3.16 (d, H-3x), 2.43 (q, H-5), 2.29 (s, H-6), 1.60 (m, H-7n), 1.07 (q, H-7x), 1.60 (m, H-8n), 1.07 (q, H-8x), 2.32 (s, H-9), 2.47 (q, H-10), 2.38 (q, H-11A), 2.28 (d, H-11S), 1.18 (d, H-12A), 1.88 (d, H-12S); ^{13}C NMR δ 84.88 (s, C-1), 56.63 (t, C-3), 66.59 (s, C-4), 57.93 (d, C-5), 34.22 (d, C-6), 29.69 (t, C-7), 30.02 (t, C-8), 35.04 (d, C-9), 60.71 (d, C-10), 54.61 (t, C-11), 30.29 (t, C-12).

Anal. Calcd for $C_{19}H_{15}NCl_2$: C, 56.9; H, 6.5; N, 6.0. Found: C, 57.0; H, 6.5; N, 5.6.

X-ray Crystallography. Crystal data: $C_{11}H_{11}Cl_4N$, M_r 299.03; crystal size 0.40 × 0.37 × 0.30 mm; orthorhombic, space group *Pbca* (No. 61), with a = 10.872 (3) Å, b = 15.074 (3) Å, c = 15.571 (3) Å; U = 2551.8 Å^3; Z = 8, D_{calcd} = 1.56 g cm^{-3}; μ(Mo Kα) = 9.0 cm^{-1}; Mo Kα radiation (λ = 0.71073 Å); Enraf-Nonius CAD4 diffractometer. The data were corrected for *Lp*, decay (average −10% due to X-ray damage), and absorption (program DIFABS). The structure was solved by direct methods and Fourier techniques and refined to a conventional R = 0.036 (R_w = 0.045). The refinements were carried out by full-matrix least-squares on the basis of 1035 unique observed [$I > 3\sigma(I)$] data and 146 parameters; all calculations were made with SDP/VAX; H atoms included as fixed contribution to the structure factor.

Supplementary Material Available: Tables of crystallographic experimental details, positional and thermal parameters, and bond lengths and angles (5 pages). Ordering information is given on any current masthead page.

A Stereospecific Total Synthesis of the Anthracyclinones (±)-Daunomycinone and (±)-Isodaunomycinone

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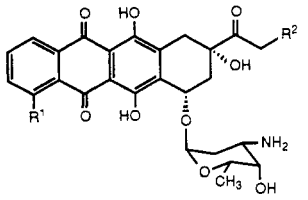
Received May 6, 1987

The complete synthesis of the anthracyclinones (±)-daunomycinone (**5**) and (±)-isodaunomycinone (**6**) is described. The construction of ring A was accomplished through a Diels–Alder cycloaddition using *trans*-4-(trimethylsilyl)-2-acetoxy-1,3-butadiene (**31**) as the diene and 5-methoxy-1,4,9,10-anthracenetetrone (**29**) as the dienophile. The 7-hydroxyl was introduced by the stereospecific replacement of the 7-trimethylsilyl function by acetate through the use of lead tetraacetate.

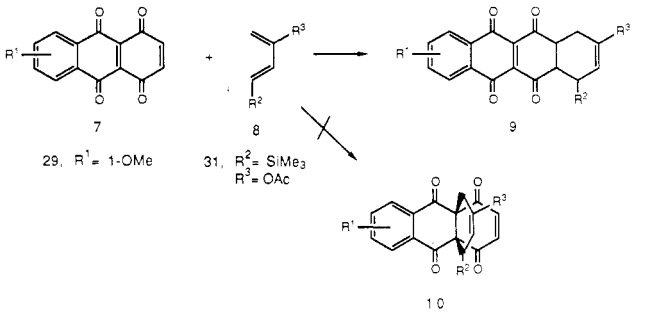
The family of anthracycline antibiotics, of which doxorubicin (adriamycin (**1**)),[1] daunorubicin (daunomycin (**2**)),[2] and carminomycin (**3**)[3,4] are important representative



1, R^1 = OCH_3; R^2 = OH
2, R^1 = OCH_3; R^2 = H
3, R^1 = OH; R^2 = H
4, R^1 = H; R^2 = H

members, has attracted considerable attention because of their remarkable efficacy against a wide variety of human cancers.[5] These cytotoxic agents are also plagued with unwanted side effects, the most serious being their cardiotoxicity.[5,6] A low therapeutic index, and surprising efficacy, has sparked great interest in the development of synthetic pathways to the natural clinically useful anthracyclines as well as analogues with improved activity profiles. This effort has been further stimulated by the fact that small structural differences can produce dramatic activity effects. For example, the synthetic analogue 4-desmethoxydaunorubicin (idarubicin (**4**)) is between 4 and 8 times more active than daunorubicin.[7]

Scheme I



The anthracycline structures are composed of a tetracyclic aglycon attached to the amino sugar L-daunosamine.[8,9] Since a variety of syntheses of this sugar[10] and its coupling to daunomycinone (**5**) have been described,[11]

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(2) (a) Cassinelli, G.; Orezzi, P.; Gior, P. *Microbiology* **1963**, *11*, 167. (b) Arcamone, F.; Francschi, G.; Orezzi, P.; Cassinelli, G.; Barbier, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334. (c) Bernard, J.; Paul, R.; Boiron, M.; Jacquillot, C.; Masal, R., Ed. *Rubidomycin*; Springer-Verlag: New York, 1969.

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(7) (a) Arcamone, F.; Bernardi, L.; Giardino, P.; Patelli, B.; DeMarco, A.; Casazza, A. M.; Pratesi, G.; Reggiani, R. *Cancer Treat. Rep.* **1976**, *60*, 829. (b) Casazza, A. M. *Cancer Treat. Rep.* **1979**, *63*, 835. (c) Umezawa, H.; Takahashi, Y.; Kinoshita, M.; Naganawa, H. *J. Antibiot.* **1980**, *33*, 1581.

(8) Iwamoto, R. H.; Lim, P.; Bhacca, N. S. *Tetrahedron Lett.* **1968**, 3891.

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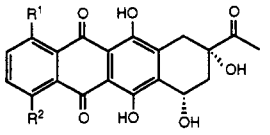
(10) (a) Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35 and references therein. (b) Samnes, P. G.; Thetford, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 111 and references therein.

0022-3263/88/1953-4244$01.50/0



5, R^1= H; R^2= OCH_3
6, R^1=OCH_3; R^2= H

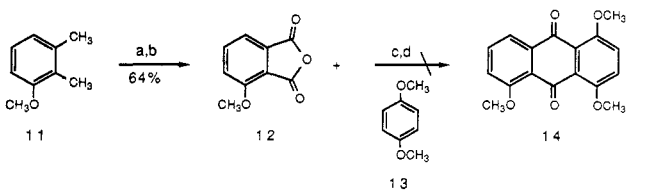
we directed our efforts toward the synthesis of the aglycon. In particular we were interested in developing a synthetic strategy that would not only generate both isomeric daunomycinones **5** and **6** but be general enough for analogue preparation and additionally incorporate a high-yielding stereospecific introduction of the 7-hydroxyl function. This previously difficult hydroxylation has been accomplished in our synthesis of 4-desmethoxydaunomycinone.[12] In this paper we report the full details of our total synthesis of both daunomycinone **5** and its regioisomer **6**.

