# A Unified Strategy for the Synthesis of Phenanthroizidine Alkaloids: Preparation of Sterically Congested Pyridines

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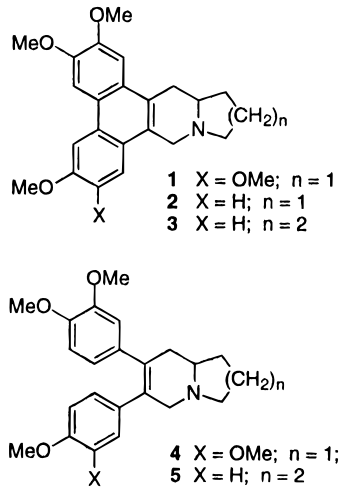
**Abstract:** Total syntheses of the representative phenanthroizidine alkaloids, tylophorine and antofine, and of their seco congeners, septicine and julandine, have been completed from sterically congested 3,4-diarylpyridines prepared by a modified Knoevenagel−Stobbe synthesis. Central to the success of this effort was the ability of α-dicarbonyl enones to combine in a formal [4 + 2]-cycloaddition with sterically demanding vinyl ethers.

## Introduction

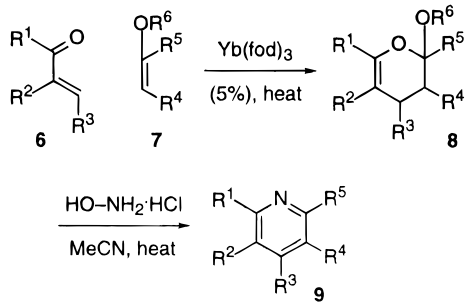
Phenanthroizidine alkaloids are found primarily in plants belonging to the *Asclepiadaceae* family.[1] Most members of this small group of natural products display a phenanthroindolizidine framework, e.g., tylophorine, **1**, and antofine, **2**, though more rare phenanthroquinolizidines such as cryptopleurine, **3**, are also known. Seco congeners of **1**−**3**, e.g. septicine, **4**, and julandine, **5**, occur in the same plant family and indeed, they are the putative biogenetic precursors of phenanthroizidines (Scheme 1).[2] It is also well recognized that oxidative conversion of the seco alkaloids to full-fledged phenanthroizidines may be readily accomplished by chemical methods; therefore seco substances may be also regarded as synthetic precursors to **1**−**3**. Phenanthroizidines exhibit interesting biological properties[1] ranging from antitumor activity,[2] seemingly through inhibition of protein synthesis, to nerve growth stimulation, to unusual cardiovascular and immunological effects, and to probable antiinflammatory action,[3] and as a consequence of their bioactivity and unusual architecture they have engendered a great deal of synthetic work.[4]

Alkaloids **1**−**5** appear to be within the scope of our pyridine synthesis, which can furnish end-products **9** with many permutations of groups $R^1$−$R^5$ (Scheme 2).[5] The retrosynthetic construct of Scheme 3 shows that a pyridine **12** suitable for the creation of a phenanthroizidine **10** could arise through the merger of enone **13** with ether **14**, followed, in some appropriate order, by izidine formation, controlled reduction of the pyridine, and oxidative cyclization. Problems and solutions pertaining to the present formulation are detailed herein.

**Scheme 1**




**Scheme 2**




## Background

The hypothesis of Scheme 3 was initially explored by attempting the cycloaddition[6] of benzalacetone, **21**, with ether

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1996.

(1) Reviews: (a) Gellert, E. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley & Sons: New York, New York, 1987; Vol. 5, p 55. (b) Suffness, M.; Cordell, G. A. *The Alkaloids*; Brossi, A., Ed.; Academic Press, Orlando, FL, 1985; Vol. 25, p 156; (c) Bick, R. C.; Sinchai, W. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 19, p 193. (d) Govindachari, T. R.; Viswanathan, N. *Heterocycles* **1978**, *11*, 587. (e) Govindachari, T. R. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 517.

(2) Detailed discussion: Suffness, M.; Cordell, G. A. In *The Alkaloids;* Brossi, A., Ed.; Academic Press: Orlando, FL, 1985; Vol. 25, ch. 1, pp 3−355.

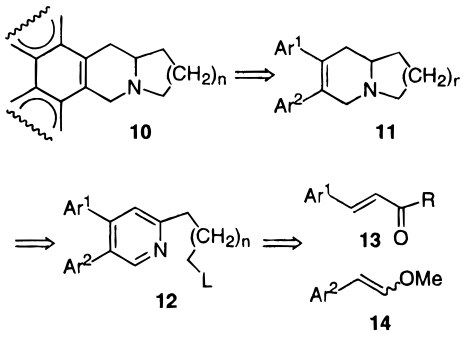
(3) Duan, J.; Yu, L. *Zhongcaoyao* **1991**, *22*, 316 (*Chem. Abstr.* **1992**, *116*, 386u).

(4) The literature cited in ref 2 contains extensive discussion of earlier syntheses of these alkaloids. More recent reports containing new strategic ideas: (a) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387. (b) Cragg, J. E.; Hedges, S. H.; Herbert, R. B. *Tetrahedron Lett.* **1981**, *22*, 2127. (c) Bremmer, M. I.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661. (d) Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; de Silva, S. O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955. (e) Iida, H.; Watanabe, Y.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 2412. (f) Iwasa, K.; Kamigauchi, M.; Takao, N. *J. Nat. Prod.* **1988**, *51*, 172. (g) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325. (h) Ihara, M.; Takino, Y.; Tomotake, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2287. (i) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (j) Snieckus, V. *Pure Appl. Chem.* **1990**, *62*, 2047. (k) Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* **1991**, *32*, 5919. (l) Yerxa, B. R.; Yang, K.; Moore, H. W. *Tetrahedron* **1994**, *50*, 6173. (m) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **1994**, *50*, 12293. This last work contains an extensive bibliography of synthetic activity in the phenanthroizidine area.

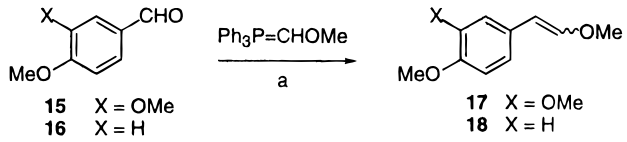
(5) Cf. Ciufolini, M. A.; Shen, Y.-C.; Bishop, M. J. *J. Am. Chem. Soc.* **1995**, 117, 12460, and references cited therein. See also ref 10.

S0002-7863(96)02757-6 CCC: $12.00 

**Scheme 3**




**Scheme 4**

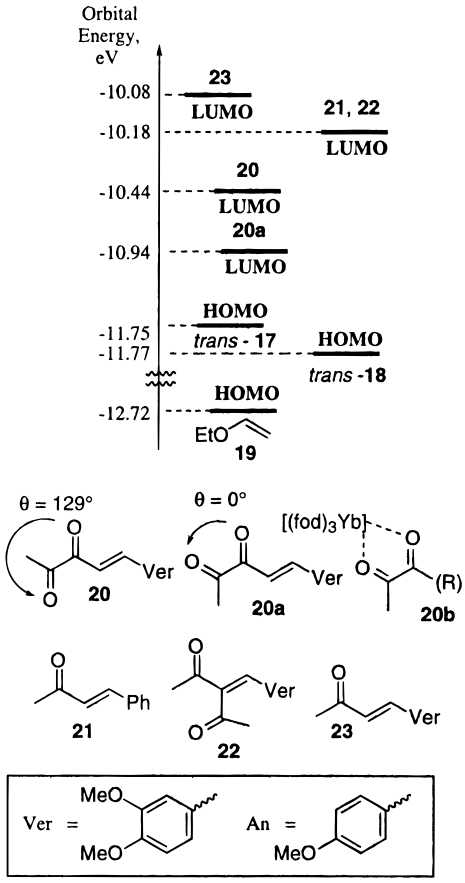



**17**, obtained as a mixture of geometric isomers in 90% distilled yield by Wittig reaction of veratraldehyde with (methoxymethylene)triphenylphosphorane (Scheme 4). A similar protocol furnished ether **18** from anisaldehyde. This second ether was later to be used in the synthesis of alkaloids **2** and **5**. Disappointingly, addends **21** and **17** failed to combine under our standard catalytic conditions.

In an effort to determine whether this might be due to electronic problems, to steric effects, or to a combination of both, we examined electronic aspects of the reaction at the EHMO level on MM+ structures. Under standard approximations,[7] the $HOMO_{(ether)}-LUMO_{(enone)}$ energy gap is a good predictor of relative reaction rates, barring adverse steric interactions. Results of an estimate of molecular orbital energies for relevant enones and vinyl ethers are summarized in Scheme 5.[8] It is apparent that the failure of **17** to combine with **21** does not augur well for the feasibility of a cycloaddtion of the ether with veratralacetone, **23**, (greater HOMO−LUMO gap), a computationally convenient analogue of an enone, wherein a short chain suitable for completion of the izidine framework would be present in lieu of a methyl group. However, concern about unfavorable electronics (i.e., excessive HOMO−LUMO gap) was dispelled by the experimental observation that benzalacetone does react, albeit slowly, with ethyl vinyl ether (EVE, **19**) under our standard cycloaddition protocol, even though the HOMO of EVE is almost 1 eV lower in energy than that of **17**. It thus seemed that in all likelihood our initial attempt had failed *primarily* because of unfavorable steric interactions between the aryl groups of the cycloaddends at or near the transition state for the reaction.

