Rearrangements of Cyclobutenones. Synthesis of *N*-Methyl-7,8-dihydrobenzophenanthridine-9,12-diols and Related Compounds

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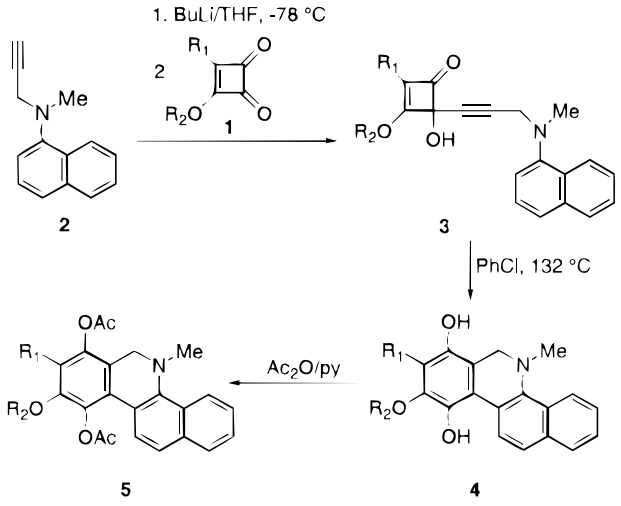
A useful synthetic route to benzophenanthridines and annulated derivatives is reported. These arise from the thermolysis (refluxing chlorobenzene) of squaric acid-derived 4-(3-*N*-methyl-*N*-arylpropynyl)-cyclobutenones via a mechanism which involves an electrocyclic ring opening of the cyclobutenone to the corresponding enynylketenes. Subsequent ring closure to a diradical intermediate followed by radical arylation gives the benzophenanthridines.

Reported here is a potentially general synthetic route to benzophenanthridines and annulated derivatives from appropriately substituted 4-alkynylcyclobutenones.[1] The method rests on a previously reported synthesis of 10,11-dimethoxy-*N*-methyl-7,8-dihydrobenzophenanthridine-9,12-diol (**4a**) from dimethyl squarate (**1a**) which has now been expanded to include a number of examples as generally outlined in Scheme 1.[2] Specifically, squaric acid-derived[3] cyclobutenones **1a**−**d** were treated with the lithium salt of *N*-methyl-*N*-(2-propynyl)-1-naphthylamine (**2**) in THF at −78 °C to give the corresponding 4-alkynylcyclobutenones **3a**−**d**. Thermolysis of these (refluxing chlorobenzene) gave the respective 7,8-dihydrobenzophenanthridine-9,12-diol **4a**−**d** in yields ranging from 42 to 71%. In two cases, the 4-alkynylcyclobutenones **3c**,**d** were not isolated but subjected directly to the thermolysis conditions to give **4c** and **4d**, respectively, in 61 and 42% overall yield. This significantly increases the yields of **4c**,**d** since the intermediate cyclobutenones **3c**,**d** were relatively unstable. For example, **3c** could be isolated in pure form in only 35% yield.

The initially formed 7,8-dihydrobenzophenanthridine-9,12-diols are difficult to isolate since they readily undergo partial oxidation to the corresponding purple quinhydrones as evidenced by mass spectral analysis; i.e., **4a** showed a molecular ion *m*/*z* at 337.4 as well as a *m*/*z*-2 peak at 335.4 of approximately equal intensity. However, when the crude reaction mixture was treated with acetic anhydride in pyridine, the more stable acylated derivatives **5a**−**c** were obtained in overall yields ranging from 31 to 53%.

The method was extended to include the synthesis of the annulated derivatives **8** and **10** (Scheme 2). That is, treatment of the lithium salt of *N*-methyl-*N*-(2-propynyl)-1-anthranylamine (**6**) with dimethyl squarate followed by direct thermolysis of the resulting cyclobutenone **7** and subsequent treatment with acetic anhydride gave **8** in 34% overall yield. In an analogous fashion **10** was obtained in 41% overall yield from *N*-methyl-*N*-(2-propynyl)-9-phenanthrylamine (**9**).

