Synthesis of the Tetracyclic Carbon Core of Menogaril Utilizing the Benzannulation Reaction of a Fischer Carbene Complex and an Alkyne

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The synthesis of the 2-bromoanthracyclinone **3** containing the tetracyclic core of menogaril is achieved with a strategy that is formulated around the benzannulation reaction of a Fischer carbene complex and an alkyne. This benzannulation requires a 2,5-dimethoxyphenyl carbene complex that bears an additional functional group at the 4-position that is the nascent 2-bromo substituent in **3**. The evaluation of 4-bromo- and 4-trimethysilyl-substituted complexes with 1-pentyne revealed that the benzannulation was more efficient with the silyl complex. The synthesis of **3** is achieved with methoxy and acetoxy substituents at the C-9 position, which begins with the methoxy- and benzyloxy-substituted alkynes **14** and **30** that contain the A ring of the menogaril core. The closure of the last ring is accomplished by a Friedel−Crafts reaction on an in situ generated acid chloride. Adjustment of the oxidation states of the B and C rings failed according to procedures that had been developed in model studies. This was accomplished in an unexpected fashion with novel bromination reactions that occurred at a benzylic position with the C-9 methoxyl derivative and alpha to a ketone in the C-9 acetoxy derivative.

Introduction

The anthracycline antitumor antibiotics are among the most important clinical agents used in cancer chemotherapy.[1] Menogaril is a semisynthetic derivative of the natural product nogalamycin and has activity against tumor systems that is substantially greater than nogalamycin.[2] The activity of menogaril is somewhat superior to that of adriamycin, the most widely used anthracycline, and at the same time is much less cardiotoxic than adriamycin. Recent studies have revealed that menogaril has unique aspects as a member of the anthracycline family. Menogaril has been shown to bind in the major groove of DNA, whereas all other anthracyclines have been found to bind in the minor groove.[3] Menogaril has been shown to poison topoisomerase II but not topoisomerase I, while its parent, nogalamycin, poisons topoisomerase I but not II.[4] Recently it has been reported that menogaril is different from other anthracyclines in that it is active after oral administration.[5] Oral treatment with menogaril is expected to be useful for outpatient treatment of lymphoma and breast cancer, and this is supported by the finding that the combination of cyclophosphamide, menogaril, and 5-fluorouracil is superior to the first choice in breast cancer chemotherapy of cyclophosphamide, adriamycin, and 5-fluorouracil as measured by activity against human breast cancer xenographs in mice.[6]

The biological activity of menogaril has stimulated the development of various strategies for the synthesis of menogaril and analogues. There have been two total syntheses of menogaril reported[7] along with a number of other synthetic studies.[8] Our approach to the synthesis of menogaril involves the bromoanthracyclinone **3** as an advanced intermediate which contains the tetracyclic core of menogaril. Introduction of the sugar unit is planned by a Grignard addition, and introduction of the C-9 methoxyl group will be accomplished as previously described.[7] In this paper, we report the utilization of the benzannulation of the highly functionalized carbene complex **4** with alkyne **5** as the key step in the synthesis of **25** and **40**, the methyl and acetoxy analogues of **3,** respectively (Scheme 1).

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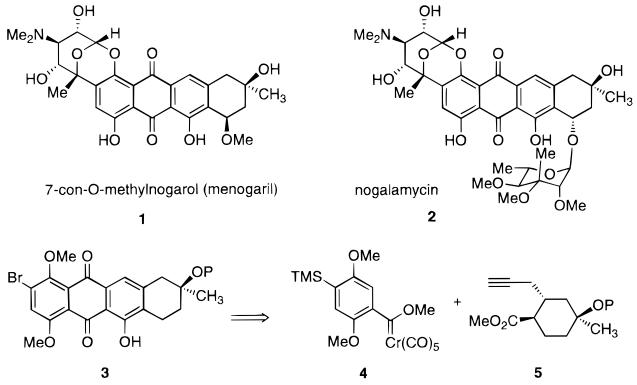
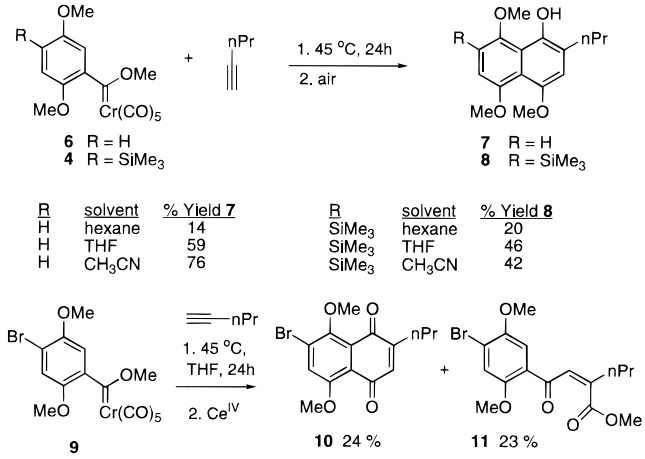
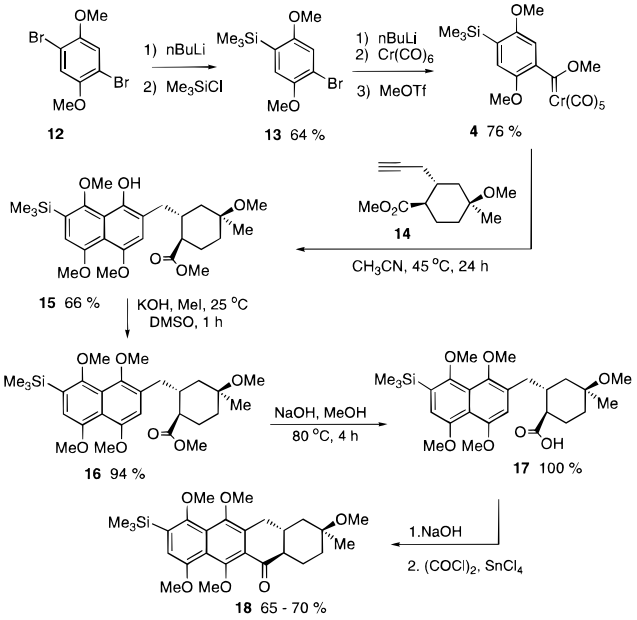
Scheme 1



Scheme 2



Scheme 3



Synthesis of Menogaril Core 25

From the systematic studies by our group and others it is known that the product distribution of the benzannulation reaction depends on many factors.[9−11] One of these factors is the electronic nature of the substituents on the arene ring of the carbene complex. Therefore, in an initial consideration of options for the synthesis of **3** via a benzannulation reaction, a model study was performed that evaluated the reaction of 1-pentyne with the carbene complexes **4**, **6**, and **9**, which contain a trimethylsilyl, hydrogen, or bromine substituent para to the carbene carbon, respectively. Interestingly, it was found that for carbene complex **6** (R = H) the yield of the phenol product increased as the polarity of the solvent increased. The highest yield of 76% was obtained in acetonitrile, and the yield dropped to 14% in hexane. Other products were observed by TLC and NMR, but no attempt was made to characterize them. The benzannulation reaction has been extensively studied by several groups over the last twenty years and, with only two known exceptions,[9,11c] higher yields of phenol products are found in nonpolar solvents such as hexane and benzene. At this time it is not known why the presence of the 2,5-dimethoxy substituents in complex give rise to the third known example of this effect.[12] An increase in the yield of the phenol product was also seen for the reaction of complex **4** bearing the para trimethylsilyl group upon going from hexane to THF but not from THF to acetonitrile. In the case of the reaction with carbene complex **9**, the naphthol product was oxidized to the quinone **10** due to the difficulties in purifying the naphthol. The reaction of the para-bromo complex **9** in THF gave a much lower yield than the para-trimethylsilyl complex **4** (24 vs 46%). One of the side products in the reaction of complex **9** was the keto ester **11**, which is indicative of furan formation (Scheme 2).[9−11] On the basis of the above results, it was decided to pursue the synthesis of **3** with the para-trimethylsilyl complex **4**.

