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Synthesis of (±)-Tylophorine by the Intramolecular Cycloaddition of an Azide with an ω-Chloroalkene

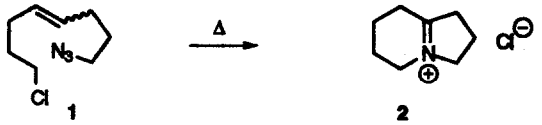
William H. Pearson* and Rajesh Walavalkar

Department of Chemistry, University of Michigan, Ann Arbor, Michigan, USA 48109-1055

Abstract: Cyclization of (*Z*)-1-(2-chloromethyl)phenyl-5-azidopent-1-ene **10** in benzene at 120 °C followed by treatment with sodium borohydride produced 1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline **11** in 71% yield. A similar cyclization of (*Z*)-2,3,6,7-tetramethoxy-9-(5-azido-1-pentenyl)-10-chloromethylphenanthrene **3** gave the phenanthroindolizidine alkaloid (±)-tylophorine **5** in 82% yield. These reactions proceed by intramolecular 1,3-dipolar cycloaddition of the azide onto the alkene followed by loss of nitrogen from the triazoline intermediate to give an imine The imine is *N*-alkylated *in situ* by the pendant benzyl chloride to provide an iminium ion, which is reduced with sodium borohydride to afford the indolizidines. The synthesis of (±)-tylophorine was accomplished in 11 steps from homoveratric acid in 5% overall yield.

INTRODUCTION

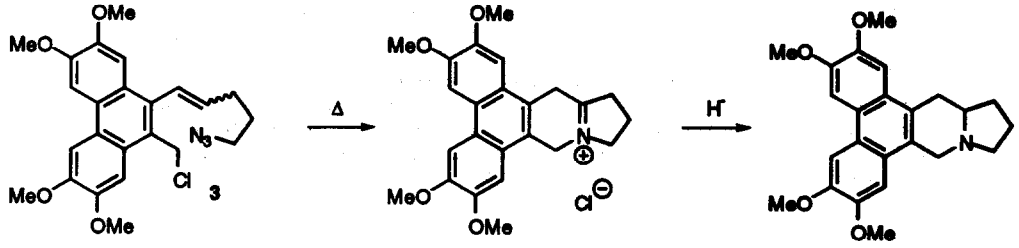
We have recently described a method for the generation of bicyclic iminium ions **2** in one operation from azides **1**.[1-3] The reaction proceeds by an intramolecular 1,3-dipolar cycloaddition of an azide onto an alkene, producing an intermediate triazoline. Fragmentation of the triazoline and rearrangement of the resultant zwitterion to a monocyclic imine occurs, which is internally N-alkylated by the pendant alkyl chloride, producing the iminium ion **2**. We have used this method for the synthesis of (–)-swainsonine[1] and (±)-γ-lycorane.[2] This report describes the application of this chemistry to the synthesis of (±)-tylophorine **5**.



1 **2**

Tylophorine **5** (Scheme 1) belongs to the phenanthroindolizidine group of alkaloids.[4] It has been isolated from, and is the major constituent of, *Tylophora asthmatica* Wight et Arn. (syn. *Tylophora indica*). The genus *Tylophora* belongs to the Asclepiadaceae family and grows wild in the forest plains of eastern and southern India. In addition, tylophorine has also been isolated from *Ficus Septica*, a plant belonging to the Moraceae family. Extracts of *Tylophora* alkaloids exhibit a range of physiological activities and these have been recorded in the Bengal, Indian, and Philippine pharmacopoeias.[4d] Interest in this group of alkaloids stems in particular from their reported antitumor activity. Specifically, tylophorine inhibits the incorporation of ^{14}C leucine into proteins of Ehrlich tumor cells, but does not affect RNA synthesis at the same

concentration.[4d] It also inhibits, irreversibly, protein synthesis in HeLa cells, in yeasts, and in Chinese hamster ovary cells.[4d] Unfortunately, along with its antitumor activity, tylophorine is also highly toxic. It has been reported to be toxic to *Paramecium caudatum* in a dilution of 1:50,000 and is lethal to frogs at a dose of 0.4 mg/Kg.[4c] Its toxicity to mice and pigs, however, is very small. Tylophorine has a paralyzing action on heart muscles and a stimulating effect on the muscles of blood vessels which is reflected by an initial drop in blood pressure followed by a rise to a level above normal.[4c] A variety of syntheses of tylophorine in both racemic and optically active form have been reported.[5] Of particular relevance to the current work, Liepa,[5d] Weinreb,[5e,g] and Fukumoto[5o-q] have described routes to tylophorine where both rings of the indolizidine nucleus are assembled with a single reaction. We wish to report an alternative method for construction of the indolizidine nucleus (Scheme 1). Our strategy involves the thermal double-cyclization of an azide **3** as discussed above, which should afford the pentacyclic iminium ion **4**. Hydride reduction will then produce tylophorine **5**.

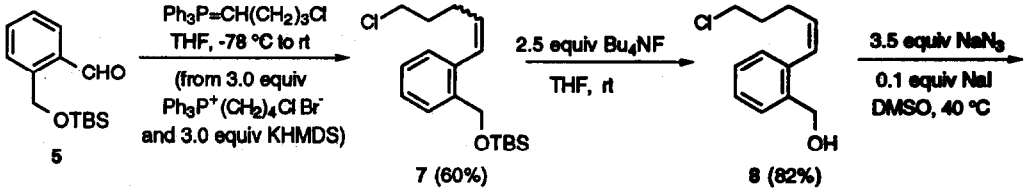


Scheme 1. Synthetic Plan for the Indolizidine Nucleus of Tylophorine

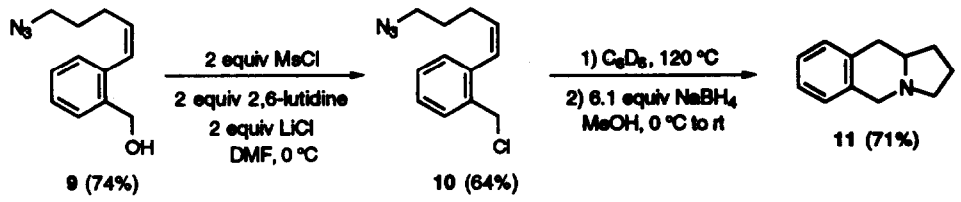
RESULTS AND DISCUSSION

A Model Cyclization

The synthesis of the cyclization precursor **3** was considered to be relatively challenging due to the requirement of carbon substitutents at both C(9) and C(10) of the phenanthrene ring. We decided to test the feasibility of the azide double cyclization method by studying the simpler benzo-fused indolizidine **11** (Scheme 2). Wittig reaction of the known aldehyde **5**[6] with the phosphorane[1] derived from 4-bromo-1-chlorobutane gave the alkene **7** as an inseparable mixture of isomers (*Z*:*E* = 5:1). Removal of the silyl protecting group with fluoride ion gave **8**, which upon purification was found to be exclusively the *Z*-isomer. Displacement of the chloro group gave the azide **9**, which was converted to the benzylic chloride **10** in one