Scheme 1



	R_1	R_2	% Yield **3**	% Yield **4**	% Yield **5***
a	OMe	Me	70	66	45
b	O-i-Pr	i-Pr	85	71	53
c	n-Bu	i-Pr	35	61*	31
d	Ph	i-Pr	--	42*	--

*=overall yield from 2

Finally, the method was extended to include the synthesis of selected examples of benzophenanthridinium ions, a ring system commonly found in naturally occurring alkaloids such as chelilutine (**15**).[4] For example, **12** was obtained from the propargyl anion of **11** and was converted to the corresponding tetramethoxybenzophenanthridine **13** in 30% overall yield via the dihydroxybenzophenanthridine followed by treatment with methyl iodide. Oxidation of **13** with DDQ followed by treatment with HCl (aqueous) gave **14** in 75% yield. Analogously, **17** was obtained in 74% yield from its tetramethoxy precursor **16** which, in turn, stems from **3a** (Scheme 3).

The structure assignments for the benzophenanthridines and related benzophenanthridinium salts re-

(1) For a recent review on the ring expansion of cyclobutenones see: Moore, H. W.; Yerxa B. R. *Adv. Strain Org. Chem.* **1995**, *4*, 81.
(2) Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 1, 9168.
(3) For an efficient synthesis of dialkyl squarates see: Liu, H.; Tomooka, C. S.; Moore, H. W. *Synth. Commun.* **1997**, *27*, 2177.
(4) (a) Dostal, J.; Slavik, J.; Potacek, M.; Marek, R.; Humpa, O.; Sklenar, V.; Tousek, J.; de Hoffmann, E.; Rozenberg, R. *Collect. Czech. Chem. Commun.* **1998**, *63*, 1045. (b) Krane, B. D.; Fagbule, M. O.; Shamma, M. *J. Nat. Prod.* **1984**, *47*, 1.

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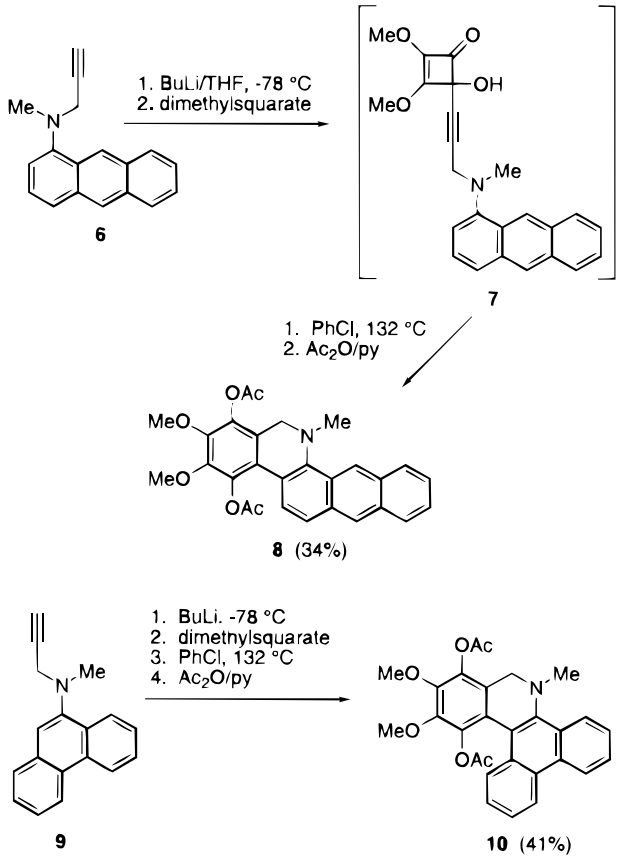
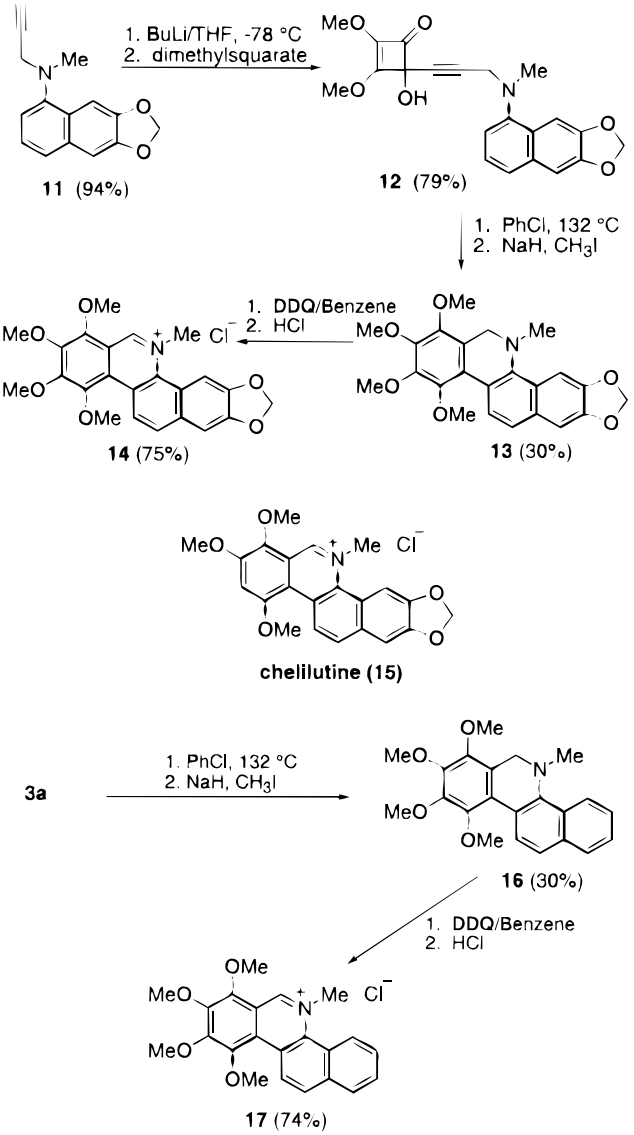
Scheme 2



