, 3 H), 4.12 (s, 3 H), 4.13 (s, 3 H), 4.55 (d, J = 17 Hz, 1 H), 5.31 (d, J = 17 Hz, 1 H), 7.15 (s, 1 H), 7.28 (s, 1 H), 7.82 (s, 1 H), 7.83 (s, 1 H); MS (EI, m/e rel intensity) 407 (M^+, 100) 394 (9), 392 (7), 376 (6), 327 (15), 326 (81), 325 (19), 324 (70), 311 (5), 309 (6), 298 (7), 283 (9), 281 (12), 208 (7), 207 (19), 204 (11), 203 (21), 201 (5), 200 (13), 195 (6), 192 (10), 185 (7), 183 (11), 165 (10), 163 (13), 162 (17), 152 (8), 151 (10), 141 (6), 140 (15), 137 (11), 135 (9), 126 (8), 125 (13), 123 (15), 121 (9), 119 (9), 112 (12), 111 (21), 110 (3), 109 (19), 107 (9), 105 (11), 99 (13), 98 (12), 97 (38), 96 (10), 95 (25), 83 (38), 81 (30), 71 (42), 69 (68).

Racemic Tylophorine (2). To a suspension of 9.33 mg (0.0229 mmol) of lactam **21** in 4.0 mL of dry THF was added 3.0 mg of lithium aluminum hydride and the mixture was stirred at room temperature for 1.25 h. A saturated solution of NH_4Cl was added to the reaction mixture followed by dilution with chloroform, and the mixture was filtered to remove inorganic salts. The chloroform layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The crude product was purified by preparative TLC on slilica gel using $CHCl_3$/MeOH (9:1) containing 1 drop of concentrated NH_4OH in 100 mL of solution, yielding 5.78 mg (64%) of racemic tylophorine (**2**) which had TLC, IR, NMR, mass spectrum, and UV identical with those of natural tylophorine.

Dimethyl (2-Oxopentyl)phosphonate (24). To 400 mL of dry THF at −70 °C under N_2 was added *n*-butyllithium (236 mL, 0.40 mol, 1.7 M in hexanes) followed by the dropwise addition of dimethyl methylphosphonate (49.6 g, 0.40 mol) with stirring over 0.5 h.[23] The resulting white mixture was stirred for 0.5 h at −70 °C under N_2, and redistilled ethyl *n*-butyrate (55.6 g, 0.48 mol) was added dropwise. Stirring was continued for 0.5 h at −70 °C and for an additional hour while the mixture was warmed to room temperature. The resulting clear reaction mixture was concentrated in vacuo to a mobile oil, diluted with 200 mL of ethyl acetate, and washed with three 60-mL portions of 10% acetic acid. The combined aqueous layer was saturated with NaCl and back-extracted with three 60-mL portions of ethyl acetate. The original organic layers were combined and washed with three 60-mL portions of saturated $NaHCO_3$ which were also combined and back-extracted as above. All of the various organic layers were then combined and washed with three 60-mL portions of brine. The ethyl acetate extract was dried over anhydrous $MgSO_4$, concentrated in vacuo, and distilled through a 20-cm Vigreux column to yield a clear oil, bp 93–96 °C (0.2 Torr), (35.5 g, 46%). Half of this product was redistilled, bp 87–88 °C (0.15 Torr), to afford analytically pure **24**: IR (film) 3000–2850, 1720, 1260, 1030 cm^{-1}; ^1H NMR δ 3.75 (d, 6 H, J = 11 Hz), 3.08 (d, 2 H, J = 22 Hz), 2.6 (t, 2 H, J = 7 Hz), 1.6 (h, 2 H, J = 7 Hz), 0.92 (t, 3 H, J = 7 Hz).

Anal. Calcd for $C_7H_{15}O_4$: C, 43.51; H, 7.82. Found: C, 43.57; H, 7.97.

