powder, 94% yield. HPLC assay shows this material is 98.8% pure by weight (96.7% pure by area). The product can be purified further by recrystallization from ethyl acetate/hexanes (1:2): HPLC conditions [Zorbax Rx C-8, CH_3CN/H_2O/phosphoric acid, 30:70:0.1 gradient elution to 95:5:0.1 in 15 min, maintain 95:5:0.1 for 5 min; flow in 1.5 mL/min; UV detection at 292 nm) MK-287 TBS ether t_R = 18.1 min, MK-287 t_R = 11.8 min. The optical purity of the product can be determined by chiral HPLC: HPLC conditions [Pirkle type IA D-phenylglycine, three analytical columns in series, hexane/chloroform/2-isopropanol, 55:45:5, isocractic; flow = 0.6 mL/min; UV detection at 292 nm] MK-287 t_R = 42 min, *RR* enantiomer t_R = 41 min; $[\alpha]_D$ = -72.8 (c = 1.0, MeOH); mp 110-112 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (d, J = 2.0 Hz, 1 H), 7.29 (d, J = 2.0 Hz, 1 H), 6.61 (s, 2 H), 5.24 (m, 1 H), 5.22 (m, 1 H), 4.11 (t, J = 7.1 Hz, 2 H, $CH_3CH_2CH_2O$), 3.92 (broad m, 2 H, CH_2OH), 3.92 (s, 3 H, OCH_3), 3.88 (s, 6 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.66 (m, 2 H, CH_2SO_2), 2.90 (broad t, 1 H, OH), 2.50 (m, 2 H), 1.99 (m, 2 H), 1.87 (sextet, J = 7.1 Hz, 2 H, $CH_3CH_2CH_2O$), 1.04 (t, J = 7.1 Hz, 3 H, $CH_3CH_2CH_2O$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.2 (s), 151.8 (s), 144.3 (s), 138.8 (s), 137.5 (s), 135.9 (s), 131.4 (s), 116.7 (d), 114.4 (d), 101.9 (d), 81.6 (d), 80.5 (d), 76.3 (t), 61.1 (q), 57.8 (t), 56.8 (t), 56.6 (q), 56.5 (q), 36.38 (t), 36.35 (t), 24.1 (t), 11.5 (q); IR (KBr) 3524, 3050-2800, 1597, 1460, 1310, 1130, 1280, 1234, cm^{-1}. Anal. Calcd for $C_{25}H_{34}O_9S$: C, 58.85; H, 6.66; S, 6.28. Found: C, 58.79; H, 6.72; S, 6.20.

Acknowledgment. We would like to thank Miss Marian Spears for preparing the manuscript.

Studies in the Benzannulation of a Cycloalkynone: An Approach to the Synthesis of Antibiotics Containing the Benz[*a*]anthracene Core Structure

Dana M. Gordon and Samuel J. Danishefsky*

Department of Chemistry, Yale University, New Haven, Connecticut 06511

Gayle K. Schulte

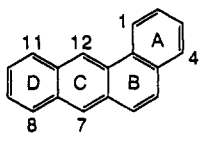
Yale University Center for Chemical Instrumentation, New Haven, Connecticut 06511

Received June 25, 1992

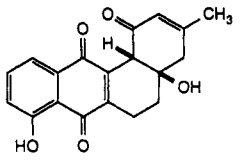
The chromium(0)-carbene complex benzannulation reaction was shown to be applicable to cyclodec-4-yn-1-one. Significant regioselectivity was realized in this reaction with ortho-substituted benzylchromium complexes. Reactions of a novel resultant fused cyclodecenone-naphthoquinone with several bases have been studied. Products apparently arising from either intramolecular Michael addition of a ketone enolate to the quinone or intramolecular aldol condensation of a quinone-stabilized anion with the ketone have been observed. The latter mode constitutes a route to the title substructure and, in principle, provides a route to reach certain angucycline antibiotics.