Scheme 3



ported here are based upon their spectral properties as well as complete X-ray crystallographic structure for **8** and **10**.[5] The nonplanarity of **10** is sufficient to cause the methylene protons in this hexahelicen-type molecule to become diastereotopic as evidenced in its ^{1}H NMR spectrum. That is, the methylene proton absoptions appear as doublets (J = 14.9 Hz) at δ 3.87 and 4.25 ppm. In contrast, the methylene proton absorptions in **8** appear as a singlet at δ 4.11 ppm even though the X-ray structure shows some nonplanar helical character.

The mechanism envisaged for the thermal rearrangement of, for example, 4-deuterioxy-2,3-dimethoxy-4-[3-(*N*-methyl-*N*-(1-naphthylamino)-1-propynyl]-2-cyclobuten-1-one (**3a(OD)**) to 10,11-dimethoxy-*N*-methyl-7,8-dihydrobenzophenanthridine-9,12-diol (**4a**) is outlined in Scheme 4. The cyclobutenone **3a(OD)** undergoes a torqueselective[6] electrocyclic ring opening to the vinylketene **18**. Ring closure of this leads to the diradical **19**.[7] Attack of the ring-based radical in **19** on the proximal aromatic ring gives **20** which would lead directly to **4a** upon loss of a hydrogen atom. Alternatively, hydrogen atom abstraction from the OD group by the aryl radical in **20** would give the quinone **21** which would provide **4a** upon disprotonation.

The former mechanism finds precedence in radical arylation reactions,[8] but in the case outlined here such analogies may not hold due to the nature of the unique diradical intermediates. An analogy for the latter mechanism is found in the reported rearrangement of **22** to **23**.[9] Here, the initially formed diradical intermediate attacks the alkene double bond, and the resulting radical center abstracts a deuterium atom from the proximal OD group to give quinone **23**. To test these possibilities, **3a-(OD)** was prepared and subjected to the thermal rearrangement conditions. The product was isolated using aqueous workup conditions which would cause exchange of deuterons for protons at all OD-centers. Mass spectroscopic analysis of the benzophenanthridine **4a** showed no incorporation of deuterium. Thus, direct loss of a hydrogen atom from **20** best accounts for the formation of **4a**.

In conclusion, we wish to note the following significant points: (1) A new benzophenanthridine synthesis is outlined herein. It utilizes readily available starting material and can be employed to prepare annulated derivatives. (2) The method is of potential importance as

(5) Similar nonplanar structures have been reported for other dihydrophenanthridines. See, for example: (a) Chen, Y.; Tang, G.; Xu, B.; Wu, Q.; Lu, C.; Li, J.; Huang, Z. *Sci. China, Ser. B* **1992**, *35*, 1101. (b) Chen, Y.; Xu, B.; Yang, L.; Huang, Z. *Chin. Sci. Bull.* **1989**, *34*, 1182. (c) Chen, Y.; Yang, L.; Xu, B. *Acta Chim. Sin.* **1989**, *47*, 1048.