Dimethyl [1-(1-Oxobutyl)-1,5-hexadienyl]phosphonate (25). Phosphonate **24** (23.2 g, 0.12 mol), piperidine (0.3 g), and glacial acetic acid (2.0 mL) were dissolved in benzene (200 mL) in a flask equipped with a Dean-Stark apparatus and the mixture was brought to reflux. Using a Hirschberg funnel, 4-pentenal[24] (12.6 g, 0.15 mol) was added dropwise over 1 h, and the mixture was heated at reflux for 5 h longer under N_2.[25b] The resulting light-yellow solution was cooled to room temperature and washed with 50 mL of saturated $NaHCO_3$ and 50 mL of brine. Each aqueous layer was back-extracted with 50 mL of $CHCl_3$ and the combined organic extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on 150 g of silica gel (hexanes–ethyl acetate, 1:1) to yield a slightly impure fraction (16.1 g) and pure fraction (9.64 g). Rechromatography of the first fraction on 100 g of silica gel produced 14.08 g of vinyl phosphonate **25**: total yield, 23.7 g (76%); IR (film) 2960, 1720, 1660, 1610, 1595, 1460, 1260, 1060–1020, 920, 830, 790 cm^{-1}; ^1H NMR δ 6.0–4.7 (m, 4 H), 3.82, (d, 3 H, J = 11 Hz), 3.66 (d, 3 H, J = 11 Hz), 3.0–2.2 (m, 6 H), 1.8–1.4 (m, 2 H), 0.92 (t, 3 H, J = 7 Hz).

1-[2-(3-Butenyl)-2,5-dihydro-3-thienyl]-1-butanone (26). A mixture of phosphonate **25** (20.75 g, 0.080 mol), *p*-dithiane-2,5-diol (7.3 g, 0.48 mol), and triethylamine (10.5 g, 0.104 mol) dissolved in CH_2Cl_2 (600 mL) was refluxed for 6 h under N_2.[25] The reaction solution was cooled and extracted with 200 mL of 5% HCl and 200 mL of brine. The aqueous layers were each extracted with 100 mL of CH_2Cl_2. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Chromatography of the resulting light yellow oil on 150 g of silica gel (2:1, then 1:1, hexanes–ethyl acetate) yielded dihydrothiophene **26** as a clear oil homogeneous by TLC (9.36 g, 56%): IR (film) 3080, 2980–2850, 1680, 1640–1630, 1350–1335, 1280, 1200, 1170, 1000, 920 cm^{-1}; 1 H NMR δ 6.78 (m, 1 H), 6.0–5.4 (m, 1 H), 5.2–4.7 (m, 2 H), 4.5–4.3 (m, 1 H), 3.8 (m, 2 H), 2.65 (t, 2 H, J = 7 Hz), 2.4–1.2 (m, 6 H), 0.92 (t, 3 H, J = 7 Hz); MS (EI, m/e measured, rel intensity, m/e

calcd) 210.1080 (M^+, 46, 210.1078), 155.0515 ($M^+ - C_4H_7$, 75, 155.0531), 139.0560 ($M^+ - C_4H_6O$, 30, 139.0548), 125.0141 (12, 125.0140), 97.0107 (28, 97.0112), 71.0510 (100, 71.0497).

1-[2,5-Dihydro-2-(2-oxiranylethyl)-3-thienyl]-1-butanone *S,S*-Dioxide (27). A solution of *m*-chloroperbenzoic acid (52.9 g, 0.26 mol, Aldrich, ca. 85%) in CH_2Cl_2 (250 mL) was added to a solution of dihydrothiophene **26** (9.1 g, 0.0433 mol) in CH_2Cl_2 (600 mL). After stirring for 24 h, the mixture was filtered, concentrated *at room temperature*, refiltered, and extracted with saturated $NaHCO_3$, followed by brine. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to yield a cloudy oil (11.0 g). The crude product was dissolved in 150 mL of CH_2Cl_2, treated with 5.0 g of activated charcoal for 10 min, and filtered through Celite which was then rinsed with 50 mL of CH_2Cl_2. Concentration of the filtrate in vacuo provided sulfone epoxide **27** as a clear oil homogeneous by TLC and suitable for the next step (10.42 g, 92%): IR (film) 3000–2900, 1720, 1680, 1620, 1450, 1400, 1380, 1310, 1260, 1160, 930 cm^{-1}; ^1H NMR δ 6.8 (t, 1 H, J = 3 Hz), 3.9 (d, 2 H, J = 3 Hz), 3.9 (m, 1 H), 3.0–2.3 (m, 5 H), 2.2–1.3 (m, 6 H), 0.92 (t, 3 H, J = 7 Hz); MS (CI, m/e 1, rel intensity) 258 (M^+, 38), 194 ($M^+ - SO_2$, 100), 176 (64), 148 (33).