Background of the Problem

The angucyclines are antibiotics whose aglycon moieties are derivatives of benz[*a*]anthracene 1.[1] The antibiotics are divided into two major subclasses on the basis of structural features. The members of the first subclass,



1

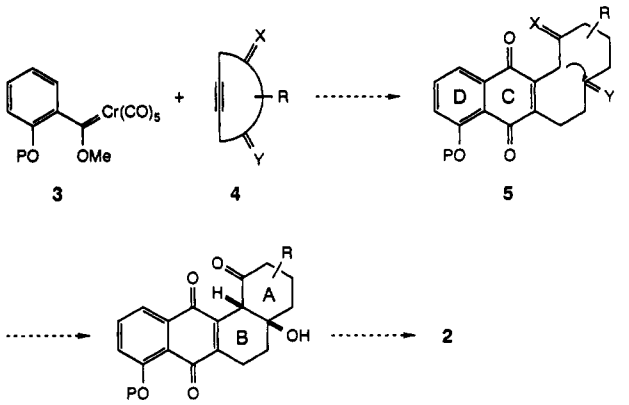


2

the angucyclinones, possess the benz[*a*]anthracene core structure but bear no *C*- or *O*-glycosyl domains. The members of the second subclass, the angucyclines, differ from the first in that they are glycosylated. Angucyclines are further divisible into systems bearing *C*- or *O*-glycosides as well as some which bear both *C*- and *O*-glycosidic linkages. Presently, more than 100 such antibiotics have been reported. All of the angucyclines isolated to date are secondary metabolites of the *Actinomycetes* group of microorganisms. In most cases, the organism which produces the antibiotic is a species of *Streptomycetes*. The angucyclines have been the subject of a recent comprehensive review.[2]

As a group the angucyclines display a wide range of biological activities. Individual members of this family of

Scheme I



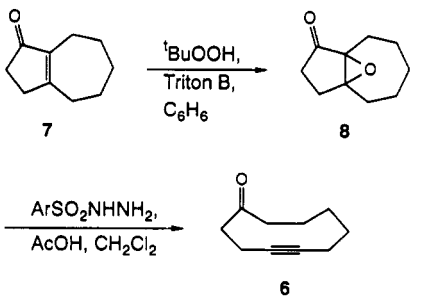
antibiotics exhibit cytostatic, enzyme inhibitory, antibacterial, or antiviral activities. Additionally, a small number of angucyclinones inhibit platelet aggregation. OM-4842[3] and saquayamycins A-D[4] are perhaps the most compelling angucyclines, from a therapeutic standpoint, due to their activities against doxorubicin-resistant and adriamycin-resistant cell lines, respectively.

In proportion to the large number of structurally intriguing angucyclines, previous synthetic work in the area has been relatively sparse.[5] Our attention was drawn to

(1) Drautz, H.; Zähner, H.; Rohr, J.; Zeeck, A. *J. Antibiot.* **1986**, *39*, 1657.
(2) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103.
(3) Omura, S.; Nakagawa, A.; Fukamachi, N.; Miura, S.; Takahashi, Y.; Komiyama, K.; Kobayashi, B. *J. Antibiot.* **1988**, *41*, 812.
(4) Uchida, T.; Imoto, M.; Watanabe, Y.; Miura, K.; Dobashi, T.; Matsuda, N.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 1171.

0022-3263/92/1957-7052$03.00/0

Scheme II



the angucyclinone SF 2315A[6] **2**. This compound exhibits mild antibacterial activity against Gram-positive bacteria and moderate antiviral activity against reverse transcriptase of the Avian myeloblastosis virus (IC_{50} 100 μg/mL).[6b] Its synthesis could perhaps serve as a model for approaches to more complicated goals.

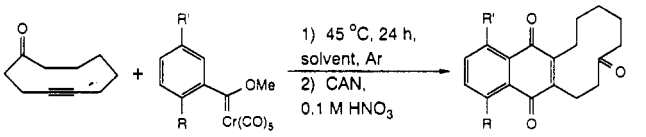
Consideration of the structure of SF 2315A **2** suggested a synthetic plan in which rings C and D of the benz[*a*]anthracene core would be appended onto a cycloalkyne **4** via a chromium carbene derivative **3** (see Scheme I).[7] For goal structure **2**, the acetylene **4** would be functionalized such that a system of the type **5** would be accessible after annulation. The A/B ring junction of SF 2315A might be formed at a late stage of the synthesis by aldolization of an intermediate **5** wherein X = Y = O. While the stereochemistry to be anticipated from such an aldolization was not necessarily clear, the outcomes of related cyclizations have been influenced by the choice of counterion.[8]