Scheme 2. Model Cyclization to Afford the Benzoindolizidine Ring System

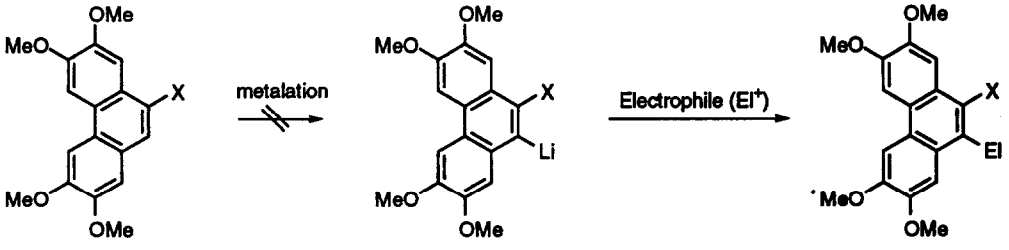


Scheme 2 (Continued). Model Cyclization to Afford the Benzoindolizidine Ring System

operation using Meyers' method.[7] Heating **10** in a sealed tube in benzene-d_6 produced an iminium ion which was reduced with methanolic sodium borohydride to afford the benzoindolizidine **11** in good yield. With this precedent in hand, we then turned to the preparation of the tylophorine precursor **3**.

Synthesis of (±)-Tylophorine

It appeared that the simplest route to a suitable 9,10-disubstituted phenanthrene was by functionalization of a known 9-substituted phenanthrene at the 10-position. Formation of a C(10) organolithium derivative (e.g., **15**, Scheme 3) by directed metalation at the ortho position was examined first. Metalation of benzylic alcohols in the ortho position is a well-precedented process.[8] However, attempts to form the dianion of **12**[5g] failed, returning either unreacted starting material or uncharacterized mixtures. It is known that methoxy groups may lead to undesired side-reactions in the metalation of benzylic alcohols.[8a] The ortho metalation of aromatic aldehydes has been reported by Comins,[9] who showed that α-amino alkoxides, formed by the addition of amide bases to the carbonyl group, were excellent ortho directing groups. Addition of the lithium amides of *N*-methylpiperazine or *N,N',N'*-trimethylethylenediamine to 2,3,6,7-tetramethoxyphenanthrene-9-carboxyaldehyde[5g] followed by addition of 3 equivalents of *n*-BuLi and quenching with formaldehyde or D_2O led to recovery of starting materials and decomposition products. Finally, the N,N-diethylcarboxamide **14** was prepared[10] and metalation was attempted using Snieckus' conditions.[11] No metalation was observed after numerous attempts. This result was disappointing since Snieckus had reported the successful ortho metalation of a phenanthrene amide which lacked the 2-methoxy substituent of **14**.[12] Electrophilic substitution reactions on a variety of 9-substituted phenanthrenes at C(10) were also unsuccessful, returning multiple products. It therefore seemed prudent to examine routes to 9,10-disubstituted phenanthrenes that incorporated both of the carbon substitutents at an earlier stage.

