JOC*Note*

Total Synthesis of Antofine Using the Net [5+5]-Cycloaddition of γ,δ-Unsaturated Carbene Complexes and 2-Alkynylphenyl Ketones as a Key Step

Alejandro Camacho-Davila and James W. Herndon*

Department of Chemistry and Biochemistry, New Mexico State University, MSC 3C, Las Cruces, New Mexico 88003

jherndon@nmsu.edu

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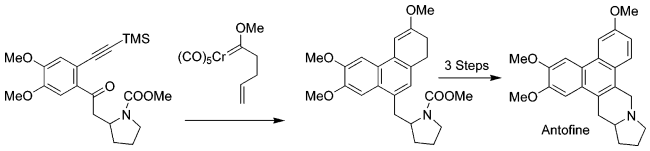
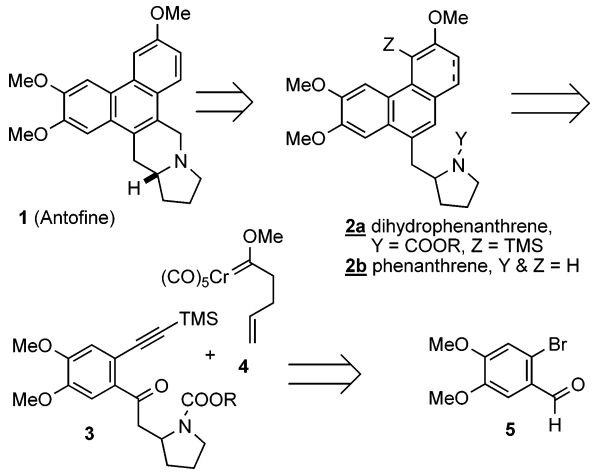


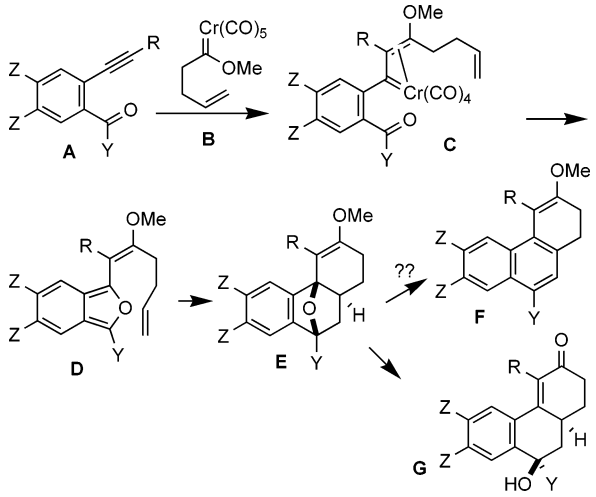
A compound containing all of the carbons of the anticancer agent antofine was produced in a single step from the coupling of a γ,δ-unsaturated carbene complex with a 2-alkynylphenyl ketone derivative. Subsequent conversion to antofine was effected in three steps.

Antofine (**1**, Scheme 1) is a potent anticancer agent[1] of the phenanthroindolizidine alkaloid family of natural products.[2] The anticancer activity of antofine arises through inhibition of protein and nucleic acid synthesis.[3] Antofine also displays other medicinal properties, including antibiotic and antifungal activity,[4] and antiviral activity.[5] Antofine has been the subject of numerous synthetic investigations. Most of the syntheses of antofine have involved the preparation of substrates where the middle aromatic ring of phenanthrene is closed in an early step of the synthesis. Diverse strategies have been employed for appending the pyrrolidine ring system. These methods include strategies based on the alkylation of pyrrole,[6] alkylation of proline,[7] use of a pyrrole-substituted Wittig-like reagent,[8] and ortho metalation.[9] Other strategies include a pyridine-based strategy[10] and a cyclohexadienone photorearrangement approach.[11] Enantioselective approaches based on alkene metathesis have recently been reported.[12]