Such a problem may be remedied by decreasing the steric demand of the addends, through replacement of one or both aryl groups with smaller implements that would later allow arylation of the intermediate pyridine. However, cures of this type were unattractive, because they would substantially lengthen the synthesis. A better approach was to augment the reactivity of the enone through drastic lowering of its LUMO, but in a manner consonant with our ultimate synthetic goal. This objective seemed attainable by buttressing the electron-withdrawing power of the carbonyl subunit directly connected to the olefin. To that end, we considered Knoevenagel-type enone **22** and the isomeric α-diketone **20**. Not only would enone **20** ultimately be more suitable as a synthetic precursor to **1**−**5**, since its substitution pattern better coincides with that of intermediate **12**, but its LUMO energy turned out to appreciably lower than that of **22**.[9] Our calculations also revealed that the LUMO energy of **20** drops from −10.44 eV to −10.94 eV when the dihedral angle between the carbonyls tends to 0° (conformer **20a**). Therefore, it may be speculated that if activation of this enone by $Yb(fod)_3$ in the course of the cycloaddition were to involve a chelating interaction of the type shown in structure **20b**, the combined effects of conformation and Lewis acid coordination would bring the LUMO of the molecule to within less than 1 eV away from the HOMO of ether **17**. This should greatly favor the cycloaddition step.

**Scheme 5**




Enone **20** necessary to test our prediction was prepared by Wadsworth−Emmons reaction of **15** with phosphonate **24**,[10] followed by acid hydrolysis (Scheme 6). Indeed, diketone **20** combined slowly (2 days), but cleanly, with the mixture of geometric isomers of **17** to furnish almost exclusively the *all-*

(6) The term "cycloaddition" is used throughout this paper only to describe the gross outcome of reactions between α,β-unsaturated carbonyl compounds and vinyl ethers. No mechanistic inferences should be drawn from such usage, particularly with respect to concertedeness or other intimate electronic details of the reactions.

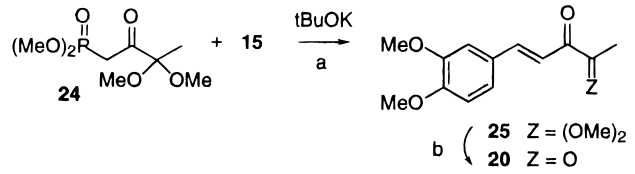
(7) Because the reaction proceeds with inverse demand, the major frontier orbital interaction is assumed to be the one between the HOMO of the electron-rich ether and the LUMO of the electron-deficient enone.

(8) Calculations were carried out with the Hyperchem package (version 4.0) available from Hypercube, Inc., Ontario, Canada.

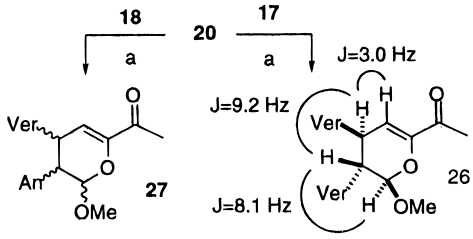
(9) This may reflect the fact that in structure **20** the enone system is essentially planar, though the dihedral angle between the vicinal carbonyl groups is approximately 129°; therefore, excellent conjugations exists throughout the π network involved in the cycloaddition. By contrast, significant out-of-plane distortion of aryl, olefin, and carbonyl groups is apparent in the MM+ structure of **22**: conjugation is thus likely to be disrupted. Indeed, the LUMO energy of **22** is identical to that of **21**, indicating that the activation provided by the second carbonyl is barely sufficient to counterbalance the presence of two electron-releasing OMe groups on the phenyl ring.

(10) Ciufolini, M. A.; Bishop, M. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1463.

**Scheme 6**




**Scheme 7**




*trans* diastereomer of pyran **26**. The stereochemistry of this material rests on the magnitude of the homonuclear vicinal coupling constants between the ring hydrogens (Scheme 7). Relative to the "anomeric" methoxy group, compound **26** may be regarded as the *endo* adduct of the enone with the (*E*)-isomer of ether **17**. The formation of an adduct arising from substantially only one isomer of the ether reaffirms the principle that facile isomerization of vinyl ethers may occur under lanthanide-promoted cycloadditions and ene-like processes, and that often, one particular regio- or stereoisomer of the ether is seen as reacting considerably faster than the other(s).[11] In sharp contrast, reaction of **20** with ether **18** completed much faster (6 h), but produced pyran **27** as a mixture of diastereomers. Fortunately, this was inconsequential, because conversion of **27** to a pyridine would ultimately eliminate all stereocenters.

## A Common Intermediate for Phenanthroizidines Emerges

Pyran **26** formed pyridine oxime **34** when refluxed in a suspension of hydroxylamine hydrochloride in acetonitrile. We were unable to retrieve the more synthetically useful ketone **35** from **34** in a clean fashion; accordingly, reduction of **26**/**27** and benzoylation of the intermediate alcohol were conducted prior to pyridine formation, resulting in the ultimate creation of heterocycles **30a** (X = OMe) and **30b** (X = H). Vinylpyridines of the type **33** were soon identified as especially good intermediates for side-chain elongation, due to the well-known propensity of their olefinic linkage to undergo nucleophilic addition.[12] Either indolizidines or quinolizidines would therefore be made from **33** through addition of a $C_1$ or a $C_2$ unit, respectively. The vinylpyridines emerged in good overall yield from **30a**,**b** through a sequence involving benzoate ester cleavage, chloride formation by reaction of the intermediate alcohol with $SOCl_2$, and E2-type reaction with tBuOK as the base (Scheme 8).

Two aspects of the chemistry of Scheme 8 deserve further comment. First, benzoylation of intermediates **28** was necessary because substantial quantities of oxime **34** again resulted when pyridine formation was attempted from the free alcohols. The oxime probably forms through events that parallel those leading to osazone formation in carbohydrate chemistry[13] (Scheme 9).

Second, reaction of both **29a** and **29b** with hydroxylamine hydrochloride produced small amounts (ca. 5% of total product) of abnormal pyridines **37a** and **37b**, respectively. Their structure was assigned on the basis of spectral evidence summarized in Scheme 10.[14] Our mechanistic rationale for the formation of **37** envision competition between simple deprotonation (path a, major) and aryl migration/deprotonation (path b, minor) during dehydrative aromatization of intermediate **36**, which may arise as indicated earlier in Scheme 9.[15]

We conclude this section by pointing out that the introduction of an α-dicarbonyl motif as a means to increase the reactivity of an enone that is otherwise disinclined to undergo lanthanide-mediated heterocycloaddition appears to be a general solution. For instance, enone **38** refused to combine with 1-ethoxypropene under our standard conditions, but compound **39** reacted smoothly to form adduct **40**, and thence pyridine **41** in good overall yield (Scheme 11).[16]

## Synthesis of Phenanthroizidines and Their Seco Congeners

With quantities of vinylpyridines **33a**,**b** now secured, we set out to reach some of the natural products. Access to phenanthroindolizidines dictated the introduction of a $C_1$ unit. To that end, exposure of **33a** to a mixture of LiCN in hot DMF containing a small amount of AcOH (*in situ* formation of HCN) induced smooth hydrocyanation to nitrile **42**. Completion of the molecular framework was accomplished in a straightforward manner through acidic hydrolysis of the nitrile to an acid, LAH reduction to the alcohol, and cyclization to pyridinium salt **45**. The precise nature of the anion in **45** was not defined, hence $X^-$ may be either $Cl^-$ or $MsO^-$. Indeed, this salt was not characterized beyond a proton NMR spectrum; rather, it was reduced with $NaBH_4$ in hot ethanol to afford fully synthetic (±)-septicine, **4**, which was converted to totally synthetic (±)-tylophorine, **1**, in 74% recrystallized yield via a Liepa-type oxidation with vanadium(V) oxyfluoride in the presence of trifluoroacetic acid.[17] We found that the success of the Liepa protocol depended critically on the precise order of addition of the reagents, an aspect of this chemistry that does not appear to have been explicitly addressed in the literature. It was crucial to introduce the TFA last, 5 to 10 min after $VOF_3$ had been added: reversal of the order of addition led to total destruction of the 1,2-diarylethylene derivatives. In a like fashion and yields, vinylpyridine **33b** was advanced to compound **50**, which underwent oxidative cyclization to synthetic (±)-antofine, **2**, in 51% recrystallized yield (Scheme 12).

Addition of a $C_2$ unit in the interest of creating an ultimate quinolizidine was accomplished through addition of the enolate of acetonitrile to **33b**. This operation was best effected in DMSO at room temperature with excess acetonitrile and tBuOK as the base, and it furnished compound **51** in high yield. A sequence identical to that shown in Scheme 12 above advanced **51** to fully synthetic (±)-julandine, **5**. Methods for the oxidative cyclization of julandine to cryptopleurine are known,[18] therefore a synthesis of **5** amounts also to a formal synthesis of **3**.[19]

(11) Ciufolini, M. A. In *Advances in Heterocyclic Natural Product Synthesis;* Pearson. W. H., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 3, ch. 1, pp 1−55. See also ref 10.

(12) Cf., e.g., Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1975**, *97*, 5282.

(13) Discussion: Jones, J. K. N. In *Chemistry of Carbon Coumpounds*; Rodd, E. H., Ed.; Elsevier: Amsterdam, The Netherlands, 1952; Vol. I, Part B, Ch. 19; see especially p 1238.

(14) We thank Dr. Larry Alemany, of this department, for valuable assistance with the NOE measurements.

