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Expedient Syntheses of Antofine and Cryptopleurine via Intramolecular 1,3-Dipolar Cycloaddition

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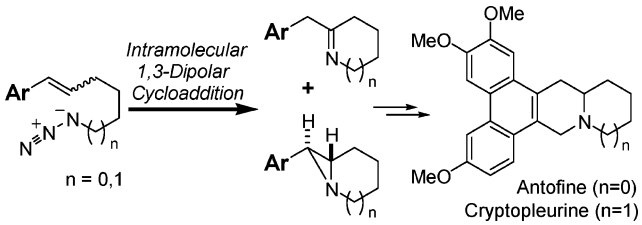
Received April 2, 2007



The practical and expedient total syntheses of the representative phenanthroindolizidine and phenanthroquinolizidine alkaloids, antofine and cryptopleurine, are described. Construction of the pyrrolidine and piperidine ring of each alkaloid was achieved by using an intramolecular 1,3-dipolar cycloaddition of an azide onto an alkene and subsequent reduction of the resulting imine and aziridine.

Introduction

It is now over 70 years since the phenanthroindolizidine alkaloid, tylophorine (**1**, Figure 1), was first described in the literature.[1] Nowadays, numerous phenanthroindolizidine alkaloids and structurally related phenanthroquinolizidine alkaloids have been isolated from various natural sources. These pentacyclic natural products exhibit a variety of biological effects including antitumor, antiamoebic, antibacterial, and antifungal activities.[2,3] Among these interesting biological activities, the most intriguing property is the profound cytotoxic activity against various cancer cell lines. For example, (−)-antofine ((−)-**2**, Figure 1) has IC_{50} values in the low nanomolar range against drug-sensitive KB-3-1 and multidrug-resistant KB-V1 cancer cell lines, comparable to that of clinically employed cytotoxic drugs.[4] Because of the profound cytotoxic activity and interesting biochemical aspects, phenanthroindolizidine alkaloids together with phenanthroquinolizidine alkaloids have received significant attention as potential therapeutic leads. However, these classes of natural products have not yet been developed for clinical use. The major drawbacks to the potential therapeutic use of these compound classes are the serious central nervous side effects[5] and low water solubility. To overcome these pharmacologically unsuitable properties, more intense investigations are deemed necessary from a medicinal chemical viewpoint.[6]

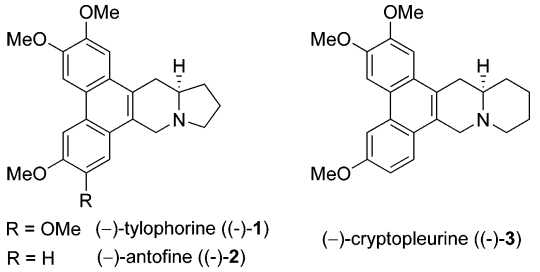


FIGURE 1. Chemical structures of compounds **1**−**3**.

* To whom correspondence should be addressed. Tel: 82-2-740-8913. Fax: 82-2-762-8322.

(1) Ratnagiriswaran, A. N.; Venkatachalam, K. *Indian J. Med. Res.* **1935**, *22*, 433−441.

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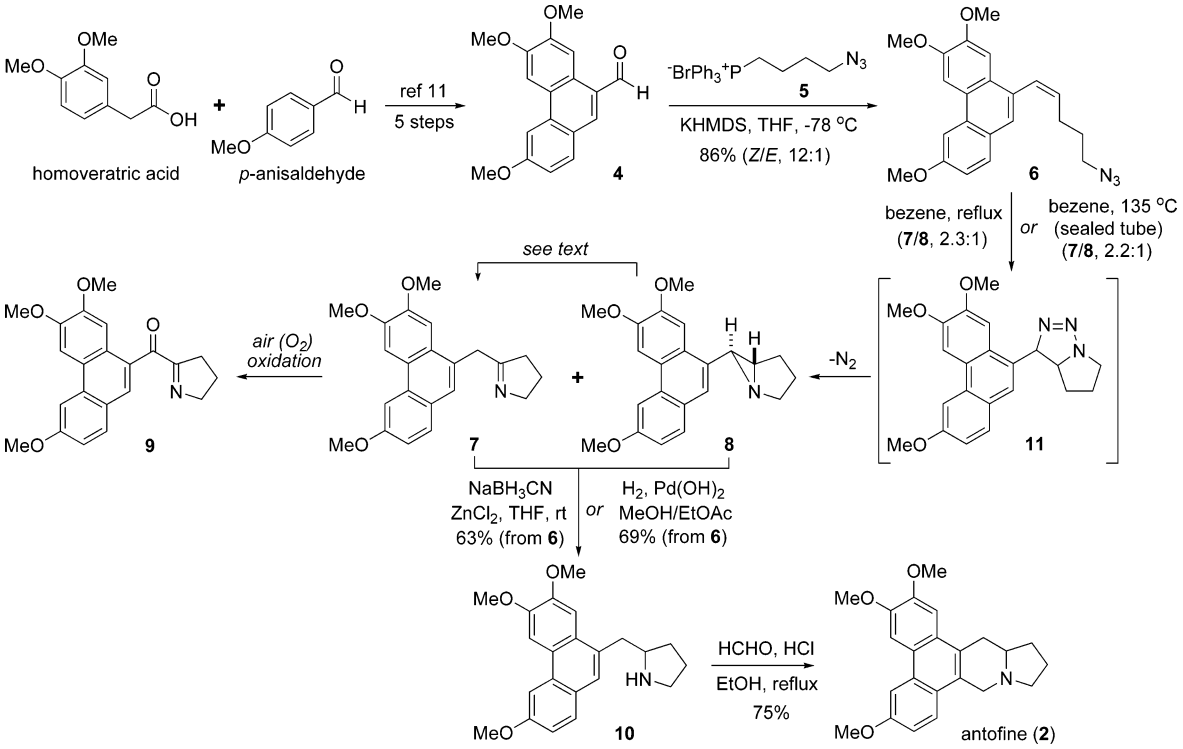
10.1021/jo070668x CCC: $37.00
Published on Web 05/25/2007