SCHEME 1



SCHEME 2



Synthesis of the hydrophenanthrene ring systems through the coupling of γ,δ-unsaturated carbene complexes with 2-alkynylphenylbenzoyl systems in a net [5+5]-cycloaddition process was recently reported (Scheme 2).[13] This complex tandem process involves carbene−alkyne coupling (**A** + **B** to **C**), followed by isobenzofuran formation (**C** to **D**), followed by

(1) (a) Tanner, U.; Wiegrebe, W. *Arch. Pharm. Chem. Life Sci.* **1993**, *326*, 67−72. (b) Stark, D.; Lykkeberg, A. K.; Christensen, J.; Budnik, B. A.; Abe, F.; Jaroszewski, J. W. *J. Nat. Prod.* **2002**, *65*, 1299−1302. (c) Lee, S. K.; Nam, K. A.; Heo, Y. H. *Planta Med.* **2003**, *69*, 21−25. (d) Lou, H.; Li, X.; Chu, X.; Jiang, Z.; Zhao, Y. *Shandong Yike Daxue Xuebao* **1995**, *33*, 158−62. (e) Fang, S.; Zhang, R.; Chen, Y.; Xu, C.; Lu, S. *Zhiwu Xuebao* **1989**, *31*, 934−938.

(2) For a recent review of this class of compounds, see: Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365−2378.

(3) Xi, Z.; Zhang, R.; Yu, Z.; Ouyang, D.; Huang, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2673−2677.

(4) (a) Baumgartner, B.; Erdelmeier, C. A. J.; Wright, A. D.; Rali, T.; Sticher, O. *Phytochemistry* **1990**, *29*, 3327−3330. (b) Capo, M.; Saa, J. M. *J. Nat. Prod.* **1989**, *52*, 389−390.

(5) An, T.; Huang, R.; Yang, Z.; Zhang, D.; Li, G.; Yao, Y.; Gao, J. *Phytochemistry* **2001**, *58*, 1267−1269.

(6) Govindachari, T. R.; Ragade, I. S.; Viswanathan, N. *J. Chem. Soc.* **1962**, 1357−1360.

(7) (a) Chauncey, B.; Geller, E. *Aust. J. Chem.* **1970**, *23*, 2503−2513. (b) Faber, L.; Weigerebe, W. *Helv. Chim. Acta* **1973**, *56*, 2882−2884. (c) Faber, L.; Wiegerebe, W. *Helv. Chim. Acta* **1976**, *59*, 2201−2212.

(8) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1999**, *55*, 2659−2670.

(9) Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; De Silva, S. O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955−1962.

(10) Ciufolini, M. A.; Roschangar, F. *J. Am. Chem. Soc.* **1996**, *118*, 12082−12089.

(11) Bhakuni, D. S.; Gupta, P. K. *Indian J. Chem., B* **1982**, *21B*, 393−395.

(12) (a) Kim, S.; Lee, J.; Lee, T.; Park, H. G.; Kim, D. *Org. Lett.* **2003**, *5*, 2703−2706. (b) Kim, S.; Lee, T.; Lee, E.; Lee, J.; Fan, G.; Lee, S. K.; Kim, D. *J. Org. Chem.* **2004**, *69*, 3144−3149. (c) For synthesis of the enantiomer, see ref 7b.

(13) For the most recent example, see: Li, R.; Zhang, L.; Camacho-Davila, A.; Herndon, J. W. *Tetrahedron Lett.* **2005**, *46*, 5117−5120.

10.1021/jo061053n CCC: $33.50
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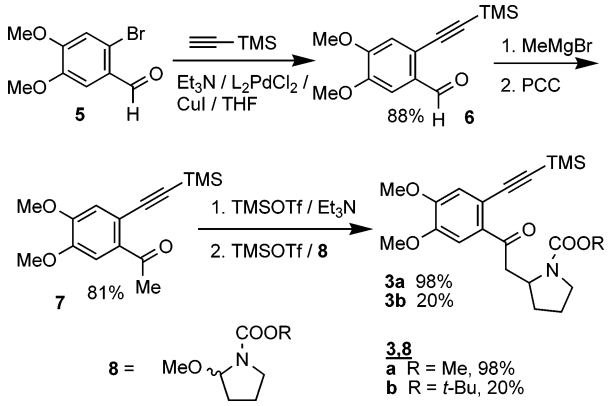
SCHEME 3