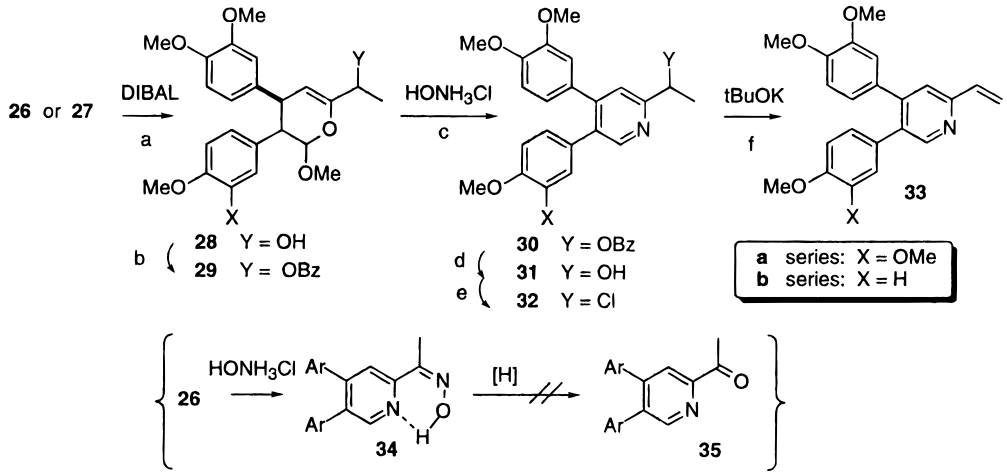
(15) The abnormal products displayed the same chromatographic mobility as the major pyridines under a variety of conditions, rendering their isolation quite arduous, but they were found to undergo benzoate cleavage at a considerably slower rate than "normal" pyridines **30a**,**b**, probably for steric reasons, and were thus separated from the major product at the stage of alcohols **31**.

(16) Bishop, M. J. Unpublished results from these laboratories.

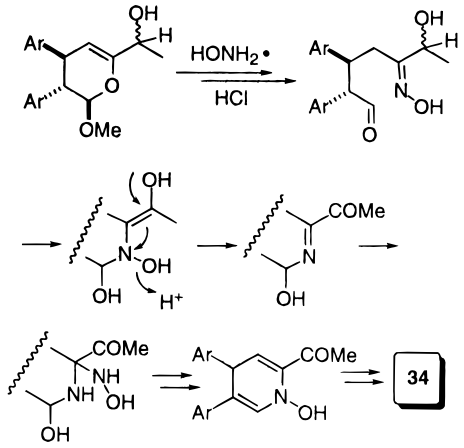
(17) Liepa, A. J.; Summons, R. E. *J. Chem. Soc., Chem. Commun.* **1977**, 826.

(18) Cragg, J. E.; Herbert, R. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2487.

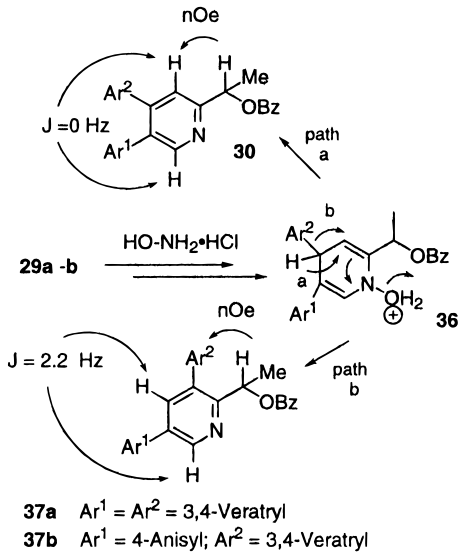
**Scheme 8**




**Scheme 9**



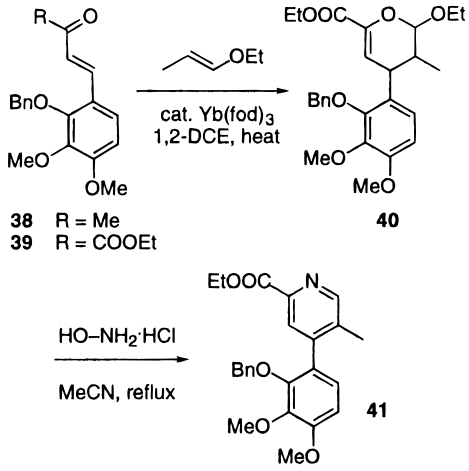

**Scheme 10**




In summary, we have shown that our pyridine-forming reaction may be used to prepare sterically congested 3,4-diarylpyridine, and therefore it can play a central role in defining a unified approach to a number of phenanthroizidine alkaloids and their *seco* relatives. The scope of the methodology, the value of which has already been demonstrated in connection with the total synthesis of diverse heterocyclic natural products,[20] is thus further expanded.

(19) It was not possible to compare the spectra of our synthetic final products with spectra of authentic natural materials. However, all of these alkaloids have been synthesized several times, and physical and spectral data obtained by us were in complete agreement with those reported by previous workers. As further detailed in ref 22, controversy exists regarding the melting point (but not the *spectral properties*) of (±)−tylophorine, literature values for which span almost 30 °C.

**Scheme 11**



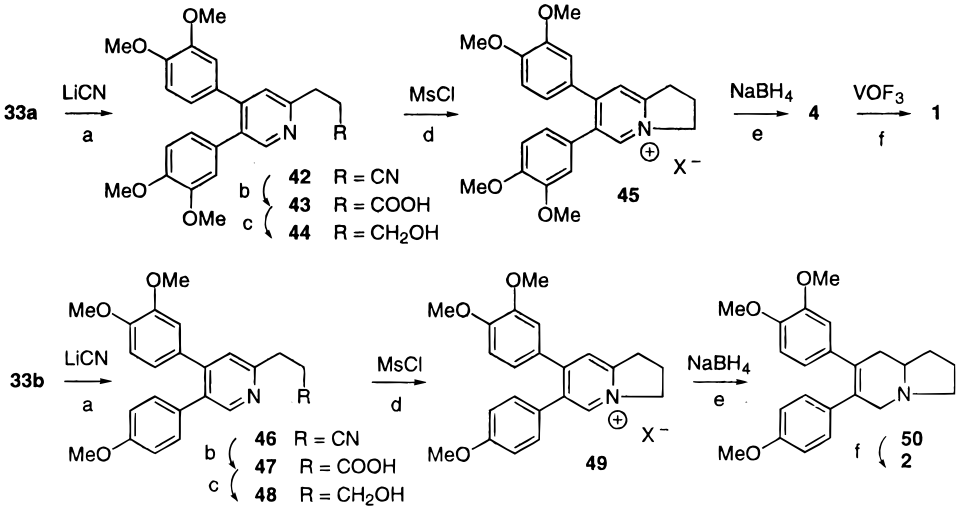

## Experimental Section[21]

**Vinyl Ether 17.** *tert*-Butyllithium (1.7 M in pentane, 104 mL, 176 mmol) was added to a cold (−78 °C) suspension of $Ph_3P^+CH_2OMe\ Cl^-$ (61.7 g, 180.1 mmol) in THF (100 mL) and the mixture was warmed to 0 °C. After 2 h, veratraldehyde (14.3 g, 85.5 mmol) in THF (30 mL) was added. The mixture was refluxed until the reaction was completed (TLC, ca. 12 h), and then it was cooled to room temp, quenched ($H_2O$), and extracted (hexanes). The combined extracts were sequentially washed with $H_2O$, saturated aqueous $NaHCO_3$, $H_2O$, and saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography with 1% → 20% EtOAc/hexanes followed by concentration and Kugelrohr distillation gave 15.0 g (90%) of **17**, colorless oil. $^1H$ (major peaks only, *cis*:*trans* ∼ 76:24): 7.25−7.24 (d, $J$ = 1.7 Hz),

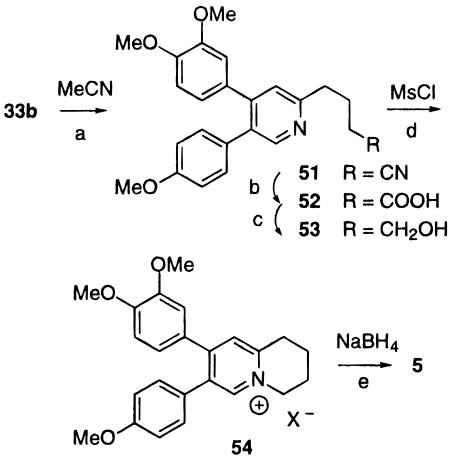
(20) (a) Ciufolini, M. A.; Byrne, N. E. *J. Am. Chem. Soc.* **1991**, *113*, 8016 (cystodytins). (b) Bishop, M. J.; Ciufolini, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 10081 (dercitins and kuanoniamines). (c) Ciufolini, M. A.; Shen, Y.-C. *Tetrahedron Lett.* **1995**, *36*, 4709 (diplamine and shermilamine), as well as refs 5, 10 (lavendamycin methyl ester), and 11.

(21) Experimental Protocols. Melting points (uncorrected) were measured on a Fischer-Johns hot stage apparatus. NMR spectra (ppm on the $\delta$ scale) were recorded at room temperature at 250 MHz for $^1H$ and 62.5 MHz for $^{13}C$ in $CDCl_3$ solutions. Analytical and preparative TLC employed Merck $SiO_2$ 60 plates with fluorescent indicator. THF was distilled from Na/$Ph_2$-CO; DCE, DME, pyridine, and $CH_2Cl_2$ were distilled from $CaH_2$; DMSO was vacuum distilled from $CaH_2$; MeOH was dried over 4 Å mol sieves. All other reagents and solvents were used as received.

**Scheme 12**




**Scheme 13**




7.09−7.05 (dd, $J_1$ = 8.3 Hz, $J_2$ = 1.8 Hz), 6.97−6.92 (d, $J$ = 12.9 Hz), 6.81 (s) 6.78 (s), 6.07−6.05 (d, $J$ = 7.0 Hz), 5.80−5.75 (d, $J$ = 13.0 Hz), 5.18−5.15 (d, $J$ = 7.0 Hz) 3.88 (s), 3.86 (s), 3.85 (s), 3.76 (s), 3.66 (s). $^{13}$C (major peaks only): 149.0, 148.4, 147.7, 147.3, 147.1, 146.5, 129.3, 129.0, 120.7, 117.5, 111.5, 110.9, 108.3, 105.4, 104.8, 60.5, 56.4, 55.9, 55.8, 55.7. IR: 1655, 1534, 1453, 1259. MS: 194 ($M^+$, 100%), 179, 151. HRMS: Calcd for $C_{11}H_{14}O_3$: 194.0943 ($M^+$). Found: 194.0942 ($M^+$). EA (Calcd): C: 67.46 (68.02); H: 7.20 (7.27).