Following the first synthesis of **1**,[13] a number of general approaches for the construction of the tetrahydro-5,12-naphthacenedione ring system, some demonstrating regiochemical control in the orientation of the A- and D-ring substituents, have been described.[14] In our approach, we chose 5-methoxy-1,4,9,10-anthradiquinone (**29**)[15] as our Diels–Alder dienophile and *trans*-4-(trimethylsilyl)-2-acetoxy-1,3-butadiene (**31**)[12a,b] as the diene for ultimate conversion to isodaunomycinone (**6**) and daunomycinone (**5**), respectively. We noted that relatively electron rich dienes add to the internal double bond (Scheme I) of anthradiquinones (**7**) to produce **10** while relatively electron deficient dienes prefer the terminal double bond, generating (**9**).[15-17,22] Since diene **31** is electron poor, we expected it to add predominantly to the terminal double bond. The trimethylsilyl (TMS) functionality of **31** also represents a "disguised" hydroxyl since we had previously shown that the TMS group of benzyl trimethylsilanes[12a,b] was replaced by acetate on treatment with lead tetraacetate.

Initially, our synthesis of anthradiquinone **29** was accomplished by the method of Kende et al.[15] (Scheme II). Efforts to effect a Friedel–Crafts reaction between **12** and 1,4-dimethoxybenzene (**13**) followed by treatment with concentrated sulfuric acid gave poor yields of mixtures of 1,4,5-trimethoxyanthraquinone (**14**)[18] and their dealkylated derivatives.

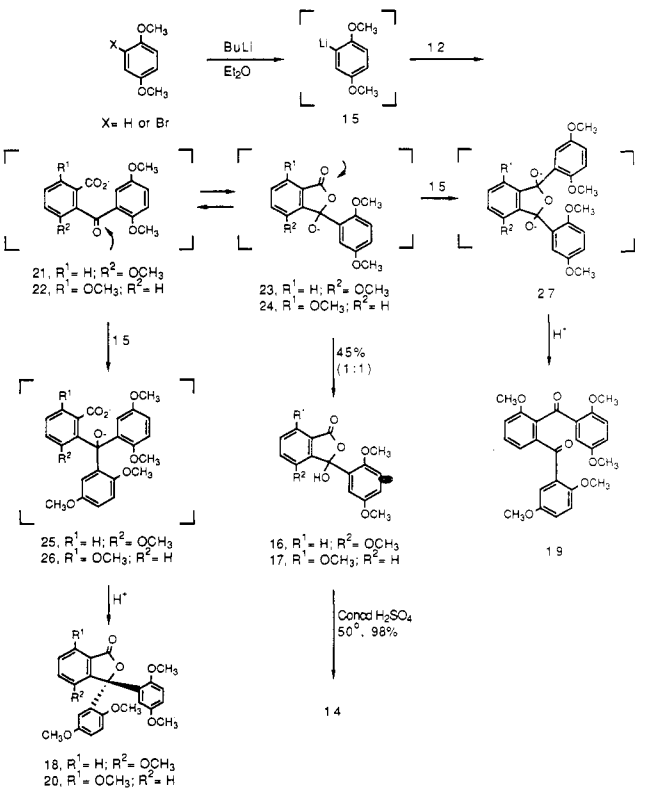
A successful synthesis of **14** was developed by lithiation of **13** either directly or through its bromo analogue. The anion **15** was condensed with anhydride **12**, providing in 45% yield a 1:1 ratio of lactols **16** and **17**. These lactols were quantitatively converted by concentrated sulfuric acid to the anthraquinone **14**. A detailed investigation of this

Scheme II



[a] $KMnO_4$, H_2O, 100 °C. [b] Ac_2O, 25 °C. [c] Various Lewis acids and solvents. [d] Concentrated H_2SO_4.

Scheme III



[a] Excess $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux. [b] $Ag^IAg^{III}O_2$, HNO_3, acetone, 50 °C. [c] $Pb(OAc)_4$, CH_2Cl_2, HOAc, 25 °C. [d] Silica gel–air or NaI–HOAc or $NaHSO_3$, HOAc.

reaction led to the isolation of lactones **18** and **20** and diketone **19**. These products suggested the mechanism described in Scheme III, where anion **15** indiscriminately attacks both carbonyl groups of **12** (route a or b), generating ketone carboxylates **21** and **22**. Addition of a second mole of anion **15** to the ketone in **21** and **22** ultimately forms the lactones **18** and **20**. The dione **19** is formed by addition of anion **15** to the anions of the lactols **16** and **17**, intermediates **23** and **24**.

An alternate approach to **14** was investigated starting from a crude sample of dye intermediate 1,4,5-tri-

(11) Acton, E. M.; Fujiwara, A. N.; Henry, D. W. *J. Med. Chem.* **1974**, *17*, 659.
(12) (a) Garland, R. B.; Palmer, J. R.; Schulz, J. A.; Sollman, P. B.; Pappo, R. *Tetrahedron Lett.* **1978**, *39*, 3669. (b) Pappo, R.; Garland, R. B. U.S. Patent 4 161 480, 1979. (c) Bulman-Page, P. C.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1847.
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(15) Kende, A. S.; Tsay, Y.-G.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967.
(16) Lee, W. W.; Martinez, A. P.; Smith, T. H.; Henry, D. W. *J. Org. Chem.* **1976**, *41*, 2297.
(17) Inhoffen, H. H.; Muxfeldt, H.; Koppi, V.; Heimann-Trosien, J. *Chem. Ber.* **1957**, *90*, 1448.
(18) Wiles, L. A.; Thomas, L. C. *J. Chem. Soc.* **1956**, 4811.

hydroxyanthraquinone (**28**).[19] This material (Scheme IV), without purification, was methylated with excess dimethyl sulfate to give **14** (72%). The required dienophile, 5-methoxy-1,4,9,10-anthradiquinone (**29**),[15] was formed by oxidative demethylation of **14** with argentic oxide (Ag^{I}-$Ag^{III}O_2$)[20] using the procedure of Rapoport and Snyder.[21]

It is interesting to note that **30**, isolated as a byproduct both in the synthesis of **14** and in the subsequent Diels–Alder reactions of **29**, could be recycled by oxidation back to **29**. Diquinone **29** is relatively unstable and was slowly reduced to **30** on contact with silica gel and air but could be stored unchanged for weeks if kept cold, under argon, and protected from light. Compound **30** was quantitatively obtained by treatment of **29** with NaI or $NaHSO_3$ in acetic acid.