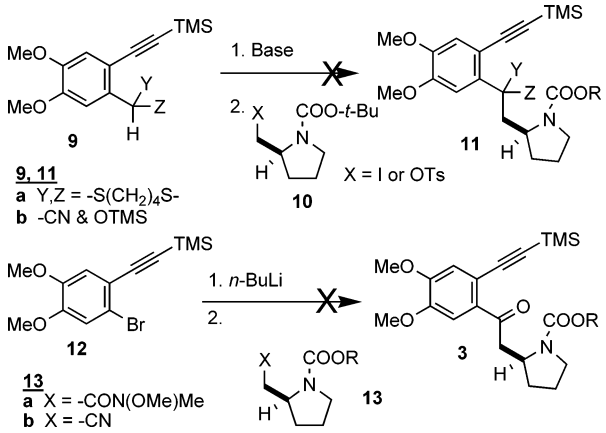


intramolecular Diels−Alder reaction (**D** to **E**), followed by opening of the oxanorbornene ring to afford **G**. Use of this reaction for the synthesis of antofine will require that the oxanorbornene intermediate undergo an alternative pathway, dehydration (**E** to **F**).[14] This pathway was observed in cases where the Y group is strongly electron donating.[15]

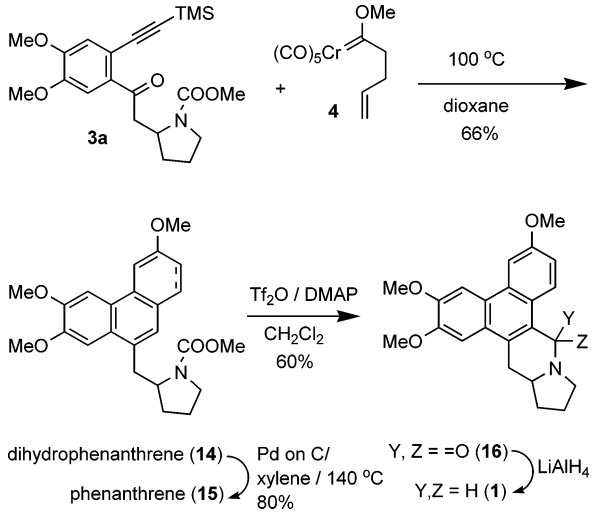
In this manuscript, the use of the process in Scheme 2 as the key step in a short total synthesis of antofine will be described. The retrosynthetic analysis for antofine is depicted in Scheme 1. Coupling of ketone **3** and butenylcarbene complex **4** will afford dihydrophenanthrene **2a**, assuming that the presence of the electron-rich aromatic ring will result in dehydration (conversion of **E** to **F** in Scheme 2). The cyclization precursor **3** should be readily prepared from commercially available 6-bromo-3,4-dimethoxybenzaldehyde **5** through alkynylation and introduction of the pyrrolidine group. Successful transformation of initial adduct **2a** to secondary amine−phenanthrene **2b**, the penultimate synthetic intermediate in several of the previous total syntheses, would constitute a formal total synthesis of antofine. Simple condensation of amine **2b** with formaldehyde leads to antofine in high yield.[7b,8,12]

The alkyne−ketone−carbamate **3** was rapidly assembled through the sequence of reactions in Scheme 3. Commercially available 6-bromoveratraldehyde (**5**)[16] was transformed to the ketone **7** via Sonogashira coupling[17] followed by conversion of the alkyne−aldehyde **6** to the corresponding methyl ketone. For the introduction of the pyrrolidine unit, only the silyl enol ether−acyliminium ion coupling depicted in Scheme 3 was successful. The synthesis of the carbomethoxy-protected adduct **3a** was more efficient than the attempted synthesis of Boc-protected analogue **3b**. Methods using proline-derived sources of the heterocyclic ring were also attempted but were unsuccessful (Scheme 4). Coupling of carbonyl anion equivalents derived from aldehyde **6** (e.g., **9a** and **9b**) and Boc-protected homoproline iodide or tosylate (**10**) was unsuccessful despite demonstrated success with similar compounds.[18]