**Vinyl Ether 18.** *tert*-Butyllithium (1.7 M in pentane, 34 mL, 58 mmol) was added to a cold (−78 °C) suspension of $Ph_3P^+CH_2OMe$ $Cl^-$ (19.8 g, 57.8 mmol) in THF (80 mL), and the mixture was warmed to 0 °C. After 2 h, *p*-anisaldehyde (4.7 mL, 38.5 mmol) in THF (16 mL) was added and the mixture handled as described above for **17** to furnish 4.5 g (71%) of **18**, a colorless oil, which solidifies upon storage at −20 °C. $^1$H (major peaks only, *cis*:*trans* ∼19:81): 7.55−7.51 (d, $J$ = 8.8 Hz), 7.18−7.14 (m), 6.97−6.92 (d, $J$ = 13.0 Hz), 6.87−6.81 (m) 6.78 (s), 6.07−6.05 (d, $J$ = 7.0 Hz), 5.82−5.77 (d, $J$ = 13.0 Hz), 5.20−5.17 (d, $J$ = 7.0 Hz) 3.80 (s), 3.79 (s), 3.77 (s), 3.75 (s), 3.67 (s). $^{13}$C: 157.8, 147.5, 146.3, 129.3, 128.3, 126.1, 114.0, 113.5, 105.2, 104.5, 60.2, 56.4, 55.2. IR: 1642, 1511, 1463, 1246. MS: 164 ($M^+$, 100%), 149, 121. HRMS: Calcd for $C_{10}H_{12}O_2$: 194.0837 ($M^+$). Found: 164.0837 ($M^+$). EA (Calcd): C: 73.53 (73.15); H: 7.29 (7.37).

**Enone Ketal 25.** Phosphonate **24** (12.9 g, 54.0 mmol) in 1,2-dimethoxyethane (DME, 15 mL) was cannulated into a cold (0 °C) solution of tBuOK (6.4 g, 54.0 mmol) in DME (47 mL) in a flame-dried flask, and the mixture was stirred at 0 °C for 30 min. The ice-bath was removed, and veratraldehyde (6.9 g, 41.5 mmol) in DME (15 mL) was added. The mixture was refluxed until the reaction was completed (TLC), and then it was cooled, poured into saturated aqueous $NaHCO_3$, and extracted with ether. The extracts were sequentially washed with saturated aqueous $NaHCO_3$, $H_2O$, and saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography (20% EtOAc/hexanes) provided 10.9 g (94%) of **25**, yellow oil. $^1$H: 7.76−7.70 (d, 1H, $J$ = 15.9 Hz), 7.20−7.16 (dd, 1H, $J_1$ = 8.3 Hz, $J_2$ = 1.9 Hz), 7.12−7.05 (d, 1H, $J$ = 15.9 Hz), 7.10−7.09 (d, 1H, $J$ = 2.0 Hz), 6.87−6.83 (d, 1H, $J$ = 8.3 Hz), 3.91 (s, 3H), 3.89 (s, 3H), 1.44 (s, 3H). $^{13}$C: 196.6, 151.5, 149.1, 145.1, 127.5, 123.6, 118.0, 110.9, 110.0, 102.3, 55.9, 49.7, 20.1. IR: 1693, 1593, 1511, 1463, 1265, 1140, 1042. MS: 280 ($M^+$), 249, 221, 191, 89 (100%). HRMS: Calcd for $C_{15}H_{20}O_5$: 280.1310 ($M^+$). Found: 280.1313 ($M^+$).

**Diketone 20**. A mixture of **25** (1.135 g, 4.05 mmol), $CHCl_3$ (20 mL) and 70% aqueous trifluoroacetic acid (20 mL) was stirred at 0 °C for 2 h and then poured into saturated aqueous NaCl and extracted with $CHCl_3$. The extracts were sequentially washed with $H_2O$ and saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. The residue was recrystallized from toluene/hexanes to provide 718 mg (76%) of **20**, bright yellow solid, mp 124 °C. $^1$H: 7.75−7.69 (d, 2H, $J$ = 16.3 Hz), 7.20−7.09 (m, 3H), 6.84−6.81 (d, 1H, $J$ = 8.3 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 2.39 (s, 3H). $^{13}$C: 199.1, 186.3, 152.1, 149.2, 147.7, 127.3, 124.3, 115.4, 110.9, 109.8, 55.8 (2 signals), 24.3: IR: 1711, 1671, 1576, 1510, 1265, 1244. MS: 234 ($M^+$), 191 (100%). HRMS: Calcd for $C_{13}H_{14}O_4$: 234.0892 ($M^+$). Found: 234.0891 ($M^+$) EA: (Calcd) C: 66.52 (66.66); H: 6.13 (6.02).

**Cycloadduct 26.** A solution of **20** (4.8 g, 20.5 mmol), **17** (12.0 g, 61.8 mmol), and Yb(fod)$_3$ (2.2 g, 2.0 mmol) in 1,2-dichloroethane (DCE, 45 mL) was gently refluxed until the reaction completed (TLC, 36 h). The cooled mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were sequentially washed with saturated aqueous $NaHCO_3$, $H_2O$ and saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) provided **26** (7.479 g, 91%), yellow foam. $^1$H: 6.80−6.15 (m), 5.28−5.11 (m), 3.96−3.45 (m), 2.91−2.84 (t, $J$ = 8.7 Hz), 2.42−2.39 (m). $^{13}$C: 194.0, 148.7, 148.5 (2 signals), 147.8, 133.5, 131.8, 120.0 (2 signals), 113.2, 111.5, 111.2, 111.0, 110.8, 103.7, 56.6, 55.7, 55.3, 47.4, 25.7. IR: 1696, 1643, 1521, 1267. MS: 428 ($M^+$), 194 (100%). HRMS: Calcd for $C_{24}H_{28}O_7$: 428.1835 ($M^+$). Found: 428.1833 ($M^+$).

**Cycloadduct 27.** A solution of **20** (2.2 g, 9.4 mmol), **18** (4.7 g, 28.5 mmol), and Yb(fod)$_3$ (1.0 g, 0.9 mmol) in DCE (20 mL) was gently refluxed until the reaction completed (TLC, 7 h). Workup as described above for **26** and chromatography with 40% EtOAc/hexanes provided **27** (3.7 g, 99%), yellow foam, mixture of diastereomers. $^1$H (major peaks only): 7.13−6.06 (m), 5.21−5.06 (m), 4.12−3.20 (m), 2.90−2.83 (t, $J$ = 8.6 Hz), 2.40−2.35 (m). $^{13}$C (major peaks only): 193.7, 158.3, 147.7, 147.6, 132.2, 131.0, 130.1, 128.8, 128.7, 122.3, 120.9, 119.8, 114.1, 113.8, 113.3, 113.2, 113.0, 112.3, 111.1, 109.9, 101.2, 55.8, 55.6, 55.5, 55.0, 45.9, 39.0, 25.8, 25.7, 25.6. IR: 1687,-1632, 1514, 1246. MS: 398 ($M^+$), 310, 164 (100%). HRMS: Calcd for $C_{23}H_{26}O_6$: 398.1729 ($M^+$). Found: 398.1728 ($M^+$).

**Alcohol 28a.** Diisobutylaluminum hydride (DIBAL, 1.5 M in toluene, 13.1 mL, 19.6 mmol) was added at a slow dropwise rate into

a cold (−78 °C) solution of **26** (6.5 g, 15.1 mmol) in $CH_2Cl_2$ (50 mL). The mixture was stirred at −78 °C for 10 min (TLC: reaction complete) and then treated with cold MeOH (−78 °C, 3.5 mL) and poured into cold (0 °C) saturated aqueous $NaHCO_3$ with vigorous swirling over 15 min. The resulting slurry was extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated to give 6.4 g (99%) of **28a**, pale yellow foam, mixture of diastereomers, which was used in crude form. $^1$H (major peaks only): 6.92−6.23 (m), 5.14−5.02 (m), 4.41−4.32 (br q, $J$ = 5.9 Hz), 3.96−3.38 (m), 2.85−2.76 (m), 2.5−2.1 (br s, chemical shift depending on concentration), 1.51−1.44 (b). $^{13}$C (major peaks only): 154.1, 154.0, 148.5, 148.3, 147.5, 147.4, 135.3, 132.4, 119.8, 119.7, 111.5, 111.0, 110.6, 103.6, 100.3, 67.4, 56.3, 55.6, 55.5, 52.3, 52.2, 45.8, 45.7, 21.1, 20.7. IR: 1687,1632, 1514, 1246. MS: 430 ($M^+$), 194 (100%). HRMS Calcd for $C_{24}H_{30}O_7$: 430.1992. Found: 430.1992 ($M^+$).