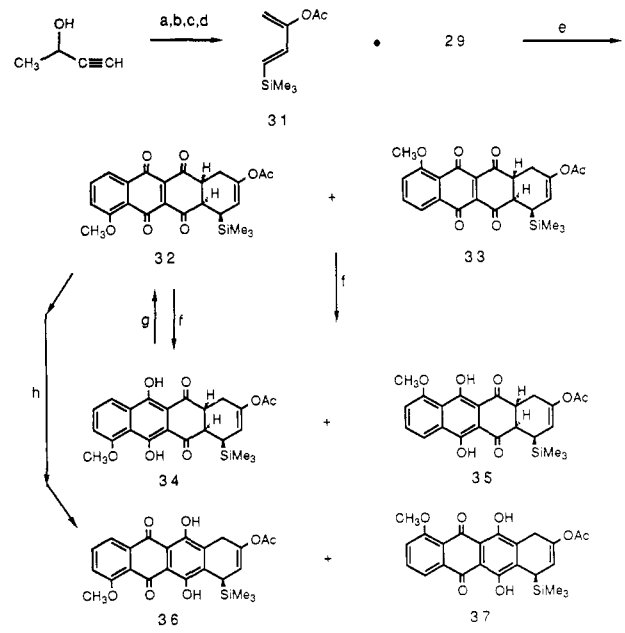
The Diels–Alder reaction between **29** and 2 equiv of **31** gave a 1:1 mixture of cis-endo regioisomeric adducts **32** and **33** after a 17-h reflux in methylene chloride. Other solvents (HOAc, benzene, CH_3CN, acetone) and various ratios of **29**:**31** all produced an approximate 1:1 mixture of **32** and **33**. The above procedure was one of the most successful and used because of its compatability with subsequent reactions. All efforts to separate this mixture led to decomposition and reversion to starting materials and their subsequent decomposition products.[24] The isomeric mixture was therefore reduced with zinc in methylene chloride–acetic acid directly to the corresponding yellow dihydro derivatives **34** and **35**. Alternatively this reduction could be accomplished by hydrogenation over 5% Pd/C. The use of methylene chloride as solvent in the cycloaddition of **29** and **31** and cosolvent in the subsequent Zn–HOAc reduction of adducts **32** and **33** permitted the conversion of **29** and **31** to the dihydro adducts **34** and **35** in a single reaction vessel.

These yellow diketones **34** and **35** were isolated by silica gel chromatography along with small amounts of the red aromatic diketones **36** and **37** and orange byproducts **30**. These latter aromatic diketones were not present in the original reduction mixture and are evidently produced during the silica gel isolation. Dry column liquid chromatography (DCLC) gave better results than HPLC but the efficient separation of isomers remained a serious problem.

Though tetracyclic adducts **34**–**37** were each isolated and possessed characteristic color and TLC R_f's, spectroscopic techniques were unable to distinguish between the 1-methoxy and 4-methoxy isomeric pairs. We were, however, able to correlate **32**, **34**, and **36** and demonstrate that each of these compounds had an R_f greater than the corresponding members of the other series **33**, **35**, and **37**. These compounds were related as indicated in Scheme V. We will discuss the chemistry of **34** that ultimately produced daunomycinone (**5**) before dealing with the synthesis of isodaunomycinone.

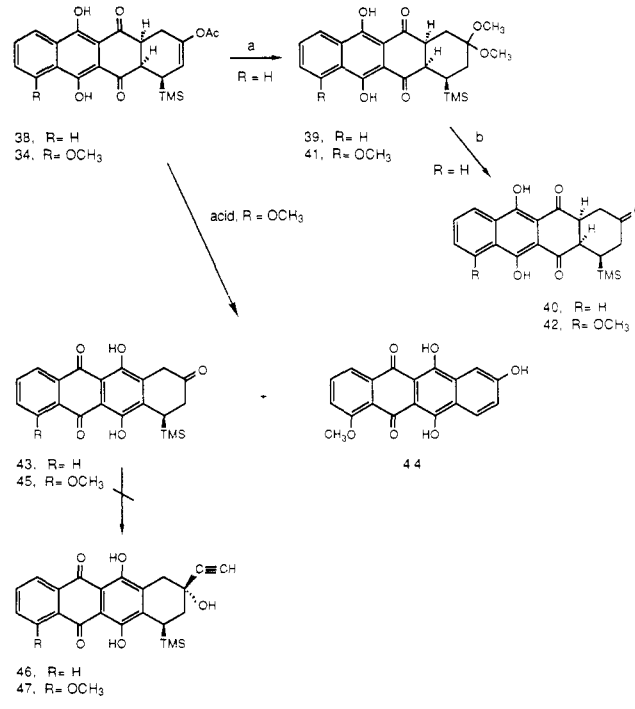
To introduce the requisite 9-acetyl group, it was necessary to convert enol acetate **34** to dihydro ketone **42** (Scheme VI). We initially attempted to use the methodology developed in our synthesis of 4-desmethoxydaunomycinone (**4**)[12a,b] where enol acetate **38** was converted

Scheme V



[a] *n*-BuLi, $ClSiMe_3$, CH_3OH, HCl. [b] H_2, benzene, 0.5% quinoline, 5% $Pd/BaSO_4$. [c] CrO_3, acetone. [d] Isopropenyl acetate, pTSA. [e] **29**, CH_2Cl_2, reflux 17 h. [f] Zn, HOAc, CH_2Cl_2. [g] $Pb(OAc)_4$, HOAc. [h] KOAc, HOAc (satd).

Scheme VI

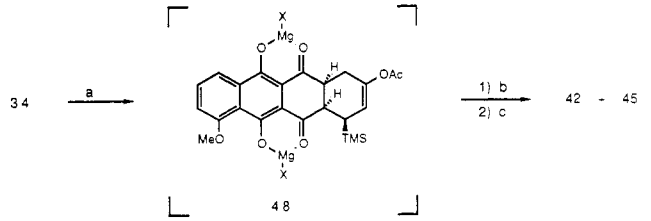


[a] HCl, CH_3OH, reflux. [b] CF_3CO_2H, H_2O.

to the dimethyl ketal **39** followed by hydrolysis to dihydro ketone **40**. All our attempts at converting **34** to ketone **42** under acidic conditions either directly or via intermediate ketal **41** led to aromatic ketone **45** as the major product, along with a small amount of an A-ring aromatized material **44**. Ketone **45** proved to be an unsuitable precursor to ethynylated adduct **47**, and previously we demonstrated[12a,b] that desmethoxy analogue **43** could also not be converted to **46**. Presumably, formation of the enolate stabilized by conjugation with the aromatic B ring prevents acetylide anion addition to C-9.

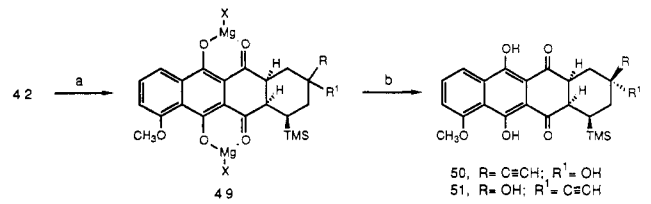
(19) We greatly appreciate the gift of a very generous sample of 1,4,5-trihydroxyanthroquinone from Drs. R. Price and P. Woolluen of ICI's Organics Division.
(20) Crivello, J. V. *Synth. Commun.* **1976**, *6*, 543.
(21) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.
(22) (a) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16. (b) Sustman, R. *Tetrahedron Lett.* **1971**, 2717.
(23) Kalman, J. R.; Pinhey, J. T.; Sternhell, S. *Tetrahedron Lett.* **1972**, 5369.
(24) The major material derived from diquinone **29** was hydroquinone **30**.

Scheme VII



[a] EtOH, MeMgBr/Et_2O (2 equiv). [b] EtOMgBr (1 equiv). [c] HOAc, H_2O.

Scheme VIII



[a] EtMgBr, THF, C_2H_2 (excess), −78 to −20 °C. [b] NH_4Cl, HCl.

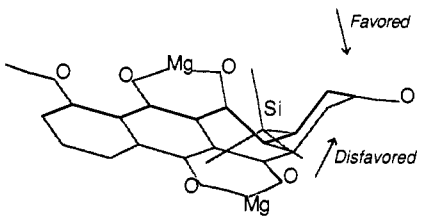


Figure 1.