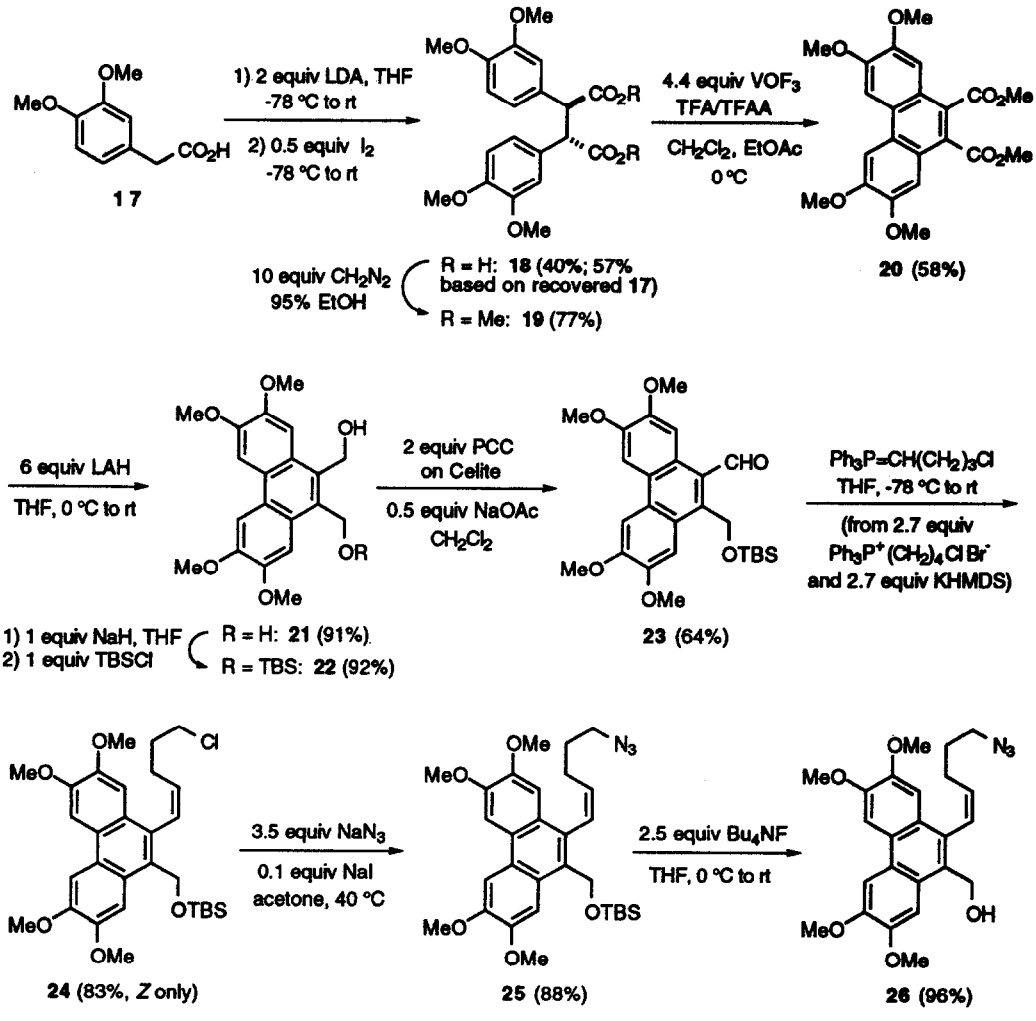


12 X = CH_2OH
13 X = $CH(OLi)NR_2$
14 X = $CONEt_2$

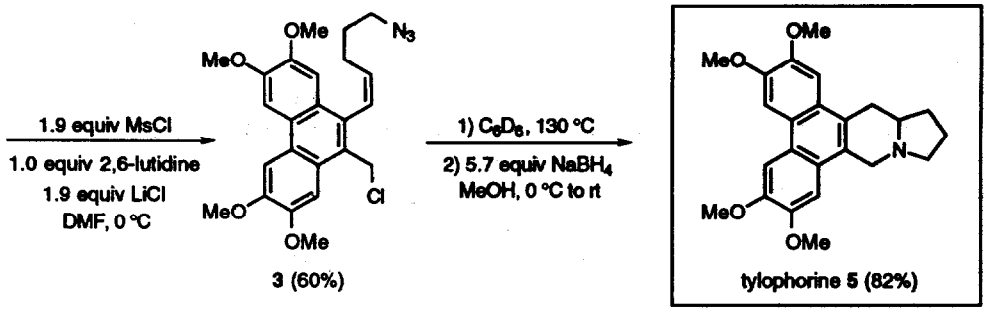
15 **16**

Scheme 3. Attempted Installation of Side-Chain by Functionalization of Phenanthrene Nucleus

A successful route to tylophorine is shown in Scheme 4. Oxidative coupling of the dianion of homoveratric acid **17** using iodine according to the procedure of Belletire[13] gave the diacid **18** in 40% isolated yield (57% based on recovered **17**). One stereoisomer was isolated which was assigned as the dl-isomer based on literature precedent.[13a] Esterification of **18** with diazomethane gave the diester **19**. Initial attempts to carry out the oxidative coupling of **19** with 2.2 equiv of VOF_3 followed by DDQ oxidation of the resulting dihydrophenanthrene proved capricious. This problem was solved by using 4.4 equiv of VOF_3,[5d,14] which resulted in ring closure with concomitant dehydrogenation to give the desired 9,10-disubstituted phenanthrene **20** in 58% yield. Reduction to the diol **21** and selective monoprotection using McDougal's procedure[15] gave the monosilylated compound **22** in excellent yield.



Scheme 4. Synthesis of (±)-Tylophorine



Scheme 4 (continued). Synthesis of (±)-Tylophorine

Oxidation[16] to the aldehyde **23** followed by Wittig reaction as in Scheme 2[1] produced the ω-chloroalkene **24** in good yield. Azide displacement afforded **25**, which was deprotected to the alcohol **26**. One-pot conversion to the benzylic chloride **3** was accomplished using Meyers' technique.[7] As precedented in the model study in Scheme 2, heating the azide **3** at 130 °C produced a solution of the iminium ion **4** (see Scheme 1) which was reduced with sodium borohydride to yield (±)-tylophorine **5** in 82% yield.

CONCLUSION

The double cyclization of ω-chloro azidoalkenes to produce fused-bicyclic iminium ions has been shown to be successful in two benzo-fused indolizidine examples (**10** → **11** in Scheme 2 and **3** → **5** in Scheme 3). The synthesis of tylophorine **5** using this method represents a new disconnection for this pentacyclic alkaloid in that the indolizidine ring was assembled in one step from a 9,10-disubstituted phenanthrene.

EXPERIMENTAL SECTION

General. Reagents and starting materials were obtained from commercial suppliers, and were used without further purification. Tetrahydrofuran and ether were distilled from sodium / benzophenone ketyl. Methylene chloride and triethylamine were distilled from calcium hydride. Dimethylformamide was distilled from barium oxide at reduced pressure. Dimethyl sulfoxide was distilled from calcium hydride at reduced pressure. All reactions were conducted under an atmosphere of dry nitrogen. Chromatography refers to flash column chromatography on silica gel (230-400 mesh) unless otherwise noted. Combustion analyses were performed by Spang Microanalytical Laboratories (Eagle Harbor, Michigan) or by the microanalytical facility operated by the University of Michigan. J-Modulated Spin Echo Fourier Transform (JMOD) ^{13}C NMR experiments are reported as (+) (for CH_3 and CH) or (-) (for CH_2 and C) and are used as an alternative to off resonance decoupling experiments.

(*Z*)- and (*E*)-1-{2-[(*tert*-Butyldimethylsilyl)oxy]methylphenyl}-5-chloropent-1-ene (7). Potassium bis(trimethylsilyl)amide (24.0 mL of a 0.5 M solution in toluene, 12.0 mmol) was added to a solution of (4-chlorobutyl)triphenylphosphonium bromide[1] (5.20 g, 12.0 mmol) in THF (60 mL) at -20 °C. After 40 min, the orange mixture was cooled to -78 °C and a solution of aldehyde **5**[6] (1.0 g, 4.0 mmol) in THF (20 mL) was added. After 10 min, the mixture was warmed to 0 °C for 30 min, and then to rt for 1 h. Saturated aqueous

NH_4Cl (20 mL) was added and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Chromatography (2% EtOAc/hexane) provided 0.20 g (60%) of the title compound as an inseparable 5:1 mixture of *Z* and *E* isomers as determined by integration of the benzylic olefinic protons at δ 6.65 (d, J = 15.8 Hz, 0.2 H, *E* isomer) and 6.49 (d, J = 11.4 Hz, 1 H, *Z* isomer), R_f= 0.5 (10% EtOAc/hexane). Data for major (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.50 (d, J = 7.4 Hz, 1 H), 7.2-7.4 (m, 2 H), 7.13 (d, J = 7.4 Hz, 1 H), 6.49 (d, J = 11.4 Hz, 1 H), 5.69 (dt, J = 11.4, 7.9 Hz, 1 H), 4.67 (s, 2 H), 3.49 (t, J = 6.8 Hz, 2 H), 2.27 (app q, J = 7.7 Hz, 2 H), 1.85 (m, 2 H), 0.94 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 139.1 (–), 134.5 (–), 131.4 (+), 128.7 (+), 128.0 (+), 127.1 (+), 126.4 (+), 126.2 (+), 62.9 (–), 44.4 (–), 32.7 (–), 25.9 (+), 25.8 (–), 18.4 (-), -5.3 (+); IR (neat) 2954 (s), 2928 (s), 2855 (s), 1658 (m), 1470 (m), 1255 (s), 1117 (s), 837 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 342 [$(M + NH_4)^+$, 9.7], 325 [$(M + H)^+$, 2.6], 212 (40.4), 211 (19.9), 210 (100.0), 195 (21.2), 193 (45.8), 174 (20.2), 157 (48.7), 91 (15.7); HRMS calcd for $C_{18}H_{29}{}^{35}ClOSiH$ 325.1754, found 325.1754. ^{1}H NMR data for the (*E*)-isomer: ($CDCl_3$, 360 MHz) δ 6.65 (d, J = 15.8 Hz, 1 H), 6.05 (dt, J = 15.8, 7.0 Hz, 1 H), 4.76 (s, 2 H), 3.60 (t, J = 6.8 Hz, 2 H), 2.40 (app q, J = 7.7 Hz, 2 H), 1.95 (m, 2 H).