SCHEME 1. Synthesis of Antofine (2)



The promising biochemical profiles of phenanthroindolizidine and phenanthroquinolizidine alkaloids coupled with their low natural abundance and unusual architecture have prompted impressive synthetic efforts to date from a number of laboratories.[3,7] As part of our ongoing research, we have previously developed two different asymmetric synthetic approaches to (−)-antofine.[8] Although our previous approaches are efficient enough to apply to the synthesis of phenanthroindolizidine and phenanthroquinolizidine analogues, we needed to explore a different and expedient synthetic route for the rapid preparation of analogues in racemic form. Indeed, with the new facile synthetic route, we have synthesized and evaluated a series of antofine analogues with different substituents on the phenanthrene ring to define the features of the molecule that are essential for cytotoxicity.[9] In this paper, we wish to describe full details of our new synthetic route to the representative phenanthroindolizidine and phenanthroquinolizidine alkaloids, antofine (**2**) and cryptopleurine (**3**), which was briefly mentioned in our recent report.

Results and Discussion

We employed the intramolecular 1,3-dipolar cycloaddition of an azide onto an alkene as a key step in our new synthesis (Scheme 1). Indeed, a similar cycloaddition reaction has been employed in the synthesis of tylophorine (**1**).[10] The starting material for our synthesis was the known phenanthryl aldehyde **4**, which was obtained from the commercially available homoveratric acid and *p*-anisaldehyde via the conventional five-step sequence according to the previously reported procedure.[11] Wittig reaction of aldehyde **4** with the known azidophosphonium salt **5**[12] in the presence of KHMDS in THF gave mainly (*Z*)-*ω*-azidoalkene **6** as an inseparable *Z/E* mixture (86%, *Z*/*E*, 12:1). Upon heating the obtained azidoalkene **6** in refluxing benzene for 5 days, a mixture of imine **7** and aziridine **8** were obtained in a 2.3:1 ratio, as determined by the crude ^{1}H NMR spectrum. At the elevated temperature (135 °C) and pressure by means of a sealed tube reactor, the reaction proceeded faster to give **7** and **8** in only 15 h in a similar ratio. We isolated just one isomer of aziridine **8**, and the small coupling constant of the hydrogens attached to the aziridine ring (2.7 Hz) seems to suggest the trans configuration. The isolated imine **7** was unstable and underwent spontaneous oxidation in the presence of atmospheric oxygen to furnish the keto-imine **9**.[13] Even though the full reduction of the unwanted keto-imine **9** to the previously known pyrrolidine **10** was plausible, the crude reaction mixture of the above reaction was directly subjected to reducing conditions to establish an expedient process. The $ZnCl_2$ and $NaBH_3CN$

(6) For recent examples, see: (a) Wei, L.; Brossi, A.; Kendall, R.; Bastow, K. F.; Morris-Natschke, S. L.; Shi, Q.; Lee, K.-H. *Bioorg. Med. Chem.* **2006**, *14*, 6560−6569. (b) Chuang, T.-H.; Lee, S.-J.; Yang, C.-W.; Wu, P.-L. *Org. Biomol. Chem.* **2006**, *4*, 860−867. (c) Banwell, M. G.; Bezos, A.; Burns, C.; Kruszeknicki, I.; Parish, C. R.; Su, S.; Sydnes, M. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 181−185. (d) Gao, W.; Lam, W.; Zhong, S.; Kaczmarek, C.; Baker, D. C.; Cheng, Y.-C. *Cancer Res.* **2004**, *64*, 678−688.

(7) For representative recent examples, see: (a) Fürstner, A.; Kennedy, J. W. J. *Chem. Eur. J.* **2006**, *12*, 7398−7410. (b) Camacho-Davila, A.; Herndon, J. W. *J Org. Chem.* **2006**, *71*, 6682−6685. (c) Jin, Z.; Li, S. P.; Wang, Q. M.; Huang, R. *Chin. Chem. Lett.* **2004**, *15*, 1164−1166. (d) Banwell, M. G.; Sydnes, M. O. *Aust. J. Chem.* **2004**, *57*, 537−548.

(8) (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.-j.; Lee, S. K.; Kim, D. *J. Org. Chem.* **2004**, *69*, 3144−3149.

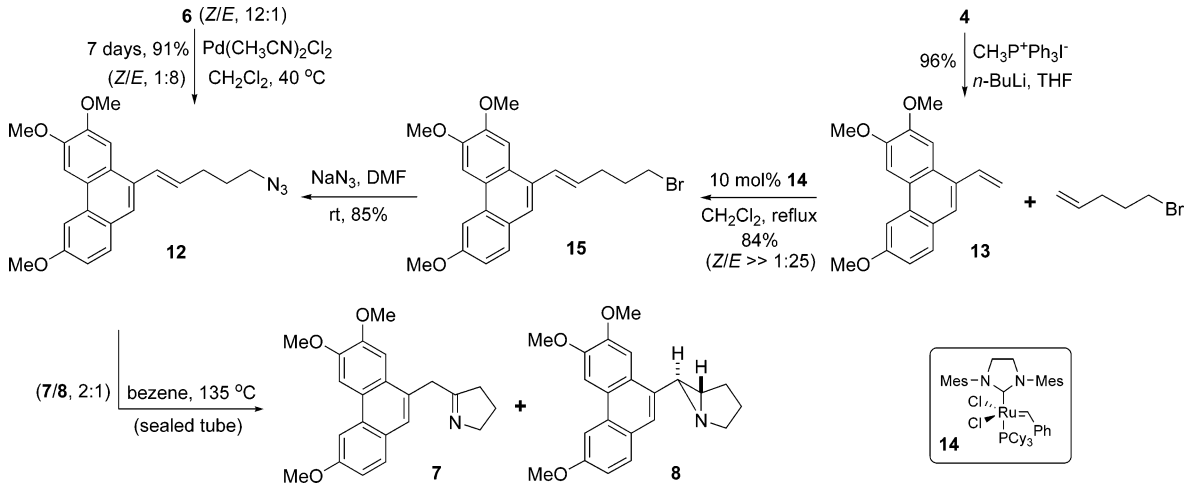
(9) Fu, Y.; Lee, S. K.; Min, H.-Y.; Lee, T.; Lee, J.; Cheng, M.; Kim, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 97−100.