SCHEME 4



SCHEME 5



Methods based on the addition of the organolithium reagent derived from **12** to Weinreb amide **13a** or the corresponding nitrile **13b** were similarly unsuccessful.[19]

The key step of the reaction (coupling of **3a** and **4**, Scheme 5) led to dihydrophenanthrene **14** in 66% yield. As expected, the presence of the electron-rich aromatic ring in **3a** resulted in only a dehydration product, dihydrophenanthrene **14**. The trimethylsilyl substituent was also removed in the key carbene complex coupling step, possibly during chromatographic purification.[20] Dehydrogenation to form phenanthrene **15** was effected by treatment with palladium on carbon in refluxing xylene. The reaction employing DDQ afforded a complex mixture of products. Formal total synthesis of antofine required only the removal of the carbomethoxy protecting group from **15** to afford **2b** (see Scheme 1). This proved to be very challenging, and no conditions were found where this process

(14) This pathway is frequently observed for isobenzofuran−alkene Diels−Alder adducts. Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, *73*, 1−96.

(15) Ghorai, B. K.; Herndon, J. W. *Organometallics* **2003**, *22*, 3951−3957.

(16) It is far more economical to brominate veratraldehyde for large-scale reactions (Br_2 in acetic acid). Charlton, J. L.; Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490−3493.

(17) This is a known compound. Martin, N.; Altable, M.; Filippone, S.; Martin-Domenech, A.; Poater, A.; Sola, M. *Chem.−Eur. J.* **2005**, *11*, 2716−2729.

(18) Jones, K.; Woo, K. C. *Tetrahedron* **1991**, *47*, 7179−7184.

(19) Nucleophilic addition of hydride to the nitrile has been reported; however, we are not aware of successful addition of aryllithium reagents. Toujas, J. L.; Jost, E.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 713−717.

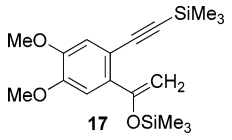
(20) This is anticipated to be a facile process because of the strain associated with forcing a bulky trimethylsilyl group into the bay region and because protonation of the silicon-bearing carbon of compound **2** (Scheme 1) would afford a carbocation stabilized by an α-methoxy group and a *β*-silyl group. For a recent reference to alkoxyvinylsilanes, see: Barluenga, J.; Alvarez-Garcia, L. J.; Romanelli, G. P.; Gonzalez, J. M. *Tetrahedron Lett.* **1997**, *38*, 6763−6766. These authors did not note any unusual acid sensitivity for these compounds.

could be accomplished in respectable yield. An alternative synthetic route was explored that employs the conversion of carbamate **15** to the lactam **16** through the Bischler−Napieralski reaction. Classical conditions using phosphorus oxychloride failed in this reaction; however, the use of triflic anhydride allowed for successful ring closure.[21] The resulting amide was utilized in previous total syntheses of antofine,[9,11] and treatment with lithium aluminum hydride completed the total synthesis.

In summary, a short total synthesis that affords racemic[22] antofine in 23% overall yield in seven steps[23] from commercially available chemicals has been presented. The key step in this reaction is the carbene complex coupling in Scheme 5, which incorporates all of the carbons of antofine in a net [5+5]-cycloaddition process.

Experimental Section[24]

Preparation of Ketone 3a. To a solution of ketone **7**[25] (2.00 g, 7.23 mmol) in dichloromethane (25 mL) was added triethylamine (2 mL). This mixture was cooled to 0 °C in an ice-water bath, and a solution of trimethylsilyl trifluoromethanesulfonate (1.7 mL, 8.8 mmol) dissolved in dichloromethane (5 mL) was added dropwise over 5 min. The mixture was stirred at 0−5 °C for 30 min and at room temperature for 1 h. The reaction mixture was then diluted with hexanes (75 mL) and poured into saturated aqueous sodium bicarbonate solution (25 mL). The organic phase was washed with water (4 × 25 mL), dried over sodium sulfate, and concentrated on a rotary evaporator to afford 2.49 g (98%) of silyl enol ether **17** as an oil, which was used in the next step without purification. ^{1}H NMR ($CDCl_3$): δ 0.20 (s, 9H), 0.22 (s, 9H), 3.86 (s, 6H), 4.65 (d, 1H, J = 1.3 Hz), 5.15 (d, 1H, J = 1.3 Hz), 6.93 (s, 1H), 7.01 (s, 1H). ^{13}C NMR ($CDCl_3$): δ −0.2, 0.0, 55.7, 55.8, 96.2, 96.7, 105.1, 110.5, 112.5, 115.7, 134.3, 147.9, 149.0, 153.6. IR (neat): 2147 (m), 1600 (s) cm^{-1}. To a solution of **8a**[26] (1.095 g, 6.88 mmol)