2,5-Dihydro-3-(1-oxobutyl)-2-thiophenepropanoic Acid 1,1-Dioxide (28). A solution of chromium trioxide (8.0 g, 0.08 mol) and periodic acid (36.5 g, 0.16 mol) in distilled H_2O (400 mL) was added dropwise to a solution of epoxide **27** (10.32 g, 0.040 mol) in acetone (400 mL).[26] The orange solution gradually turned green as it was stirred at room temperature for 4 h. Solid $NaHSO_3$ was added and the mixture was stirred for 0.5 h, then concentrated in vacuo at room temperature. The resulting clear, deep blue-green solution was extracted with three 250-mL portions of CH_2Cl_2 which were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield acid **28** as a clear oil of sufficient purity for subsequent reactions (8.84 g, 84%): IR (film) 3500–3000, 2950–2800, 1720, 1680, 1620, 1310, 1160, 1130 cm^{-1}; ^1H NMR δ 10.2–9.5 (br s, 1 H), 6.95 (t, 1 H, J = 3 Hz), 4.0 (d, 2 H, J = 3 Hz) 4.0 (m, 1 H), 3.0–2.4 (m, 4 H), 2.4–2.0 (m, 2 H), 2.0–1.3 (m, 2 H), 0.92 (t, 3 H, J = 7 Hz).

2,5-Dihydro-3-(1-oxobutyl)-2-thiophenepropanamide 1,1-Dioxide (29). The acid **28** (6.88 g, 0.0264 mol) in CH_2Cl_2 (400 mL) was cooled to −15 °C and triethylamine (3.0 g, 0.03 mol, distilled from CaH_2) and redistilled ethyl chloroformate (3.26 g, 0.03 mol) were added in succession under nitrogen. Stirring at −15 to −5 °C was continued for 1 h. The light yellow solution was cooled again to −15 °C and ca. 2 mL of dry NH_3 in 5 mL of CH_2Cl_2 was added dropwise. After warming to room temperature over 0.5 h, the mixture was filtered and extracted successively with 200 mL of 5% HCl, 200 mL of $NaHCO_3$, and 200 mL of brine. Each aqueous phase was back-extracted with 50 mL of CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4, concentrated in vacuo, and chromatographed on 75 g of silica gel (1:1, hexanes–ethyl acetate then 2% methanol–ethyl acetate) to produce a clear oil, homogeneous by TLC, which crystallized upon refrigeration for several days to form a white solid, mp 76–78 °C (3.6 g). Another crop was obtained by acidifying the $NaHCO_3$ layer and extracting with 200 mL of CH_2Cl_2 and 200 mL of ethyl acetate, drying and chromatographing as above on 10 g of silica gel to give an additional 0.40 g of amide **29** (total yield: 4.0 g, 58%). Amide **29** was recrystallized from ether–methylene chloride giving small, shiny white crystals, mp 80.5–81.5 °C: IR ($CHCl_3$) 3430, 3350, 2900–2850, 1680, 1620, 1400, 1310, 1160, 1120 cm^{-1}; ^1H NMR δ 7.08 (t, 1 H, J = 3 Hz), 6.5–6.2 (br s, 2 H), 4.2–4.0 (d, 2 H, J = 3 Hz, m, 1 H), 2.8–2.0 (m, 6 H), 2.0–1.4 (h, 2 H, J = 7 Hz), 0.97 (t, 3 H, J = 7 Hz); ^{13}C NMR δ 195.9, 174.2, 142.0, 132.2, 62.8, 56.9, 39.8, 31.7, 24.7, 17.0, 13.3; MS (CI, m/e − 1, rel intensity) 259 (M^+, 100), 242 (52), 223 (23), 195 ($M^+ - SO_2$, 80), 178 (82).

Anal. Calcd for $C_{11}H_{17}O_4NS$: C, 50.95; H, 6.61; N, 5.40. Found: C, 50.74; H. 6.57; N, 5.25.