(10) For, a previous application of intramolecular 1,3-dipolar cycloaddition in synthesis of phenanthroindolizidine alkaloids, see: Pearson, W. H.; Walavalkar, R. *Tetrahedron* **1994**, *50*, 12293−12304.

(11) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661−3666.

(12) Vaultier, A. C. M.; Carrié, R. *Tetrahedron Lett.* **1989**, *30*, 4953−4956.

SCHEME 2. Intramolecular 1,3-Dipolar Cycloaddition of Trans Isomer 12



reduction condition[14] successfully provided the desired pyrrolidine **10**[8,15] in 63% yield over two steps. Under this reaction condition, reduction of aziridine **8** was sluggish even at the elevated temperature and required excess reagents to complete. On the other hand, catalytic hydrogenation of the crude reaction mixture ($Pd(OH)_2/H_2$ balloon pressure) resulted in the facile reduction of both imine **7** and aziridine **8** to give pyrrolidine **10** in high overall yield (69% from **6**). Having successfully constructed the pyrrolidine ring of phenanthroindolizidine alkaloid, we then converted the known pyrrolidine **10** to antofine (**2**) in 75% yield, using the previously reported reaction conditions[8,15] (formaldehyde, HCl, EtOH, reflux). The spectroscopic data (^1H and ^{13}C NMR) obtained for the synthetic material were in agreement with those reported in the literature.[4,7,8,15]

The formation of both imine **7** and aziridine **8** could be a result of a 1,3-dipolar cycloaddition of the alkyl azide onto the olefin as the first step to give the unstable triazoline intermediate **11**, which undergoes decomposition under the reaction conditions to produce the products **7** and **8** through nitrogen extrusion. The ultimate product distribution of 1,3-dipolar cycloaddition is known to be affected by many factors, including solvent and temperature.[16] To understand the obtained product distribution result, the isolated aziridine **8** was subjected to the same reaction conditions (135 °C in a sealed tube) with the notion that imine **7** could arise from aziridine **8** during the reaction. Heating the pure aziridine for 12 h afforded the imine **7** but with very low conversion (<5%). After prolonged heating for an additional 24 h, the conversion was increased to ca. 20%, but unidentifiable decomposed byproducts were also detected in the ^1H NMR spectrum of the crude product. These results suggested that the observed product distribution might be determined mainly by the triazoline decomposition mode, not by product interconversion.

Although the factors that determine which products are formed depend on many variables, we were particularly interested in the olefin geometry of ω-azidoalkene. The 1,3-dipolar cycloadducts of *trans*- and *cis*-olefin isomers would have different stereochemistry, if the reaction proceeds via a concerted mechanism. The subsequent decomposition of each triazoline isomer would have a chance to proceed in different modes, thus affecting the product distribution. On the basis of these considerations, we prepared the *trans*-azidoalkene **12** and examined its cycloaddition reaction (Scheme 2). The *cis*-azidoalkene **6**, contaminated with a slight amount of the trans isomer (*Z*/*E*, 12:1), was isomerized to the corresponding trans isomer utilizing $Pd(CH_3CN)_2Cl_2$ in CH_2Cl_2.[17] Heating the mixture to 40 °C for 7 days provided the desired olefin isomerization product **12** (*Z*/*E*, 1:8) in 91% yield. Alternatively, we could prepare the *trans*-azidoalkene **12** selectively by using a cross-metathesis reaction.[18] Wittig methylenation of aldehyde **4** afforded olefin **13** in 96% yield. Exposure of **13** to 4 equiv of 5-bromopentene in the presence of 10 mol % of the second-generation Grubbs catalyst **14** in refluxing CH_2Cl_2 for 3 days provided the (*E*)-alkene **15** as the sole isolable isomer in 84% yield. Finally, azide displacement of the obtained product **15** with NaN_3 afforded the desired *trans*-azidoalkene **12** in 85% yield.

Interestingly, under the same reaction conditions as that of the cis isomer **6** (135 °C in a sealed tube), the trans isomer **12** also provided imine **7** and aziridine **8** in a similar ratio (2:1) observed for the cis isomer. This outcome indicated that the olefin geometry of azidoalkene does not significantly affect the product distribution. At this stage, we were unable to establish unambiguously the origin of the observed product distribution, since the possible cycloadduct intermediates of the initial dipolar

(13) The spontaneous oxidation of the C−H bond flanked between an imine and an aromatic ring has been observed by others, see: (a) Andreu, I.; Cabedo, N.; Atassi, G.; Pierre, A.; Caignard, D. H.; Renard, P.; Cortes, D.; Bermejo, A. *Tetrahedron Lett.* **2002**, *43*, 757−759. (b) Leboeuf, M.; Ranaivo, A.; Cavé, A.; Moskowitz, H. *J. Nat. Prod.* **1989**, *52*, 516−521. (c) Uff, B. C.; Kershaw, J. R.; Chhabra, S. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 479−483.

(14) (a) Bytschkov, I.; Sven, D. *Tetrahedron Lett.* **2002**, *43*, 3715−3718. (b) Kim, S.; Yoon, J.-Y. *Synthesis* **2000**, 1622−1630. (c) Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927−1932.