**Alcohol 28b.** DIBAL (1.5 M solution in toluene, 7.1 mL, 10.6 mmol) was added at a slow dropwise rate into a cold (−78 °C) solution of **27** (3.8 g, 9.6 mmol) in $CH_2Cl_2$ (32 mL). The same procedure detailed above for **28a** furnished 3.8 g (99%) of **29b**, pale yellow foam, mixture of diastereomers, which was used in crude form. $^1$H (major peaks only): 7.00−6.11 (m), 5.15−4.99 (m), 4.37−4.30 (br q, $J$ = 5.8 Hz, 3.86−3.19 (m), 2.85−2.76 (m), 2.5−2.1 (br s, chemical shift depends on concentration), 1.51−1.15 (m). $^{13}$C (major peaks only): 158.1, 154.1, 154.0, 148.2, 147.3, 135.2, 131.8, 131.1, 128.9, 119.5, 113.6, 111.0, 110.6, 103.8, 100.4, 67.7, 67.5, 56.3, 55.6, 55.5, 55.0, 52.0, 51.9, 45.9, 45.7, 21.1, 20.7. IR: 3480 (br), 1680, 1611, 1514, 1464, 1248. MS: 400 ($M^+$), 386, 270, 164 (100%). HRMS: Calcd for $C_{23}H_{28}O_6$: 400.1886 ($M^+$). Found: 400.1886 ($M^+$).

**Benzoate 29a.** Benzoyl chloride (BzCl, 3.5 mL, 30.2 mmol) was added at room temp to a solution of **28a** (6.5 g, 15.1 mmol) and pyridine (4.9 mL, 60.4 mmol) in $CH_2Cl_2$ (36 mL). The mixture was stirred at room temp for 30 min and then added to saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with $H_2O$ and with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 6.3 g (78%) of **29a**, yellow foam, mixture of diastereomers. $^1$H (major peaks only): 8.16−8.01 (m), 7.60−7.15 (m), 6.79−6.40 (m), 5.61−5.53 (q, $J$ = 6.6 Hz), 4.85−4.81 (d, $J$ = 7.7 Hz), 3.91−3.32 (m), 2.85−2.71 (m), 2.23−2.02 (m), 1.69−1.27 (m). $^{13}$C (major peaks only): 165.3, 148.4, 148.2, 147.1, 135.0, 132.8, 131.7, 130.0, 129.4, 128.1, 119.9, 119.4, 112.0, 110.8, 101.7, 101.4, 100.4, 100.2, 70.7, 69.9, 56.3, 56.0, 55.5, 52.7, 52.3, 41.5, 36.3, 15.4, 15.3, 14.3. IR: 1723, 1522, 1270. MS: 534 ($M^+$), 300 (100%), 194. HRMS: Calcd for $C_{31}H_{34}O_8$: 534.2253 ($M^+$). Found: 534.2252 ($M^+$).

**Benzoate 29b.** BzCl (2.2 mL, 19.1 mmol) was added at room temp to a solution of **29b** (3.8 g, 9.5 mmol) and pyridine (3.1 mL, 38.2 mmol) in $CH_2Cl_2$ (32 mL), and the mixture was handled as described above for **29a** to give 3.7 g (85%) of **29b**, yellow foam, mixture of diastereomers. $^1$H (major peaks only): 8.12−8.01 (m), 7.56−7.41 (m), 6.99−6.43 (m), 5.75−5.60 (m), 5.19−5.06 (m), 3.80−3.31 (m), 2.93−2.80 (m), 1.67−1.29 (m). $^{13}$C (major peaks only): 165.6, 165.5, 158.2, 151.0, 150.7, 148.3, 147.3, 135.3, 135.2, 133.4, 132.9, 132.0, 131.9, 130.0, 129.5, 128.9, 128.3, 119.7, 113.7, 113.4, 111.0, 110.8, 110.5, 103.7, 103.5, 102.8, 102.1, 70.1, 70.0, 56.0, 55.8, 55.6, 55.4, 55.0, 52.0, 45.8, 45.6, 18.5, 18.0. IR: 1719, 1514, 1269. MS: 504 ($M^+$), 270, 164 (100%). HRMS: Calcd for $C_{30}H_{32}O_7$: 504.2148 ($M^+$). Found: 504.2149 ($M^+$).

**Pyridine 30a.** A mixture of **29a** (6.2 g, 11.7 mmol) and hydroxylamine hydrochloride (4.9 g, 70.3 mmol) in acetonitrile (MeCN, 117 mL) was refluxed for 1.5 h and then cooled to room temp, quenched (saturated aqueous $NaHCO_3$), and extracted with $CHCl_3$. The combined extracts were washed with $H_2O$ and with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 4.7 g (80%) of **30a**, pale yellow foam. $^1$H: 8.58 (s, 1H), 8.11−8.08 (d, 2H, $J$ = 7.5 Hz), 7.54−7.36 (m, 5H), 6.81−6.73 (m, 5H, $J_1$ = 8.4 Hz, $J_2$ = 1.5 Hz), 6.25−6.17 (q, 1H, $J$ = 6.6 Hz), 3.82 (s, 3H), 3.81 (s, 3H), 3.58 (s, 3H), 3.53 (s, 3H), 1.79−1.77 (d, 3H, $J$ = 6.6 Hz). $^{13}$C: 165.6, 159.0, 150.2, 148.6, 148.4, 148.3, 148.2, 147.9, 134.3, 132.8, 131.1, 130.1, 130.0, 129.5, 128.2, 121.7, 121.5, 120.7, 113.0, 112.6, 110.9, 110.8, 73.3, 55.6, 55.5, 55.4, 20.6. IR: 1717, 1601, 1515, 1252. MS: 499 ($M^+$), 394, 105 (100%). HRMS: Calcd for $C_{30}H_{29}NO_6$: 499.1995 ($M^+$). Found: 499.1995 ($M^+$).

**Pyridine 30b.** A mixture of **29b** (3.7 g, 7.4 mmol) and hydroxylamine hydrochloride (3.1 g, 44.7 mmol) in MeCN (75 mL) was treated as detailed above for **30a**. Chromatography (30% EtOAc/hexanes) gave 2.0 g (59%) of **30b**, pale yellow foam. $^1$H: 8.58 (s, 1H), 8.15−8.11 (d, 2H, $J$ = 7.0 Hz), 7.55−7.36 (m, 5H), 7.09−7.06 (d, 2H, $J$ = 8.7 Hz), 6.85−6.77 (m, 5H), 6.55−6.54 (d, $J$ = 1.5 Hz) 6.29−6.21 (q, 1H, $J$ = 6.6 Hz), 3.85 (s, 3H), 3.82 (s, 3H), 3.53 (s, 3H), 1.82−1.80 (d, 3H, $J$ = 6.6 Hz). $^{13}$C: 165.8, 159.0, 158.8, 150.4, 148.7, 148.2, 147.9, 134.3, 132.9, 131.1, 130.7, 130.1, 129.9, 129.6, 128.3, 128.1, 121.6, 120.8, 114.4, 113.8, 112.7, 110.8, 73.5, 55.7, 55.4, 55.1, 20.7. IR: 1717, 1606, 1514, 1253. MS: 469 ($M^+$), 364 (100%). HRMS: Calcd for $C_{29}H_{27}NO_5$: 469.1889 ($M^+$). Found: 469.1890 ($M^+$).

**Alcohol 31a.** A mixture of **30a** (2.0 g, 4.1 mmol), MeOH (41 mL), and 1% aqueous NaOH (14 mL) was stirred at room temperature for 1.5 h and then poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. Chromatography (0.5% MeOH/$CHCl_3$) gave 1.6 g (99%) of **32a**, pale yellow foam. $^1$H: 8.52 (s, 1H), 7.32 (s, 1H), 6.83−6.73 (m, 4H), 6.60−6.58 (m, 2H), 5.00−4.92 (q, 1H, $J$ = 6.5 Hz), 3.85 (s, 6H), 3.61 (s, 3H), 3.59 (s, 3H), 1.58−1.55 (d, 3H, $J$ = 6.6 Hz). $^{13}$C: 161.9, 149.1, 148.8, 148.5, 148.4, 148.3, 148.2, 134.2, 131.2, 130.2, 121.9, 121.6, 120.2, 113.1, 112.6, 111.0, 110.9, 68.9, 55.8, 55.6, 24.2. IR: 3450 (br), 1600, 1524, 1252. MS: 395 ($M^+$, 100%), 380. HRMS Calcd for $C_{23}H_{25}NO_5$: 395.1733 ($M^+$). Found: 395.1733 ($M^+$).

**Alcohol 31b.** A mixture of **30b** (2.0 g, 4.30 mmol), MeOH (43 mL), and 1% aqueous NaOH (14 mL) was processed as described above for **31a** to give 1.5 g (94%) of **31b**, pale yellow foam. $^1$H: 8.49 (s, 1H), 7.32 (s, 1H), 7.08−7.05 (d, 2H, $J$ = 8.7 Hz), 6.86−6.78 (m, 4H), 6.56−6.55 (d, 1H, $J$ = 1.4 Hz), 5.01−4.93 (q, 1H, $J$ = 6.5 Hz), 3.87 (s, 3H), 3.78 (s, 3H), 3.57 (s, 3H), 1.59−1.56 (d, 3H, $J$ = 6.5 Hz). $^{13}$C: 161.8, 158.9, 149.3, 148.8, 148.3, 148.1, 134.1, 131.2, 130.8, 130.0, 121.6, 120.2, 113.8, 112.8, 110.9, 68.9, 55.7, 55.6, 55.2, 24.2. IR: 3377 (br), 1607, 1515, 1253. MS: 365 ($M^+$), 350 (100%). HRMS Calcd for $C_{22}H_{23}NO_4$: 365.1627 ($M^+$). Found: 365.1626 ($M^+$).