2,5-Dihydro-*N*-[(methylthio)methyl]-3-(1-oxobutyl)-2-thiophenepropanamide 1,1-Dioxide (31). Amide **29** (0.40 g, 1.54 mmol) was dissolved in CH_2Cl_2 (4.0 mL). Trifluoroacetic acid (4.0 mL) and chloromethyl methyl sulfide (4.0 mL) were added slowly in succession, followed by stirring for 4 h. The solution was diluted with 25 mL of CH_2Cl_2 and extracted with 20 mL of H_2O. Further extractions of the aqueous layer (three 40-mL portions of ethyl acetate) were added to the original organic layer and the combined extract was dried over anhydrous Na_2SO_4, evaporated in vacuo for 40 min at 30–35 °C, diluted with another 100 mL of ethyl acetate followed by slow evaporation under vacuum for another 30 min. The residual oil was evacuated at 0.1 Torr for 20 min, then immediately chromatographed on 120 g of silica gel (ethyl acetate) to yield sulfide **31** as a clear oil (304 mg, 62%): IR (film) 3400–3300, 2950–2800, 1680, 1620, 1540, 1400, 1310, 1205, 1160, 1120 cm^{-1}; ^1H NMR δ 7.03 (t, 1 H, J = 3 Hz), 6.8–6.5 (t, 1 H, J = 6 Hz), 4.40 (d, 2 H, J = 6 Hz), 4.2–4.0 (d, 2 H, J = 3 Hz) (m, 1 H), 3.0–2.0 (m, 4 H), 2.2 (s, 3 H), 2.0–1.4 (m, 4 H), 0.96 (t, 3 H, J = 7 Hz); MS (CI, m/e − 1, rel intensity) 283 (32), 267 (65), 255 ($M^+ - SO_2$, 38), 207 ($M^+ - SO_2 - NHSCH_3$, 100), 148 (74).

***N*-[(Acetyloxy)methyl]-2,5-dihydro-3-(1-oxobutyl)-2-thiophenepropanamide 1,1-Dioxide (32).** Mercuric acetate (39 mg, 0.122 mmol) was added to sulfide **31** (39 mg, 0.122 mmol) in glacial acetic acid (1 mL). The resulting solution was stirred for 2 h under N_2. Water (5 mL) was added and the mixture was extracted with three 10-mL portions of ethyl acetate. The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Chromatography of the resulting oil on 5 g of silica gel (ethyl acetate) provided **32** (35 mg, 87%): IR (film) 3500–3200, 3000–2850, 1720, 1680, 1530, 1380, 1300, 1120, 1020, 910 cm^{-1}; ^1H NMR δ 6.90 (t, 1 H, J = 3 Hz) 6.9–6.8 (m, 1 H), 5.20 (d, 2 H, J = 7 Hz), 4.0 (d, 2 H, J = 3 Hz), 4.0 (m, 1 H), 3.0–2.2 (m, 4 H), 2.10 (s, 3 H), 2.0–1.3 (m, 4 H), 1.0 (t, 3 H, J = 7 Hz).

2,5-Dihydro-3-(1-hydroxybutyl)-*N*-[(methylthio)methyl]-2-thiophenepropanamide 1,1-Dioxide (33). Solid sodium borohydride (26.5 mg, 0.70 mmol) was added to a stirred solution of keto sulfide **31** (224 mg, 0.70 mmol) in 0.4 N $CeCl_3$ in methanol (3 mL). Stirring was continued for 1 min after initial effervescence. The reaction was quenched with 10 mL of H_2O, and extracted with three 40-mL portions of ethyl acetate. The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield alcohol sulfide **33** as an *inseparable 5:1* mixture of diastereomers of sufficient purity for the next step (202 mg, 90%): IR (film) 3500–3200, 2960–2800, 1660, 1540, 1305, 1260, 1160, 1120 cm^{-1}; ^1H NMR δ 6.8 (t, 1 H, J = 7 Hz), 6.0 (m, 1 H), 5.0–4.8 (m, 1 H), 4.3 (d, 2 H, J = 7 Hz), 3.8–3.7 (m, 3 H), 2.8–2.3 (m, 3 H), 2.2 (s, 3 H), 1.8–1.2 (m, 6 H), 1.2–0.80 (m, 3 H): ^{13}C NMR δ 172.3′, 171.7, 154.2′, 145.2, 122.4′, 115.8, 69.5, 64.2, 55.5, 42.8, 37.4, 32.2, 23.5, 18.2, 14.4, 137 (′ = observable minor diastereomer peaks); MS (CI, m/e − 1, rel intensity) 239 ($M^+ - SO_2 - H_2O$, 82), 207 (100), 191 (57), 178 (57).