17

and silyl enol ether **17** (2.76 g, 7.91 mmol, 1.15 equiv) in dichloromethane (25 mL) at −78 °C and under an argon atmosphere was added trimethylsilyl trifluoromethanesulfonate (0.50 mL, 2.6 mmol). The resulting purple solution was stirred for 1 h at −78 °C, and saturated aqueous sodium bicarbonate solution (25 mL) was added. The reaction mixture was allowed to warm to room temperature, then extracted with dichloromethane (3 × 15 mL) and dried over sodium sulfate. After concentration, the residue was purified by flash chromatography on silica gel, eluting with hexanes−ethyl acetate (3:2). A yellowish syrup identified as alkyne−ketone−carbamate **3a** (3.17 g, 100% yield) was obtained. ^{1}H NMR ($CDCl_3$): δ 0.25 (s, 9H), 1.70−1.93 (m, 3H), 2.20 (m, 1H), 3.20−3.57 (m, 4H), 3.60 (s, 3H), 3.94 (s, 6H), 4.39 (m, 1H), 6.97 (s, 1H), 7.42 (nearly coalescing singlets,[27] 1H). ^{13}C NMR ($CDCl_3$): δ −0.4, 22.9*, 23.7*, 31.0*, 31.9*, 46.3*, 46.7, 52.1, 54.1*, 54.7*, 56.0, 56.2, 104.7, 111.3*, 115.4*, 116.2, 133.7, 142.4, 149.4, 151.5*, 155.3*, 198.7. IR (neat): 2147 (m), 1698 (s), 1668 (m), 1592 (m), 1512 (m) cm^{-1}. MS (EI): 403 (M, 33), 388 (23), 372 (12), 344 (18), 330 (73), 301 (12), 261 (64), 149 (54), 128 (95), 69 (100). HRMS: Calcd for $C_{21}H_{29}NO_5Si$, 403.1815; found, 403.1804. *These peaks are broadened due to dynamic processes.

Synthesis of Dihydrophenanthrene 14 through Coupling of Alkyne−Ketone 3a with Carbene Complex 4. To a refluxing solution of alkyne−ketone **3a** (568 mg, 1.40 mmol) in dioxane (15 mL) was added over a 1 h period a solution of carbene complex **4**[25] (450 mg, 1.55 mmol) in dioxane (15 mL). After the addition was complete, the reflux was continued for 24 h and the mixture was then allowed to cool to room temperature. The dioxane was removed on a rotary evaporator, and the residue was suspended in hexanes−ethyl acetate and filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using 1:1 hexane/ethyl acetate as eluent. Dihydrophenanthrene **14** was isolated as a white powder (380 mg, 66%). Mp 173−175 °C. ^{1}H NMR ($CDCl_3$): δ 1.60−2.00 (m, 4H), 2.47 (t, 2H, J = 4.0 Hz), 2.57 (m, 1H), 2.97 (t, 2H, J = 4.0 Hz), 3.34 (m, 1H), 3.45−3.75 (m, 2H), 3.76 (s, 1.5 H, one rotamer of $R_2NCOOCH_3$), 3.85 (s, 3H), 4.03 (s, 6H), 4.15 (s, 1.5H, one rotamer of $R_2NCOOCH_3$), 4.27 (m, 1H), 6.09 (s, 1H), 6.93 (s, 1H), 7.28 (s, 1H), 7.97 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.5, 27.7, 29.1, 29.5, 37.9, 46.6, 52.1, 54.8, 55.8, 56.5, 57.9, 91.9, 102.1, 104.9, 125.0, 126.8, 127.6, 128.1, 130.1, 149.0, 155.7, 160.8. IR (neat): 1693 (s), 1636 (m) cm^{-1}. MS (EI): 411 (M, 40), 283 (100), 268 (3), 128 (77). HRMS: Calcd for $C_{24}H_{29}NO_5$, 411.2036; found, 411.2045.