(*Z*)-1-(2-Hydroxymethyl)phenyl-5-chloropent-1-ene (8). Tetrabutylammonium fluoride (32.5 mL, 1.0 M in THF, 32.5 mmol) was added to a solution of **7** (4.22 g, 13.0 mmol) in THF (25 mL). After 12 h, water (12 mL) was added, and the resultant mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (20 mL) and brine (30 mL), then dried ($MgSO_4$), and concentrated. Chromatography (5%-20% EtOAc/hexane gradient) afforded 2.24 g (82%) of the title compound as a colorless liquid. The (*E*)-isomer was not isolated. R_f = 0.2 (20% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.42 (m, 1 H), 7.2-7.3 (m, 2 H), 7.19 (m, 1 H), 6.60 (d, J = 11.4 Hz, 1 H), 5.75 (dt, J = 11.4, 7.9 Hz, 1 H), 4.65 (s, 2 H), 3.49 (t, J = 6.8 Hz, 2 H), 2.32 (app q, J = 7.7 Hz, 2 H), 1.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 138.5 (–), 135.5 (–), 132.0 (+), 129.3 (+), 127.9 (+), 127.8 (+), 127.5 (+), 127.3 (+), 63.3 (–), 44.3 (–), 32.4 (–), 25.7 (–); IR (neat) 3345 (s), 3063 (s), 3009 (s), 2956 (s), 1646 (w), 1601 (w), 1485 (m), 1455 (s), 1308 (m), 1202 (m), 1100 (m), 1038 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 210 [$(M)^+$, 28.5], 209 (22.6), 133 (34.7), 129 (100.0), 128 (28.9), 117 (30.4), 91 (27.4), 86 (59.3), 83 (85.4), 49 (87.8); HRMS calcd for $C_{12}H_{15}{}^{35}ClO$ 210.0811, found 210.0811.

(*Z*)-1-(2-Hydroxymethyl)phenyl-5-azidopent-1-ene (9). Sodium azide (0.12 g , 1.9 mmol) was added to a solution of **8** (0.11 g, 0.54 mmol) and sodium iodide (8 mg, 0.05 mmol) in DMSO (2.7 mL) at 40 °C. After 12 h, water (4 mL) was added and the mixture was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (5%-20% EtOAc/hexane gradient) provided 86 mg (74%) of the title compound as colorless liquid, R_f = 0.2 (20% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.42 (m, 1 H), 7.2-7.3 (m, 2 H), 7.19 (m, 1 H), 6.62 (d, J = 11.4 Hz, 1 H), 5.76 (dt, J = 11.4, 7.9 Hz, 1 H), 4.70 (s, 2 H), 3.24 (t, J = 6.8 Hz, 2 H), 2.23 (app q, J = 7.7 Hz, 2 H), 1.69 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 138.6 (–), 135.7 (–), 132.2 (+), 129.3 (+), 128.0 (+), 127.7 (+), 127.4 (+), 127.3 (+), 63.4 (–), 50.9 (–), 28.7 (–), 25.5 (–); IR (neat) 3584 (m), 3361 (m), 3009 (m), 2935 (m), 2095 (s), 1644 (w), 1485 (s), 1454 (s), 1257 (m), 1040 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel int) 235 [$(M + NH_4)^+$, 36.3], 228 (4.18), 200 (6.2), 188 (7.0), 190 (36.1), 173 (13.7), 172 (90.9), 137 (7.56), 136 (100.0); HRMS calcd for $C_{12}H_{15}N_3ONH_4$ 235.1558 [$(M + NH_4)^+$], found 235.1556.

(*Z*)-1-(2-Chloromethyl)phenyl-5-azidopent-1-ene (10) Methanesulfonyl chloride (0.08 g, 0.7 mmol) was added dropwise to a cold (0 °C) solution of alcohol **9** (0.080 g, 0.35 mmol), 2,6-lutidine (0.08 g, 0.08 mL, 0.7 mmol), and LiCl (0.03 g, 0.7 mmol) in DMF (0.5 mL). After 2 h, water (1 mL) was added and the resulting mixture was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (4 mL), dried ($MgSO_4$), and concentrated. Chromatography (3% EtOAc/hexane) gave 53 mg (64%) of the title compound as a pale yellow liquid, R_f = 0.5 (5% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.42 (m, 1 H), 7.2-7.3 (m, 2 H), 7.19 (m, 1 H), 6.67 (d, J = 11.4 Hz, 1 H), 5.78 (dt, J = 11.4, 7.9 Hz, 1 H), 4.57 (s, 2 H), 3.25 (t, J = 6.8 Hz, 2 H), 2.22 (app q, J = 7.7 Hz, 2 H), 1.69 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 136.8 (–), 135.2 (–), 132.9 (+), 129.8 (+), 129.7 (+), 128.5 (+), 127.6 (+), 127.5 (+), 50.8 (–), 44.5 (–), 28.7 (-), 25.6 (–); IR (neat) 3065 (m), 3013 (m), 2934 (s), 2868 (m), 2096 (s), 1644 (w), 1486 (m), 1453 (m), 1347 (m), 1262 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel int) 253 [(M + NH_4)$^+$, 41.5], 210 (46.5), 209 (21.4), 208 (100.0), 174 (43.8), 173 (20.6), 172 (74.4), 138 (18.1), 130 (19.7), 129 (16.1); HRMS calcd for $C_{12}H_{14}{}^{35}ClN_3NH_4$ 253.1219 [(M + NH_4)$^+$], found 253.1210.