***N*-[(Acetyloxy)methyl]-2,5-dihydro-3-(1-hydroxybutyl)-2-thiophenepropanamide 1,1-Dioxide (34).** The diastereomeric mixture of alcohol–sulfide **33** (200 mg, 0.622 mmol) was dissolved in glacial acetic acid (22 mL). Solid mercuric acetate (198 mg, 0.622 mmol, recrystallized from glacial acetic acid) was added and the resulting light yellow solution was stirred for 1 h, then partitioned between 10 mL of H_2O and four 25-mL $CHCl_3$ portions. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude acetate was chromatographed on 5 g of silica gel (ethyl acetate) to yield **34** as a clear oil which had ^1H and ^{13}C NMR indicating a mixture of diastereomers (170 mg, 82%): IR (film) 3500–3200, 2950–2800, 1740, 1680, 1540, 1370, 1300, 1160, 1120, 1020, 960 cm^{-1}; ^1H NMR (200 MHz) δ 7.23 (t, 1 H, J = 7 Hz), 6.0 (t, 1 H, J = 1.5 Hz), 5.21 and 5.20 (2 d, 2 H, J = 7.2 Hz), 4.2 (m, 1 H), 3.76 (br s, 2 H), 3.69 (t, 1 H), 2.8–2.12 (m, 3 H), 2.06 (s, 3 H), 1.98–1.06 (m, 6 H), 0.94 (t, 3 H, J = 7 Hz, two triplets overlapping); MS (CI, m/e − 1, rel intensity) 273 (M^+ − HOAc, 43), 251 ($M^+ - H_2O - SO_2$, 32), 209 (M^+ − HOAc − SO_2, 60), 191 (M^+ − HOAc − $SO_2 - H_2O$, 100).

***N*-[(Acetyloxy)methyl]-2,5-dihydro-3-[1-[(trimethylsilyl)oxy]butyl]-2-thiophenepropanamide 1,1-Dioxide (35).** Hexamethyldisilazane (3 mL) and trimethylsilyl chloride (1.5 mL) were added to alcohol acetate **34** (170 mg, 0.510 mmol) dissolved in anhydrous pyridine (5 mL). After 5 min the reaction mixture was quenched with 10 mL of H_2O and extracted with three 25-mL portions of $CHCl_3$. The organic extract was dried over anhydrous Na_2SO_4 and evaporated in vacuo. Rapid chromatography of the resulting clear oil through 0.5 g of silica gel ($CHCl_3$) yielded silyl ether **35** as a clear, colorless oil (198 mg, 96%). This material was sensitive to hydrolysis and was used immediately with no further purification in the next step: IR (film) 3360, 2950–2850, 1740, 1690, 1540, 1370, 1300, 1160, 1120, 961, 900, 840 cm^{-1}; ^1H NMR δ 7.2 (m, 1 H), 6.0–5.7 (m, 1 H), 5.2 (d, 2 H, J = 17 Hz), 4.25 (m, 1 H), 3.8–3.5 (m, 3 H), 2.7–2.2 (m, 2 H), 2.1 (s, 3 H), 1.8–1.2 (m, 6 H), 1.1–0.8 (m, 3 H); MS (EI, m/e) 186 ($M^+ - SO_2$ − HOAc); MS (CI, m/e − 1, rel intensity) 345 (M^+ − HOAc, 100).

1,5,6,8a-Tetrahydro-8-(1-hydroxybutyl)-3(2*H*)-indolizinone (37b/39b). A dilute solution of the acetate **35** (140 mg, 0.345 mmol) in toluene (50 mL) was added slowly (1 drop/3–4 s) through a column of glass helices as described for conversion of **8** to **9**. The addition was conducted over 2 h while maintaining a column temperature of 370 °C. Concentration of the condensed solution in vacuo yielded a clear, slightly yellow oil showing a single TLC spot (66 mg, 68%). This crude oil was further purified by preparative TLC using ethyl acetate as eluant, giving a mixture of silyl ethers **37a/39a** as a clear, colorless oil in a 5:4 ratio (52.0 mg, 0.185 mmol, 54%): IR (film) 3100–2850, 1680, 1430, 1250–1200, 910, 840 cm^{-1}; ^1H NMR (200 MHz) δ 5.75 (d, ~1/2 H, J = 4.1 Hz), 5.67 (minor epimer) (d, ~1/2 H, J = 5.5 Hz), 4.3–3.9 (m, 3 H), 2.77–2.66 (m, 1 H), 2.47–1.14 (m, 10 H), 0.90 and 0.89 (2 t, 3 H); MS (CI, m/e − 1, rel intensity) 282 (M^+ + 1, 27), 281 (M^+, 100), 265 (13), 191 (20), 190 (13), 179 (20).