However, when **34** was treated with 3 equiv of EtOMgBr (Scheme VII), the desired ketone **42** was obtained (86%) along with a small amount of aromatized ketone **45**. We believe that the first 2 equiv of EtOMgBr reacted with the phenolic hydroxyls of **34**, forming the stabilized intermediate **48**. The third equivalent of base was most likely responsible for hydrolysis of the acetate.

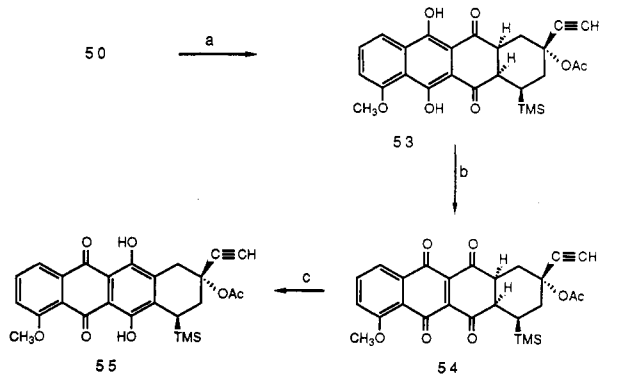
The 9-carbonyl of **42** (Scheme VIII) was stereospecifically ethynylated by taking advantage of the magnesium cation. The first 2 of 3 equiv of ethynylmagnesium bromide presumably reacted with the phenolic hydroxyl groups. The third equivalent then added to the 9-ketone, producing an intermediate resembling **49**. When careful attention to reaction temperatures was taken and the reaction was quenched with NH_4Cl and HCl, yellow ethynyl alcohol **50** was isolated in 91% yield along with a small amount (0.6%) of stereoisomer **51**. The high degree of stereospecificity achieved in the generation of **50** was not expected.

Calculations[25] suggest that the favored direction for attack by an ethynyl anion (Figure 1) is that which leads to the equatorial ethynyl product **50**. Molecular mechanics studies[25] on models on the two possible products **50** and **51** suggest there is <0.5 kcal difference in energy between them. The course of the reaction appears to be kinetically controlled.

This remarkable 152:1 (**50**:**51**) specificity was not essential for the success of the synthesis. Chirality at the AB ring juncture was destroyed by aromatization of ring B and at C-7 during introduction of the 7-acetate (vide infra). Therefore either **50**, **51**, or a mixture thereof was adequate for the synthesis.

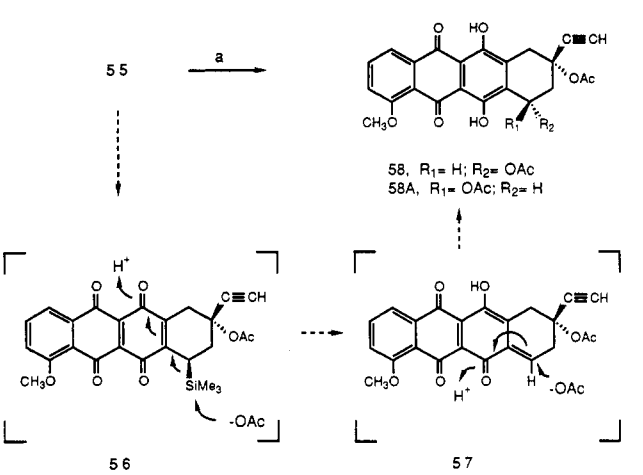
(25) MM2 calculations, private communication with M. Clare, Drug Design Dept., G. D. Searle & Co.

Scheme IX



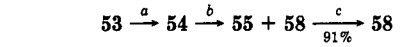
[a] Isopropenyl acetate, PTSA, room temperature. [b] $Pb(OAc)_4$, CH_2Cl_2, 0 °C. [c] KOAc, HOAc, 90 °C, 2.5 h.

Scheme X



[a] $Pb(OAc)_4$ (20% excess), HOAc, KOAc, 25 °C, 3 days.

Scheme XI

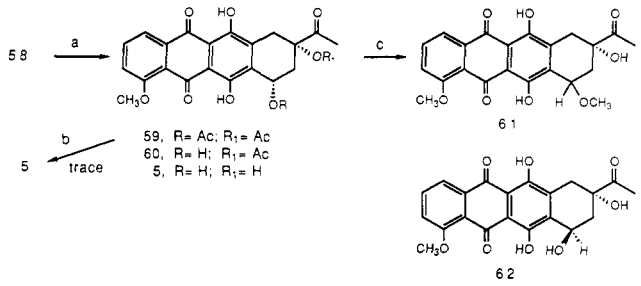


[a] $Pb(OAc)_4$, HOAc, KOAc, 25 °C. [b] 90 °C, 1.75 h. [c] $Pb(OAc)_4$, 25 °C, 2 days.

The 9-hydroxyl of **50** (Scheme IX) was protected from subsequent oxidative conditions by its conversion to acetate **53**. Treatment of ethynyl alcohol **50** with isopropenyl acetate at room temperature and under acid catalytic conditions produced the yellow crystalline **53** in quantitative yield. This material was oxidized (98%) with $Pb(OAc)_4$ to the rust-colored quinone **54** in methylene chloride at 0 °C. The B ring of **54** was then cleanly aromatized by KOAc in HOAc to produce the red crystalline ethynyl acetate **55**.

When **55**, dissolved in HOAc, was treated with KOAc and a 20% excess of $Pb(OAc)_4$ for 3 days at 25 °C, the red crystalline diacetate **58** was obtained in essentially quantitative yield. The most probable mechanistic interpretation for this conversion is shown in Scheme X in which **55** was initially oxidized to diquinone **56**. The electrophilic silicon was attacked by acetate to produce the key *o*-quinone methide intermediate **57**, which subsequently accepted an acetate from below to generate **58**, containing an axial acetate. It is interesting to note that none of the alternative isomer **58A** was isolated. Examination of models suggest that attack by acetate from the axial direction may be preferred. In addition, thermodynamic control in this reaction would favor the more stable isomer

Scheme XII



[a] $HgCl_2$, CH_2Cl_2, H_2O, 25 °C. [b] Alcohols, H_2O, HCl/various concentrations and temperatures. [c] CH_3OH, 10% HCl, reflux.

58.[26] Regardless of the nature of the transition state, the reaction is remarkably efficient and stereospecific.

Because of the commonality of reagents and the very high yields obtained in each individual step from **53** to **58**, we were able to effect the conversion of **53** to **58** (Scheme XI) in one reaction vessel. The yellow ethynyl acetate **53** dissolved in HOAc was oxidized with 1.2 equiv of $Pb(OAc)_4$ in the presence of KOAc. After 5 min, TLC suggested that the generation of quinone **54** was complete. The mixture was then heated at 90 °C for 1.75 h, forming **55** plus a trace of **58**. After the mixture cooled, an additional 1.1 equiv of $Pb(OAc)_4$ was added, and the mixture was stirred for 2 days at 25 °C to produce a 91% yield of **58**.