1,2,3,5,10,10a-Hexahydropyrrolo[1,2-*b*]isoquinoline (11). A solution of azidoalkene **10** (30 mg, 0.13 mmol) in benzene-d_6 (1.5 mL) in a sealable NMR tube was degassed with three freeze-thaw cycles,and then sealed under vacuum. The tube was heated in a silicone-oil bath to 120 °C for 7 h, then cooled to rt and opened. The contents were taken up in methanol (2.5 mL) and the resulting solution was added to sodium borohydride (0.03 g, 0.8 mmol) at 0 °C. After 20 min, the mixture was warmed to rt for 12 h, then cooled to 0 °C and treated with aqueous NaOH (15%, 4 mL). The resulting mixture was extracted with EtOAc (3 x 4 mL) and the combined organic extracts were washed with brine (5 mL), then dried (K_2CO_3) and concentrated. Chromatography (2%-10% $CH_3OH/CHCl_3$ gradient) provided 16 mg (71%) of the title compound as a colorless liquid, R_f = 0.3 (10% $CH_3OH/CHCl_3$): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.0-7.15 (m, 4 H), 4.13 (d, J = 14.8 Hz, 1 H), 3.44 (d, J = 15.5 Hz, 1 H), 3.26 (t, J = 9.2 Hz, 1 H), 2.98 (dd, J = 15.5, 5.4 Hz, 1 H), 2.71 (dd, J = 16.2, 1.6 Hz, 1 H), 2.27 (m, 2 H), 2.09 (m, 1 H), 1.9 (m, 2 H), 1.55 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 135.0, 128.9, 126.9, 126.5, 125.5, 60.8, 56.0, 54.9, 36.2, 31.3, 21.5; IR ($CDCl_3$) 2966 (s), 2923 (s), 2879 (s), 2795 (m), 1446 (m), 1340 (m), 1315 (m), 1157 (m), 1138 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel int) 174 [(M + H)$^+$, 100.0], 173 (M$^+$, 46.5), 172 (34.1), 145 (5.5), 144 (3.6), 130 (4.7), 117 (2.7), 105 (5.1), 104 (15.2), 91 (3.0); HRMS calcd for $C_{12}H_{15}NH$ 174.1283 [(M + H)$^+$], found 174.1281.

***d,l*-2,3-Bis-(3,4-dimethoxyphenyl)butanedioic acid (18).** *n*-Butyllithium (39.1 mL of a 2.1 M solution in hexane, 82.0 mmol) was added to a cold (0 °C) solution of diisopropylamine (8.30 g, 11.5 mL, 82.0 mmol) in THF (400 mL). After 30 min, the solution was cooled to -78 °C and (3,4-dimethoxyphenyl)acetic acid (homoveratric acid, 7.85 g, 40.0 mmol) in THF (220 mL) was added. After 1 h, the mixture was warmed to 0 °C for 1 h, then cooled to -78 °C, and a solution of iodine (5.07 g, 20.0 mmol) in THF (100 mL) was added. After 30 min, the yellowish-brown mixture was warmed to rt for 24 h, and then concentrated. The resulting brown froth was acidified to pH 1 with 1 N HCl and extracted with chloroform (3 x 100 mL). The combined organic extracts were washed with aqueous $NaHSO_3$ (10%, 50 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated. Chromatography (0%-10% $CH_3OH/CHCl_3$ gradient) provided 3.12 g (40% isolated, 57% based on recovered starting acid) of the title compound as a frothy viscous oil. A single stereoisomer was evident based on ^{1}H NMR and ^{13}C NMR analysis. ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.7 (s, 4 H), 6.6 (s, 2 H), 4.2 (s, 2 H), 3.7 (s, 6 H), 3.6 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 179.8, 148.8, 148.6, 126.7, 120.7, 111.3, 111.1, 55.8, 55.7, 54.4; IR ($CDCl_3$) 3744 (br, s), 2939 (m), 1703 (s), 1596 (m), 1515 (s), 1460 (m), 1257 (s),

1146 (s), 1025 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 390 (M^+, 2.41), 300 (16.7), 196 (12.9), 195 (100.0), 178 (36.0), 167 (8.1), 163 (9.5), 151 (6.8), 139 (11.8), 83 (7.3); HRMS calcd for $C_{20}H_{22}O_8$ 390.1314, found 390.1319.

Dimethyl *d,l*-2,3-Bis-(3,4-dimethoxyphenyl)butanedicarboxylate (19). Diazomethane (approx. 16.6 mmol generated from 5.0 g of Diazald®, Aldrich) was added to a solution of diacid **18** (0.65 g, 1.66 mmol) in 95% ethanol (4 mL). After the addition was complete, excess diazomethane was destroyed by quenching with 10% aqueous acetic acid. Water (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with 10% aqueous Na_2CO_3 (15 mL), dried (K_2CO_3), and concentrated. Chromatography (0-1% $CH_3OH/CHCl_3$ gradient) provided 0.54 g (77%) of diester **19** as a viscous oil, R_f = 0.3 (1% $CH_3OH/CHCl_3$): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.63 (m, 2 H), 6.53 (m, 4 H), 4.13 (s, 2 H), 3.78 (s, 6 H), 3.73 (s, 6 H), 3.70 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 173.8 (–), 148.8 (–), 148.3 (–), 128.1 (–), 120.8 (+), 111.1 (+), 111.0 (+), 55.8 (+), 55.7 (+), 54.4 (+), 52.4 (+); IR (neat) 2952 (s), 1732 (s), 1514 (s), 1504 (s), 1470 (s), 1454 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 418 (M^+, 18.2), 223 (4.3), 211 (3.9), 210 (15.8), 209 (100.0), 181 (17.6), 151 (6.9), 85 (29.2), 83 (42.7), 47 (9.6); HRMS calcd for $C_{22}H_{26}O_8$ 418.1628, found 418.1614.

Dimethyl 2,3,6,7-Tetramethoxyphenanthrene-9,10-dicarboxylate (20). A solution of VOF_3 (1.09 g, 8.84 mmol) in CH_2Cl_2 (12 mL) and EtOAc (6 mL) containing trifluoroacetic acid (0.2 mL) and trifluoroacetic anhydride (1 drop) was added in a dropwise fashion to a cold (0 °C) solution of the diester **19** (0.84 g, 2.0 mmol) in CH_2Cl_2 (6 mL) containing trifluoroacetic anhydride (1 drop). After 5 h, the mixture was poured into crushed ice and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated. Chromatography ($CHCl_3$) provided 0.48 g (58%) of the title compound as an oil, R_f = 0.27 (5% $CH_3OH/CHCl_3$): ^1H NMR ($CDCl_3$, 360 MHz) δ 7.68 (s, 2 H), 7.53 (s, 2 H), 4.10 (s, 6 H), 3.99 (s, 12 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 168.8 (–), 150.5 (–), 149.4 (–), 126.9 (–), 125.8 (–), 121.6 (–), 106.3 (+), 102.4 (+), 55.9 (+), 55.8 (+), 52.6 (+); IR ($CDCl_3$) 3014 (m), 2853 (m), 1725 (s), 1621 (m), 1511 (s), 1428 (s), 1411 (m), 1180 (s), 1141 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 415 (27.8), 414 (M^+, 100.0), 383 (18.5), 398 (8.9), 371 (13.5), 341 (8.0), 339 (8.5), 325 (14.2), 311 (15.7), 209 (10.4); HRMS calcd for $C_{22}H_{22}O_8$ 414.1315, found 414.1322; Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.47; H, 5.56.