**Chloride 32a.** A mixture of $SOCl_2$ (256 $\mu$L, 3.5 mmol), **31a** (697 mg, 1.8 mmol), pyridine (284 $\mu$L, 3.5 mmol), and benzene (18 mL) was refluxed for 20 min and then poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with $H_2O$ and with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 670 mg (92%) of **33a**, yellow foam. $^1$H: 8.59 (s, 1H), 7.51 (s, 1H), 6.86−6.77 (m, 4H), 6.62−6.61 (m, 2H), 5.27−5.19 (q, 1H, $J$ = 6.8 Hz), 3.88 (s, 6H), 3.64 (s, 3H), 3.62 (s, 3H), 1.98−1.95 (d, 3H, $J$ = 6.9 Hz). $^{13}$C: 159.4, 150.2, 148.8, 148.6, 148.5, 148.4, 148.3, 134.8, 131.0, 130.0, 121.9, 121.7, 121.6, 113.0, 112.6, 111.0, 110.9, 58.7, 55.8, 55.6, 24.8. IR: 1522, 1251. MS: 413 ($M^+$, 100%), 378. HRMS Calcd for $C_{23}H_{24}ClNO_4$ 413.1394 ($M^+$). Found: 413.1393 ($M^+$).

**Chloride 32b.** A mixture of $SOCl_2$ (572 $\mu$L, 7.9 mmol), **31b** (1.4 g, 3.9 mmol), pyridine (637 $\mu$L, 7.9 mmol) and benzene (40 mL) was processed as discussed above for **32a**. Chromatography (30% EtOAc/hexanes) gave 1.4 g (91%) of **32b**, yellow foam. $^1$H: 8.53 (s, 1H), 7.48 (s, 1H), 7.08−7.05 (d, 2H, $J$ = 8.7 Hz), 6.87−6.78 (m, 4H), 6.55−6.54 (d, 1H, $J$ = 1.7 Hz), 5.24−5.16 (q, 1H, $J$ = 6.8 Hz), 3.85 (s, 3H), 3.76 (s, 3H), 3.55 (s, 3H), 1.95−1.92 (d, 3H, $J$ = 6.8 Hz). $^{13}$C: 159.2, 158.9, 150.2, 148.7, 148.3, 148.2, 134.7, 130.9, 130.7, 129.7, 121.7, 121.6, 113.8, 112.6, 110.9, 58.7, 55.7, 55.5, 55.1, 24.8. IR: 1608, 1514, 1249. MS: 383 ($M^+$, 100%), 348. HRMS Calcd for $C_{22}H_{22}ClNO_3$ 383.1288 ($M^+$). Found: 383.1288 ($M^+$).

**Vinylpyridine 33a**. A solution of **32a** (670 mg, 1.6 mmol) and tBuOK (1.9 g, 16.2 mmol) in THF (16 mL) was refluxed for 10 min, and then it was cooled and poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with $H_2O$ and with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 431 mg (71%) of **33a**, yellow foam. $^1$H: 8.60 (s, 1H), 7.38 (s, 1H), 6.95−6.86 (dd, 1H, $J_1$ = 17.5 Hz, $J_2$ = 10.3 Hz), 6.91−6.77 (m, 4H), 6.63−6.61 (d, 2H, $J$ = 6.8 Hz), 6.30−6.23 (d, 1H, $J$ = 17.5 Hz), 5.54−5.50 (d, 1H, $J$ = 10.7 Hz), 3.88 (s, 6H), 3.62 (s, 6H). $^{13}$C: 154.4, 150.5, 148.7, 148.5, 148.3, 147.6, 136.5, 134.2, 131.3, 130.3, 121.9, 121.6, 118.1, 113.1, 112.6, 111.0, 110.9, 55.8, 55.6. IR: 1517, 1252. MS: 377 ($M^+$, 100%). HRMS Calcd for $C_{23}H_{23}NO_4$: 377.1627 ($M^+$). Found: 377.1629 ($M^+$).

**Vinylpyridine 33b.** A solution of **32b** (1.343 g, 3.50 mmol) and tBuOK (2.1 g, 17.5 mmol) in THF (35 mL) was treated as discussed

above for **33a**. Chromatography (30% EtOAc/hexanes) gave 933 mg (77%) of **33b**, yellow foam. $^1$H: 8.54 (s, 1H), 7.34 (s, 1H), 7.26−7.08 (d, 2H, $J$ = 8.7 Hz), 6.92−6.83 (dd, 1H, $J_1$ = 17.4 Hz, $J_2$ = 10.8 Hz), 6.88−6.77 (m, 4H), 6.56−6.56 (d, 1H, $J$ = 1.4 Hz), 6.28−6.21 (dd, $J_1$ = 17.5 Hz, $J_2$ = 1.4 Hz), 5.51−5.46 (dd, $J_1$ = 10.8 Hz, $J_2$ = 1.2 Hz), 3.85 (s, 3H), 3.76 (s, 3H), 3.57 (s, 3H). $^{13}$C: 158.8, 154.3, 150.6, 148.6, 148.3, 147.5, 136.5, 134.0, 131.2, 130.7, 130.0, 121.8, 121.5, 117.9, 113.7, 112.7, 110.8, 55.7, 55.5, 55.1. IR: 1513, 1253. MS: 347 ($M^+$, 100%). HRMS Calcd for $C_{22}H_{21}NO_3$: 347.1521 ($M^+$). Found: 347.1521 ($M^+$).

**Nitrile 42.** AcOH (352 $\mu$L, 6.7 mmol) was added to a solution of **33a** (580 mg, 1.5 mmol) in commercial LiCN in DMF (Aldrich, 0.5 M, 31 mL, 15.5 mmol **CAUTION**: highly toxic). The mixture was heated at 140 °C for 18 h and then cooled, poured into saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extracts were washed with $H_2O$ and with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography (50% EtOAc/hexanes) gave 620 mg (99%) of **42**, yellow foam. $^1$H: 8.48 (s, 1H), 7.19 (s, 1H), 6.77−6.52 (m, 4H), 6.54−6.52 (d, 2H, $J$ = 5.7 Hz), 3.79 (s, 6H), 3.55 (s, 3H), 3.53 (s, 3H), 3.13−3.08 (t, 2H, $J$ = 7.2 Hz), 2.86−2.81 (t, 2H, $J$ = 7.1 Hz). $^{13}$C: 155.7, 150.5, 148.7, 148.5, 148.4, 148.2, 147.9, 133.9, 130.8, 130.0, 123.5, 121.8, 121.5, 119.4, 113.0, 112.5, 111.0, 110.8, 55.7, 55.6, 32.9, 16.6. IR: 1597, 1515, 1251, 1141, 1025. MS: 404 ($M^+$, 100%). HRMS Calcd for $C_{24}H_{24}N_2O_4$: 404.1736 ($M^+$). Found: 404.1737 ($M^+$).

**Nitrile 46.** AcOH (201 $\mu$L, 3.5 mmol) was added to a solution of **33b** (307 mg, 0.9 mmol) in commercial LiCN in DMF (Aldrich, 0.5 M, 18 mL, 8.8 mmol **CAUTION**: highly toxic). The mixture was heated at 140 °C for 12 h. Workup and chromatography as detailed above for **42** gave 244 mg (74%) of **46**, yellow foam. $^1$H: 8.50 (s, 1H), 7.25 (s, 1H), 7.07−7.03 (d, 2H, $J$ = 8.7 Hz), 6.84−6.79 (m, 4H), 6.55−6.54 (d, 1H, $J$ = 1.1 Hz), 3.84 (s, 3H), 3.76 (s, 3H), 3.55 (s, 3H), 3.19−3.13 (t, 2H, $J$ = 7.2 Hz), 2.92−2.86 (t, 2H, $J$ = 7.2 Hz). $^{13}$C: 158.8, 155.6, 150.5, 148.7, 148.2, 147.9, 133.8, 130.7, 129.8, 123.5, 121.6, 119.4, 113.7, 112.6, 110.8, 55.6, 55.4, 55.1, 32.9, 16.6. IR: 1609, 1515, 1251, 1026. MS: 374 ($M^+$, 100%). HRMS Calcd for $C_{23}H_{22}N_2O_3$: 374.1630 ($M^+$). Found: 374.1631 ($M^+$).

**Nitrile 51.** A solution of **33b** (634 mg, 1.83 mmol) and MeCN (191 $\mu$L, 3.66 mmol) in DMSO (18 mL) was stirred at room temp for 5 min after addition of tBuOK (647 mg, 5.49 mmol), and then it was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with $H_2O$ and with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated. Chromatography (40% EtOAc/hexanes) gave 623 mg (88%) of **51**, orange foam. $^1$H: 8.50 (s, 1H), 7.22 (s, 1H), 7.10−7.08 (d, 2H, $J$ = 8.8 Hz), 6.85−6.79 (m, 4H), 6.56 (s, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.58 (s, 3H), 3.03−2.97 (t, 2H, $J$ = 7.3 Hz), 2.50−2.44 (t, 2H, $J$ = 7.1 Hz), 2.26−2.14 (quintet, 2H, $J$ = 7.2 Hz). $^{13}$C: 158.8, 158.1, 150.6, 148.8, 148.4, 147.8, 133.4, 131.0, 130.8, 130.0, 123.6, 121.6, 119.5, 113.8, 112.7, 110.9, 55.8, 55.6, 55.2, 36.0, 25.0, 16.6. IR: 2318 (weak), 1608, 1515, 1254, 1026. MS: 388 ($M^+$), 335 (100%). HRMS Calcd for $C_{24}H_{24}N_2O_3$: 388.1787 ($M^+$). Found: 388.1789 ($M^+$).