Aside from the goal of reaching the antibiotics by total synthesis, the synthetic proposal in Scheme I raised questions as to the extension of the chromium–carbene complex technology to cycloalkynes and the regioselectivity to be expected from the coupling of nonsymmetric partners. These issues, as well as uncertainties as to the feasibility of the proposed transannular aldolization reaction, were of sufficient interest to warrant an investigation. The first two of these questions might be addressed by a systematic study of the reactions of various chromium–carbene complexes with the readily accessible cyclodec-4-yn-1-one **6**. The tricyclic naphthoquinones (cf. **5**), produced in the cycloalkyne benzannulation reaction, would provide an opportunity to explore whether the proposition of the transannular cyclization could be realized in practice.

Discussion of Results

Azulenone[9] **7** was oxidized to α,β-epoxyketone **8** by treatment with *tert*-butyl hydroperoxide and Triton B in benzene.[10] Addition of mesitylene-2-sulfonohydrazide[11] to a solution of **8** in acetic acid–CH_2Cl_2 resulted in smooth Eschenmoser fragmentation,[12] at ambient temperature, to give cycloalkyne **6**.[11]

Scheme III



6

9 R = R' = H
11 R = OMe, R' = H
14 R = CF_3, R' = H
17 R = R' = OMe

10 R = R' = H
12 R = OMe, R' = H
13 R = H, R' = OMe
15 R = CF_3, R' = H
16 R = H, R' = CF_3
18 R = R' = OMe

Solvent	12 (yield)	13 (yield)	12 : 13
THF	48%	21%	2.3 : 1
PhH	53%	25%	2.1 : 1
n-heptane	57%	20%	2.8 : 1
2,5-DMTHF	56%	24%	2.3 : 1

Access to relatively large quantities of cycloalkyne **6** set the stage for an exploration of its participation in the chromium–carbene complex benzannulation reaction. Warming a solution of cycloalkyne **6** and chromium–carbene complex[13] **9** in THF for 24 h, at 45 °C under argon, followed by oxidation with ceric ammonium nitrate (CAN), gave naphthoquinone **10** in 89% yield.

The possibility that regioselectivity might be manifested in the benzannulation reaction of the cycloalkyne was intriguing. To address this question, the reaction of **6** with *o*-methoxyphenylcarbene complex[13] **11** was carried out under the conditions described for the formation of **10**. The isomeric naphthoquinones **12** and **13** were obtained in 48 and 21% yield, respectively. The identity of naphthoquinone **12** was established unequivocally by single-crystal X-ray crystallographic analysis. The presence of any regiochemical preference in this reaction is remarkable given the only modest departure from symmetry in cycloalkyne **6**. The observed regioselectivity suggests that either steric or electronic factors are influencing the outcome of the condensation. The regioselectivity observed in intermolecular benzannulation reactions of unsymmetrical acetylenes is known to be roughly proportional to the difference in steric demands between the acetylene substituents and to be independent of electronic factors.[7] Reactions involving terminal acetylenes give rise to a single product, whereas those with internal acetylenes produce mixtures.

The effects of variation of solvent on the ratio of naphthoquinones **12** and **13** produced from **6** and **11** were evaluated. Reactions were conducted in benzene, *n*-heptane, and 2,5-dimethyl-THF (2,5-DMTHF). After oxidation of the products with CAN, naphthoquinones **12** and **13** were produced. As is demonstrated in the table associated with Scheme III, the variations in regioselectivity were minimal, thus further suggesting that the effects are not of a polar origin.

The effect of electron-withdrawing substitution on the aromatic ring of the carbene complex in the benzannulation reaction of the cycloalkyne was also studied. Combination of *o*-(trifluoromethyl)phenylcarbene complex[13] **14** and cycloalkyne **6** in THF, for 24 h at 45 °C under

(5) (a) Brown, P. M.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 997. (b) Uemura, M.; Take, K.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 858. (c) Katsuura, K.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 9. (d) Katsuura, K.; Snieckus, V. *Can. J. Chem.* **1987**, *65*, 124. (e) Guingant, A.; Barreto, M. M. *Tetrahedron Lett.* **1987**, *28*, 3107. (f) Yamaguchi, M.; Okuma, T.; Horiguchi, A.; Ikeura, C.; Minami, T. *J. Org. Chem.* **1992**, *57*, 1647.