It was satisfying to find that the benzannulation of the para-trimethylsilyl complex **4** with alkyne **14**[13] gave a higher yield than did the model study with 1-pentyne. In this reaction, acetonitrile was the superior solvent giving the desired naphthol product **15** in 66% yield along with two other products, which were not characterized. The same reaction in THF gave the phenol **15** in only 46% yield. Since the unprotected naphthol was not compatible with Friedel−Crafts reaction conditions,[14] the naphthol **15** was methylated with potassium hydroxide and methyl iodide in DMSO at room temperature to give **16** in 94% isolated yield.[15] Hydrolysis of compound **16** under the conditions in Scheme 3 gave a quantitative conversion to the acid **17** in preparation for the Friedel−Crafts reaction. However, due to the acid-sensitive TMS and tertiary methyl ether groups, standard Friedel−Crafts cyclization conditions were not successful. In addition, acid **17** could not be directly converted to the acid chloride in a clean fashion. The acid chloride was generated by treatment of the acid with 1 equiv of NaOH followed by addition of oxalyl chloride. A variety of Lewis acids were screened for the Friedel−Crafts cyclization on this in situ generated acid chloride ($FeCl_3$,$TiCl_4$, $ZnCl_2$,

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(12) The benzannulation of the 2,5-dimethoxy complex **6** has been previously reported, but only in THF solvent.[10]

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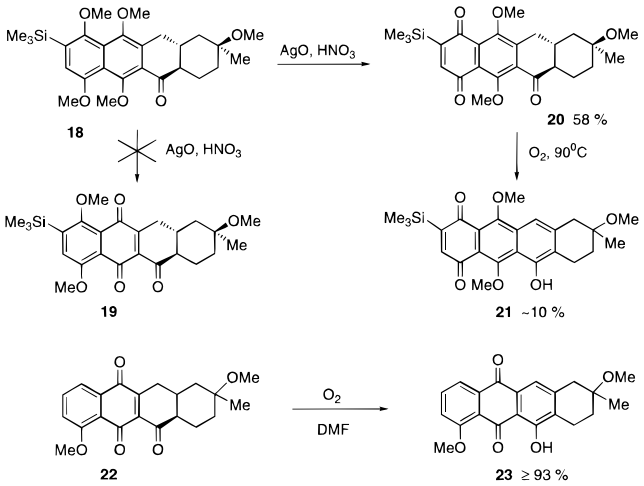
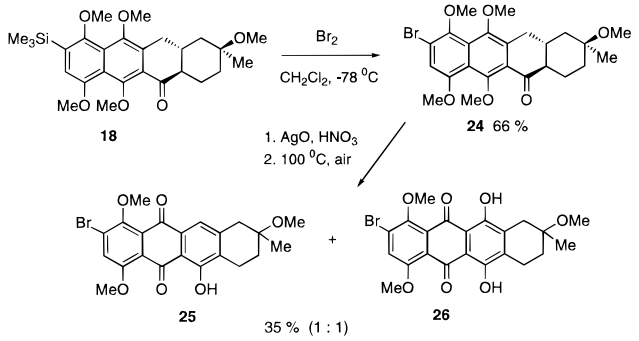
Scheme 4



Scheme 5



$(CF_3CO)_2O$, $HgCl_2$, $AlCl_3$, TMSOTf), but unfortunately all of the yields were in the range 20−40%. Milder reagents such as polyphosphorus ester (PPE) afforded only 10% of the desired product **18**.[16] All of the side products that were isolated had lost the tertiary methyl ether, and this is believed to be due to elimination under the reaction conditions. It was finally found that the cyclization product **18** could be obtained in 65−70% yield by using $SnCl_4$ on the in situ generated acid chloride if a nonaqueous workup was employed.

Finishing the synthesis of the tetracyclic core of menogaril **25** from the intermediate **18** required an adjustment of the oxidation states of the B and C rings. This was initially attempted by a two-step approach that had been successful in model studies.[13] The first step involved the oxidation of the C ring with silver oxide in nitric acid.[17] This gave a 58% yield of a compound that was expected to be the quinone **19**. This product was originally assigned the structure **19**; however, it was surprising to find that the second oxidation of the B ring was quite difficult. This oxidative aromatization by molecular oxygen[18] gave more than five products, and the desired product was obtained in only 10% yield. Other oxidizing agents such as DDQ[19] or SeO_2[20] failed to improve the yield. This failure was surprising given the ease with which the B ring in the model compound **22** could be oxidized.[13] Furthermore, dehydrogenation with Pd−C was attempted under many different conditions, but in each case only the starting material was recovered.[19,21] All of these results taken together led to the suspicion that the structural assignment for the oxidation product of **18** may not have been made correctly. A single crystal of this compound was grown in pentane, and an X-ray diffraction study gave an unexpected but perhaps not surprising result: the oxidation of **18** occurred at the D ring instead of the C ring to give the quinone **20** (Scheme 4).

The selective oxidation of intermediate **18** at the D ring presumably occurred as a result of the high electron density on this ring, which results from the presence of two methoxyl and one trimethylsilyl group. If this is correct, then it may be possible to direct the oxidation of **18** by decreasing the electron density of the D ring by exchanging the trimethylsilyl group for a bromide. This exchange reaction was already designed into the retrosynthetic plan to provide a functional handle for the installation of the amino sugar subunit at a later step, and therefore, this change in the synthesis would not increase the number of synthetic steps. The reaction of bromine with compound **18** in CH_2Cl_2 at −78 °C gave the desired product **24** in 66% yield (Scheme 5).[22] The oxidation of **24** with AgO/HNO_3 indeed only took place at the C ring. Subsequent air oxidation of this quinone gave the desired product **25** along with the inseparable overoxidation product **26** (35% yield, 1:1). In the synthesis of a similar model compound this overoxidation could be avoided by performing the air oxidation without solvent,[13] but unfortunately it was not possible to minimize the side product **26** by this procedure.

Despite the fact that the oxidation of **24** occurred at the C ring, the overall conversion of **18** to **25** (11%) was not synthetically viable. This problem was solved by the following discovery. It was found that the reaction of 2 equiv of bromine with compound **18** in a nonpolar solvent such as pentane at 0 °C gave the benzylic bromination product **27** in 51% yield, while the same reaction of **18** with bromine in polar solvent such as CH_2Cl_2 or HOAc at 0 °C gave the dibromo product **28** in 60−70% yield (Scheme 6). This dibromo compound **28** could be generated from **18** by either of the two methods outlined in Scheme 6 in which each bromine was introduced in a single step and in either order. The best method for the synthesis of compound **28** involved the two-step protocol.