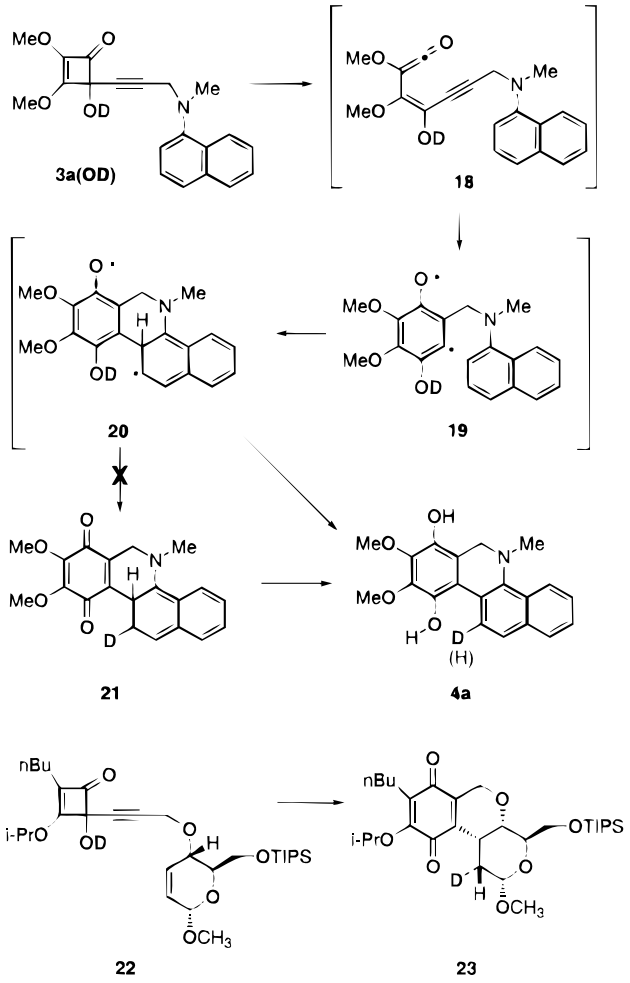
(6) Niwayama, S.; Kallel, E. A.; Sheu, C. M.; Houk, K. N.; *J. Org. Chem.* **1996**, *61*, 2517.

(7) Foland, L. D.; Karlsson J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.

(8) For a review of radical arylations, see: Waters, W. A. *Free Radicals Reactions*; Butterworth: London, 1987; Chapter 3, pp 25−45.

(9) Xiong, Y.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 6460.

Scheme 4



a route to analogues of benzophenanthridine and benzophenanthridinium salts in which ring-A (squarate-derived) can be easily modified. The method may find practical use since a number of naturally occurring alkaloids in this series show biological properties, e.g., nitidine, fagaronine, sanguinarine, and chelerythrine (Figure 1).[10] Nitidine and fagaronine received detailed attention a few years ago as a result of their potent activity against several tumor cell lines, but interest waned due to their narrow antitumor spectrum as well as certain toxicity and instability. However, renewed interest in alkoxy- and hydroxy-ring-A analogues of benzophenanthridinium salts has surfaced due to the recent report that NK109 shows potent antitumor activity and has long-term stability for potential clinical use.[11]

Experimental Section

General. All air- or water-sensitive reactions were carried out in flame-dried glassware under nitrogen. Tetrahydrofuran (THF) was dried by passing it through two 4 × 36 in. columns of anhydrous neutral A-2 alumina. Chlorobenzene was distilled over calcium hydride. Flash column chromatography was performed with silica gel (230−400 mesh) according to the procedure of Still, Kahn, and Mitra.[12] ^{1}H and ^{13}C NMR spectra

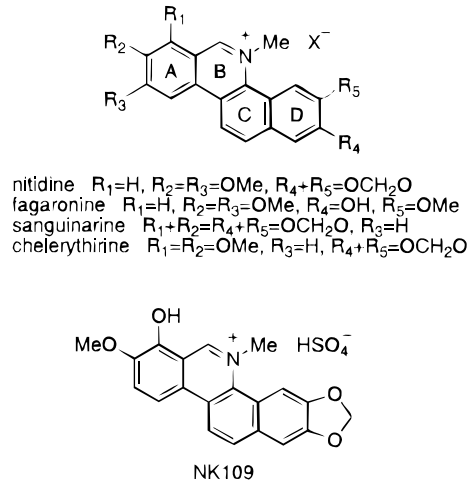


Figure 1.

were recorded at 500 and 125 MHz respectively in $CDCl_3$ unless specified otherwise. All NMR spectra were referenced to $CHCl_3$ resonance (7.26 and 77.0 ppm) unless specified otherwise and are reported in units of δ with coupling constants in hertz (Hz).

Experimental procedures and characterization of compounds **3c**, **4d**, **5b**,**c**, **8**, **9**, **10**, **11**, **16**, and **17** are supplied in the Supporting Information.