2,3,6,7-Tetramethoxy-9,10-bis(hydroxymethyl)phenanthrene (21). $LiAlH_4$ (0.36 g, 9.6 mmol) was added to a solution of the diester **20** (0.66 g, 1.6 mmol) in THF (16 mL) at 0 °C. After 15 min, the solution was warmed to rt for 3 h, then cooled to 0 °C. Water (1 mL) and concentrated HCl (0.5 mL) were carefully added. The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic extracts were washed with 10% aqueous Na_2CO_3 (10 mL) and brine (25 mL), then dried ($MgSO_4$) and concentrated. Crystallization (methanol) provided 0.52 g (91%) of the title compound as a white powder, mp 220 °C, R_f = 0.2 (5% $CH_3OH/CHCl_3$): ^1H NMR ($CDCl_3$, 360 MHz) δ 7.76 (s, 2 H), 7.6 (s, 2 H), 5.26 (s, 4 H), 4.12 (s, 6 H), 4.06 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 149.5, 149.0, 131.0, 125.5, 112.5, 105.1, 103.1, 59.2, 56.0; IR ($CHCl_3$) 3417 (br, w), 2938 (w), 1620 (s), 1512 (s), 1468 (s), 1426 (s), 1253 (s), 1152 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 359 (30.4), 358 (M^+, 100.0), 343 (38.1), 340 (52.3), 339 (19.6), 338 (26.3), 311 (55.0), 211 (42.4), 165 (34.5), 43 (65.0); HRMS calcd for $C_{20}H_{22}O_6$ 358.1416, found 358.1418.

2,3,6,7-Tetramethoxy-9-(hydroxymethyl)-10-[(*tert*-butyldimethylsilyl)oxy]methylphenanthrene (22). Sodium hydride (0.050 g, 60% dispersion in mineral oil, 1.13 mmol) was added to a solution of the diol **21** (0.40 g, 1.13 mmol) in THF (25 mL). After 2 h, *tert*-butyldimethylchlorosilane (0.17 g, 1.13 mmol) was added. After 2.5 h, water (10 mL) was added and the resulting mixture was extracted with chloroform (3 x 10 mL). The combined organic extracts were washed with aqueous Na_2CO_3 (10%, 15 mL) and brine (20 mL), then dried (K_2CO_3) and concentrated. Chromatography (0-10% $CH_3OH/CHCl_3$ gradient) provided 0.49 g (92%) of the title compound as a white solid, mp 118 °C (on a small sample recrystallized from EtOAc/hexane). R_f = 0.5 (5% $CH_3OH/CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.73 (s, 2 H), 7.61 (s, 1 H), 7.52 (s, 1 H), 5.17 (s, 4 H), 4.10 (s, 6 H), 4.05 (s, 3 H), 4.02 (s, 3 H), 0.9 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 149.2 (–), 149.1 (–), 149.0 (–), 148.7 (–), 131.6 (–), 131.1 (–), 125.2 (–), 125.1 (-), 125.0 (–), 105.5 (+), 105.3 (+), 103.0 (+), 59.5 (–), 59.3 (–), 56.0 (+), 55.9 (+), 55.8 (+), 26.0 (+), 18.4 (–), -5.0 (+); IR ($CHCl_3$) 3614 (m), 3020 (s), 2858 (s), 1620 (m), 1511 (s), 1468 (s), 1425 (s), 1253 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 472 (M^+, 48.2), 415 (26.2), 340 (16.3), 324 (26.4), 323 (100.0), 308 (8.6), 292 (13.6), 151 (5.6), 75 (26.6), 73 (15.1); HRMS calcd for $C_{26}H_{36}O_6Si$ 472.2281, found 472.2281.

2,3,6,7-Tetramethoxy-10-[(*tert*-butyldimethylsilyl)oxy]methyl phenanthrene-9-carboxaldehyde (23). A solution of the alcohol **22** (0.20 g, 0.40 mmol) in CH_2Cl_2 (0.4 mL) was added to a suspension of pyridinium chlorochromate (0.18 g, 0.80 mmol), sodium acetate (0.01 g, 0.2 mmol), and Celite (0.01 g) in CH_2Cl_2 (1.1 mL). After 40 min, ether (10 mL) was added and the mixture was filtered through a plug of Celite, washing repeatedly with ether, then chloroform. Chromatography ($CHCl_3$) afforded 0.12 g (64%) of the title compound, mp 220 °C, R_f = 0.8 (5% $CH_3OH/CHCl_3$): ^1H NMR ($CDCl_3$, 360 MHz) δ 10.97 (s, 1 H), 8.46 (s, 1 H), 7.76 (s, 2 H), 7.68 (s, 1 H), 5.38 (s, 2 H), 4.14 (s, 3 H), 4.11 (s, 3 H), 4.05 (s, 6 H), 0.9 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 194.6 (+), 151.1 (–), 149.7 (–), 149.5 (–), 149.0 (–), 138.6 (–), 127.9 (–), 127.0 (–), 124.9 (–), 124.5 (–), 122.8 (–), 106.3 (+), 106.1 (+), 102.8 (+), 102.6 (+), 57.9 (–), 56.0 (+), 55.9 (+), 25.8 (+), 18.3 (–), -5.1 (+); IR ($CDCl_3$) 2956 (m), 1618 (m), 1509 (s), 1423 (s), 1255 (s), 1197 (m), 1047 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 470 (M^+, 24.3), 414 (37.3), 413 (100.0), 340 (16.4), 339 (51.5), 86 (14.4), 84 (21.3), 75 (17.4), 57 (11.3), 41 (10.8); HRMS calcd for $C_{26}H_{34}O_6Si$ 470.2125, found 470.2148.