The reaction of bromine with compound **18** in pentane at 0 °C provided **27**, which, without purification, was treated immediately with bromine in CH_2Cl_2 at −78 °C to provide the product **28** in overall 70% yield. Oxidation of compound **28** with AgO in HNO_3 gave the quinone **29**, which could not be isolated and subsequently eliminated HBr to afforded the final product **25** in 69% yield from **28**. Apparently, the elimination is driven by the thermodynamic favorability of the aromatic B ring, which is apparently greater than that for **28**. No overoxidation product was observed for this reaction. The discovery of the benzylic bromination obviates the final aromatization step in **24**, which requires more forcing reaction conditions and therefore provides a more efficient synthesis of the target tetracycle **25**.

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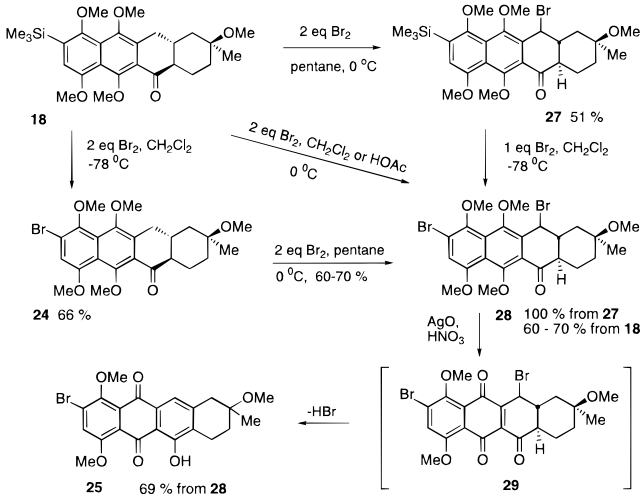
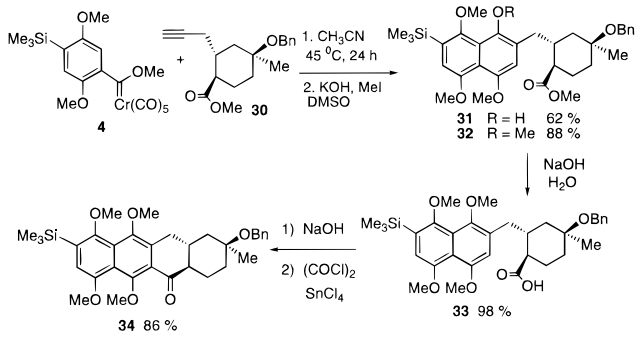
(22) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

Scheme 6



Scheme 7

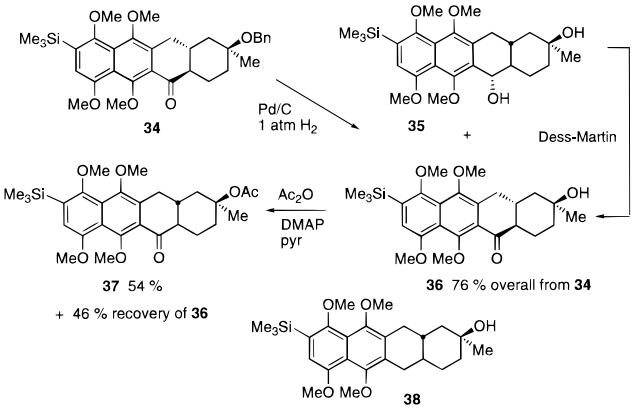


Synthesis of Menogaril Precursor 40

The reaction of carbene complex **4** and alkyne **30**[13] in acetonitrile, like the same reaction with alkyne **14**, gave the desired benzannulation product in good yields. Over a number of runs the yields of naphthol **31** varied from 59 to 68%. Two byproducts were isolated, and their spectroscopic data showed that they were likely alkyne oligomers. The naphthol **31** was protected as the methyl ether by using the same method as developed for naphthol **15**. Hydrolysis of ester **32** took much longer than for the analogous ester **16**. After **32** was refluxed in NaOH and MeOH at 80 °C for 36 h and neutralized with concentrated HCl, the corresponding acid was obtained in near quantitative yield. The Friedel−Crafts cyclization reaction proceeded very smoothly utilizing the conditions optimized for **17** and provided the tetracyclic intermediate **34** in 86% yield (Scheme 7). Whereas methoxyl elimination products were observed as side products in the Friedel−Crafts reaction of **17**, products resulting from the elimination of the benzyloxy group were not detected in the reaction of **33**.

The benzyl protecting group was removed prior to the oxidation of the B ring since it was found that if these steps were reversed, the benzyl group could not be removed without substantial decompositon of the starting material. Thus, compound **34** was treated with Pd−C under H_2, which was found to give the desired alcohol **36**. If the mixture was stirred too long (12 h), a significant amount of the reduced product **38** was isolated (64%). Shortening the reaction time to 1 h eliminated **38**; however, even with a 1 h reaction time, the desired product **36** was accompanied by the diol **35** on some occasions. The diol **35** could be oxidized to **36** by the Dess−Martin reaction, and by so doing the tertiary alcohol **36** could be prepared in 76% yield. The use of hydrogen transfer hydrogenations (such as ammonium formate)[23] did not improve the total yield from **34**. The diol **35** was always observed when **34** was treated with ammonium formate (15−32 equiv) on Pd/C in MeOH at 90 °C for 1−2 h. It was surprising to encounter difficulty in the acylation of the alcohol **36** with DMAP/pyridine or $(^iPr)_2NEt/Ac_2O$.[24] When a catalytic amount of DMAP was used, only the starting material was recovered after chromatography. Even with a large excess of DMAP (4 equiv), this reaction could not be driven to completion: the acetate **37** was isolated in 54% yield and 46% of **36** was recovered. However, when this starting material was recycled, efficient throughput to the acetate **37** could be achieved (Scheme 8).

Scheme 8



Completion of the synthesis of the target tetracycle **40** from intermediate **37** requires only the oxidation of the B ring and the substitution of silicon with bromine. Given the success in effecting both steps via bromination in the synthesis of **25** from **18,** this was the first and only approach we investigated for **37**. In principle, this dibromination could be carried out on either the alcohol **36** or the acetate **37**. However, attempts to dibrominate the alcohol **36** ended with the formation of a complex mixture of products. Hence, the focus of the dibromination became the acetate **37**. Given the experience gained in the bromination of **18**, it was expected that the treatment of **37** with bromine in pentane at 0 °C and then with bromine in methylene chloride at −78 °C should provide the dibromide **41**. However, the crude reaction mixture was found to contain a mixture of compounds none of which were the desired product **41** nor the starting material. Nonetheless, when this mixture was subjected to oxidation with AgO/HNO_3, the target tetracyclic compound **40** was isolated in 48% overall yield from **37** (Scheme 9). The mixture of isomers obtained from the bromination of **37** in CH_2Cl_2 is tentatively assigned as **39** where bromination of the ketone function in **37** occurred. Since the bromine in **39** can be eliminated to form the aromatic B ring, this bromination of the ketone, like the benzylic bromination of **18** (Scheme 6), serves to avoid the difficult aromatization step that was encountered in the synthesis of **24** by oxidative methods (Scheme 5).