**Carboxylic Acid 43.** A solution of **42** (365 mg, 0.90 mmol) in concd HCl (5 mL) and dioxane (20 mL) was heated at 40 °C for 18 h. The cooled mixture was poured into saturated aqueous $NaHCO_3$ (**CAUTION**: vigorous foaming) and extracted with ether. The extracts were discarded and the aqueous mixture was acidified to pH 2, saturated with solid NaCl, and repeatedly extracted with EtOAc. The extracts were dried ($Na_2SO_4$) and concentrated to afford **43** (332 mg, 87%) as a greenish foam that was advanced to the next step without purification. $^1$H: 12.39 (br s, 1H), 8.51 (br s, 1H), 7.48 (s, 1H), 6.89−6.72 (m, 4H), 6.60−6.58 (d, 2H, $J$ = 6.3 Hz), 3.85 (s, 6H), 3.62 (s, 3H), 3.58 (s, 3H), 3.31 (br s, 2H), 2.96 (br s, 2H). $^{13}$C: 174.7, 156.1, 152.0, 149.5, 148.8, 148.7, 148.5, 145.2, 134.9, 129.3, 128.2, 125.3, 121.9, 121.8, 112.6, 112.3, 111.1, 110.9, 55.7, 33.7, 30.0. IR: 3590 (br), 1723, 1601, 1516, 1465, 1254, 1024. MS: 423 ($M^+$), 378 (100%). HRMS Calcd for $C_{24}H_{25}NO_6$: 423.1682 ($M^+$). Found: 423.1680 ($M^+$).

**Carboxylic Acid 47.** A solution of **46** (205 mg, 0.55 mmol) in concd HCl (2.2 mL)/dioxane (8.8 mL) was heated at 40 °C for 20 h. Workup as described above for **43** afforded **47** (207 mg, 96%), yellow foam, which was advanced to the next step without purification. $^1$H: 11.08 (br s, 1H), 8.47 (br s, 1H), 7.57 (s, 1H), 7.04−7.01 (d, 2H, $J$ = 6.4 Hz), 6.87−6.77 (m, 4H), 6.54 (s, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.51 (s, 3H), 3.34 (br s, 2H), 2.95 (br s, 2H). $^{13}$C ($CDCl_3$): 174.5, 159.5, 155.0, 153.5, 149.9, 148.5, 143.7, 135.4, 130.5, 128.7, 127.3, 126.0, 122.2, 114.1, 112.4, 111.0, 55.7, 55.5, 55.2, 33.5, 29.3. IR: 3511 (br), 1724, 1609, 1516, 1257. MS: 393 ($M^+$), 348 (100%). HRMS Calcd for $C_{23}H_{23}NO_5$: 393.1576 ($M^+$). Found: 393.1576 ($M^+$).

**Carboxylic Acid 52.** A solution of **51** (235 mg, 0.6 mmol) in concd HCl (2.4 mL)/dioxane (9.6 mL) was heated at 40 °C for 2 days. Workup as described above for **43** afforded acid **52** (240 mg, 99%), orange foam, which was advanced to the next step without purification. $^1$H: 9.05 (br s, 1H), 8.53 (br s, 1H), 7.43 (s, 1H), 7.06−7.04 (d, 2H, $J$ = 6.4 Hz), 6.87−6.77 (m, 4H), 6.55 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.55 (s, 3H), 3.10 (br s, 2H), 2.48 (br s, 2H), 2.18 (br s, 2H). $^{13}$C: 175.9, 159.8, 155.1, 154.7, 150.2, 148.6, 142.8, 135.8, 130.6, 128.4, 127.0, 126.1, 122.3, 114.3, 112.4, 111.2, 55.8, 55.6, 55.2, 33.2, 32.8, 24.6. IR: 3504 (br), 1723 (medium intensity), 1609, 1517, 1258. MS: 407 ($M^+$), 348, 335 (100%). HRMS Calcd for $C_{24}H_{25}NO_5$: 407.1733 ($M^+$). Found: 407.1731 ($M^+$).

**Alcohol 44.** A solution of **43** (332 mg, 0.8 mmol) in THF (16 mL) was treated with lithium aluminum hydride (LAH, 187 mg, 4.7 mmol). After gas evolution ceased, the mixture was refluxed for 15 min and then cooled, poured into saturated aqueous $NaHCO_3$ (**CAUTION**: vigorous $H_2$ evolution), and extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated to afford highly polar **44** (yellow foam; 280 mg, 87%), which was not further purified. $^1$H: 8.47 (s, 1H), 7.21 (s, 1H), 6.80−6.71 (m, 4H), 6.57−6.56 (d, 2H, $J$ = 5.9 Hz), 3.84 (s, 6H), 3.77−3.73 (t, 2H, $J$ = 6.9 Hz), 3.60 (s, 3H), 3.58 (s, 3H), 3.03−2.98 (t, 2H, $J$ = 6.9 Hz), 2.08−1.98 (t, 2H, $J$ = 6.5 Hz). $^{13}$C: 160.1, 149.6, 148.7, 148.5, 148.4, 148.2, 148.0, 133.0, 131.7, 130.2, 123.5, 121.8, 121.6, 113.1, 112.6, 111.0, 110.8, 62.2, 55.7, 55.6, 34.9, 31.7. IR 3359 (br), 1601, 1514, 1251, 1026. MS: 409 ($M^+$), 365 (100%). HRMS Calcd for $C_{24}H_{27}NO_5$: 409.1889 ($M^+$). Found: 409.1889 ($M^+$).

**Alcohol 48.** A solution of **47** (207 mg, 0.5 mmol) in THF (11 mL) was treated with LAH (127 mg, 3.2 mmol). The same procedure described above for **44** delivered highly polar **48** (orange foam; 177 mg, 89%), which was not further purified. $^1$H: 8.47 (s, 1H), 7.22 (s, 1H), 7.07−7.03 (d, 2H, $J$ = 8.7 Hz), 6.82−6.78 (m, 4H), 6.54 (s, 1H), 3.86 (s, 3H), 3.79−3.74 (t, 2H, $J$ = 6.7 Hz), 3.77 (s, 3H), 3.56 (s, 3H), 3.05−2.99 (t, 2H, $J$ = 6.7 Hz), 2.09−1.99 (quintet, 2H, $J$ = 6.4 Hz). $^{13}$C: 160.0, 158.8, 149.7, 148.7, 148.3, 148.0, 133.0, 131.2, 130.7, 130.0, 123.6, 121.6, 113.8, 112.7, 110.9, 62.3, 55.7, 55.5, 55.2, 34.9, 31.7. IR: 3387 (br), 1608, 1515, 1252. MS: 379 ($M^+$), 335 (100%). HRMS Calcd for $C_{23}H_{25}NO_4$: 379.1784 ($M^+$). Found: 379.1780 ($M^+$).

**Alcohol 53.** A solution of **52** (132 mg, 0.4 mmol) in THF (8 mL) was treated with LAH (94 mg, 2.3 mmol). The same procedure described above for **44** delivered highly polar **53** (thick yellow oil; 113 mg, 89%), which was not further purified. $^1$H: 8.46 (s, 1H), 7.53 (br s, 1H), 7.19 (s, 1H), 7.07−7.04 (d, 2H, $J$ = 7.7 Hz), 6.84−6.74 (m, 4H), 6.54 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.73−3.68 (t, 2H, $J$ = 6.3 Hz), 3.55 (s, 3H), 2.92−2.86 (t, 2H, $J$ = 6.8 Hz), 1.95−1.83 (quintet, 2H, $J$ = 6.6 Hz), 1.74−1.64 (quintet, 2H, $J$ = 6.5 Hz). $^{13}$C: 160.6, 158.7, 150.0, 148.6, 148.3, 147.7, 132.8, 131.3, 131.1, 130.8, 130.2, 123.4, 121.6, 113.8, 112.8, 112.6, 110.8, 62.2, 56.1, 55.7, 55.5, 55.2, 37.1, 32.2, 25.9. IR: 3401 (br), 1607, 1515, 1251. MS: 393 ($M^+$), 335 (100%). HRMS Calcd for $C_{24}H_{27}NO_4$: 393.1940 ($M^+$). Found: 393.1937 ($M^+$).

**Pyridinium Salt 45.** Methanesulfonyl chloride (MsCl, 102 $\mu$L, 1.3 mmol) was added to a cold (0 °C) mixture of crude **45** (270 mg, 0.7 mmol) and $Et_3N$ (275 $\mu$L, 2.0 mmol) in $CH_2Cl_2$ (13 mL) with good stirring. After 30 min (TLC: reaction complete), the mixture was poured into saturated aqueous NaCl and extracted with $CHCl_3$. The extracts were dried ($Na_2SO_4$) and concentrated to afford **45** (245 mg), orange-brown foam, which was advanced to the next step without purification or characterization beyond a $^1$H NMR spectrum. The nature of the counterion was not determined. $^1$H: 9.21 (s, 1H), 7.75 (s, 1H), 6.96−6.55 (m, 6H), 5.16−5.11 (t, 2H, $J$ = 7.3 Hz), 3.89−3.49 (m, 14H), 2.56−2.45 (quintet, 2H, $J$ = 7.3 Hz).

**Pyridinium Salt 49.** MsCl (70 $\mu$L, 0.9 mmol) was added to a cold (0 °C) mixture of crude **48** (172 mg, 0.4 mmol) and $Et_3N$ (187 $\mu$L, 1.3 mmol) in $CH_2Cl_2$ (9 mL). The same protocol detailed above for **45** furnished **49** (191 mg), orange-brown foam, which was advanced to

the next step without purification or characterization beyond a $^1$H NMR spectrum. The nature of the counterion was not determined $^1$H: 9.26 (s, 1H), 7.78 (s, 1H), 7.26−6.81 (m, 6H), 6.58 (d, 1H, $J$ = 1.3 Hz), 5.29−5.24 (t, 2H, $J$ = 7.1 Hz), 3.87−3.53 (m, 11H), 2.66−2.51 (quintet, 2H, $J$ = 7.2 Hz).