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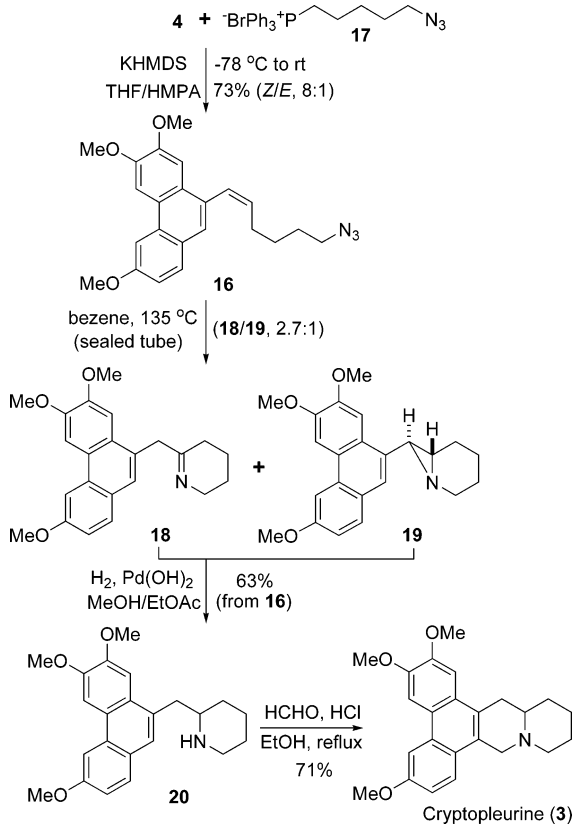
(17) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627−4629.

(18) For recent reviews, see: (a) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

SCHEME 3. Synthesis of Cryptopleurine (3)



cycloaddition, triazolines, were never detected because of the thermal lability. Although more systematic studies are needed to elucidate the observed outcome, one possible explanation may be that extrusion of nitrogen occurs prior to a hydrogen migration or an aziridine ring formation to give the benzylic carbocation or radical intermediate, regardless of the stereochemistry of the triazoline intermediate.

Having demonstrated the feasibility of the intramolecular cycloaddition of azidoalkene for the construction of the five-membered ring (pyrrolidine) of phenanthroindolizidine alkaloid, we then turned our attention to the preparation of the six-membered ring (piperidine) analogue. Thus, we synthesized the one-carbon homologated azidoalkene **16** and examined its cycloaddition reaction (Scheme 3). Generation of ylide from azidophosphonium salt **17**[19] using KHMDS in THF followed by addition of aldehyde **4** resulted in the formation of the desired ω-azidoalkene **16** in a poor yield (19%) with mostly unreacted starting material **4** after 10 h, in contrast to the previous reaction of **5** and **4**. This can be ascribed, in part, to the relatively lower solubility of ylide of **17** in THF compared to that of **5**. This difficulty was easily overcome by employing HMPA as a cosolvent. Under optimized conditions (KHMDS in THF/HMPA (7:1), at −78 °C to room temperature), Wittig coupling of the ylide from **17** with aldehyde **4** afforded azidoalkene **16** in 73% yield as a mixture of *Z*/*E* isomers (8:1) in which the (*Z*)-isomer was the major product. At this stage, the *Z*/*E* selectivity was not important, because *cis*-azidoalkene **6** and its trans isomer **12** afforded both two products, **7** and **8**, in a similar ratio and effectiveness as mentioned above. Heating the *Z*/*E* mixture of azidoalkene **16** at 135 °C in a sealed tube successfully provided imine **18** and aziridine **19** in a similar ratio (2.7:1) observed for **7** and **8**.[20] Analogous to the preparation of antofine **2**, a two-step sequence viz. catalytic hydrogenation (overall 63% from **16**) of the crude reaction mixture and Pictet−Spengler cyclomethylenation (71%) of the resulting **20**,[8b,15] transformed the cyclized products **18** and **19** into the phenanthroquinolizidine alkaloid, cryptopleurine (**3**), whose ^{1}H and ^{13}C NMR spectra were in agreement with those reported in the literature.[7a,8b,15,21]

In conclusion, the expedient total syntheses of the representative naturally occurring phenanthroindolizidine and phenanthroquinolizidine alkaloids, antofine and cryptopleurine, were accomplished. Construction of the pyrrolidine and piperidine rings was successfully achieved by using an intramolecular 1,3-dipolar cycloaddition of an azide onto an alkene and subsequent reduction of the resulting imine and aziridine. The chemistry described herein provides a practical synthetic method of phenanthroindolizidine and phenanthroquinolizidine alkaloids synthesis, and we were able to accomplish the synthesis of other modified analogues in useful quantities and high overall yield for biochemical and pharmaceutical studies.

Experimental Section

(*Z*)-10-(5-Azidopent-1-enyl)-2,3,6-trimethoxyphenanthrene (6). To a solution of phosphonium salt **5** (820 mg, 1.86 mmol) in dry THF (20 mL) was added KHMDS (4 mL, 2.00 mmol, 0.5 M solution in toluene) at −78 °C. After the reaction mixture was stirred for 30 min at −78 °C, a solution of aldehyde **4** (184 mg, 0.621 mmol) in dry THF (12 mL) was added dropwise over 10 min. After 30 min, this reaction mixture was warmed to room temperature over 1 h. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice (2 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane/EtOAc, 4:1) provided the desired product **6** (202 mg, 86%) as a waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) (*Z*/*E* mixture, ratio 12:1) (*Z*)-isomer δ 1.72 (tt, J = 7.2, 7.2 Hz, 2H), 2.31 (dtd, J = 1.2, 7.2, 7.5 Hz, 2H), 3.22 (t, J = 7.2 Hz, 2H), 4.03 (s, 3H), 4.04 (s, 3H), 4.13 (s, 3H), 5.94 (td, J = 7.5, 11.1 Hz, 1H), 6.88 (dd, J = 1.2, 11.4 Hz, 1H), 7.20 (dd, J = 2.4, 8.7 Hz, 1H), 7.34 (s, 1H), 7.43 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 2.1 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (*Z*)-isomer δ 25.8, 28.8, 50.8, 55.5, 55.8, 55.9, 103.5, 103.7, 105.6, 115.4, 124.3, 124.8, 125.6, 126.5, 128.7, 129.5, 130.0, 130.5, 132.5, 148.7, 149.1, 158.0; MS (FAB) (*m*/*z*) 377 (M^+, 26), 350 (35), 334 (100), 322 (42); HRMS (FAB) calcd for $C_{22}H_{23}N_3O_3$ (M^+) 377.1739, found 377.1728.