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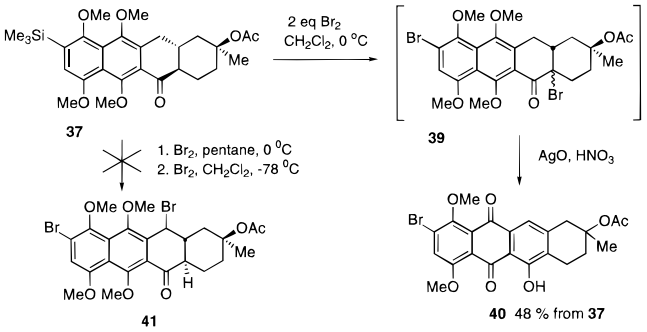
Scheme 9



Summary

A synthesis of the 2-bromoanthracyclinone **40** was achieved in 10 steps and 8% overall yield from 2,5-dibromo-1,4-dimethoxybenzene. The key steps are the benzannulation of the 2,4-dimethoxy-4-*p*-(trimethylsilyl)-phenyl carbene complex **4** with alkyne **30**, the subsequent Friedel−Crafts cyclization to give the tetracyclic intermediate **34**, and a novel bromination that provides the proper final oxidation state of the B ring of the anthracyclinone core. The results of this study demonstrate that the benzannulation reaction of Fischer carbene complexes can provide an attractive strategy for the synthesis of menogaril.

Experimental Section

Unless otherwise stated, all chemicals were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran, benzene, and diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. Methylene chloride, diisopropylamine, and HMPA were distilled from calcium hydride. Some of the high-resolution mass spectra were obtained at the Midwest Center for Mass Spectrometry in Lincoln, NE. Elemental analysis were done by Galbraith Laboratories in Knoxville, TN.

Synthesis of 1-Bromo-2,5-dimethoxy-4-(trimethylsilyl)-benzene 13. A solution of 1,4-dibromo-2,5-benzene (7.15 g, 24.15 mmol) in 150 mL of THF was cooled to −78 °C under a nitrogen atmosphere. This solution was treated with ^{n}BuLi (15.9 mL, 1.6 M, 1.1 equiv) and stirred for 1 h. Freshly distilled trimethylsilyl chloride (6.13 mL, 48.30 mmol, 2 equiv) in 30 mL of THF was added, and the mixture was stirred at −78 °C for 50 min. The cold bath was removed and the solution was stirred for additional 20 min before 5 mL of H_2O was added. The solvent was removed, and the residue was washed with brine and extracted three times with ether. The organic layer was dried over $MgSO_4$ and filtered through Celite. Removal of solvent gave the desired product **13** (6.77 g, 97%), which appeared to be a single compound by ^{1}H NMR. However, further purification by chromatography on silica gel with a 1:1:60 mixture of ether/dichloromethane/hexane as eluent gave 4.50 g of pure **13** in 64% yield, a 5% yield of 1,4-bis(trimethylsilyl)-2,5-dimethoxybenzene, and a 10% yield of 1-(trimethylsilyl)-2,5-dimethoxybenzene. Spectral data for **13**: ^{1}H NMR ($CDCl_3$) δ 0.28 (s, 9 H), 3.76 (s, 3 H), 3.86 (s, 3 H), 6.90 (s, 1 H), 6.99 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ −0.40, 56.60, 57.84, 114.15, 115.96, 119.60, 129.07, 150.78, 159.47; mass spectrum *m*/*z* (% rel intensity) 290 M^+ (^{81}Br), (66), 245 (100). Anal. Calcd for $C_{11}H_{17}O_2SiBr$: C, 45.68; H, 5.92. Found: C, 45.55; H, 5.70. White solid, mp 48−49 °C. R_f = 0.15 (ether/dichloromethane/hexane = 1:1:60).

Synthesis of (Methoxy(2,5-dimethoxy-4-(trimethylsilyl))phenylmethylene)pentacarbonylchromium(0) (4). The aryl bromide **13** (6.12 g, 21.18 mmol) was dissolved in 100 mL of THF and cooled to −78 °C. A solution of ^{n}BuLi (13.90 mL, 1.6 M, 22.24 mmol, 1.05 equiv) was added, and the mixture was stirred for 40 min. The solution was transferred via cannula to a solution of $Cr(CO)_6$ (4.66 g, 21.18 mmol, 1 equiv) in 100 mL of THF at room temperature and stirred for 1.5 h. The solvent was removed, and 100 mL of dichloromethane was added at 0 °C. Methyl triflate (2.64 mL, 23.30 mmol, 1.1 equiv) was added, and the solution was stirred for 10 min. The reaction was quenched with H_2O and extracted with dichloromethane. The organic layer was washed with brine. After removal of the solvent, the residue was chromatographed with a 1:1:30 mixture of ether/dichloromethane/hexane as eluent to give 7.15 g (76%) of **4** as a red solid. Spectral data for **4**: ^{1}H NMR ($CDCl_3$) δ 0.30 (s, 9 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.20 (br s, 3 H), 6.26 (s, 1 H), 6.86 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ −0.31, 56.42, 66.16, 104.15, 118.18, 130.27, 142.30, 158.99, 216.82, 225.81, 354.58; IR (neat) 1930 vs cm^{-1}; mass spectrum *m*/*z* (% rel intensity) 444 M^+ (6), 416 (7), 388 (15), 360 (6), 332 (66), 304 (100). Anal. Calcd for $C_{18}H_{20}CrO_8Si$: C, 48.65; H, 4.54. Found: C, 48.33; H, 4.57. Red solid, mp 75−76 °C (dec). R_f = 0.27 (ether/dichloromethane/hexane = 1:1:30).

Preparation of 2-(Methyl 4-methoxy-4-methyl-2-methylene-1-cyclohexane carboxylate)-1-hydroxy-4,5,8-trimethoxy-7-(trimethylsilyl)naphthalene (15). A mixture of carbene complex **4** (0.8678 g, 1.95 mmol) and alkyne **14**[13] (0.4816 g, 2.15 mmol, 1.1 equiv) was diluted with 3.90 mL of CH_3CN to give a 0.5 M solution in carbene complex. This solution was added to a single-necked flask in which the ground glass joint had been replaced with a threaded high-vacuum Teflon stopcock and deoxygenated by the freeze−thaw method (3 cycles, −196−25 °C). The flask was sealed under 1 atm of argon at 25 °C and heated to 45 °C for 36 h. The reaction mixture was strirred open to the air for 30 min. Solvent was removed, and chromatography on silica gel with ethyl acetate/petroleum ether (1:5) gave 0.65 g of **15** as a yellow viscous oil in 66% yield. Spectral data for **15**: ^{1}H NMR ($CDCl_3$) δ 0.41 (s, 9 H), 1.03 (s, 3 H), 1.20−1.23 (m, 1 H), 1.70−1.73 (m, 1 H), 1.82−1.89 (m, 4 H), 2.15−2.19 (m, 1 H), 2.36−2.39 (m, 1 H), 2.65 (dd, 1 H, J = 9.6, 13.3 Hz), 2.72 (dd, 1 H, J = 5.5, 13.3 Hz), 2.98 (s, 3 H), 3.65 (s, 3 H), 3.77 (s, 3 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 6.71 (s, 1 H), 6.76 (s, 1 H), 9.50 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.87, 25.13, 25.66, 32.34, 35.02, 35.17, 37.12, 42.35, 49.15, 51.67, 57.74, 58.92, 65.52, 74.00, 111.22, 114.75, 119.59, 120.41, 122.86, 127.82, 145.35, 149.64, 153.94, 155.82, 176.01; IR (CH_2Cl_2) 1730 s cm^{-1}; mass spectrum *m*/*z* (% rel intensity) 505 $(M + 1)^+$ (100); *m*/*z* calcd for $C_{27}H_{40}O_7Si$ 504.2544, measured 504.2543. Anal. Calcd for $C_{27}H_{40}O_7Si$: C, 64.26; H, 7.99. Found: C, 64.00; H, 8.08. R_f = 0.13 (ethyl acetate/petroleum ether = 1:5).