Hydrolysis of the silyl group was effected by dissolving **37a/39a** (40.0 mg, 0.142 mmol) in freshly distilled THF (3 mL) followed by addition of 3 drops of H_2O and 1 drop of 1 M HCl and allowing the solution to stand for 5 min. The product was obtained by concentration in vacuo and preparative TLC ($CHCl_3$/MeOH, 9:1) yielding a mixture of lactam alcohols **37b/39b** as a clear, colorless oil (28.5 mg, 96%) in the same 5:4 diastereomeric ratio: IR (film) 3600–3200, 3000–2800, 1680, 1430, 1310, 1260, 860 cm^{-1}; ^1H NMR (200 MHz) δ 5.87 (d, 1/2 H, J = 4.78 Hz), 5.81 (minor epimer) (d, ~1/2 H, J = 5.48 Hz), 4.32–4.08 (m, 3 H), 2.82–2.65 (m, 1 H), 2.50–2.0 (m, 5 H), 2.0–1.28 (m, 6 H), 0.96 and 0.95 (2 t, 3 H); ^{13}C NMR δ 173.1, 172.7, 140.9, 140.5, 121.1, 118.1, 72.7, 70.24, 55.5, 55.4, 38.1, 36.4, 35.7, 35.5, 31.4, 31.2, 28.9, 26.2, 25.5, 23.60, 18.7, 18.1, 13.4, 13.4; MS (CI, m/e - 1, rel intensity) 209 (M^+, 100), 191 ($M^+ - H_2O$, 21).

It was found that 10 mg of lactams could be separated by employing a medium-pressure liquid chromatography apparatus[31] using a 2 × 30 cm column filled with silica gel (Woelm 0.023–0.063 mm), eluting with 20:1 $CHCl_3$–MeOH, providing 5 and 4 mg of each diastereomer. The 200-MHz ^1H NMR spectra of these isomers were very similar to that of the mixture.

(±)-1,5,6,8a-Tetrahydro-8-(1-oxobutyl)-3(2*H*)-indolizinone (22a). Pyridinium chlorochromate (15 mg, 0.07 mmol) was added to the mixture of alcohols **37b/39b** (10.5 mg, 0.05 mmol) dissolved in CH_2Cl_2 (1 mL) and the mixture was stirred for 1 h.[14] The mixture was chromatographed on 2 g of Florisil (ethyl acetate) yielding lactam enone **22a** (6.75 mg, 66%): IR (film) 3000–2850, 1680, 1420 cm^{-1}; ^1H NMR δ 6.9 (t, 1 H, J = 3 Hz), 4.5–4.0 (m, 2 H), 2.9–2.0 (m, 7 H), 2.20–1.0 (m, 4 H), 0.90 (t, 3 H, J = 7 Hz).

1,2,3,5,6,8a-Hexahydro-α-propyl-8-indolizinemethanol (elaeokanine B) (4). Diisobutylaluminum hydride (0.6 mL, 0.6 mmol, 1.0 M in hexanes) was added dropwise under N_2 to a solution of epimeric lactams **37b/39b** (25.2 mg, 0.120 mmol) in THF at room temperature. Stirring was continued for an additional 0.5 h. The solution was hydrolyzed with 5 mL of 1 M HCl and extracted with 10 mL of $CHCl_3$. The aqueous layer was basified with solid Na_2CO_3 and extracted with three 20-mL $CHCl_3$ portions. Drying over anhydrous Na_2SO_4 and concentration in vacuo yielded the diastereomeric amino alcohols (elaeokanine B) (**4**) as a clear oil which decomposed slowly at room temperature but was stable for several weeks below 0 °C (21.2 mg, 91%): IR (film) 3500–3200, 3000–2700, 1260, 1050, 800 cm^{-1}; ^1H NMR (200 MHz) δ 5.65 (s, 1 H), 4.04–3.74 (m, 2 H), 3.10–1.28 (m, 15 H), 0.86 (t, 3 H, J = 6 Hz); MS (CI, m/e - 1, rel intensity) 195 (P, 40), 194 (20), 193 (33), 177 (P - H_2O, 100); MS (EI, m/e measured, rel intensity, m/e calcd) 195.1607 (M^+, 14, 195.1623), 194.1582 (M^+ - 1, 23, 194.1545), 122.0967 (100, 122.0970).