Intramolecular 1,3-Dipolar Cycloaddition of ω-Azidoalkene 6. Method A: A solution of azidoalkene **6** (26 mg, 0.069 mmol) in degassed benzene (4 mL) was heated to reflux for 5 days. The reaction was cooled to room temperature and concentrated in vacuo to provide a light yellow syrup as a mixture of imine **7** and aziridine **8** in a ratio of 2.3:1. The crude mixture was used in the next step without further purification.

Method B: Azidoalkene **6** (130 mg, 0.344 mmol) was dissolved in benzene (8 mL). This solution was transferred to a sealed tube,

(19) The azidophosphonium salt **17** was prepared as described in ref 12, and see also: Chhen, A. I.; Soufiaoui, M.; Carrié, R. *Bull. Soc. Chim. Fr.* **1992**, *129*, 308−314.

(20) For the construction of the seven-membered ring (azepine) analogue, we prepared the two-carbon homologated azidoalkene, 10-(7-azidohept-1-enyl)-2,3,6-trimethoxyphenanthrene, as a mixture of *Z*/*E* isomers (4:1). Unfortunately, heating the two-carbon homologated azidoalkene at 135 °C in a sealed tube did not provide any noticeable cyclized product, and increasing the temperature higher than 200 °C resulted only in unreacted starting material and decomposed material.

(21) (a) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1995**, *60*, 6114−6122. (b) Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 935−936.

degassed with N_2 gas, and heated at 135 °C in an oil bath for 15 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to provide a light yellow syrup as a mixture of imine **7** and aziridine **8** in a ratio of 2.2:1. The crude mixture was used in the next step without further purification.

Imine **7** and aziridine **8** were isolated by column chromatography on silica gel (hexane/EtOAc, 1:6) for analytical purposes. The isolated imine **7** was unstable and underwent spontaneous oxidation to furnish keto-imine **9**.

5-(3,6,7-Trimethoxyphenanthren-9-ylmethyl)-3,4-dihydro-2*H*-pyrrole (7). As a light yellow waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 2H), 2.34 (app. t, J = 8.1 Hz, 2H), 3.91 (tt, J = 1.5, 7.2 Hz, 2H), 4.02 (s, 3H), 4.03 (s, 3H), 4.11 (s, 3H), 4.20 (br s, 2H), 7.20 (dd, J = 2.4, 8.7 Hz, 1H), 7.54 (s, 1H), 7.58 (s, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.92 (s, 1H); MS (FAB) (*m*/*z*) 350 ([M + 1]$^+$, 100); HRMS (FAB) calcd for $C_{22}H_{24}NO_3$ ([M + H]$^+$) 350.1756, found 350.1760.

6-(3,6,7-Trimethoxyphenanthren-9-yl)-1-aza-bicyclo[3.1.0]-hexane (8). As a light yellow waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69−1.91 (m, 2H), 2.10 (m, 1H), 2.37 (dd, J = 8.1, 12.9 Hz, 1H), 2.56 (dd, J = 3.0, 4.5 Hz, 1H), 2.73 (d, J = 2.7 Hz, 1H), 3.19 (ddd, J = 7.5, 7.8, 12.0 Hz, 1H), 3.33 (dddt, J = 1.2, 8.1, 12.0 Hz, 1H), 3.97 (s, 3H), 4.04 (s, 3H), 4.08 (s, 3H), 7.16 (dd, J = 2.4, 8.7 Hz, 1H), 7.41 (s, 1H), 7.66 (s, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 26.5, 38.1, 48.4, 53.0, 55.4, 55.5, 55.8, 103.6, 103.7, 104.3, 115.2, 123.0, 124.3, 125.9, 126.5, 130.0, 130.2, 130.5, 148.5, 149.0, 157.8; MS (FAB) (*m*/*z*) 350 ([M + 1]$^+$, 26), 334 (33), 281 (28), 154 (100); HRMS (FAB) calcd for $C_{22}H_{24}NO_3$ ([M + H]$^+$) 350.1756, found 350.1763.

(4,5-Dihydro-3*H*-pyrrol-2-yl)-(3,6,7-trimethoxyphenanthren-9-yl)methanone (9). As a light yellow waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (m, 2H), 3.08 (tt, J = 2.4, 8.4 Hz, 2H), 4.02 (s, 3H), 4.04 (s, 3H), 4.10 (s, 3H), 4.25 (tt, J = 2.1, 7.5 Hz, 2H), 7.18 (dd, J = 2.4, 9.0 Hz, 1H), 7.79 (d, J = 2.4 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.86 (s, 1H), 8.28 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 35.8, 55.5, 55.80, 55.82, 63.0, 103.2, 103.7, 106.8, 115.9, 123.8, 124.6, 125.1, 127.5, 132.4, 133.6, 134.4, 149.0, 150.0, 160.5, 175.6, 193.8; MS (FAB) (*m*/*z*) 364 ([M + 1]$^+$, 8), 154 (100); HRMS (FAB) calcd for $C_{22}H_{22}NO_4$ ([M + H]$^+$) 364.1549, found 364.1548.

2-(3,6,7-Trimethoxyphenanthren-9-ylmethyl)pyrrolidine (10).