2,3-Diisopropoxy-4-hydroxy-4-[3-[*N*-methyl-*N*-(1-naphthyl)amino]-1-propynyl]-2-cyclobuten-1-one (3b). In analogy to the synthesis of **3a**[2], compound **3b** (1.02 g, 85%, chromatography, CH_2Cl_2/EtOAc 10:1) was obtained as a yellow oil from **2** (0.60 g, 3.07 mmol) and diisopropyl squarate[3] (0.60 g, 3.00 mmol): IR (neat) 3356, 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.29 (t, J = 6.2 Hz, 6H), 1.36 (d, J = 6.2 Hz, 3H), 1.38 (d, J = 6.2 Hz, 3H), 2.68 (s, 1H), 2.96 (s, 3H), 4.01 (s, 2H), 4.86 (sept, J = 6.2 Hz, 1H), 4.90 (sept, J = 6.2 Hz, 1H), 7.2 (dd, J = 0.7, 7.4 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.44−7.50 (m, 2H), 7.56 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 9.3 Hz, 1H), 8.17 (dd, J = 1.2, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.9, 164.5, 147.9, 134.6, 133.6, 128.8, 128.3, 125.7, 125.5, 123.8, 123.4, 116.5, 84.5, 80.2, 78.4, 77.8, 74.0, 46.9, 40.8, 22.6, 22.6, 22.5, 22.4; exact mass calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1936.

10,11-Diisopropoxy-*N*-methyl-7,8-dihydrobenzophenanthridine-9,12-diol (4b). A solution of **3b** (0.20 g, 0.50 mmol) in chlorobenzene (20 mL) was added dropwise (N_2) to refluxing chlorobenzene (100 mL) over a 1.5 h period, and the resulting solution was then refluxed for an additional 20 min. The solution was cooled to room temperature and concentrated in vacuo. Chromatography (hexanes/EtOAc = 15:1) gave **4b** (0.142 g, 71%) as a light purple solid: mp 113−118 °C dec; IR (KBr) 3507, 1448, 1373 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (d, J = 6.1 Hz, 12H), 2.66 (s, 3H), 4.24 (s, 2H), 4.67−4.75 (m, 2H), 5.35 (s, 1H), 6.02 (s, 1H), 7.45 (dd, J = 6.9, 8.0 Hz, 1H), 7.50 (dd, J = 6.9, 8.2 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 8.2 Hz, 1H), 8.54 (dd, J = 1.0, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.0, 140.8, 140.0, 136.1, 135.6, 133.5, 129.2, 127.9, 126.1, 125.6, 125.6, 124.5, 123.9, 123.5, 114.4, 114.0, 75.1, 75.0, 48.3, 41.0, 22.4; exact mass calcd for $C_{24}H_{27}NO_4$ 393.1940, found 393.1933.

10-Butyl-11-isopropoxy-*N*-methyl-7,8-dihydrobenzophenanthridine-9,12-diol (4c). Method A. In analogy to the above procedure, compound **4c** (0.073 g, 42%) was obtained after chromatography (hexanes/EtOAc = 15:1) as a dark purple solid from **3c** (0.175 g, 0.45 mmol): mp 157−159 °C; IR (KBr) 3495, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (t, J = 7.3 Hz, 3H), 1.41 (d, J = 6.2 Hz, 6H), 1.46 (sex, J = 7.3 Hz, 2H), 1.62 (tt, J = 7.3, 8.0 Hz, 2H), 2.68 (s, 3H), 2.69 (t, J = 8.0 Hz, 2H), 4.23 (sep, J = 6.2 Hz, 1H), 4.25 (s, 2H), 6.04 (s, 1H), 7.46

(10) (a) Arthur, H. R.; Hui, W. H.; Ng, Y. L. *Chem. Ind.* (London) **1958**, 1514. (b) Messmer, W. M.; Tin-Wa, M.; Fong, H. H. S.; Bevelle, C.; Farnsworth, N. R.; Abraham, D. J.; Trojanek, J. *J. Pharm. Sci.* **1972**, *61*, 1858.

(11) Nakanishi, T.; Suzuki, M.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem.* **1998**, *63*, 4235.

(12) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 3, 2923.