(6) (a) Sasaki, T.; Gomi, S.; Sezaki, M.; Takeuchi, Y.; Kodama, Y.; Kawamura, K. *J. Antibiot.* **1988**, *41*, 843. (b) Sasaki, T.; Yoshida, J.; Itoh, M.; Gomi, S.; Shomura, T.; Sezaki, M. *J. Antibiot.* **1988**, *41*, 835.

(7) (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (b) Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813. (c) Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, *27*, 3471. (d) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293.

(8) (a) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310. (b) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767. (c) Stork, G.; Winkler, J. D.; Saccomano, N. A *Tetrahedron Lett.* **1983**, *24*, 465. (d) Stork, G.; Saccomano, N. A. *Nouv. J. Chim.* **1986**, *10*, 677.

(9) Hiyama, T.; Shinoda, M.; Nozaki, H. *J. Am. Chem. Soc.* **1979**, *101*, 1599.

(10) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845.

(11) Reese, C. B.; Sanders, H. P. *Synthesis* **1981**, 276.

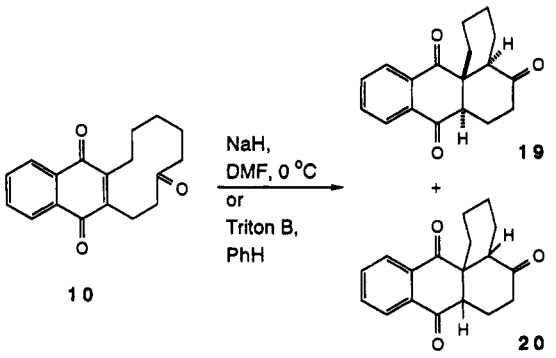
(12) (a) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708. (b) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, *8*, 3943.

(13) Fischer, E. O.; Kreiter, C. G.; Kollmeier, H. J.; Müller, J.; Fischer, R. D. *J. Organomet. Chem.* **1971**, *28*, 237.

argon, followed by oxidation with CAN, gave naphthoquinones **15** and **16** in 25 and 17% yield, respectively. A single-crystal X-ray crystallographic analysis of naphthoquinone **15** established its identity. Thus, the electron-deficient carbene complex **14** had produced the naphthoquinones **15** and **16**, though with diminished preference and in lower chemical yield, relative to the two examples described above.

Finally, condensation of cycloalkyne **6** with highly electron-rich 2,5-dimethoxyphenylcarbene complex[14] **17** in THF, for 24 h at 45 °C under argon, followed by oxidation with CAN, gave naphthoquinone **18**, though only in 27% yield. Related reactions with *p*-dimethoxyphenyl carbene complex **17** have typically been less efficient than those with less electron-rich carbenes.[7c]

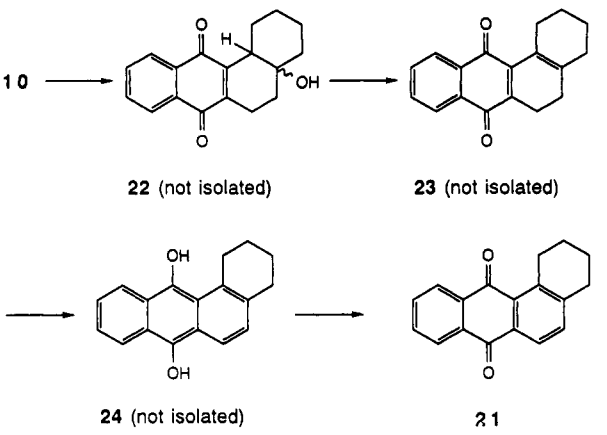
We next investigated cyclization reactions of quinone **10**. Although this compound lacks a ketone which would be present in goal substrates of type **5**, we felt that it might still undergo the transannular aldolization. In an attempt to generate a quinone-stabilized anion,[15] naphthoquinone **10** was treated with sodium hydride in DMF at 0 °C. These conditions gave trione **19** and an isomer **20** (stereochemistry undetermined) in 44 and 22% yield, respectively. The identity of trione **19** was established unambiguously by single-crystal X-ray crystallographic analysis. Triones **19** and **20** ostensibly arise from Michael addition of a ketone enolate to the quinone. Treatment of a solution of naphthoquinone **10** in benzene with Triton B, at ambient temperature, gave triones **19** and **20** in 22 and 46% yield, respectively.