Method A: To a solution of the above crude imine **7** and aziridine **8** (from **6** by Method B, 0.15 mmol) in THF (2 mL) were added $NaBH_3CN$ (20 mg, 0.61 mmol) and $ZnCl_2$ (0.20 mL, 0.20 mmol, 1.0 M solution in diethyl ether). The reaction mixture was stirred at room temperature for 2 days. It was diluted with CH_2Cl_2 (10 mL) and 1 N HCl solution (10 mL) and then stirred at room temperature for 2 h. After the resulting layers were separated, the aqueous layer was neutralized to pH 7 by using 1 N NaOH solution and extracted with CH_2Cl_2 twice (2 × 10 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1, 1% NH_4OH) afforded pyrrolidine **10** (33 mg, 63% from **6**) as a white solid.

Method B: A solution of the above crude imine **7** and aziridine **8** (from **6** by Method B, 0.344 mmol) in MeOH/EtOAc (1:1, 4 mL) was charged with palladium hydroxide (260 mg, 200 wt %). The reaction mixture was stirred for 7 h under a balloon filled with hydrogen gas at room temperature. It was diluted with MeOH/EtOAc and filtered through a pad of Celite. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1, 1% NH_4OH) to give pyrrolidine **10** (83 mg, 69% from **6**) as a white solid: mp 144−145 °C (lit.[15] mp 145−146 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (m, 1H), 1.74 (m, 1H), 1.88 (m, 2H), 2.85−2.94 (m, 2H), 3.11 (m, 1H), 3.22 (dt, J = 6.9, 14.1 Hz, 2H), 3.56 (dt, J = 14.1, 6.6 Hz, 1H), 3.99 (s, 3H), 4.05 (s, 3H), 4.09 (s, 3H), 7.17 (dd, J = 2.4, 8.7 Hz, 1H), 7.41 (s, 1H), 7.48 (s, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 30.9, 37.4, 45.2, 55.4, 55.9, 56.4, 59.2, 103.7, 103.8, 104.5, 115.4, 124.6, 125.2, 125.7, 126.2, 128.9, 129.8, 130.5, 148.7, 149.5, 158.0; MS (FAB) (*m*/*z*) 352 ([M + H]$^+$, 51), 282 (23), 70 (100); HRMS (FAB) calcd for $C_{22}H_{26}NO_3$ ([M + H]$^+$) 352.1913, found 352.1905.

Antofine (2). To a solution of pyrrolidine **10** (31 mg, 0.088 mmol) in EtOH (2 mL) were added 37% formaldehyde (0.50 mL) and concd HCl (0.050 mL). The reaction mixture was refluxed for 2 days in the dark. The reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 and treated with 10% HCl. The aqueous layer was extracted with CH_2Cl_2 twice, and the combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) afforded the desired product, antofine (**2**) (24 mg, 75%), as a white solid: mp 196−199 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.74 (m, 1H), 1.89 (m, 1H), 2.02 (m, 1H), 2.21 (m, 1H), 2.42 (m, 2H), 2.86 (m, 1H), 3.28 (dd, J = 2.4, 15.6 Hz, 1H), 3.44 (dt, J = 1.8, 8.5 Hz, 1H), 3.64 (d, J = 14.7 Hz, 1H), 3.99 (s, 3H), 4.04 (s, 3H), 4.08 (s, 3H), 4.66 (d, J = 14.7 Hz, 1H), 7.18 (dd, J = 2.5, 9.0 Hz, 1H), 7.27 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 2.5 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 31.2, 33.6, 53.8, 55.0, 55.4, 55.8, 55.9, 60.1, 103.8, 103.9, 104.6, 114.8, 123.5, 124.1, 124.2, 125.5, 126.6, 127.0, 130.1, 148.3, 149.3, 157.4; MS (EI) (*m*/*z*) 363 (M$^+$, 24), 294 (100); HRMS (CI) calcd for $C_{23}H_{26}NO_3$ ([M + H]$^+$) 364.1912, found 364.1913.

2,3,6-Trimethoxy-10-vinylphenanthrene (13). To a solution of methyl(triphenyl)phosphonium iodide (409 mg, 1.01 mmol) in dry THF (4 mL) was added *n*-BuLi (0.63 mL, 0.96 mmol, 1.6 M solution in hexane) at 0 °C. After the reaction mixture was stirred for 1 h at 0 °C, a solution of aldehyde **4** (100 mg, 0.34 mmol) in dry THF (4 mL) was added dropwise. After 30 min, this reaction mixture was warmed to room temperature over 1 h. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice (2 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane/EtOAc, 4:1) to provide vinylphenanthrene **13** (95 mg, 96%) as a white solid: mp 116.5−118.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 3H), 4.06 (s, 3H), 4.12 (s, 3H), 5.49 (dd, J = 1.8, 10.8 Hz, 1H), 5.84 (dd, J = 1.5, 17.1 Hz, 1H), 7.20 (dd, J = 2.4, 8.7 Hz, 1H), 7.39 (dd, J = 10.8, 17.1 Hz, 1H), 7.44 (s, 1H), 7.71 (s, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 2.7 Hz, 1H), 7.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 55.7, 55.9, 103.5, 103.6, 104.6, 115.5, 116.6, 122.7, 124.2, 125.8, 125.9, 130.2, 130.8, 131.4, 135.2, 148.6, 149.1, 158.1; MS (FAB) (*m*/*z*) 294 (M$^+$, 100), 263 (11); HRMS (FAB) calcd for $C_{19}H_{18}O_3$ (M$^+$) 294.1256, found 294.1255.