Formation of Phenanthrene 15 through Dehydrogenation of 14. Compound **14** (0.841 g, 2.00 mmol) was dissolved in xylenes (15 mL), and 10% palladium on carbon (0.5 g) was added. The mixture was refluxed for 48 h. Concentration under reduced pressure and purification by flash column chromatography eluting with hexane/ethyl acetate 3:2 on silica gel afforded 0.67 g (80%) of phenanthrene **15**. Mp 177−180 °C. ^{1}H NMR ($CDCl_3$): δ 1.83−2.05 (m, 2H), 2.16 (m, 1H), 2.43 (m, 1H), 2.91 (dd, 1H, J = 15.7, 13.5 Hz), 3.54 (dd, 1H, J = 15.8, 4.5 Hz), 3.80−4.00 (m, 4H), 4.01 (s, 3H), 4.06 (s, 6H), 4.12 (s, 3H), 7.26 (dd, 1H, J = 9.3, 2.4 Hz), 7.32 (s, 1H), 7.85 (d, 1H, J = 2.4 Hz), 7.90 (s, 1H), 9.30 (d, 1H, J = 9.3 Hz). ^{13}C NMR ($CDCl_3$): δ 14.1, 23.4, 28.9, 38.2, 46.5, 52.0, 55.4, 55.9, 56.6, 57.4, 60.2, 103.6, 103.8, 106.3, 115.2, 124.5, 125.9, 127.0, 129.4, 130.5, 148.7, 149.8, 155.6, 157.9, 170.9. IR (neat): 1693 cm^{-1}. MS (EI): 409 (M^+, 15), 281 (8), 128 (100). HRMS: Calcd for $C_{24}H_{27}NO_5$, 409.1892; found, 409.1889.

Formation of Amide 16 through Bischler−Napieralski Cyclization of 15. To a cooled (0 °C) solution of **15** (200 mg, 0.48 mmol) in dichloromethane (25 mL) containing (dimethylamino)-pyridine (176 mg, 2.40 mmol, 3 equiv) was added over 15 min a solution of trifluoromethanesulfonic anhydride (677 mg, 2.4 mmol, 3 equiv) in dichloromethane (10 mL). The solution was stirred for 16 h while the ice-water bath was kept in place but without any further addition of ice. The reaction was diluted with dichloromethane (20 mL) and washed successively with saturated aqueous sodium carbonate solution (10 mL), 20% aqueous acetic acid (10 mL), and again with saturated aqueous sodium carbonate solution. This solution was dried over sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 100% ethyl acetate gave 108 mg (60%) of

(21) Banwell, M. G.; Bisset, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *Chem. Commun.* **1995**, 2551−2553.

(22) Because of the failed reactions noted in Scheme 4, use of the synthesis in this manuscript for preparation of optically pure antofine must await advances in the enantioselective addition of acetophenone-derived silyl enol ethers to acyliminium ions. A report of moderately enantioselective additions (53% ee in best case) to acyliminium ions recently appeared. Onomura, O.; Ikeda, T.; Matsumura, Y. *Heterocycles* **2005**, *66*, 81−86.

(23) The overall synthesis is six steps from known compound **6**, seven steps from commercially available 6-bromoveratraldehyde (**5**), and eight steps from cheap 3,4-dimethoxybenzaldehyde.

(24) For a general experimental, see the Supporting Information.

(25) See Supporting Information.

(26) Boto, A.; Hernandez, R.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930−4937.