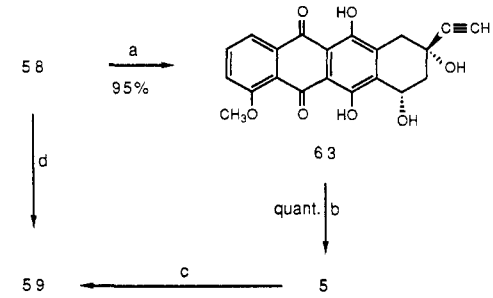
The hydration of the 9-ethynyl side chain was accomplished (Scheme XII) in >90% yield by treatment of **58** with $HgCl_2$[27] in wet methylene chloride. The HCl workup necessary to liberate the red acetyl product (**59**) from the Hg salts also produced small amounts of monoacetate **60** and trace amounts of daunomycinone (**5**) itself. The detection of **5** after HCl treatment strongly suggested that some combination of an aqueous alcoholic HCl treatment should give the desired daunomycinone (**5**) in respectable yield. Yet all efforts to optimize this acid-catalyzed conversion were unsuccessful. One trial using methanol as solvent produced traces of **5** from **59** within 5 min of contact with 10% HCl. In attempts to drive the reaction to **5** as acetate **59** disappeared, the amount of **5** remained constant while two new products, identified as methoxy derivative **61** and epidaunomycinone **62**, appeared.

To solve this potential roadblock, the removal of the 7- and 9-acetates of ethynyl diacetate **58** prior to the hydration of the ethynyl function was investigated. After numerous attempts using a wide variety of conditions, the action of concentrated HCl in refluxing THF (41 h) on **58** produced the red crystalline ethynyl diol **63** in >95% yield (Scheme XIII). The ethynyl group of **63** was subsequently hydrated to give **5** in quantitative yield by the action of Hg^{2+} bound to a Dowex 50W-X8 resin.[28] Our synthetic daunomycinone (**5**) was identical in all respects with authentic samples.[29]

As additional proof of structure, an authentic sample of **5** was converted to diacetate **59** by treatment with isopropenyl acetate. This material was also identical with that generated by hydration of diacetate **58**.

With the identification of **5** and **59** as daunomycinone and its diacetate, respectively, the structural assignment of the methoxy at C-4 in **34**, the isomer possessing the greater TLC R_f, was confirmed. Its isomer, **35**, was subsequently converted as described in Scheme XIV to isodaunomycinone (**6**). The physical and spectral properties of our isodaunomycinone (**6**) are consistent with those reported by Krohn et al.[35] Since methods for the introduction of the hydroxyl function at C-14 have been described,[30] this route also formally constitutes the synthesis of adriamycinone and isoadriamycinone.

Scheme XIII



[a] Concentrated HCl, H_2O, THF, reflux. [b] Dowex 50W-C8/Hg^{2+}, H_2O, HOAc, CH_3OH, THF, 25 °C. [c] Isopropenyl acetate, *p*-toluenesulfonic acid (cat.), 25 °C. [d] $HgCl_2$, CH_2Cl_2, H_2O, 25 °C.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary apparatus and are not corrected. Unless otherwise stated, IR spectra were taken in $CHCl_3$ using a Perkin-Elmer Model 283

(26) It has been shown[15] that 7-epidaunomycinone can be epimerized by dissolving in trifluoroacetic acid (25 °C, 2 h).

(27) Stavely, H. E. *J. Am. Chem. Soc.* **1941**, *61*, 3127.

(28) (a) Newman, M. S. *J. Am. Chem. Soc.* **1953**, *75*, 4740. (b) Hajos, Z. G.; Doebel, K. J.; Goldberg, M. W. *J. Org. Chem.* **1964**, *29*, 2527.

(29) We thank Professors David Watt and James Daniel for authentic samples of daunomycinone.

(30) Smith, T. H.; Fujiwara, A. N.; Henry, D. W.; Lee, W. W. *J. Am. Chem. Soc.* **1976**, *98*, 1969.

(31) The coupling constant between the two ring junction protons of **34** is 5.2 Hz, too small for a diaxial trans coupling. Because of the difficulty in determining the A-ring conformation of **34**, the relative stereochemistry of the 7-TMS and adjacent ring junction proton was determined from the NMR data for **53**. Compound **53** was prepared from **34** without compromising the configurations of the ring junction carbons or C-7. The 7-H of **53** has 3- and 14-Hz couplings to the C-8 protons and a 3-Hz coupling to the adjacent ring junction proton. The C-10 protons have 13- and 3-Hz couplings to the adjacent ring junction proton. The large couplings establish that the 7-H, one of the 8-H's, one of the 10-H's, and the ring junction proton adjacent to C-10 are axial. Clearly, the A ring is in a chair conformation with the TMS group equatorial and the adjacent ring junction proton equatorial and thus trans to the TMS.

(32) The relative orientations of the TMS and C-9 substituents of **50** and **51** were assigned on the basis of the similarity of ^1H NMR data for **55** to data for the corresponding desmethoxy analogue and $Eu(fod)_3$ studies of the C-9 diastereomers of the desmethoxy analogue. Compound **55** was prepared from **50** without compromising the C-7 and C-9 configurations.

Coupling data for the desmethoxy diastereomers indicate that the A rings of both compounds exist in a twisted-chair conformation. The vicinal couplings of the 7-H of both diastereomers are similar in magnitude (8.0, 8.5 Hz and 8.2, 9.5 Hz), which is consistent with an axial TMS group and an equatorial 7-H. If the 7-H were axial, one of the vicinal couplings should be larger than the other. The relatively large magnitudes of the axial,equatorial and equatorial,equatorial couplings are probably due to the silicone. There is a long-range coupling of about 3 Hz between the 8-H and 10-H of both diastereomers. These protons couple through a planar W geometry of the intervening bonds, and the optimum planar W is formed when the two protons are cis to each other and equatorial.

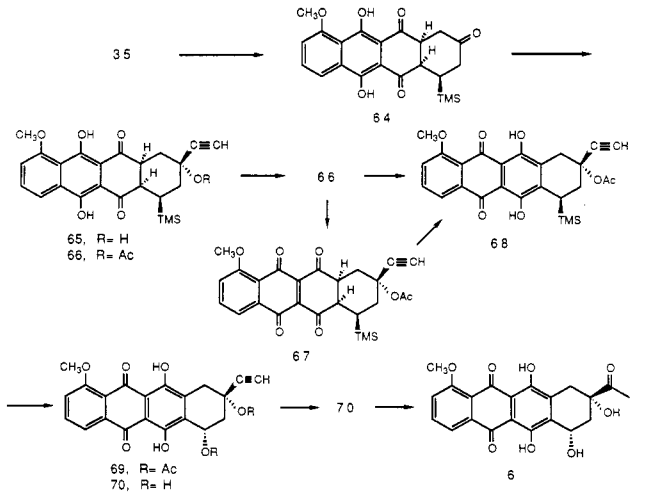
Evidence for assignments of stereochemistries at C-9 was obtained from $Eu(fod)_3$ studies of the desmethoxy diastereomers. When the OAc moiety is equatorial, it roughly bisects the angle between the 10-protons, and the two-protons shift at roughly the same rate. When the OAc is axial, the 10-proton cis to the OAc shifts more rapidly than the trans 10-proton. A similar phenomenon is observed for the 8-protons.

(33) Conversion of **58** to daunomycinone, whose structure is well established, provides proof that the configurations assigned to C-7 and C9 of **58** are correct. Although the ^1H NMR data for **58** are not useful in proving the C-7 and C-9 configurations, coupling data do indicate that the A ring is in a twisted-chair conformation and the 7-OAc is axial. Since a similar conformation and axial orientation of the $Si(CH_3)_3$ moiety have been shown for **55**, replacement of the $Si(CH_3)_3$ moiety must have been accompanied by conversion of the A ring from one twisted-chair conformer to the other. This might be expected since there would by unfavorable steric interactions between a bulky equatorial C-7 substituent and the C-6 substituent.