(*E*)-10-(5-Bromopent-1-enyl)-2,3,6-trimethoxyphenanthrene (15). A solution of vinylphenanthrene **13** (80 mg, 0.27 mmol), 5-bromopentene (0.13 mL, 1.10 mmol), and the second-generation Grubbs catalyst **14** (23 mg, 10 mol %, 0.03 mmol) in CH_2Cl_2 (27 mL) was stirred at 40 °C for 3 days. The reaction mixture was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to give bromopentenyl phenanthrene **15** (95 mg, 84%) as a waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (tt, J = 6.6, 6.9 Hz, 2H), 2.56 (ddt, J = 1.2, 6.9, 7.2 Hz, 2H), 3.57 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 4.07 (s, 3H), 4.12 (s, 3H), 6.17 (td, J = 6.9, 15.6 Hz, 1H), 7.11 (d, J = 15.6 Hz, 1H), 7.19 (dd, J = 2.1, 8.4 Hz, 1H), 7.45 (s, 1H), 7.63 (s, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 31.8, 33.3, 55.5, 55.9, 56.0, 103.7, 103.8, 104.9, 115.5, 122.6, 124.3, 126.0, 126.1, 129.7, 130.0, 130.7, 131.11, 131.13, 148.8, 149.3, 158.0; MS (FAB) (*m*/*z*) 414 (M$^+$, 95), 416 (100), 307 (20),

154 (45); HRMS (FAB) calcd for $C_{22}H_{23}BrO_3$ (M^+) 414.0831, found 414.0837.

(*E*)-10-(5-Azidopent-1-enyl)-2,3,6-trimethoxyphenanthrene (12). From **6**: A solution of (*Z*)-azidoalkene **6** (22 mg, 0.058 mmol, *Z*/*E* mixture, ratio 12:1) and $Pd(CH_3CN)_2Cl_2$ (3 mg, 0.012 mmol, 20 mol %) in CH_2Cl_2 (3 mL) was stirred at 40 °C for 7 days. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to provide (*E*)-azidoalkene **12** (20 mg, 91%) as a waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) (*Z*/*E* mixture, ratio 1:8) (*E*)-isomer δ 1.89 (tt, J = 6.9, 7.2 Hz, 2H), 2.48 (dt, J = 6.9, 7.2 Hz, 2H), 3.43 (t, J = 6.9 Hz, 2H), 4.02 (s, 3H), 4.07 (s, 3H), 4.12 (s, 3H), 6.22 (td, J = 6.9, 7.2 Hz, 1H), 7.07 (d, J = 15.6 Hz, 1H), 7.19 (dd, J = 2.4, 8.4 Hz, 1H), 7.44 (s, 1H), 7.64 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.92 (s, 1H).

From **15**: To a solution of bromopentenyl phenanthrene **15** (85 mg, 0.21 mmol, *Z*/*E* mixture, ratio [dmt] 1: 25) in DMF (10 mL) was slowly added sodium azide (20 mg, 0.31 mmol). After the reaction mixture was stirred for 3 h at rt, water (30 mL) was added. The resulting mixture was extracted with EtOAc twice (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to provide (*E*)-azidoalkene **12** (66 mg, 85%, *Z*/*E* mixture, ratio [dmt] 1:25) as a waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (tt, J = 6.9, 7.2 Hz, 2H), 2.46 (dt, J = 6.9, 7.5 Hz, 2H), 3.43 (t, J = 6.9 Hz, 2H), 4.02 (s, 3H), 4.07 (s, 3H), 4.12 (s, 3H), 6.22 (td, J = 6.9, 7.2 Hz, 1H), 7.06 (d, J = 15.3 Hz, 1H), 7.19 (dd, J = 2.4, 8.7 Hz, 1H), 7.44 (s, 1H), 7.64 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 30.3, 50.8, 55.6, 55.9, 56.0, 103.8, 103.9, 104.9, 115.6, 122.7, 124.4, 126.07, 126.1, 129.2, 130.1, 130.7, 131.1, 131.8, 148.8, 149.3, 158.1; MS (FAB) (*m*/*z*) 377 (M^+, 21), 350 (46), 334 (100); HRMS (FAB) calcd for $C_{22}H_{23}N_3O_3$ (M^+) 377.1739, found 377.1736.

(*Z*)-10-(6-Azidohex-1-enyl)-2,3,6-trimethoxyphenanthrene (16). To a solution of phosphonium salt **17** (2.50 g, 5.50 mmol) in dry THF/HMPA (40 mL, 7:1) was added KHMDS (13 mL, 6.50 mmol, 0.5 M solution in toluene) at −78 °C. After the reaction mixture was stirred for 30 min at −78 °C, a solution of aldehyde **4** (550 mg, 1.86 mmol) in dry THF (20 mL) was added dropwise over 10 min. After 30 min, this reaction mixture was warmed to room temperature over 1 h. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (hexane/EtOAc, 4:1) provided ω-azidoalkene **16** (532 mg, 73%) as a waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) (*Z*/*E* mixture, ratio 8:1) (*Z*)-isomer δ 1.44−1.59 (m, 4H), 2.25 (dtd, J = 1.2, 6.9, 7.5 Hz, 2H), 3.15 (t, J = 6.6 Hz, 2H), 4.02 (s, 3H), 4.04 (s, 3H), 4.12 (s, 3H), 5.94 (td, J = 7.5, 11.1 Hz, 1H), 6.84 (dd, J = 1.2, 11.1 Hz, 1H), 7.20 (dd, J = 2.4, 8.7 Hz, 1H), 7.35 (s, 1H), 7.42 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.91 (s, 1H), (*E*)-isomer δ 1.61−1.75 (m, 4H), 2.39 (app. q, J = 7.2 Hz, 2H), 3.35 (t, J = 6.6 Hz, 2H), 4.00 (s, 3H), 4.07 (s, 3H), 4.11 (s, 3H), 6.23 (td, J = 6.9, 15.6 Hz, 1H), 7.00 (d, J = 15.6 Hz, 1H), 7.18 (dd, J = 2.4, 8.7 Hz, 1H), 7.42 (s, 1H), 7.62 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (*Z*)-isomer δ 26.6, 28.0, 28.2, 51.0, 55.4, 55.7, 55.9, 103.4, 103.7, 105.6, 115.4, 124.2, 124.8, 125.6, 126.5, 128.0, 129.7, 129.9, 130.4, 133.5, 148.7, 149.1, 158.0; MS (FAB) (*m*/*z*) 391 (M^+, 26), 362 (57), 348 (71), 149 (92), 57 (100); HRMS (FAB) calcd for $C_{23}H_{25}N_3O_3$ (M^+) 391.1896, found 391.1889.