The diastereomeric amino alcohols **40** and **41** could be separated, although with difficulty, by preparative TLC on silica gel ($CHCl_3$/ether/MeOH/28%NH_4OH, 40:35:20:5). Each epimer gave 200-MHz ^1H NMR spectra identical with the compound prepared by reduction of the individual lactams **37b** and **39b**. The TLC's of pure compounds **40** and **41** prepared by either method were identical. NMR spectra of each isomer was nearly identical with that of the mixture.

(±)-1-(1,2,3,4,6,8a-Hexahydro-8-indolizinyl)-1-butanone (elaeokanine A) (3). Trifluoroacetic acid (32 mg, 0.15 mmol) was added under N_2 to a stirred solution of dimethyl sulfoxide (16 mg, 0.20 mmol) in CH_2Cl_2 at -78 °C.[35] This cold solution was stirred under N_2 for 20 min. Epimeric alcohol **4** (20.0 mg, 0.102 mmol) in CH_2Cl_2 (1 mL) was then added. Stirring at -78 °C under N_2 was continued for 1 h and the reaction mixture was quenched with 3 drops of triethylamine, warmed to room temperature over 10 min, and hydrolyzed with 1 mL of H_2O. Extraction with three 3-mL portions of CH_2Cl_2, drying over anhydrous Na_2SO_4, and concentration in vacuo yielded crude racemic elaeokanine A (**3**). Chromatography on preparative silica gel G plates (saturated NH_4OH in ether, methanol, $CHCl_3$, 2:2:1) gave the alkaloid as a clear oil (12.2 mg, 62%) identical in spectral properties to natural elaeokanine A.[19,34] IR ($CHCl_3$) 3100–2800, 1665, 1200, 1040 cm^{-1}; ^1H NMR (200 MHz) δ 6.887 (d of t, 1 H, J = 4.1, 1.6 Hz), 3.30 (m, 1 H), 2.99–2.28 and 1.92–1.25 (m, 14 H), 0.925 (t, 3 H, J = 7.4 Hz); UV λ_{max} (ϵ): 229 (10,000); MS (CI, m/e - 1, rel intensity) 194 (13), 193 (M^+, 100), 192 (11), 191 (17); MS (EI, m/e measured, rel intensity, m/e calcd) 193.1463 (M^+, 35, 193.1466), 192.1391 (M^+ - 1, 17, 192.1388), 173.1239 (17, 173.1231), 165.1158 (11, 165.1154), 164.1069 ($M^+ - C_2H_5$, 9, 164.1075), 151.0949 (12.5, 151.0952), 150.0904 ($M^+ - C_3H_7$, 100, 150.0919), 123.1041 (19, 123.1048), 122.0981 ($M^+ - C_4H_7O$, 40, 122.0970), 120.0821 (9, 120.0813).

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Reaction of Benzophenone Triplets with Allylic Hydrogens. A Laser Flash Photolysis Study

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Abstract: The quenching of benzophenone by olefins having allylic hydrogens leads to hydrogen abstraction in addition to quenching by the π system. The fraction of quenching events that leads to hydrogen abstraction in benzene at 27 °C ranges from ~0 for conjugated dienes to 94% for 1,4-cyclohexadiene. For cyclohexene the rate constant for abstraction is 1.7×10^7 M^{-1} s^{-1} and accounts for 23% of the quenching events. Deuteration leads to a decrease in the fraction of abstraction, which for cyclohexene-d_{10} is 11%. Hydrogen abstraction has a higher activation energy than quenching by the double bond; as a result its importance increases with increasing temperatures. The absolute rate constants for the reactions of *tert*-butoxy radicals with the olefins were also measured.

Introduction

The interaction of carbonyl triplets with double bonds has been the subject of numerous studies.[3-18] The predominant process is known to involve interaction with the π system leading to a 1,4-biradical, probably via a charge-transfer precursor.[5-7,10] This

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