(Z)-2,3,6,7-Tetramethoxy-9-(5-chloro-1-pentenyl)-10-[(*tert*-butyldimethylsilyl)oxy]methylphenanthrene (24). Potassium bis(trimethylsilyl)amide (1.6 mL, 0.5 M in toluene, 0.80 mmol) was added to a solution of (4-chlorobutyl)triphenylphosphonium bromide[1] (0.34 g, 0.8 mmol) in THF (4 mL) at -20 °C. After 40 min, the orange mixture was cooled to -78 °C and THF (10 mL) was added, followed by a solution of aldehyde **23** (0.12 g, 0.30 mmol) in CH_2Cl_2 (5 mL). The mixture was warmed to -20 °C for 1.5 h, 0 °C for 30 min, and then to rt for 1 h. After cooling the mixture to 0 °C, acetone (1.5 mL), HCl (3%, 1 mL), and saturated aqueous NH_4Cl (5 mL) were added. The resulting mixture was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with brine (30 mL) dried ($MgSO_4$) and concentrated. Chromatography (2% EtOAc/hexane) provided 0.14 g (83%) of the title compound as a colorless solid, mp 185-187 °C (on a small sample recrystallized from EtOAc/hexane). The *E*-isomer was not detected by NMR. R_f= 0.3 (33% EtOAc/hexane); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.81 (s, 1 H), 7.80 (s, 1 H), 7.69 (s, 1 H), 7.43 (s, 1 H), 6.88 (d, J = 15.7 Hz, 1 H), 5.88 (dt, J = 15.7, 6.5 Hz, 1 H), 5.18 (s, 2 H), 4.15 (s, 6 H), 4.11 (s, 3 H), 4.06 (s, 3 H), 3.72 (t, J = 6.7 Hz, 2 H), 2.62 (app q, J = 6.7 Hz, 2 H), 2.05 (m, 2 H), 0.9 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 149.0, 148.7, 148.4, 135.7, 132.1, 129.2, 128.7, 126.1, 125.5, 124.5, 124.3,

106.9, 106.5, 102.9, 102.7, 61.5, 56.0, 55.8, 44.3, 31.7, 30.2, 25.9, 18.3, -5.1; IR ($CDCl_3$) 2957 (m), 2926 (m), 1619 (m), 1522 (m), 1502 (s), 1419 (m), 1248 (s), 1189 (m), 1047 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 544 (M^+, 82.0), 487 (10.9), 416 (12.0), 415 (44.5), 414 (52.3), 413 (100.0), 412 (60.4), 350 (10.3), 349 (29.1), 75 (28.2); HRMS calcd for $C_{30}H_{41}{}^{35}ClO_5Si$ 544.2412, found 544.2402.

(Z)-2,3,6,7-Tetramethoxy-9-(5-azido-1-pentenyl)-10-[(*tert*-butyldimethylsilyl)oxy]methylphenanthrene (25). Sodium azide (0.04 g, 0.7 mmol) was added to a solution of chloroalkene **24** (0.090 g, 0.20 mmol) and NaI (3 mg, 0.02 mmol) in DMSO (1 mL) and acetone (1 mL) at 40 °C. After 7 h, water (4 mL) was added and the resulting mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. Chromatography (20-30% EtOAc/hexane gradient) provided 0.080 g (88%) of the title compound as a yellowish white powder, mp 165-170 °C dec. (on a small sample recrystallized from EtOAc/hexane), R_f = 0.4 (33% EtOAc/hexane): ^1H NMR ($CDCl_3$, 360 MHz) δ 7.81 (s, 1 H), 7.80 (s, 1 H), 7.69 (s, 1 H), 7.41 (s, 1 H), 6.85 (d, J = 15.7 Hz, 1 H), 5.91 (dt, J = 15.7, 6.5 Hz, 1 H), 5.17 (s, 2 H), 4.18 (s, 6 H), 4.12 (s, 3 H), 4.06 (s, 3 H), 3.45 (t, J = 6.7 Hz, 2 H), 2.53 (app q, J = 6.7 Hz, 2 H), 1.90 (m, 2 H), 0.9 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 149.1 (–), 148.7 (–), 148.6 (–), 148.3 (–), 136.0 (+), 131.9 (–), 129.2 (–), 128.2 (+), 125.4 (–), 124.6 (–), 124.3 (–), 124.2 (–), 106.9 (+), 106.6 (+), 102.9 (+), 102.7 (+), 61.5 (–), 56.0 (+), 55.9 (+), 55.8 (+), 55.7 (+), 50.8 (–), 30.3 (–), 28.5 (–), 25.9 (+), 18.3 (–), -5.1 (+); IR ($CDCl_3$) 3008 (m), 2933 (m), 2099 (s), 1619 (m), 1528 (m), 1508 (s), 1421 (m), 1250 (s), 1154 (m), 1060 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel int) 524 [(M - N_2 + H)$^+$, 100.0], 523 (13.4), 508 (8.1), 395 (15.3), 394 (44.2), 393 (21.1), 392 (47.8), 390 (12.2), 379 (16.7), 378 (22.2); HRMS calcd for $C_{30}H_{41}NO_5SiH$ 524.2832 [(M - N_2 + H)$^+$], found 524.2809.

(Z)-2,3,6,7-Tetramethoxy-9-(5-azido-1-pentenyl)-10-hydroxymethylphenanthrene (26). Tetrabutylammonium fluoride (0.37 mL, 1.0 M in THF, 0.37 mmol) was added to a cold (0 °C) solution of **25** (0.080 g, 0.15 mmol) in THF (0.5 mL). After 30 min, the mixture was warmed to rt for 40 min, then cooled to 0 °C, and treated with water (2 mL). The resulting mixture was extracted with EtOAc (3 x 4 mL) and the combined organic extracts were washed with brine (30 mL), then dried ($MgSO_4$) and concentrated. Chromatography (30-60% EtOAc/hexane gradient) afforded 63 mg (96%) of the title compound as an oil, R_f = 0.1 (33% EtOAc/hexane): ^1H NMR ($CDCl_3$, 360 MHz) δ 7.82 (s, 1 H), 7.81 (s, 1 H), 7.68 (s, 1 H), 7.42 (s, 1 H), 6.88 (d, J = 15.7 Hz, 1 H), 5.92 (dt, J = 15.7, 6.5 Hz, 1 H), 5.19 (s, 2 H), 4.13 (s, 6 H), 4.08 (s, 3 H), 4.01 (s, 3 H), 3.46 (t, J = 6.7 Hz, 2 H), 2.55 (app q, J = 6.7 Hz, 2 H), 1.92 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 149.4, 149.1, 149.0, 148.5, 136.2, 132.8, 129.0, 128.1, 125.3, 124.7, 124.4, 107.0, 105.7, 103.1, 102.9, 60.9, 56.1, 56.0 , 55.8, 50.8, 30.4, 29.7, 28.6; IR ($CDCl_3$) 3599 (w), 2937 (m), 2099 (m), 1619 (m), 1508 (s), 1422 (m), 1251 (s), 1154 (m) cm^{-1}; MS (DCI, NH_3) *m/z* (rel int) 410 [(M - N_2 + H)$^+$, 100.0], 409 (16.5), 408 (20.1), 394 (26.3), 393 (11.3), 392 (26.9), 380 (12.0), 340 (18.3), 339 (35.7), 313 (13.6); HRMS calcd for $C_{24}H_{27}NO_5H$ 410.1967 [(M - N_2 + H)$^+$], found 410.1976.