(dt, J = 1.2, 7.5 Hz, 1H), 7.51 (dt, J = 1.3, 7.5 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.37 (d, J = 8.3 Hz, 1H), 8.57 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.0, 143.7, 142.0, 141.3, 133.6, 129.1, 127.9, 126.2, 125.7, 125.6, 124.8, 123.9, 123.5, 122.5, 116.7, 116.6, 77.3, 48.6, 41.2, 31.5, 25.0, 23.1, 22.6, 13.9; exact mass calcd for $C_{25}H_{29}NO_3$ 391.2147, found 391.2152.

Method B. To a solution of **2** (0.075 g, 0.38 mmol) in THF (10 mL) at −78 °C was added ^{n}BuLi (0.24 mL, 1.6 M in hexanes, 0.38 mmol). The resulting reaction mixture was stirred for 30 min (−78 °C) and then transferred via cannula to a solution of 3-butyl-4-isopropoxycyclobutenedione (0.15 g, 0.76 mmol) in THF (20 mL). The resulting reaction mixture was stirred for 1 h at −78 °C, quenched with saturated ammonium chloride (25 mL), and extracted with diethyl ether. The combined organic portion was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was dissolved in chlorobenzene (20 mL), and this solution was added dropwise (N_2) to refluxing chlorobenzene (125 mL) over a 2 h period. The solution was refluxed for an additional 20 min, cooled to room temperature and concentrated in vacuo. Chromatography (hexanes/EtOAc = 15:1) gave product **4c** (0.092 g, 61% overall yield from **2**).

9,12-Diacetoxy-10,11-dimethoxy-*N*-methyl-7,8-dihydrobenzophenanthridine (5a). To a solution of **2** (0.20 g, 1.02 mmol) in THF (5 mL) at −78 °C was added ^{n}BuLi (0.63 mL, 1.6 M in hexanes, 1.02 mmol). The resulting reaction mixture was stirred for 30 min (−78 °C) and then transferred via cannula to a solution of dimethyl squarate[3] (0.14 g, 1.00 mmol) in THF (10 mL). The resulting solution was stirred for 1 h at −78 °C, quenched with saturated ammonium chloride (20 mL), and extracted with diethyl ether. The combined organic portion was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was dissolved in chlorobenzene (40 mL) added dropwise (N_2) to refluxing chlorobenzene (150 mL) over a 2 h period. The resulting solution was refluxed for an additional 20 min, cooled to room temperature and concentrated in vacuo. The crude product was dissolved in anhydrous pyridine (10 mL), and acetic anhydride was added (10 mL, 105 mmol). This solution was stirred for 1 h to room temperature, quenched with saturated aqueous sodium bicarbonate (25 mL), and extracted with diethyl ether. The combined organic portion was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography (hexanes/EtOAc = 7:1) gave **5a** (0.19 g, 45%) as a light yellow solid: mp 121−123 °C; IR (KBr) 1768, 1471, 1366 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.38 (s, 3H), 2.43 (s, 3H), 2.65 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.05 (s, 2H), 7.49 (ddd, J = 1.2, 6.7, 8.0 Hz, 1H), 7.54 (ddd, J = 1.2, 6.7, 8.3 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8, 168.4, 145.1, 145.0, 144.9, 139.2, 139.0, 133.8, 129.2, 127.9, 126.3, 126.0, 124.2, 124.0, 123.9, 122.8, 122.6, 121.4, 60.9, 49.0, 41.0, 20.9, 20.4; exact mass calcd for $C_{24}H_{23}NO_6$ 421.1525, found 421.1522.

***N*-Methyl-*N*-(2-propynyl)-1-anthranylamine (6).** A mixture of *N*-methyl-1-anthranylamine[13,14] (1.40 g, 6.75 mmol), potassium carbonate (1.37 g, 9.94 mmol) and propargyl bromide (1.5 mL, 80% in toluene, 13.46 mmol) in acetone (75 mL) was refluxed under nitrogen for 2 days. The mixture was quenched with saturated ammonium chloride (20 mL), and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography (hexanes/EtOAc = 15:1) gave product **6** (1.26 g, 76%) as a yellow oil: IR (neat) 3292, 1618, 1556, 1458, 1402 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.32 (t, J = 2.1 Hz, 1H), 3.06 (s, 3H), 4.06 (d, J = 2.1 Hz, 2H), 7.17 (d, J = 7.1 Hz, 1H), 7.38 (dd, J = 7.1, 8.4 Hz, 1H), 7.45 (dt, J = 3.2, 6.3 Hz, 1H), 7.46 (dt, J = 3.2, 6.3 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.98 (dd, J = 3.2, 6.3 Hz, 1H), 8.05 (dd, J = 3.2, 6.3 Hz, 1H), 8.40 (s, 1H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.9, 132.8, 131.4, 131.3, 128.6, 127.7, 127.5, 126.6, 125.4, 125.2, 124.9, 124.0, 122.4, 114.8, 79.5, 73.3, 46.4, 40.7; exact mass calcd for $C_{18}H_{15}N$ 245.1204, found 245.1197.