Since the observed products from the reaction of **10** with NaH or Triton B were those formally derived from the ketone enolate serving as the nucleophile, the strength of the basic catalyst was further decreased. The hope was that the weaker base might trigger alternative cyclization modes via minor equilibrium components. In the event, heating a solution of naphthoquinone **10** and triethylamine in THF at reflux for 24 h gave no reaction. However, addition of DBU to a solution of naphthoquinone **10** in THF, at ambient temperature, gave 1,2,3,4-tetrahydrobenz[*a*]anthraquinone[16] **21** in 65% yield. *The benz*[a]*anthracene core structure of the angucycline antibiotics had thus been prepared in two steps from cycloalkyne* **6** *and carbene complex* **9**.

A reasonable mechanism for the formation of anthraquinone **21** is shown in Scheme IV. Naphthoquinone **10** is deprotonated by DBU to give a quinone-stablized anion which then adds to the ketone to give tertiary alcohol **22**. Water is then eliminated across the A/B ring junction to give dihydroanthraquinene **23**. Finally, dihydroanthraquinone tautomer **24** is oxidized, by adventitious oxygen, to anthraquinone **21**. We note that none of the proposed intermediates (**22**, **23**, or **24**) was isolated or detected.

Scheme IV



Summary

Naphthoquinones **10**, **12**, **13**, **15**, **16**, and **18** have been prepared by extending the chromium–carbene complex benzannulation methodology to cycloalkyne **6**. Treatment of naphthoquinone **10** with base provides either triones **19** and **20** or anthraquinone **21** depending upon the base utilized. Future efforts will focus on the application of the results from this model study to the synthesis of SF 2315A **2**.

Experimental Section

General Procedure for Preparation of Naphthoquinones 10, 12, 13, 15, 16, and 18. To a flame-dried flask charged with compound **9**, **11**, **14**, or **17** and blanketed with Argon was added a solution of cyclodec-4-yn-1-one **6** (1.5–2 equiv). The flask was sealed with a polystyrene cap and the solution stirred for 24 h at 45 °C. After being cooled to ambient temperature, the reaction mixture was added to a 0.5 M solution of CAN (7.5 equiv) in 0.1 M HNO_3 and stirred in air for 30 min. The mixture was washed with $CHCl_3$ (4 × 25 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 chromatography.

1,2,3,4,5,6,7,8-Octahydrocyclodeca[*b*]naphthalene-3,9,14-trione (10). Compound **9** (504 mg, 1.61 mmol) and **6** (339 mg, 2.26 mmol) in THF (5 mL), followed by oxidation with CAN (6.62 g, 12.1 mmol) in 0.1 M HNO_3 (24 mL) and SiO_2 chromatography (6:1:1 hexane–EtOAc–CH_2Cl_2), gave **10** (406 mg, 1.44 mmol, 89%): mp 159–60 °C; IR ($CHCl_3$) 3020, 2930, 2850, 1700, 1655, 1595, 1450, 1330, 1290 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.09–8.00 (m, 2 H, ArH), 7.70–7.66 (m, 2 H, ArH), 3.12–3.07 (m, 2 H, $QCH_2CH_2C(O)$), 2.75–2.70 (m, 4 H, $QCH_2CH_2C(O)$ and $QCH_2(CH_2)_4$), 2.60–2.55 (m, 2 H, $Q(CH_2)_2C(O)CH_2$), 1.83–1.73 (m, 4 H), 1.35–1.29 (m, 2 H); MS *m/z* 282 (M^+); HRMS calcd for $C_{18}H_{18}O_3$ (M^+) 282.1256, found 282.1247. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.30; H, 6.44.