Preparation of 2-(Methyl 4-methoxy-4-methyl-2-methylene-1-cyclohexanecarboxylate)-1,4,5,8-tetramethoxy-7-(trimethylsilyl)naphthalene (16). Powdered KOH (0.347 g, 6.196 mmol, 4 equiv) was dissolved in DMSO (3 mL) along with compound **15** (0.78 g, 1.548 mmol) and MeI (2.3 mL, large excess). After stirring for 5 h at room temperature, ether was added and the resulting solution was washed four times with water. The aqueous layer was extracted four times with CH_2Cl_2. The organic layer was combined, and the solvents were removed. Elution with ether through a short silica gel column gave 0.75 g of **16** as a yellow viscous oil in 94% yield. Spectral data for **16**: ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 9 H), 0.99 (s, 3 H), 1.20−1.25 (m, 1 H), 1.74−1.90 (m, 5 H), 2.16 (td, 1 H, J = 11.0, 2.5 Hz), 2.30−2.45 (br m, 1 H), 2.68−2.97 (m, 2 H), 2.97 (s, 3 H), 3.64 (s, 3 H), 3.69 (s, 3 H), 3.70 (s, 3 H), 3.92 (s, 3 H), 3.93 (s, 3 H), 6.72 (s, 1 H), 6.82 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.58, 25.40, 26.22, 34.77, 35.85, 36.21, 39.53, 49.11, 50.12, 52.18, 57.97, 58.10, 62.60, 63.67, 73.01, 110.87, 112.60, 121.37, 123.99, 129.91, 130.26, 147.40, 153.50, 153.68, 155.71, 177.22; IR (CH_2Cl_2) 1731 s cm^{-1}; mass spectrum *m*/*z* (% rel intensity) 518 M^+ (100). Anal. Calcd for $C_{28}H_{42}O_7Si$: C, 64.83; H, 8.16. Found: C, 64.74; H, 8.28. R_f = 0.13 (ethyl acetate/petroleum ether = 1:5).

Preparation of 2-(4-Methoxy-4-methyl-2-methylene-1-cyclohexanecarboxylic acid)-1,4,5,8-tetramethoxy-7-(trimethylsilyl)naphthalene (17). A sample of compound **16** (100 mg, 0.193 mmol) was dissolved in 8 mL of MeOH and treated with 4 mL of 2 N aqueous NaOH, and the resulting solution was refluxed at 80 °C for 4 h. The solution was cooled

to room temperature and neutralized with concentrated HCl. The volatiles were removed, and the residue was extracted with ether. The extract was stripped of solvent, and the residue was loaded onto a short silica gel column; elution with ether gave the desired product **17** (96 mg) as a yellow foamy solid in quantitative yield. Spectral data for **17**: ^{1}H NMR ($CDCl_3$) δ 0.38 (s, 9 H), 1.01 (s, 3 H), 1.20−1.30 (m, 1 H), 1.82−1.92 (m, 5 H), 2.18−2.22 (m, 1 H), 2.32−2.41 (m, 1 H), 2.73−2.75 (m, 1 H), 2.83−2.86 (m, 1 H), 2.97 (s, 3 H), 3.64 (s, 3 H), 3.68 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 6.72 (s, 1 H), 6.80 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.58, 25.37, 26.27, 34.66, 35.62, 36.16, 39.23, 49.10, 49.91, 57.99, 58.13, 62.57, 63.72, 73.10, 110.94, 112.72, 121.34, 124.03, 129.96, 130.16, 147.46, 153.48, 153.70, 155.76, 183.20; IR (CH_2Cl_2) 3300−3200 br m, 1730 s cm^{-1}; mass spectrum *m/z* (% rel intensity) 504 M^+ (100).

Preparation of 1,4,5,9,12-Pentamethoxy-9-methyl-2-(trimethylsilyl)-6a,7,8,10,10a,11-hexahydronaphthacen-6-one (18). The acid **17** (74 mg, 0.1468 mmol) was treated with 1 equiv (0.1468 mmol) of NaOH (1.48 mL of a 0.09925 N aqueous solution), and the resultant sodium salt was dried under high vacuum for 12 h. The salt was dissolved in 15 mL of freshly distilled benzene, and 0.25 mL of pyridine was added at 0 °C followed by addition of 0.16 mL of freshly distilled oxalyl chloride (12.6 equiv). Gas evolution subsided after 10 min before 34.4 μL of $SnCl_4$ (2 equiv) was added. The ice bath was removed, and the solution was stirred for 15 min. The mixture was quickly put onto a Et_3N-pretreated short column and washed with ether. A yellow solution was obtained. The solvent was removed, and chromatography (ethyl acetate/petroleum ether = 1:5) gave the desired product **18** (48.0 mg) in 67% yield: ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 9 H), 1.18 (s, 3 H), 1.22−1.29 (m, 2 H), 1.67−1.71 (m, 1 H), 2.02−2.20 (m, 5 H), 2.48 (dd, 1 H, J = 12.2, 17.4 Hz), 3.16 (s, 3 H), 3.36 (dd, 1 H, J = 3.9, 17.4 Hz), 3.683(s, 3 H), 3.685 (s, 3 H), 3.89 (s, 3 H), 3.95 (s, 3 H), 6.82 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.44, 21.88, 25.45, 31.68, 34.25, 34.45, 44.95, 49.27, 53.06, 57.97, 61.99, 63.81, 64.11, 73.14, 112.82, 124.02, 124.82, 125.99, 132.21, 133.02, 147.84, 154.64, 155.16, 156.03, 199.82; IR (CH_2Cl_2) 1638 s cm^{-1}; mass spectrum *m/z* (% rel intensity) 486 M^+ (100). Anal. Calcd for $C_{27}H_{38}O_6Si$: C, 66.63; H, 7.87. Found: C, 66.46; H, 7.95. Yellow solid, mp 170−171 °C. R_f = 0.10 (ethyl acetate/petroleum ether = 1:5).

Spectral Data of 5,9,12-Trimethoxy-9-methyl-2-(trimethylsilyl)-6a,7,8,10,10a,11-hexahydronaphthacene-1,4,6-trione (20). To a solution of 80 mg (0.165 mmol) of compound **18** in 21 mL of acetone was added 408 mg (20 equiv) of silver oxide and 9.86 mL of 0.5 N aqueous HCl (30 equiv), and the resultant mixture was stirred for 4 h at room temperature. The acetone and water were removed by evaporation, and the residue was extracted into ether and dried over $MgSO_4$. The ^{1}H NMR spectrum of the crude reaction mixture revealed that **20** was the major product and also the presence of a minor product, which was tentatively identified as **19** (**20**:**19** = 5:1). After removal of solvent, the residue was loaded onto a silica gel column, and elution with ethyl acetate/hexanes (1:5) gave a 58% yield of **20** as red-brown crystals. Spectral data for **20**: R_f = 0.09 (ethyl acetate/petroleum ether = 1:5); ^{1}H NMR ($CDCl_3$) δ 0.33 (s, 9 H), 1.18 (s, 3 H), 1.22−1.29 (m, 2 H), 1.67−1.70 (m, 1 H), 1.94−1.98 (m, 1 H), 2.03−2.08 (m, 2 H), 2.10−2.25 (m 2 H), 2.44 (dd, 1 H, J = 11.3, 17.2 Hz), 3.14 (s, 3 H), 3.23 (dd, 1 H, J = 4.1, 17.2 Hz), 3.81 (s, 3 H), 3.92 (s, 3 H), 6.89 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ −1.64, 20.59, 24.61, 31.37, 33.15, 44.17, 48.56, 51.53, 61.65, 63.42, 72.19, 125.80, 126.22, 133.10, 146.21, 146.83, 153.31, 153.91, 156.20, 182.90, 188.00, 197.75; IR (neat) 1700 vs, 1657 vs cm^{-1}. The structure of **20** was confirmed by X-ray diffraction. Lists of the atomic coordinates, thermal parameters, bond distances, and bond angles have been deposited with the Cambridge Crystallographic Database, Cambridge, England.