***N*-Methyl-6,7-(methylenedioxy)-1-naphthylamine.** A mixture of 1*H*-benzotriazole (1.12 g, 9.40 mmol) and 6,7-(methylenedioxy)-1-naphthylamine[15] (1.70 g, 9.08 mmol) in ethanol (20 mL) was stirred until completely dissolved. Aqueous formaldehyde (0.70 mL, 37% aqueous, 9.34 mmol) was then added at room temperature.[16] A white solid separated overnight and was collected by filtration, washed with ethanol, dried, and suspended in THF (50 mL). Sodium borohydride was then added (0.71 g, 18.76 mmol) and the mixture was refluxed overnight. The reaction was quenched with water (20 mL) and extracted with EtOAc. The combined organic portion was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography (hexanes/EtOAc = 7:1) gave the title compound a white solid (1.57 g, 86%): mp 103−104 °C; IR (KBr) 3415, 1535, 1470, 1366 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.97 (s, 3H), 4.03 (s, 1H), 6.00 (s, 2H), 6.53 (d, J = 7.7 Hz, 1H), 7.08 (s, 1H), 7.09 (s, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.23 (t, J = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.2, 147.1, 144.1, 131.1, 125.1, 119.6, 117.2, 104.8, 103.7, 101.0, 97.0, 31.2; exact mass calcd for $C_{12}H_{11}NO_2$ 201.0789, found 201.0782.

2,3-Dimethoxy-4-hydroxy-4-[3-[*N*-methyl-*N*-[1-(6,7-methylenedioxy)naphthyl]amino]-1-propynyl]-2-cyclobuten-1-one (12). To a solution of **11** (0.27 g, 1.12 mmol) in THF (10 mL) at −78 °C was added ^{n}BuLi (0.66 mL, 1.6 M in hexanes, 1.07 mmol). The resulting reaction mixture was stirred for 25 min and then transferred via cannula to a solution of dimethyl squarate (0.15 g, 1.05 mmol) in THF (10 mL). The resulting solution was stirred for 1 h at −78 °C, quenched with saturated ammonium chloride (20 mL), and extracted with diethyl ether. The combined organic portion was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography (methylene chloride/EtOAc = 15:1) gave **12** (0.32 g, 79%) as a yellow oil: IR (KBr) 3350, 1779, 1638, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.88 (s, 3H), 3.88 (s, 2H), 3.91 (s, 3H), 4.06 (s, 3H), 4.18 (s, 1H), 5.98 (s, 2H), 7.06 (s, 1H), 7.10 (d, J = 7.4 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.9, 164.9, 147.6, 147.3, 135.2, 131.5, 125.9, 124.0, 123.3, 115.8, 104.2, 100.9, 100.1, 85.2, 79.7, 78.3, 59.8, 58.4, 46.6, 40.9; exact mass calcd for $C_{21}H_{19}NO_6$ 381.1212, found 381.1213.

9,10,11,12-Tetramethoxy-4,5-(methylenedioxy)-*N*-methyl-7,8-dihydrobenzophenanthridine (13). A solution of **12** (0.25 g, 0.65 mmol) in chlorobenzene (40 mL) was added dropwise (N_2) to refluxing chlorobenzene (300 mL) in 2 h and then refluxed for an additional 20 min. The solution was cooled to room temperature and concentrated in vacuo. The crude product was dissolved in THF (15 mL) and added (−10 °C) to a mixture of THF (10 mL) and sodium hydride (0.052 g, 60% in mineral oil, 1.30 mmol, previously washed with pentanes (2 × 10 mL)). The resulting mixture was stirred for 1 h at 0 °C, and then methyl iodide (0.080 mL, 1.30 mmol) was added. This mixture was stirred for 18 h at room temperature and quenched with saturated ammonium chloride (25 mL), and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography (hexanes/EtOAc = 8:1) gave compound **13** (0.081 g, 30% overall yield from **12**) as a colorless oil: IR (neat) 2935, 1463, 1404, 1355 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.57 (s, 3H), 3.74 (s, 3H), 3.87 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 4.15 (s, 2H), 6.03 (s, 2H), 7.11 (s, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.69

(13) Grinsteins, V.; Vina, I.; Meldraja, M. *Chem. Abstr.* **1968**, *68*, 104942.