(34) Loev, B.; Goodman, M. M. *Chem. Ind. (London)* **1967**, 2026.

(35) Krohn, K.; Tolkiehn, K. *Chem. Ber.* **1979**, *112*, 3453.

Scheme XIV



or 681. A Varian Associates Model T-60, A-60A, or FT-80 NMR spectrometer was used to record all spectra, and chemical shifts are expressed in parts per million downfield from the internal standard tetramethylsilane ($\delta = 0$). Mass spectra were recorded on a Kratos MS-30 by Dr. J. Hribar, and all compounds submitted for mass spectrometric molecular weight determination were of high purity as determined by NMR analysis and TLC. High-resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry, The University of Nebraska, on a Kratos MS-50. Microanalyses were determined by the Searle Laboratories Microanalytical Department under the direction of Mr. E. Zielinski.

3-(2,5-Dimethoxyphenyl)-3-hydroxy-4-methoxy-1(3*H*)-isobenzofuranone (16), 3-(2,5-Dimethoxyphenyl)-3-hydroxy-7-methoxy-1(3*H*)-isobenzofuranone (17), 3,3-Bis-(2,5-dimethoxyphenyl)-4-methoxy-1(3*H*)-isobenzofuranone (18), [2-(2,5-Dimethoxybenzoyl)-3-methoxyphenyl](2,5-dimethoxyphenyl)methanone (19), and 3,3-Bis(2,5-dimethoxyphenyl)-7-methoxy-1(3*H*)-isobenzofuranone (20). A dried apparatus under argon was charged with 20.7 g (0.15 mol) of 4-methoxyanisole and 300 mL of dry Et_2O. To this stirred solution, 82 mL (0.13 mol) of hexane solution of *n*-BuLi (1.6 M) was added dropwise (20 min). After this reaction was stirred for 6 days at 25 °C and then cooled to −78 °C, 17.8 g (0.1 mol) of 3-methoxyphthalic anhydride was added all at once. Stirring was continued at −78 °C for 1 h before the reaction was warmed to 25 °C and stirred an additional 18 h. The heterogeneous reaction mixture was quenched with H_2O (500 mL), and the aqueous layer was brought to pH 2 with concentrated HCl. The desired product mixture was filtered, washed with Et_2O, and dried to give 15.2 g (48%) of a 1:1 mixture of **16** and **17**.

The aqueous filtrate was extracted with 400 mL of EtOAc in a continuous extraction apparatus. The extract was combined with the organic filtrate and extracted with 10% Na_2CO_3. After acidification to pH 2 with concentrated HCl, the heterogeneous mixture was extracted with EtOAc. This extract was dried (Na_2SO_4) and the solvent removed to give a white solid that after washing with cold Et_2O and drying produced an additional 3.0 g of the product mixture (total yield = 18.3 g, 58%). A sample of this 1:1 mixture of isomeric lactols was separated by pressure liquid chromatography (PLC) on silica gel, eluting with 10% EtOAc/toluene containing 0.75% of HOAc.

The neutral organic mother liquor was stripped of all solvent under reduced pressure to yield 11.2 g of a dark red oil that contained predominantly the three neutral products **18**, **19**, and **20**. These compounds were separated by HPLC on silica gel eluting with 10% EtOAc/toluene.

16: mp 176–180 °C; IR (KBr) 3400, 2940, 2830, 1760, 1750, 1620, 1505, 1492, 1470, 1290 cm^{-1}; ^1H NMR (DMSO-d_6) 3.35 (s, 3), 3.67 (s, 3), 3.75 (s, 3), 7.0–7.6 (m, 6).

Anal. Calcd for $C_{16}H_{16}O_6$ (316.31): C, 64.55; H, 5.10. Found: C, 64.81; H, 5.27.

17: mp 181–184 °C; IR (KBr) 3450, 3260, 2940, 2840, 1770, 1740, 1615, 1602, 1490, 1440, 1300, 1230, 1050, 820, 810 cm^{-1}; ^1H NMR (DMSO-d_6) 3.44 (s, 6), 3.76 (s, 3), 3.91 (s, 3), 6.75–7.75 (m, 6).

Anal. Calcd for $C_{17}H_{16}O_6$ (316.31): C, 64.55; H, 5.10. Found: C, 64.38; H, 5.30.

18: mp 193–195 °C; IR 2940, 2830, 1760, 1610, 1580, 1500, 1460, 1280, 1150, 1050, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) 3.53 (s, 3), 3.63 (split s, 12), 6.55–7.65 (m, 9); MS *m/e* (%) 438 (6), 437 (20), 436 (100, M^+), 377 (12), 361 (15), 331 (8), 315 (10), 299 (8).

Anal. Calcd for $C_{25}H_{24}O_7$ (436.32): C, 68.79; H, 5.54. Found: C, 69.19; H, 5.74.

19: mp 163–167 °C; IR 2960, 2940, 2840, 1670, 1610, 1580, 1470, 1320, 1280, 1180, 1050, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) 3.50 (s, 3), 3.62 (s, 3), 3.70 (s, 3), 3.73 (s, 3), 3.78 (s, 3), 6.7–7.5 (m, 9); MS *m/e* (%) 438 (5), 437 (25), 436 (100, M^+), 419 (8), 418 (19), 406 (8), 403 (8).

Anal. Calcd for $C_{25}H_{24}O_7$ (436.32): C, 68.79; H, 5.54. Found: C, 68.76; H, 5.70.

20: mp 126–129 °C; IR 2950, 2840, 1765, 1620, 1605, 1470, 1290, 1110, 1060, 970 cm^{-1}; ^1H NMR ($CDCl_3$) 3.43 (s, 6), 3.68 (s, 3), 6.7–7.1 (m, 7), 7.2–7.7 (m, 2); MS *m/e* (%) 438 (7), 437 (32), 436 (100, M^+), 377 (9), 361 (14), 331 (6), 299 (23).

Anal. Calcd for $C_{25}H_{24}O_7$ (436.32): C, 68.79; H, 5.54. Found: C, 68.74; H, 5.55.

1,4,5-Trimethoxy-9,10-anthracenedione (14). Method A. Either **16**, **17**, or a 1:1 mixture of **16** and **17** responded identically to the following procedure. A 1:1 mixture of **16** and **17** (0.5 g, (16 mmol)) and 30 mL of concentrated H_2SO_4 were combined in a vessel under a H_2O condenser. After the reaction flask was immersed in an oil bath maintained at 50 °C, the mixture was stirred for 2 h, cooled to room temperature, and poured into 300 mL of ice water. The aqueous mixture was extracted with CH_2Cl_2, and this extract was washed with 5% $NaHCO_3$ and H_2O and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 0.47 g (98%) of a yellow product (**14**). Though this material was very pure as judged by TLC and NMR, it was recrystallized from 2-propanol to give 0.23 g (50%) of **14**: mp 202–204 °C (lit.[18] mp 209 °C corr); IR 2960, 2930, 2840, 1670, 1580, 1570, 1470, 1320, 1270, 1060, 990 cm^{-1}; ^1H NMR ($CDCl_3$) 3.97 (s, 6), 4.00 (s, 3), 7.1–7.9 (m, 5).

Anal. Calcd for $C_{17}H_{14}O_5$ (298.30): C, 68.45; H, 4.73. Found: C, 68.22; H, 4.98.