Preparation of 2-Bromo-1,4,5,9,12-pentamethoxy-9-methyl-6a,7,8,10,10a,11-hexahydronaphthacen-6-one (24) and 11-Bromo-1,4,5,9,12-pentamethoxy-9-methyl-2-(trimethylsilyl)-6a,7,8,10,10a-pentahydronaphthacen-6-one (27). Compound **18** (41.6 mg, 0.08559 mmol) was dissolved in 10 mL of CH_2Cl_2 and cooled to −78 °C under a N_2 atmosphere. Two equivalents of bromine (0.2879 M in CH_2Cl_2, 0.59 mL) was added dropwise. The mixture was stirred at this temperature for 2.5 h and then filtered through a layer of Celite and of triethylamine-treated silica gel in a sintered glass funnel. The contents of the funnel was washed several times with ether. After removal of the solvent, the residue was chromatographed on silica gel with EtOAc/petroleum ether (1:5) to give 28.1 mg of the desired product **24** in 66% yield as a yellow solid. The other fractions collected indicated that an equal amount of the dibromide **28** and the starting material **18** were present (∼20% each). Spectral data for **24**: mp 107 °C (dec); R_f = 0.09 (ethyl acetate/petroleum ether = 1:5); ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.28−1.33 (m, 2 H), 1.69−1.72 (m, 1 H), 2.05−2.18 (m, 5 H), 2.51 (dd, 1 H, J = 11.9, 17.1 Hz), 3.17 (s, 3 H), 3.37 (dd, 1 H, J = 4.1, 17.2 Hz), 3.76 (s, 3 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 3.95 (s, 3 H), 6.94 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.18, 24.68, 31.01, 33.44, 33.75, 44.14, 48.51, 52.39, 56.91, 61.54, 61.59, 63.46, 72.36, 110.81, 118.38, 121.58, 124.37, 127.43, 133.50, 145.34, 147.11, 155.00, 155.66, 198.66; IR (CH_2Cl_2) 1688 s cm^{-1}; mass spectrum *m/z* (% rel intensity) 494 M^+ (^{81}Br) (100).

If the reaction is carried out in pentane at 0 °C with 2 equiv of bromine for 1 h, the major product of the reaction was the benzyl bromide **27** (51%), which was formed along with a small amount of the dibromide **28**. Spectral data for **27**: yellow viscous oil; R_f = 0.25 (EtOAc/petroleum ether = 1:5); ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 9 H), 1.25 (s, 3 H), 1.67 (t, 1 H, J = 12.0 Hz), 1.80 (dt, 1 H, J = 3.5, 13.7 Hz), 1.85−1.92 (m, 1 H), 2.01−2.07 (m, 1 H), 2.13−2.22 (m, 2 H), 2.33−2.37 (m, 1 H), 2.59 (dd, 1 H, J = 11.5, 16.5 Hz), 3.18 (s, 3 H), 3.20−3.22 (m, 1 H), 3.69 (s, 3 H), 3.70 (s, 3 H), 3.90 (s, 3 H), 3.97 (s, 3 H), 6.82 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.32, 24.83, 29.20, 31.14, 31.55, 37.30, 40.43, 49.17, 57.88, 61.74, 63.44, 63.68, 72.90, 75.45, 112.95, 122.46, 123.84, 126.05, 130.30, 133.48, 147.73, 154.57, 155.10, 158.14, 191.10; IR (CH_2Cl_2)1690 s cm^{-1}; mass spectrum *m/z* (% rel intensity) 566 M^+ (^{81}Br) (20), 486 (100).

Preparation of 2,11-Dibromo-1,4,5,9,12-pentamethoxy-9-methyl-6a,7,8,10,10a-pentahydronaphthacen-6-one (28). A mixture of 12.2 mg of compound **18** (0.02510 mmol), 50 mg of solid K_2CO_3, and 8 mL of pentane was cooled to 0 °C under N_2. Two equivalents of bromine (0.174 mL of a 0.2879 M solution in CH_2Cl_2, 0.050 mmol) was added dropwise, followed by addition of 0.3 mL of CH_2Cl_2. The mixture was stirred for 1 h and quickly filtered through a layer of Celite and of triethylamine-treated silica gel in a sintered glass funnel. The contents of the funnel was washed several times with ether. All washes were combined, and the solvent was removed in vacuo. The residue was taken up in 10 mL of CH_2Cl_2, and the resulting solution was cooled to −78 °C under N_2. Bromine (0.096 mL, 0.2879 M in CH_2Cl_2, 0.02764 mmol, 1.1 equiv) was added dropwise. The solution was stirred for 30 min and again filtered through a Et_3N-pretreated silica gel/Celite funnel. After removal of the solvent, the residue was chromatographed on silica gel with EtOAc/petroleum ether (1:5) to give 10.1 mg of desired product **28** in 70% yield as a yellow oil. Dibromide **28** can be obtained from **27** in quantitative yield by bromination in CH_2Cl_2 at −78 °C and in 60−70% yield by the bromination of **24** in pentane at 0 °C. Spectral data for **28**: R_f = 0.16 (EtOAc/petroleum ether = 1:5); ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.68 (t, 1 H, J = 11.9 Hz), 1.80 (td, 1 H, J = 13.8, 3.3 Hz), 1.84−1.91 (m, 1 H), 2.02−2.05 (m, 1 H), 2.14−2.20 (m, 2 H), 2.32−2.36 (m, 1 H), 2.64 (dd, 1 H, J = 11.5, 17.7 Hz), 3.18 (s, 3 H), 3.21 (d, 1 H, J = 4.6 Hz), 3.77 (s, 3 H), 3.81 (s, 3 H), 3.88 (s, 3 H), 3.96 (s, 3 H), 6.96 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.21, 28.70, 30.50, 30.83, 36.62, 39.84, 48.60, 56.98, 61.51, 61.94, 62.88, 72.26, 74.61, 111.11, 118.82, 121.83, 122.16, 127.55, 131.65, 145.46, 147.09, 154.97, 157.75, 190.15; IR (CH_2Cl_2) 1732 m, 1689 m cm^{-1}; mass spectrum *m/z* (% rel intensity) 574 M^+ (^{81}Br) (15), 492 (100).