(14) Gobert, F.; Combrisson, S. *Tetrahedron* **1974**, *30*, 2919.

(15) The synthesis of this compound differs slightly from that reported by: (a) Begley, W. J.; Grimshaw, J. *J. Chem. Soc., Perkin Trans. I* **1977**, 2324. (b) Kessar, S. V.; Gupta, Y. P.; Balakrishnan, P.; Sawal, K. K.; Mohammad, T.; Dutt, M. *J. Org. Chem.* **1988**, *53*, 1708.

(16) The procedure used is similar to that described for the synthesis of *N*-methyl-1-naphthylamine from 1-naphthylamine: (a) Katritzky, A. R.; Black, M.; Fan, W. *J. Org. Chem.* **1991**, *56*, 6, 5045. (b) Katritzky, A. R.; Rachwall, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 805.

(s, 1H), 8.32 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.8, 147.6, 147.5, 146.4, 146.4, 146.2, 130.7, 126.1, 124.1, 123.1, 122.9, 121.0, 104.0, 100.9, 100.7, 61.4, 61.4, 61.2, 60.6, 48.7, 40.6; exact mass calcd for $C_{23}H_{23}NO_6$ 409.1525, found 409.1529.

9,10,11,12-Tetramethoxy-4,5-(methylenedioxy)-*N*-methyl-benzo-phenanthridinium Chloride (14). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.046 g, 0.20 mmol) was added to a vigorously stirred mixture of **13** (0.050 g, 0.12 mmol) and 5% aqueous sodium hydroxide (1 mL) in benzene (5 mL).[17] The solution was stirred for 3 h at room temperature. The benzene layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic portion was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was dissolved in acetone (5 mL), and hydrochloric acid 12 N (1 mL) was added. The solvent was concentrated in vacuo to give a solid which was recrystallized from EtOAc/MeOH to give **14** (0.041 g, 75%) as a yellow solid: mp 175 °C dec; IR (KBr) 3000, 1581, 1473, 1406 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 3.95 (s, 3H), 4.10 (s, 3H), 4.28 (s, 3H), 4.30 (s, 3H), 4.86 (s, 3H), 6.25 (s, 2H), 7.46 (s, 1H), 8.06 (s, 1H), 8.08 (d, $J = 9.2$ Hz, 1H), 9.33 (d, $J = 9.2$ Hz, 1H), 9.83 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 159.3, 151.2, 150.8, 150.3, 150.2, 147.2, 147.1, 134.5, 134.1, 131.4, 126.1, 125.9, 122.6, 121.3, 116.9, 106.3, 105.2, 104.3, 63.4, 62.8, 62.4, 61.6, 52.5; exact mass calcd for $C_{23}H_{22}NO_6^+$ 408.1446, found 408.1442.

(17) DDQ has been employed to accomplish this reaction in related systems. See, for example: Hanaoka, M.; Kobayashi, N.; Shimada, K.; Mukai, C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 677.

Synthesis and Thermolysis of 4-Deuterioxy-2,3-dimethoxy-4-[3-[*N*-methyl-*N*-(1-naphthyl)amino]-1-propynyl]-2-cyclobuten-1-one (3a(OD)). A mixture of **3a** (0.05 g, 0.14 mmol) in dry toluene (10 mL) and deuterium oxide (2 mL) was stirred for 1 h at room temperature under nitrogen. The solvent was removed in vacuo to give a mixture of **3a-(OD)** and the starting **3a** in a respective ratio of 1:0.7 as evidenced by mass spectral analysis. Specifically, the deuterium enrichment was confirmed from the EI mass spectrum of the mixture which showed the *m*/*z* peaks at 337.4 and 338.4 to be 42.5 and 57.5%, respectively, after correction for the M + 1 peak of the protio compounds. In addition, the IR spectrum of the mixture showed an OD stretch at 2505 cm^{-1}.

The above mixture was added dropwise (N_2) to refluxing dry toluene (100 mL) over a 1.5 h period and the resulting solution was refluxed for an additional 20 min. The solution was cooled to room temperature and concentrated in vacuo. ^{1}H NMR and mass spectra of the crude reaction showed the exclusive formation of **4a** and no deuteriun incorporation.

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Supporting Information Available: Experimental procedures, ^{13}C NMR spectra for all new compounds as well as X-ray crystallographic data for compounds **8** and **10** are available free of charge via the Internet at http://pubs.acs.org.

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