1,2,3,4,5,6,7,8-Octahydro-13-methoxycyclodeca[*b*]naphthalene-3,9,14-trione (12) and 1,2,3,4,5,6,7,8-Octahydro-10-methoxycyclodeca[*b*]naphthalene-3,9,14-trione (13). Compounds **11** (263 mg, 768 μmol) and **6** (173 mg, 1.15 mmol) in THF (2.6 mL), followed by oxidation with CAN (3.16 g, 5.76 mmol) in 0.1 M HNO_3 (11 mL) and SiO_2 chromatography (2:1 hexane–EtOAc), gave **12** (116 mg, 371 μmol, 48%) and **13** (51 mg, 163 μmol, 21%).

Compounds **11** (326 mg, 953 μmol) and **6** (214 mg, 1.43 mmol) in benzene (2.4 mL), followed by oxidation with CAN (3.92 g, 7.15 mmol) in 0.1 M HNO_3 (14 mL) and SiO_2 chromatography, gave **12** (157 mg, 502 μmol, 53%) and **13** (74 mg, 236 μmol, 25%).

Compounds **11** (322 mg, 942 μmol) and **6** (212 mg, 1.41 mmol) in *n*-heptane (3 mL), followed by oxidation with CAN (3.87 g, 7.06 mmol) in 0.1 M HNO_3 (14 mL) and SiO_2 chromatography, gave **12** (168 mg, 536 μmol, 57%) and **13** (60 mg, 193 μmol, 20%).

(14) Dötz, K. H.; Sturm, W.; Popall, M.; Riede, J. *J. Organomet. Chem.* **1984**, *277*, 267.
(15) Dean, F. M.; Houghton, L. E. *J. Chem. Soc. C* **1968**, 2060.
(16) Lehr, R. E.; Kole, P. L.; Singh, M.; Tschappat, K. D. *J. Org. Chem.* **1989**, *54*, 850.

Compounds **11** (277 mg, 808 μmol) and **6** (182 mg, 1.21 mmol) in 2,5-dimethyltetrahydrofuran (2.5 mL), followed by oxidation with CAN (3.32 g, 6.06 mmol) in 0.1 M HNO_3 (12 mL) and SiO_2 chromatography, gave **12** (141 mg, 452 μmol, 56%) and **13** (62 mg, 197 μmol, 24%). **12**: mp 148–50 °C; IR ($CHCl_3$) 3020, 2930, 2860, 1705, 1655, 1585, 1470, 1450, 1330, 1270, 1065 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.64–7.54 (m, 2 H, ArH), 7.22 (dd, 1 H, J = 7.98 and 1.48 Hz, ArH), 3.96 (s, 3 H, OMe), 3.08–3.02 (m, 2 H, $QCH_2CH_2C(O)$), 2.71–2.64 (m, 4 H, $QCH_2CH_2C(O)$ and $QCH_2(CH_2)_4$), 2.57–2.52 (m, 2 H, $Q(CH_2)_2C(O)CH_2$), 1.76–1.69 (m, 4 H), 1.28–1.21 (m, 2 H); MS m/z 312 (M^+); HRMS calcd for $C_{19}H_{20}O_4$ (M^+) 312.1362, found 312.1367. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.79; H, 6.75. **13**: mp 146–8 °C; IR ($CHCl_3$) 3020, 2930, 1705, 1655, 1585, 1470, 1450, 1275 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.75 (d, 1 H, J = 7.66 Hz, ArH), 7.63 (t, 1 H, J = 7.79 Hz, ArH), 7.25 (d, 1 H, J = 8.49 Hz, ArH), 3.99 (s, 3 H, OMe), 3.10–3.05 (m, 2 H, $QCH_2CH_2C(O)$), 2.77–2.68 (m, 4 H, $QCH_2CH_2C(O)$ and $QCH_2(CH_2)_4$), 2.62–2.57 (m, 2 H, $Q(CH_2)_2C(O)CH_2$), 1.84–1.74 (m, 4 H), 1.36–1.29 (m, 2 H); MS m/z 312 (M^+); HRMS calcd for $C_{19}H_{20}O_4$ (M^+) 312.1362, found 312.1379. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.94; H, 6.23.