(27) This assignment was based on the different appearance of the 60, 200, and 400 MHz proton NMR spectra. The two peaks at δ 7.42 appear as a single peak in the 60 MHz NMR and as two broad singlets in the 200 MHz spectrum. This broadening is likely due to rotation about the aryl−CO C−C bond.

compound **16**. Mp 265−270 °C (color is significantly darker at mp). ^{1}H NMR ($CDCl_3$): δ 1.80−2.00 (m, 2H), 2.13 (m, 1H), 2.40 (m, 1H), 2.80 (dd, 1H, J = 15.0, 13.0 Hz), 3.44 (dd, 1H, J = 15.0, 4.0 Hz), 3.78−3.85 (m, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 4.09 (s, 3H), 7.22 (s, 1H), 7.23 (dd, 1H, J = 9.1, 2.5 Hz), 7.79 (d, 1H, J = 2.5 Hz), 7.82 (s, 1H), 9.28 (d, 1H, J = 9.1 Hz). ^{13}CNMR ($CDCl_3$): δ 23.5, 32.5, 33.8, 45.2, 55.1, 55.4, 55.86, 55.94, 56.1, 103.8, 104.1, 104.9, 115.2, 123.5, 124.3, 126.7, 129.6, 130.9, 132.5, 149.5, 150.1, 157.7, 164.2. IR(neat): 1631 cm^{-1}. LRMS: 377 (M+, 100), 308 (60), 280 (42), 265 (10), 222 (8), 188 (15). HRMS Calcd for $C_{23}H_{23}NO_4$, 377.1618; found, 377.1627.[28]

Antofine (1). To a solution of amide **16** (20 mg, 0.052 mmol) in THF (10 mL) was added lithium aluminum hydride (100 mg, 2.63 mmol), and the mixture was heated to reflux under an argon atmosphere for 3 h. The reaction was cooled to room temperature, and 3 N aqueous sodium hydroxide solution (5 mL) was added. The mixture was saturated with solid sodium sulfate, and the solids were extracted with THF (5 × 5 mL). Concentration under reduced pressure and purification of the residue by preparative TLC on silica gel eluting with dichloromethane/ methanol (10:1) afforded racemic antofine as a yellowish solid.[29] ^{1}H NMR ($CDCl_3$): δ 1.79 (m, 1H), 1.93 (m, 1H), 2.02 (m, 1H), 2.26 (m, 1H), 2.50 (m, 1H), 2.92 (dd, IH, J = 13.8, 10.2 Hz), 3.34 (dd, 1H, J = 13.8, 1.8 Hz), 3.48 (br t, 1H, J = 6.5 Hz), 3.63 (m, 1H), 3.72 (d, 1H, J = 14.7 Hz), 4.01 (s, 3H), 4.06 (s, 3H), 4.11 (s, 3H), 4.70 (d, 1H, J = 14.7 Hz), 7.20 (dd, 1H, J = 9.0, 2.5 Hz), 7.30 (s, 1H), 7.81 (d, 1H, J = 9.0 Hz), 7.86 (d, 1H, J = 2.5 Hz), 7.91 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 31.2, 33.5, 53.7, 55.0, 55.4, 55.9, 56.0, 60.2, 103.9, 104.1, 104.8, 114.8, 123.5, 124.1, 124.2, 125.5, 126.5, 127.0, 130.2, 148.3, 149.3, 157.4. The spectral data were in agreement with those previously reported for this compound.[12a]

(28) The spectral data are not in agreement with that reported for this compound in ref 9. A closer examination reveals that the spectral data reported for compound **16** in ref 9 are actually the spectral data for antofine.

(29) The yield for this process is reported as quantitative (see ref 9). Our yield was 75%; however, we only attempted this reaction once.

Acknowledgment. This work was supported by the SCORE program of NIH. The Universidad Autonoma de Chihuahua and PROMEP (Mexico) provided a fellowship to A.C.D. High-resolution mass spectra were acquired at the University of California at Riverside or through the Nebraska Mass Spec Facility.

Supporting Information Available: Synthetic procedures for compounds **4**−**7**. Photocopies of proton and C-13 NMR spectra for compounds **1**, **3a**, **7**, and **14**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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