(Z)-2,3,6,7-Tetramethoxy-9-(5-azido-1-pentenyl)-10-chloromethylphenanthrene (3). Methanesulfonyl chloride (0.030 g, 22 µl, 0.29 mmol) was added dropwise to a cold (0 °C) solution of alcohol **26** (0.060 g, 0.15 mmol), 2,6-lutidine (0.030 g, 34 µL, 0.15 mmol) and LiCl (0.010 g, 0.29 mmol) in DMF (0.3 mL). After 2 h, water (1 mL) was added and the resulting mixture was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (4 mL), dried ($MgSO_4$), and concentrated. Chromatography (33-60% EtOAc/hexane gradient) gave 41 mg (60%) of the title compound as an oil, R_f = 0.2 (33%

EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.82 (s, 1 H), 7.81 (s, 1 H), 7.54 (s, 1 H), 7.39 (s, 1 H), 6.86 (d, J = 15.7 Hz, 1 H), 6.10 (dt, J = 15.7, 6.5 Hz, 1 H), 5.20 (s, 2 H), 4.19 (s, 6 H), 4.13 (s, 3 H), 4.05 (s, 3 H), 3.47 (t, J = 6.7 Hz, 2 H), 2.56 (app q, J = 6.7 Hz, 2 H), 1.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 149.5, 149.0, 148.5, 136.9, 133.5, 127.6, 125.9, 125.4, 125.0, 124.5, 124.3, 117.0, 107.0, 105.3, 103.3, 102.9, 56.1, 55.9, 55.8, 50.7, 43.5, 30.5 , 28.6; IR ($CDCl_3$) 2937 (m), 2099 (s), 1619 (m), 1509 (s), 1439 (m), 1423 (s), 1250 (s), 1210 (m), 1149 (m) cm^{-1}; MS (DCI, NH_3) *m/z* (rel int) 420 [(M - Cl)$^+$, 2.3), 408 (25.5), 394 (88.5), 392 [(M - Cl - N_2)$^+$, 100.0], 389 (14.9), 388 (50.1), 379 (37.8), 378 (27.6), 377 (25.9), 182 (47.3); HRMS calcd for $C_{24}H_{25}NO_4$ 391.1784 [(M - N_2 - Cl - H)$^+$], found 391.1784.

(±)-Tylophorine (5). A solution of azidoalkene **3** (30 mg, 0.070 mmol) in benzene-d_6 (1.5 mL) in a sealable NMR tube was degassed using three freeze/thaw cycles and then sealed under vacuum. The tube was heated in a silicone-oil bath to 130 °C for 7 h, then cooled to rt, opened, and its contents were taken up in methanol (2.5 mL). The resulting solution was added to sodium borohydride (16 mg, 0.4 mmol) at 0 °C. After 20 min, the mixture was warmed to rt for 10 h, then cooled to 0 °C and treated with aqueous NaOH (15%, 2 mL). The resulting mixture was extracted with EtOAc (3 x 4 mL) and the combined organic extracts were washed with brine (5 mL), then dried (K_2CO_3) and concentrated. Chromatography (0-2% $CH_3OH/CHCl_3$ gradient) provided 24 mg (82%) of (±)-tylophorine as a light yellow solid, mp 287 °C dec (lit mp 292[5a]), R_f = 0.15 (2% $CH_3OH/CHCl_3$): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.83 (s, 2 H), 7.32 (s, 1 H), 7.17 (s, 1 H), 4.64 (d, J = 14.7 Hz, 1 H), 4.12 (s, 6 H), 4.05 (s, 6 H), 3.69 (d, J = 14.7 Hz, 2 H), 3.49 (t, J = 8.1 Hz, 1 H), 3.39 (dd, J = 16.2, 2.3 Hz, 1 H), 2.95 (t, J = 14.4 Hz, 1 H), 2.3-2.6 (m, 2 H), 1.75-2.1 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 148.7, 148.5, 148.4, 126.3, 125.9, 124.4, 123.6, 123.4, 104.1, 103.6, 103.4, 103.3, 103.2, 60.3, 56.1, 55.9, 55.2, 54.0, 33.8, 31.3, 21.6; IR ($CDCl_3$) 2962 (m), 1620 (m), 1514 (s), 1467 (m), 1246 (s), 1211 (m), 1154 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 393 (M$^+$, 30.7), 392 (9.4), 325 (25.4), 324 (100.0), 86 (30.4), 84 (45.9), 57 (9.1), 51 (17.7), 49 (53.7), 47 (8.9); HRMS calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1953. These data matched the literature data.[5l]

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(10) Prepared from (*E*)-2,3-bis-(3,4-dimethoxyphenyl)prop-2-enoic acid:[5g] (i) thionyl chloride (3 equiv), PhH, reflux, 1.5 h; (ii) diethylamine (3 equiv), CH_2Cl_2, Et_2O, -40 to 0 °C, 1 h 70 % yield of amide; (iii) VOF_3 (2 equiv), TFA, CH_2Cl_2, EtOAc, cat. TFAA, 0 °C, 82%. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81 (s, 1 H), 7.79 (s, 1 H), 7.51 (s, 1 H), 7.19 (s, 1 H), 7.15 (s, 1 H), 4.15 (s, 6 H), 4.05 (s, 3 H), 3.95 (s, 3 H), 3.4-3.5 (bs, 2 H), 3.15 (app q, J = 8 Hz, 2 H), 1.42 (t, J = 8 Hz, 3 H), 1.05 (t, J = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 149.7, 149.5, 149.1, 131.3, 125.4, 124.7, 124.5, 122.7, 121.5, 108.5, 105.3, 103.0, 102.7, 56.1, 56.0, 55.9, 55.7, 43.1, 38.8, 14.4, 13.0; IR ($CDCl_3$) 2937 (m), 1620 (s), 1508 (s), 1472 (s), 1428 (s), 1250 (s), 1126 (s), 1044 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 398 (27.3), 397 (M^+, 82.0), 326 (33.1), 325 (100.0), 267 (18.3), 142 (38.0), 86 (54.2), 84 (80.6), 55 (18.7), 47 (21.8); HRMS calcd for $C_{23}H_{27}NO_5$ 397.1889, found 397.1878.

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