1,2,3,4,5,6,7,8-Octahydro-13-(trifluoromethyl)cyclodeca[*b*]naphthalene-3,9,14-trione (15) and 1,2,3,4,5,6,7,8-Octahydro-10-(trifluoromethyl)cyclodeca[*b*]naphthalene-3,9,14-trione (16). Compounds **14** (380 mg, 1 mmol) and **6** (226 mg, 1.5 mmol) in THF (3.5 mL), followed by oxidation with CAN (4.11 g, 7.5 mmol) in 0.1 M HNO_3 (15 mL) and SiO_2 chromatography (4:1 hexane–EtOAc) gave **15** (88 mg, 251 μmol, 25%) and **16** (59 mg, 168 μmol, 17%). **15**: mp 147–9 °C; IR ($CHCl_3$) 3020, 2930, 2850, 1705, 1665, 1585, 1450, 1310, 1270, 1160, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.27 (d, 1 H, J = 7.73 Hz, ArH), 8.04 (d, 1 H, J = 7.95 Hz, ArH), 7.76 (t, 1 H, J = 7.85 Hz, ArH), 3.14–3.09 (m, 2 H, $QCH_2CH_2C(O)$), 2.75–2.65 (m, 4 H, $QCH_2CH_2C(O)$ and $QCH_2(CH_2)_4$), 2.58–2.53 (m, 2 H, $Q(CH_2)_2C(O)CH_2$), 1.78–1.68 (m, 4 H), 1.30–1.23 (m, 2 H); MS m/z 350 (M^+); HRMS calcd for $C_{19}H_{17}F_3O_3$ (M^+) 350.1130, found 350.1133. Anal. Calcd for $C_{19}H_{17}F_3O_3$: C, 65.14; H, 4.89. Found: C, 64.92; H, 4.71. **16**: mp 149–51 °C; IR ($CHCl_3$) 3020, 2930, 2860, 1705, 1665, 1585, 1450, 1325, 1275, 1160 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.34 (dd, 1 H, J = 7.95 and 1.27 Hz, ArH), 8.02 (dd, 1 H, J = 8.95 and 0.67 Hz, ArH), 7.78 (dt, 1 H, J = 7.81 and 0.68 Hz, ArH), 3.13–3.07 (m, 2 H, $QCH_2CH_2C(O)$), 2.80 (t, 2 H, J = 6.94 Hz), 2.70–2.65 (m, 2 H), 2.61–2.56 (m, 2 H, $Q(CH_2)_2C(O)CH_2$), 1.79–1.72 (m, 4 H), 1.32–1.25 (m, 2 H); MS m/z 350 (M^+); HRMS calcd for $C_{19}H_{17}F_3O_3$ (M^+) 350.1130, found 350.1132. Anal. Calcd for $C_{19}H_{17}F_3O_3$: C, 65.14; H, 4.89. Found: C, 65.20; H, 4.71.

10,13-Dimethoxy-1,2,3,4,5,6,7,8-octahydrocyclodeca[*b*]naphthalene-3,9,14-trione (18). Compounds **17** (277 mg, 743 μmol) and **6** (223 mg, 1.49 mmol) in benzene (1.5 mL), followed by oxidation with CAN (3.05 g, 5.57 mmol) in 0.1 M HNO_3 (11 mL) and SiO_2 chromatography (1:1 hexane–EtOAc), gave **18** (69 mg, 202 μmol, 27%): mp 191–2 °C; IR ($CHCl_3$) 3020, 2940, 2845, 1705, 1660, 1570, 1480, 1275, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.22 (s, 2 H, ArH), 3.93 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.08–3.02 (m, 2 H, $QCH_2CH_2C(O)$), 2.73–2.62 (m, 4 H, $QCH_2(CH_2)_4$ and $QCH_2CH_2C(O)$), 2.58–2.53 (m, 2 H, $Q(CH_2)_2C(O)CH_2$), 1.78–1.71 (m, 4 H), 1.31–1.24 (m, 2 H); MS m/z 342 (M^+); HRMS calcd for $C_{20}H_{22}O_5$ (M^+) 342.1468, found 342.1485. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.83; H, 6.05.