Preparation of 2-Bromo-6-hydroxy-1,4,9-trimethoxy-9-methyl-7,8,10-trihydronaphthacene-5,12-dione (25). A mixture of compound **28** (28.0 mg, 0.04895 mmol), nitric acid (3.4 mL, 0.5 N, 34.7 equiv), and silver oxide (140 mg, 23 equiv) was allowed to stir for 3.5 h at room temperature in the dark under N_2. The solvent was removed, the residue was extracted

with ether, and the organic layer was dried over $MgSO_4$. The solvent was removed, and the product purified by silica gel chromatography with EtOAc/petroleum ether (1:5) to give 15.5 mg of **25** as a red solid in 69% yield. Spectral data for **25**: mp 181−182 °C, R_f = 0.12 (EtOAc/petroleum ether = 1:5); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.72−1.78 (m, 1 H), 2.09−2.14 (m, 1 H), 2.78−2.89 (m, 3 H), 2.99 (dd, 1 H, J = 17.3 Hz), 3.24 (s, 3 H), 3.95 (s, 3 H), 4.03 (s, 3 H), 7.41 (s, 1 H), 7.55 (s, 1 H), 12.99 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.74, 23.05, 31.03, 41.42, 49.11, 57.14, 61.77, 72.06, 113.61, 119.61, 123.30, 128.75, 130.75, 132.42, 140.58, 141.14, 144.34, 151.31, 157.06, 160.01, 181.97, 187.83; IR (CH_2Cl_2) 3300 br w, 1720 m, 1671 s, 1628 s cm^{-1}; mass spectrum *m*/*z* (% rel intensity) 462 M^+ (^{81}Br) (22); *m*/*z* calcd for $C_{22}H_{21}O_6{}^{81}Br$ 462.0501, measured 462.0501. Anal. Calcd for $C_{22}H_{21}O_6{}^{81}Br$: C, 57.28; H, 4.59. Found: C, 57.27; H, 5.22.

An attempt was made to prepare **25** by the oxidation of **24**. Treatment of **24** with nitric acid and silver oxide as described above and then, following workup, heating the crude reaction residue at 100 °C as a thin film exposed to air gave **25** in 17% yield along with an equal amount of a compound tentatively assigned as **26**: ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.65−1.75 (m, 1 H), 2.08−2.15 (m, 1 H), 2.61 (d, 1 H, J = 17.0 Hz), 2.70−2.90 (m, 2 H), 3.15 (d, 1 H, J = 17.0 Hz), 3.25 (s, 3 H), 3.94 (s, 3 H), 4.04 (s, 3 H), 7.55 (s, 1 H), 13.65 (s, 1 H), 13.66 (s, 1 H).

Preparation of 2-(Methyl 4-(benzyloxy)-4-methyl-2-methylene-1-cyclohexanecarboxylate)-1-hydroxy-4,5,8-(trimethylsilyl)naphthalene (31). The reaction of carbene complex **4** (0.474 g, 1.068 mmol) with alkyne **30** (0.32 g, 1.068 mmol, 1 equiv) was carried out in 1.42 mL of acetonitrile at 45 °C for 24 h according to the procedure described for the reaction of **4** with **14**. The reaction mixture was stirred open to air for 1 h and then directly loaded onto a silica gel column, and elution with a 1:1:6 mixture of ether/dichloromethane/hexane gave the desired product **31** (0.384 g) in 62% yield as a yellow wax. Spectral data for **31**: R_f = 0.09 (ether/dichloromethane/hexane = 1:1:6); ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 9 H), 1.01 (t, 1 H, J = 13.4 Hz), 1.11 (s, 3 H), 1.24−1.29 (m, 1 H), 1.71−1.74 (m, 1 H), 1.90−2.05 (m, 3 H), 2.17−2.23 (m, 1 H), 2.50−2.60 (m, 1 H), 2.61−2.69 (m, 1 H), 2.71 (dd, 1 H, J = 4.3, 13.2 Hz), 3.67 (s, 3 H), 3.71 (s, 3 H), 3.74 (s, 3 H), 3.88 (s, 3 H), 4.13 (d, 1 H, J = 11.1 Hz), 4.17 (d, 1 H, J = 11.1 Hz), 6.67 (s, 1 H), 6.71 (s, 1 H), 7.14−7.28 (m, 5 H), 9.45 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 0.32, 25.73, 25.85, 34.10, 35.09, 36.25, 39.32, 49.57, 51.58, 57.18, 58.14, 62.89, 64.89, 73.11, 110.84, 113.55, 119.02, 119.82, 121.41, 127.14, 127.29, 128.34, 139.72, 144.83, 149.22, 153.46, 155.24, 176.85; IR (neat) 3330 br m, 1730 s cm^{-1}; mass spectrum *m*/*z* (% rel intensity) 580 M^+ (100). Anal. Calcd for $C_{33}H_{44}O_7Si$: C, 68.24; H, 7.64. Found: C, 68.23; H, 7.69.

Preparation of 9-Benzyloxy-1,4,5,12-tetramethoxy-9-methyl-2-(trimethylsilyl)-6a,7,8,10,10a,11-hexahdronaphthacen-6-one (34). The naphthol **31** (1.05 g, 1.808 mmol) was treated with powdered potassium hydroxide (0.40 g, 4 equiv), iodomethane (1 mL, excess), and 4 mL of methyl sulfoxide. The mixture was stirred at room temperature for 3 h. After extraction with dichloromethane, the organic layer was washed with water. The solvent was removed, and the residue was quickly eluted through a short silica gel column with ether to give the desired product **32** (0.93 g) in 86% yield. Part of this product (0.77 g, 1.294 mmol) was treated with 15 mL of 2 N NaOH and 40 mL of methanol. The mixture was refluxed at 80 °C for 36 h. After cooling, 100 mL of ether was added. Neutralization with concentrated HCl was followed by removal of solvent, which gave a yellow foamy residue, which was extracted six times with ether. The organic layer was combined, the solvent removed, and the residue eluted through a short silica gel column to give the desired acid **33** (0.74 g) in 98% yield as a yellow foam. Spectral data for **33**: ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 9 H), 1.05 (t, 1 H, J = 13.0 Hz), 1.17 (s, 3 H), 1.40−1.50 (m, 1 H), 1.89−2.05 (m, 3 H), 2.07−2.16 (m, 1 H), 2.26−2.32 (m, 1 H), 2.55−2.65 (m, 1 H), 2.77−2.82 (m, 1 H), 2.89−2.92 (m, 1 H), 3.66 (s, 6 H), 3.80 (s, 3 H), 3.93 (s, 3 H), 4.18 (d, 1 H, J = 11.1 Hz), 4.23 (d, 1 H, J = 11.0 Hz), 6.71 (s, 1 H), 6.82 (s, 1 H), 7.21−7.30 (m, 5 H), (−O*H* not seen); ^{13}C NMR ($CDCl_3$) δ 0.02, 25.62, 25.84, 34.04, 34.96, 36.02, 39.21, 49.41, 57.18, 57.62, 62.01, 62.86, 63.12, 72.94, 109.84, 112.22, 120.83, 123.48, 127.15, 128.36, 129.43, 129.56, 139.56, 146.82, 152.94, 153.20, 155.17, 212.19; IR (neat) 3200−3000 br s, 1735 m, 1701 s cm^{-1}; mass spectrum *m*/*z* (% rel intensity) 580 M^+ (100). Anal. Calcd for $C_{33}H_{44}O_7Si$: C, 68.24; H, 7.64. Found: C, 68.53; H, 7.63.