Intramolecular 1,3-Dipolar Cycloaddition of ω-Azidoalkene 16. Azidoalkene **16** (150 mg, 0.383 mmol) was subjected to the same procedure described for the intramolecular 1,3-dipolar cycloaddition of **6** (method B) to give a mixture of imine **18** and aziridine **19** in a ratio of 2.7:1 as a light yellow syrup. The crude mixture was used in the next step without further purification. Imine **18** and aziridine **19** were isolated by column chromatography on silica gel (hexane/EtOAc, 1:6) for analytical purposes.

6-(3,6,7-Trimethoxy-phenanthren-9-ylmethyl)-2,3,4,5-tetrahydro-pyridine (18). As a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 4H), 1.95 (m, 2H), 3.67 (br s, 2H), 3.94 (s, 2H), 4.00 (s, 3H), 4.02 (s, 3H), 4.10 (s, 3H), 7.18 (dd, J = 2.4, 9.0 Hz, 1H), 7.45 (s, 1H), 7.72 (s, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 21.7, 27.7, 47.8, 49.4, 55.5, 55.90, 55.91, 103.5, 103.8, 105.9, 115.3, 124.7, 125.9, 126.5, 127.2, 128.8, 129.7, 130.6, 148.6, 149.2, 158.0, 171.1; MS (FAB) (*m*/*z*) 364 ([M + 1]$^+$, 100); HRMS (FAB) calcd for $C_{23}H_{26}NO_3$ ([M + H]$^+$) 364.1913, found 364.1903.

7-(3,6,7-Trimethoxy-phenanthren-9-yl)-1-aza-bicyclo[4.1.0]-heptane (19). As a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55−1.63 (m, 4H), 2.22 (m, 2H), 3.00 (d, J = 2.1 Hz, 1H), 3.09 (m, 1H), 3.64 (m, 1H), 4.00 (s, 3H), 4.02 (m, 1H), 4.07 (s, 3H), 4.11 (s, 3H), 7.16 (dd, J = 2.4, 8.7 Hz, 1H), 7.49 (s, 1H), 7.63 (s, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 2.4 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 21.3, 22.3, 39.1, 44.2, 48.8, 55.5, 55.7, 56.0, 103.8, 104.5, 115.3, 122.4, 124.4, 126.0, 126.7, 130.0, 130.3, 130.9, 131.6, 148.6, 149.1, 157.9; MS (FAB) (*m*/*z*) 364 ([M + 1]$^+$, 25), 307 (19), 289 (11), 154 (100); HRMS (FAB) calcd for $C_{23}H_{26}NO_3$ ([M + H]$^+$) 364.1913, found 364.1915.

2-(3,6,7-Trimethoxyphenanthren-9-ylmethyl)piperidine (20). The above crude imine **18** and aziridine **19** (from **16** by method B, 0.383 mmol) were reduced following the same procedure described for **10** (method B) to give quinolizidine **20** (88 mg, 63%, from **16**) as a light yellow solid: mp 136−137 °C (lit.[15] mp 122−123 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 2H), 1.73−1.83 (m, 5H), 1.97 (m, 1H), 2.87 (dt, J = 2.4, 12.6 Hz, 1H), 3.26−3.33 (m, 2H), 3.54 (br d, J = 12.3 Hz, 1H), 3.99 (s, 3H), 4.08 (s, 3H), 4.19 (s, 3H), 7.14 (dd, J = 2.4, 9.0 Hz, 1H), 7.41 (s, 1H), 7.61 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 22.7, 28.7, 37.8, 45.1, 55.5, 55.9, 56.7, 57.1, 103.8, 103.9, 105.0, 115.4, 124.8, 125.5, 126.2, 126.8, 126.9, 129.8, 130.7, 148.8, 149.9, 158.1; MS (EI) (*m*/*z*) 365 (M^+, 1), 282 (27), 84 (100); HRMS (CI) calcd for $C_{23}H_{28}NO_3$ ([M + H]$^+$) 366.2069, found 366.2066.

Cryptopleurine (3). Following the same procedure as for **2**, from quinolizidine **20** (59 mg, 0.16 mmol) in EtOH (3 mL), 37% formaldehyde (0.70 mL), and conc. HCl (0.20 mL), after a reaction time of 2 days, cryptopleurine (**3**) (43 mg, 71%) was obtained as a white solid: mp 177−179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (m, 1H), 1.54 (m, 1H), 1.77−1.81 (m, 2H), 1.88 (d, J = 12.2 Hz, 1H), 2.03 (d, J = 11.5 Hz, 1H), 2.30 (dt, J = 3.9, 11.2 Hz, 1H), 2.39 (t, J = 10.1 Hz, 1H), 2.88 (dd, J = 10.7, 15.9 Hz, 1H), 3.08 (dd, J = 3.1, 16.4 Hz, 1H), 3.27 (d, J = 11.1 Hz, 1H), 3.63 (d, J = 15.4 Hz, 1H), 4.01 (s, 3H), 4.06 (s, 3H), 4.10 (s, 3H), 4.44 (d, J = 15.4 Hz, 1H), 7.19 (dd, J = 2.4, 9.0 Hz, 1H), 7.25 (s, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 26.2, 34.0, 34.9, 55.7, 56.1, 56.2, 56.5, 57.8, 104.1, 104.1, 105.0, 115.0, 123.6, 123.9, 124.3, 124.7, 125.8, 126.7, 130.3, 148.5, 149.6, 157.6; MS (EI) (*m*/*z*) 377 (M^+, 32), 294 (100); HRMS (EI) calcd for $C_{24}H_{27}NO_3$ (M^+) 377.1991, found 377.1992.

Acknowledgment. This work was supported by the Korea Science and Engineering Foundation (KOSEF) through the National Research Laboratory Program funded by the Ministry of Science and Technology (M10500000055-06J0000-05510).

Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **6**−**9**, **12**, **13**, **15**, **16**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070668X