(4a*R,7a*R**,13a*R**)-1,2,3,4,4a,5,6,7-Octahydrobenz[*n*]anthracene-5,8,13-trione (19) and 1,2,3,4,4a,5,6,7-Octahydrobenz[*n*]anthracene-5,8,13-trione (20).** Sodium hydride (60% dispersion, 4.7 mg, 117 μmol) was added to a stirred solution of ketone **10** (30 mg, 106 μmol) in anhydrous DMF (1.5 mL) at 0 °C and under N_2. After being stirred for 10 min at 0 °C, the reaction mixture was diluted with H_2O (20 mL) and washed with Et_2O (4 × 20 mL). The combined organics were washed with H_2O (3 × 15 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 chromatography (4:1 hexane–EtOAc) to give **19** (13.2 mg, 47 μmol, 44%) and **20** (6.6 mg, 23 μmol, 22%).

Benzyltrimethylammonium hydroxide (40% in MeOH, 5 μL, 10 μmol) was added to a stirred solution of ketone **10** (18 mg, 64 μmol) in benzene (750 μL). After being stirred for 45 min at ambient temperature under N_2, the reaction mixture was concentrated in vacuo. The residue was purified by SiO_2 chromatography to give **19** (4 mg, 14 μmol, 22%) and **20** (8.4 mg, 30 μmol, 46%). **19**: mp 189–90 °C; IR ($CHCl_3$) 3020, 2940, 2860, 1695, 1590, 1450, 1300, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.01–7.93 (m, 2 H, ArH), 7.77–7.67 (m, 2 H, ArH), 3.32 (dd, 1 H, J = 11.80 and 3.88 Hz, ArC(O)CH), 3.05 (bd, 1 H, J = 4.56 Hz, $CH_2C(O)CH$), 2.60–2.48 (m, 2 H), 2.42–2.04 (m, 4 H), 1.61–1.40 (m, 4 H), 1.35–1.23 (m, 1 H), 1.07–0.93 (m, 1 H); MS m/z 283 ($M + H)^+$; HRMS calcd for $C_{18}H_{18}O_3$ (M^+) 282.1256, found 282.1261. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.64; H, 6.73. **20**: IR ($CHCl_3$) 3010, 2940, 2860, 1710, 1690, 1590, 1450, 1290, 1255 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.02–7.98 (m, 2 H, ArH), 7.77–7.71 (m, 2 H, ArH), 3.68 (dd, 1 H, J = 12.87 and 4.25 Hz, ArC(O)CH), 3.16 (dd, 1 H, J = 12.68 and 4.26 Hz, $CH_2C(O)CH$), 2.56–2.48 (m, 1 H), 2.32–2.14 (m, 2 H), 1.89–1.74 (m, 3 H), 1.71–1.59 (m, 3 H), 1.38–1.20 (m, 2 H), 0.86–0.78 (m, 1 H); MS m/z 282 (M^+); HRMS calcd for $C_{18}H_{18}O_3$ (M^+) 282.1256, found 282.1256.

1,2,3,4-Tetrahydrobenz[*a*]anthracene-7,12-dione (21). DBU (264 μL, 1.77 mmol) was added to a solution of ketone **10** (50 mg, 177 μmol) in THF (3 mL), and the mixture was stirred at ambient temperature for 36 h under N_2. The reaction mixture was diluted with 1 N HCl (15 mL) and washed with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with 1 N HCl (10 mL), saturated $NaHCO_3$ (10 mL), and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 chromatography (2:1 hexane–CH_2Cl_2) to give **21** (30 mg, 115 μmol, 65%): mp 151–2 °C (lit.[16] mp 152–3 °C); IR ($CHCl_3$) 3020, 2940, 2870, 1665, 1580, 1325, 1280, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.22–8.18 (m, 2 H, ArH), 8.11 (d, 1 H, J = 7.96 Hz, ArH), 7.75–7.68 (m, 2 H, ArH), 7.44 (d, 1 H, J = 8.03 Hz, ArH), 3.39–3.34 (m, 2 H, $ArCH_2$), 2.93–2.88 (m, 2 H, $ArCH_2$), 1.85–1.80 (m, 4 H, $ArCH_2CH_2$); MS m/z 262 (M^+); HRMS calcd for $C_{18}H_{14}O_2$ (M^+) 262.0994, found 262.0993.

Acknowledgment. This work was supported by NIH Grant CA28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University which was supported by NSF Chemistry Division Grant CHE7916210. We would also like to gratefully acknowledge an NSF Predoctoral Fellowship to D.M.G.

Supplementary Material Available: Crystallographic data for compounds **12**, **15**, and **19** (34 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.