The acid **33** (155.7 mg, 0.2681 mmol) was stirred with 1 equiv of NaOH (2.72 mL of a 0.09867 N aqueous solution) for 5 min. The mixture was stripped of volatiles under vacuum (0.5 mmHg/25 °C) for 48 h. After addition of benzene (15 mL) and pyridine (0.46 mL, 21 equiv), the mixture was cooled to 0 °C and oxalyl chloride (0.28 mL, 12 equiv) was added. After 10 min, tin(IV) chloride (64 μL, 2 equiv) was added dropwise, and the ice bath was removed. The mixture was stirred for 15 min before it was rapidly loaded onto a short chromatography column filled with Et_3N-pretreated silica gel. Excess ether was used as the eluent to wash off the product, and after removal of the solvent, the residue was rechromatographed with a 1:1:6 mixture of ether/dichloromethane/hexane to give **34** (130 mg, 86%) as the only product. Spectral data for **34**: bright yellow solid, mp 150−151 °C; R_f = 0.12 (ether/dichloromethane/hexane = 1:1:6); ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 9 H), 1.32 (s, 3 H), 1.33−1.42 (m, 3 H), 1.70−1.91 (m, 1 H), 2.10−2.22 (m, 3 H), 2.25−2.35 (m, 1 H), 2.50 (dd, 1 H, J = 12.0, 17.0 Hz), 3.40 (dd, 1 H, J = 4.0, 17.0 Hz), 3.68 (s, 3 H), 3.69 (s, 3 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 4.39 (d, 1 H, J = 11.1 Hz), 4.41 (d, 1 H, J = 11.1 Hz), 6.81 (s, 1 H), 7.16−7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 0.37, 21.23, 25.49, 30.85, 33.54, 34.21, 44.58, 52.30, 59.17, 61.15, 62.90, 62.99, 63.24, 72.83, 112.06, 123.22, 124.00, 125.17, 126.98, 127.13, 128.14, 131.38, 132.18, 139.27, 147.06, 153.82, 154.37, 155.24, 198.94; IR (CH_2Cl_2) 1733 s, 1687 vs cm^{-1}; mass spectrum *m*/*z* (% rel intensity) 562 M^+ (100). Anal. Calcd for $C_{33}H_{42}O_6Si$: C, 70.43; H, 7.52. Found: C, 70.64; H, 7.51.

Preparation of 9-Acetoxy-1,4,5,12-tetramethoxy-9-methyl-2-(trimethylsilyl)-6a,7,8,10,10a,11-hexahydronaphthacen-6-one (37). A solution of benzyl ether **34** (200 mg, 0.355 mmol) in 60 mL of EtOH was exposed to 10% Pd−C (200 mg) under nitrogen. A hydrogen atmosphere was introduced and maintained with a balloon for 1 h at 25 °C. After filtration through Celite, the solvent was removed and the ^{1}H NMR spectrum of the crude reaction mixture showed a mixture of the deprotected tertiary alcohol **36** and the diol **35** (10:1, total 146 mg). This mixture was treated with Dess−Martin reagent (26 mg, 2 equiv wt diol **35**) and pyridine (20 μL) in 10 mL of CH_2Cl_2. The solution was stirred at room temperature under nitrogen for 1.5 h. Saturated aqueous solutions of $NaHCO_3$ and $Na_2S_2O_4$ were added (1 mL each), and the mixture was extracted with excess CH_2Cl_2. After removal of the solvent, purification on silica gel with ether as eluent gave the alcohol **36** (0.128 g, 76%), which was directly taken on to the acetate **37**.

The alcohol **36** (250 mg, 0.5289 mmol) was mixed with DMAP (270 mg, 4.18 equiv), Hunig's base (0.46 mL, 5 equiv), and Ac_2O (0.25 mL, 5 equiv) in 20 mL of CH_2Cl_2 and stirred at room temperature under nitrogen for 12 h. After removal of the solvent, the mixture was directly loaded onto a silica gel column and eluted with pure ether to give a 46% recovery of the starting material (117 mg) and the desired product **37** (146 mg), which was isolated in 54% yield as a yellow wax. Spectral data for **37**: R_f = 0.045 (ether/dichloromethane/hexane = 1:1:6); ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 9 H), 1.25−1.41 (m, 3 H), 1.57 (s, 3 H), 1.63−1.75 (m, 1 H), 1.98 (s, 3 H), 2.05−2.16 (m, 2 H), 2.20 (dt, 1 H, J = 3.8, 11.6 Hz), 2.53 (dd, 1 H, J = 12.2, 13.7 Hz), 2.63−2.68 (m, 1 H), 3.41 (dd, 1 H, J = 4.0, 17.0 Hz), 3.69 (s, 3 H), 3.70 (s, 3 H), 3.90 (s, 3 H), 3.95 (s, 3 H), 6.82 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ -0.14, 21.35, 22.47, 26.18, 30.96, 34.07, 35.67, 43.81, 52.18, 57.43, 61.47, 63.28, 63.58, 80.41, 112.38, 123.48, 124.16, 125.48, 131.24, 132.65, 147.38, 154.08, 154.63, 155.50, 170.60, 198.91; IR (CH_2Cl_2) 1736 s, 1687 s cm^{-1}; mass spectrum *m*/*z* (% rel intensity) 514 M^+ (100). Anal. Calcd for $C_{28}H_{38}O_7Si$: C, 65.34; H, 7.44. Found: C, 65.19; H, 7.26.

Preparation of 9-Acetoxy-2-bromo-6-hydroxy-1,4-dimethoxy-9-methyl-7,8,10-trihydronaphthacene-5,12-dione (40). Compound **37** (88 mg, 0.1709 mmol), potassium carbonate (50 mg), and bromine (1.25 mL, 0.288 N in CH_2Cl_2, 2.1 equiv) were combined in 20 mL of CH_2Cl_2 under nitrogen at 0 °C. The mixture was stirred for 2 h and filtered through a short column packed with Et_3N-pretreated silica gel. TLC of the crude reaction mixture showed two products (R_f = 0.38, 0.40, ether/dichloromethane/hexane = 1:1:2). This mixture was treated with AgO (424 mg, 20 equiv) and HNO_3 (5 mL, 0.5 N) in 10 mL of acetone and stirred at room temperature for 5 h. The solvent was removed, and the residue was extracted with excess ether. The ether layer was dried over $MgSO_4$, and filtration through Celite gave a red solution. Chromatography on silica gel with a 1:1:2 mixiture of ether/dichloromethane/hexane gave the desired product **40** (40 mg) as a red solid in 48% yield. Spectral data for **40**: mp 152 °C; R_f = 0.24 (ether/dichloromethane/hexane = 1:1:2); ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 3 H), 1.94 (s, 3 H), 2.52−2.60 (m, 1 H), 2.72−2.81 (m, 1 H), 2.90−2.95 (m, 2 H), 2.94 (d, 1 H, J = 17.7 Hz), 3.39 (d, 1 H, J = 17.7 Hz), 3.95 (s, 3 H), 4.04 (s, 3 H), 7.40 (s, 1 H), 7.56 (s, 1 H), 12.99 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.49, 24.41, 29.66, 31.76, 41.49, 57.08, 61.77, 78.95, 113.55, 119.44, 123.04, 128.40, 128.95, 130.75, 131.65, 141.76, 143.45, 151.10, 156.95, 159.84, 170.47, 181.83, 187.79; IR (CH_2Cl_2) 3054 s, 1729 w cm^{-1}; mass spectrum (CI) for $C_{23}H_{21}O_7{}^{81}Br$ m/z (% rel intensity) 491 $(M + 1)^+$ (55), 431 (100).

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