Method B. A 2.0-g (8 mmol) sample of crude (~74%) 1,4,5-trihydroxyanthraquinone **28**,[19] 30 g (210 mmol) of K_2CO_3, 100 mL of acetone, and 20 mL (210 mmol) of dimethyl sulfate were combined. This stirred mixture was refluxed for 5.5 h, cooled to room temperature, and stirred overnight. The yellow-green reaction was poured into a mixture of 300 mL of H_2O and 150 mL of CH_2Cl_2. After filtration, the solid was washed with CH_2Cl_2. The aqueous layer of the filtrate was separated, washed with CH_2Cl_2, and discarded. The combined organic fractions were washed with H_2O, treated with charcoal, filtered through Celite, dried (Na_2SO_4), and stripped of solvent under reduced pressure to give a dark red solid. This material, chromatographed (PLC) on silica gel eluting with 3% acetone/CH_2Cl_2, gave 1.68 g (72%) of analytically pure **14**.

1,4-Dihydroxy-5-methoxy-9,10-anthracenedione (30). To a solution of 50 mg (0.19 mmol) of **29** in 30 mL of glacial HOAc was added 0.5 g of $NaHSO_3$. After 1 h the light orange mixture reaction was poured into 100 mL of H_2O and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to give 20 mg of **30** (mp 216–223 °C (lit.[35] mp 247–249 °C)), whose NMR, IR, and MS spectra were indistinguishable from those of **30** isolated in the synthesis of **34** and **35**.

5-Methoxy-1,4,9,10-anthracenetetrone (29). To a stirred mixture of 0.36 g (1.3 mmol) of **30** in 25 mL of glacial HOAc under an argon atmosphere was added 0.71 g (1.6 mmol) of $Pb(OAc)_4$. Within 5 min the red-orange solution turned the brick red color characteristic of **29**.[15] After 35 min, all solvent was evaporated and the residue in water was extracted twice with CH_2Cl_2. The CH_2Cl_2 fractions were dried (Na_2SO_4) and evaporated under reduced pressure to produce the red-brown product **29**, which was identical with that produced from **14**.[18]

(±)-3-(Acetyloxy)-1,4,4aβ,12aβ-tetrahydro-10-methoxy-1α-(trimethylsilyl)-5,6,11,12-naphthacenetetrone (32) and (±)-3-(Acetyloxy)-1,4,4aβ,12aβ-tetrahydro-7-methoxy-1α-(trimethylsilyl)-5,6,11,12-naphthacenetetrone (33). To 9.25 g (35 mmol) of diquinone **29** in 300 mL of CH_2Cl_2 was added 12.7

g (67 mmol) of 4-(trimethylsilyl)-2-acetoxy-1,3-butadiene (**31**).[12a,b] The mixture was refluxed under argon for 17 h for complete reaction. The TLC (20% EtOAc/toluene) of the solution after cooling to room temperature suggested that the resulting two rust-colored adducts **32** and **33** were formed in an approximately 1:1 ratio. Since all efforts at isolating and separating these materials led to decomposition, they were converted directly to dihydro derivatives **34** and **35** as described below.

(±)-3-(Acetyloxy)-1,4,4aβ,12aβ-tetrahydro-6,11-dihydroxy-10-methoxy-1α-(trimethylsilyl)-5,12-naphthacenedione (34), (±)-3-(Acetyloxy)-1,4,4aβ,12aβ-tetrahydro-6,11-dihydroxy-7-methoxy-1α-(trimethylsilyl)-5,12-naphthacenedione (35), (±)-8-(Acetyloxy)-7,10-dihydro-6,11-dihydroxy-1-methoxy-10-(trimethylsilyl)-5,12-naphthacenedione (36), and (±)-9-(Acetyloxy)-7,10-dihydro-6,11-dihydroxy-1-methoxy-7-(trimethylsilyl)-5,12-naphthacenedione (37). To the complete reaction mixture from the preceding experiment were added 75 mL of HOAc and 4.5 g (69 mmol) of zinc dust (300–400 mesh, Fisher Scientific). After 7 min of vigorous stirring, the Zn salts were filtered and washed with CH_2Cl_2. The combined filtrate was washed with water, dried (Na_2SO_4), and evaporated to give 21.9 g of an orange solid product mixture. A combination of PLC (Biosil A silica gel, eluting with 5% EtOAc/toluene) and DCLC[34] (CC-4 silica, eluting with 3% EtOAc/toluene) was used to isolate the yellow major products **34** and **35** as well as small amounts of the red aromatic regioisomers **36** and **37** and tricyclic **30**. TLC's were run on Analtech 25 Woelm silica gel GF and developed in 20% EtOAc/benzene (toluene) with 0.3% HOAc.

34: 5.4 g, 35%; mp 214–222 °C; IR 2940, 2840, 1750, 1640, 1600, 1580, 1460, 1400, 1360, 1110, 1060 cm^{-1}; ^1H NMR ($CDCl_3$)[31] 0.12 (s, 9), 1.8–2.2 (m, 1), 2.07 (s, 3), 2.3–2.6 (m, 2), 3.1–3.6 (m, 2), 4.02 (s, 3), 5.4–5.6 (m, 1), 7.1–8.2 (m, 3), 13.32 (s, 1), 14.38 (s, 1); MS *m/e* (%) 455 (8), 454 (M^+, 25), 439 (26), 426 (17), 412 (15), 411 (39), 395 (30), 353 (15), 327 (22), 322 (28), 73 (100).

Anal. Calcd for $C_{24}H_{26}O_7Si$ (454.56): C, 63.42; H, 5.77. Found: C, 63.43; H, 5.78.

35: 4.2 g, 27%; mp 119–129 °C; IR 2940, 2840, 1750, 1630, 1600, 1580, 1460, 1400, 1360, 1340, 1120, 1090, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) 0.12 (s, 9), 1.8–2.2 (m, 1), 2.07 (s, 3), 2.3–2.6 (m, 2), 3.0–3.6 (m, 2), 4.03 (s, 3), 5.4–5.6 (m, 1), 7.0–8.2 (m, 3), 13.25 (s, 1), 14.45 (s, 1); MS *m/e* (%) 455 (1), 454 (M^+, 5) 412 (17), 397 (54), 393 (13), 281 (11), 73 (100).

Anal. Calcd for $C_{24}H_{26}O_7Si$ (454.56): C, 63.42; H, 5.77. Found: C, 63.73; H, 5.88.

36: 0.3 g, 2%; IR 3700, 2930, 2860, 1770, 1740, 1590, 1470, 1380, 1360, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) 0.08 (s, 9), 2.18 (s, 3), 3.53 (bs, 2), 4.07 (s, 3), 7.2–8.1 (m, 3), 13.50 (s, 1); MS *m/e* (%), 452 (M^+, 1), 435 (4), 393 (13), 379 (21), 378 (78), 338 (25), 337 (26), 336 (100), 319 (20), 318 (73), 317 (32).

37: 0.6 g, 4%; mp 218–219 °C; IR 3700, 2960, 2840, 1750, 1620, 1590, 1450, 1440, 1380, 1350, 1290, 1140, 1110, 1090, 1070, 1020, 1010, 990 cm^{-1}; ^1H NMR ($CDCl_3$) 0.08 (s, 9), 2.18 (s, 3), 3.52 (bs, 2), 4.03 (s, 3), 7.2–8.1 (m, 3), 13.50 (s, 1), 13.85 (s, 1); MS *m/e* (%) 453 (2), 452 (M^+, 7) 435 (13), 410 (23), 393 (60), 379 (40), 377 (28), 73 (100).