**Pyridinium Salt 54.** MsCl (46 $\mu$L, 0.6 mmol) was added to a cold (0 °C) mixture of crude **54** (113 mg, 0.3 mmol) and $Et_3N$ (121 $\mu$L, 0.9 mmol) in $CH_2Cl_2$ (6 mL). The same protocol detailed above for **45** furnished **54** (127 mg), orange-green foam, which was advanced to the next step without purification or characterization beyond a $^1$H NMR spectrum. The nature of the counterion was not determined. $^1$H: 9.05 (s, 1H), 7.67 (br s, 1H), 7.31−7.26 (m, 2H), 6.92−6.82 (m, 4H), 6.61 (s, 1H), 4.98 (br s, 2H), 3.87−3.54 (m, 11H), 3.31 (br s, 2H), 2.22 (br s, 2H), 2.14−2.02 (br m, 2H).

**(±)-Septicine (1).** $NaBH_4$ (182 mg, 4.6 mmol) was added at room temp to a suspension of crude **45** (164 mg) in EtOH (9 mL). Strong gas evolution ensued. When gas evolution subsided, the mixture was refluxed for 30 min to complete reduction (TLC), and then it was cooled, poured into 10% aqueous NaOH, and extracted with $CH_2Cl_2$. The extracts were dried ($Na_2SO_4$) and concentrated. Chromatography (2% MeOH/$CHCl_3$) gave 106 mg (62% from **44**) of (±)-septicine, **1**, mp 135−137 °C. $^1$H: 6.71−6.65 (m, 4H), 6.57−6.53 (d, 2H, $J$ = 5.0 Hz), 3.93−3.87 (d, 1H, $J$ = 15.9 Hz), 3.80 (s, 6H), 3.59 (s, 3H), 3.57 (s, 3H), 3.36−3.29 (t, 1H, $J$ = 6.8 Hz), 3.14−3.08 (d, 1H, $J$ = 16.1 Hz), 2.78−2.71 (d, 1H, $J$ = 12.6 Hz) 2.46−1.84 (m, 6H), 1.65−1.52 (m, 1H). $^{13}$C: 148.2, 148.1, 147.5, 134.9, 133.5, 132.9, 132.3, 121.0, 120.7, 113.0, 112.8, 110.6 (2 signals), 60.4, 57.3, 55.7, 55.6, 54.1, 38.2, 30.7, 29.7, 21.5. IR: 1513, 1261, 1027. MS: 395 ($M^+$), 326, 295 (100%), 264. HRMS Calcd for $C_{24}H_{29}NO_4$: 395.2097 ($M^+$). Found: 395.2097 ($M^+$).

**(±)-Seco-Antofine (50).** $NaBH_4$ (192 mg, 4.8 mmol) was added at room temp to a suspension of crude **50** (180 mg) in EtOH (10 mL). Strong gas evolution ensued. The mixture was handled as detailed above for **1** to give 139 mg (84% from **48**) of (±)-seco-antofine **50**, pale orange foam. $^1$H: 6.98−6.94 (d, 2H, $J$ = 6.9 Hz), 6.69−6.63 (m, 4H), 6.46 (s, 1H), 6.57−6.53 (d, 2H, $J$ = 5.0 Hz), 3.90−3.83 (d, 1H, $J$ = 15.9 Hz), 3.80 (s, 3H), 3.72 (s, 3H), 3.54 (s, 3H), 3.34−3.27 (dt, 1H, $J_1$ = 8.3 Hz, $J_2$ = 2.0 Hz), 3.11−3.05 (d, 1H, $J$ = 15.9 Hz), 2.81−2.65 (m, 1H) 2.44−1.80 (m, 6H), 1.65−1.48 (m, 1H). $^{13}$C ($CDCl_3$): 157.9, 147.8, 147.1, 135.0, 133.5, 132.6, 130.1, 120.6, 113.3, 113.0, 110.4, 60.4, 57.8, 55.6, 55.4, 55.1, 54.2, 38.4, 30.8, 29.7, 21.5. IR: 1509, 1247. MS: 365 ($M^+$), 296, 265 (100%). HRMS Calcd for $C_{23}H_{27}NO_3$: 365.1991 ($M^+$). Found: 365.1990 ($M^+$).

**(±)-Julandine (5).** $NaBH_4$ (116 mg, 2.9 mmol) was added at room temp to a suspension of crude **54** (118 mg) in EtOH (6 mL). Strong gas evolution ensued. The mixture was handled as detailed above for **1** to give 91 mg (86% from **53**) of pale yellow (±)-julandine, **5**, mp 135−137 °C. $^1$H: 7.00−6.95 (dd, 2H, $J_1$ = 8.6 Hz, $J_2$ = 1.9 Hz), 6.71−6.63 (m, 4H), 6.46 (s, 1H), 3.81 (s, 3H), 3.73−3.54 (m, 10 H, of which 3 s with 3H each), 3.21−3.09 (m, 2H), 2.54−1.25 (m, 10H). $^{13}$C: 158.0, 147.8, 147.2, 134.3, 133.1, 131.2, 130.1, 129.4, 129.3, 120.5, 113.4, 112.9, 110.4, 60.2, 57.9, 55.9, 55.6, 55.4, 55.1, 39.3, 33.1, 25.7, 24.2. IR: 3502 (br), 1606, 1511, 1248. MS: 379 ($M^+$, 100%), 296, 265. HRMS Calcd for $C_{24}H_{29}NO_4$: 379.2147 ($M^+$). Found: 379.2147 ($M^+$).

**(±)-Tylophorine (1).** A cold (0 °C) solution of (±)-septicine, **4** (54 mg, 0.14 mmol) and $VOF_3$ (84 mg, 0.6 mmol) in $CH_2Cl_2$ (3 mL) was stirred for 15 min, and then trifluoroacetic acid (136 $\mu$L) was slowly introduced and stirring was continued at 0 °C for an additional 15 min. The mixture was poured into 10% aqueous NaOH and extracted with $CH_2Cl_2$. The extracts were dried ($Na_2SO_4$) and concentrated. Recrystallization of the crude product from acetonitrile gave 40 mg (74%) of beige (±)-tylophorine, **1**, mp 272−274 °C dec. (lit. mp's range from 263−265 °C to 292−294 °C).[22] $^1$H: 7.83 (s, 2H), 7.32 (s, 1H), 7.16 (s, 1H), 4.66−4.60 (d, 1H, $J$ = 14.5 Hz), 4.12 (s, 6H), 4.06 (two s, each 3H), 3.57 (s, 3H), 3.70−3.64 (d, 1H, $J$ = 14.6 Hz), 3.51−3.45 (t, 1H, $J$ = 7.4 Hz), 3.42−3.34 (dd, 1H, $J_1$ = 5.7 Hz, $J_2$ = 2.4 Hz), 2.97−2.86 (t, 1H, $J$ = 13.0 Hz), 2.56−2.41 (m, 2H), 2.31−2.19 (m, 1H), 2.09−1.70 (m, 3H). $^{13}$C: 148.7, 148.5, 126.3, 126.0, 125.8, 124.3, 123.6, 123.4, 104.0, 103.4, 103.3, 103.1, 60.2, 56.0, 55.9, 55.2, 54.1, 33.8, 31.3, 21.6. IR: 1513, 1248. MS: 393 ($M^+$), 324(100%). HRMS Calcd for $C_{24}H_{27}NO_4$: 393.1940 ($M^+$). Found: 393.1939 ($M^+$).

**(±)-Antofine (2).** A cold (0 °C) solution of (±)-seco-antofine (**50**) (83 mg, 0.23 mmol) and $VOF_3$ (143 mg, 1.1 mmol) in $CH_2Cl_2$ (5 mL) was stirred for 15 min, and then trifluoroacetic acid (230 $\mu$L) was slowly introduced and stirring was continued at 0 °C for an additional 15 min. The same workup described above for **1** and recrystallization from acetonitrile furnished 42 mg (51%) of pale yellow (±)-antofine, **2**, mp 205−207 °C (dec; lit. 213−215 °C, dec.).[23] $^1$H: 7.91−7.89 (m, 2H), 7.83−7.80 (d, 1H, $J$ = 9.1 Hz), 7.31 (s, 1H), 7.22−7.18 (dd, 1H, $J_1$ = 9.1 Hz, $J_2$ = 2.5 Hz), 4.72−4.66 (d, 1H, $J$ = 14.9 Hz), 4.11 (s, 3H), 4.06 (s, 3H), 4.02 (s, 3H), 3.57 (s, 3H), 3.72−3.66 (d, 1H, $J$ = 14.9 Hz), 3.49−3.42 (dt, 1H, $J_1$ = 7.6 Hz, $J_2$ = 1.9 Hz), 3.36−3.30 (dd, 1H, $J_1$ = 5.7 Hz, $J_2$ = 2.3 Hz), 2.94−2.84 (t, 1H, $J$ = 12.9 Hz), 2.50−2.39 (m, 2H), 2.26−2.18 (m, 1H), 2.08−1.71 (m, 3H). $^{13}$C: 157.4, 149.4, 148.3, 130.1, 127.1, 126.7, 125.5, 124.2, 124.1, 123.5, 114.8, 104.6, 104.0, 103.8, 60.2, 56.0, 55.9, 55.5, 55.1, 53.9, 33.7, 31.3, 29.7, 21.6. IR: 3402 (br), 1616, 1512, 1469, 1257, 1205. MS: 363 ($M^+$), 294 (100%). HRMS Calcd for $C_{23}H_{25}NO_3$:363.1834 ($M^+$). Found: 363.1834 ($M^+$).

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**Supporting Information Available:** Hardcopy $^1$H and $^{13}$C spectra of selected compounds (30 pages). See any current masthead page for ordering and Internet access instructions.

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(22) Discord exists in the literature regarding the melting point of (±)-**1**, e.g.: 292−294 °C (ref 4k); 287 °C (ref 4m); 273 °C (ref 17); 263−265 °C (ref 4f).

(23) Govindachari, T. R.; Ragade, I. S.; Viswanathan, N. *J. Chem. Soc.* **1962**, 1356.