Oxidation of 35 to 33 (Oxidation of 34 to 32). To a yellow solution of **35** (70 mg, 0.15 mmol) dissolved in 25 mL of HOAc under N_2 was added 70 mg (0.16 mmol) of $Pb(OAc)_4$. After stirring for 20 min at room temperature, the resulting orange-red mixture was combined with 50 mL of H_2O and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with H_2O (20 mL), dried (Na_2SO_4), and evaporated. The resulting brick red solid was redissolved in benzene, and TLC's (20% EtOAc/benzene with 0.3% HOAc) of this solution and a benzene solution of a mixture of Diels–Alder adducts **32** and **33** were run. The product of this reaction had an R_f identical with that of the slower moving isomer **33**.

When regioisomer **34** was substituted for **35** in this reaction, **32**, the isomer with the greater R_f value, was formed.

Conversion of 33 to 37 (Conversion of 32 to 36). A 10-mg sample of **33**, the product from the preceding reaction, was dissolved in 10 mL of HOAc. One milliliter of a saturated solution of KOAc in HOAc was added to the reaction vessel. This mixture was stirred under N_2 at room temperature for 1.5 h before dilution with H_2O (50 mL) and extraction with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give red solid **37**. After this product was dissolved in CH_2Cl_2, a comparison TLC (20% EtOAc/benzene with 0.3% HOAc) of this material and a mixture of **36** and **37** showed that the product of this reaction had an R_f identical with that of the slower regioisomer.

When isomer **32** was substituted for **33** in an identical reaction, **36**, the regioisomer with the greater R_f value, was formed.

(±)-3,4,4aβ,12aβ-Tetrahydro-6,11-dihydroxy-7-methoxy-4α-(trimethylsilyl)-2,5,12(1*H*)-naphthacenetrione (42) and (±)-3,4-Dihydro-5,12-dihydroxy-7-methoxy-4-(trimethylsilyl)-2,6,11(1*H*)-naphthacenetrione (45). Dry EtOH (200 mL) was deoxygenated by bubbling argon through for 4 h at room temperature followed by refluxing for 1 h under Ar. After the EtOH was cooled to room temperature, **34** (2.46 g, 5 mmol) was dissolved in the EtOH, and the yellow solution was cooled to 0 °C in an ice bath. A 7.6-mL (16.2 mmol) sample of MeMgBr in Et_2O (Alfa, 2.15 M) was slowly (10 min) injected into the stirred reaction mixture. The resulting purple solution was stirred at 0 °C for 3 h before it was poured into 300 mL of a 2:1 mixture of 2% aqueous HOAc and CH_2Cl_2. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a yellow-orange solid. This material was chromatographed (DCLC) on CC-4 silica, eluting with 3% EtOAc/toluene, to give 1.86 g (86%) of **42** after recrystallization from CH_2Cl_2/hexane and 37 mg of **45**.

42: mp 220–222 °C; IR 3680, 2940, 2900, 2840, 1710, 1630, 1600, 1580, 1460, 1440, 1360, 1330, 1160, 1120, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) 0.13 (s, 9), 1.1–1.65 (m, 1), 2.3–2.7 (m, 4), 4.03 (s, 3), 7.1–8.2 (m, 3), 13.40 (s, 1), 14.58 (s, 1); MS *m/e* (%) 413 (5), 412 (M^+, 21) 410 (5), 398 (26), 397 (100), 384 (6), 382 (6), 294 (4), 73 (43).

Anal. Calcd for $C_{22}H_{24}O_6Si$ (412.52): C, 64.06; H, 5.86. Found: C, 63.95; H, 5.92.

45: mp 236–239 °C; IR 3680, 2960, 2900, 2840, 1710, 1610, 1580, 1450, 1380, 1340, 1280, 1270, 1070, 1020, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) 0.05 (s, 9), 2.6–2.8 (m, 2), 3.1–3.7 (m, 3), 4.07 (s, 3), 7.2–8.1 (m, 3), 13.40 (s, 1), 13.92 (s, 1); MS *m/e* (%) 411 (29), 410 (M^+, 100), 395 (37), 393 (16), 382 (41), 367 (53), 365 (63), 351 (22), 349 (15), 309 (53), 307 (32), 73 (49).

Anal. Calcd for $C_{22}H_{22}O_6Si$ (410.37): C, 64.37; H, 5.40. Found: C, 64.71; H, 5.55.

(±)-3,4,4aβ,12aβ-Tetrahydro-6,11-dihydroxy-10-methoxy-4α-(trimethylsilyl)-2,5,12(1*H*)-naphthacenetrione (64) and (±)-3,4-Dihydro-5,12-dihydroxy-10-methoxy-4-(trimethylsilyl)-2,6,11(1*H*)-naphthacenetrione (71). In a procedure identical with that used to prepare **42**, **35** was converted to **64** and a small amount of **71**.

64: mp 199–208 °C; IR 3680, 2950, 2900, 2840, 1710, 1630, 1610, 1580, 1460, 1440, 1400, 1370, 1340, 1280, 1150, 1120, 1080, 960 cm^{-1}; ^1H NMR ($CDCl_3$) 0.17 (s, 9), 1.1–1.5 (m, 1), 2.2–2.8 (m, 4), 3.1–3.7 (m, 2), 4.03 (s, 3), 7.0–8.2 (m, 3), 13.37 (s, 1), 14.46 (s, 1); MS *m/e* (%) 413 (16), 412 (M^+, 43), 410 (9), 398 (15), 397 (100), 384 (6), 294 (12), 73 (46).

Anal. Calcd for $C_{22}H_{24}O_6Si$ (412.52): C, 64.06; H, 5.86. Found: C, 64.15; H, 5.83.

71: mp 182–210 °C; IR 3680, 2950, 2840, 1720, 1610, 1580, 1450, 1380, 1350, 1280, 1150, 1070, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) 0.05 (s, 3), 2.6–2.8 (m, 2), 3.1–3.7 (m, 3), 4.05 (s, 3), 7.1–8.1 (m, 3), 13.44 (s, 1), 13.72 (s, 1); MS *m/e* (%) 411 (11), 410 (M^+, 37), 395 (16), 393 (10), 382 (7), 367 (18), 365 (19), 351 (11), 349 (6), 309 (2), 73 (100).

Anal. Calcd for $C_{22}H_{22}O_6Si$ (410.37): C, 64.37; H, 5.40. Found: C, 64.45; H, 5.45.

(±)-3-Ethynyl-1,2,3,4,4aβ,12aβ-hexahydro-3β,6,11-trihydroxy-10-methoxy-1α-(trimethylsilyl)-5,12-naphthacenedione (50). Approximately 15 mL of dry acetylene was condensed in 30 mL of THF (distilled from Na) contained in an oven-dried flask cooled to −78 °C. An ethereal solution of EtMgBr (6.3 mL, 16 mmol) was added dropwise (5 min) to the stirred mixture maintained at −78 °C under Ar. After the reaction temperature was allowed to rise slowly to 10 °C and excess acetylene was allowed to escape, the pink mixture was cooled to −20 °C and ketone **42** (2.06 g, 5.0 mmol), suspended in 30 mL of THF, was added over 10 min. The resulting dark red solution was stirred at −20 °C for 30 min and 0 °C for 1 h and then poured

into 60 mL of cold (0 °C) saturated NH_4Cl. After dilution with 1 N HCl (90 mL) and water (200 mL), a slow stream of N_2 was bubbled through the solution for 12 h. The resulting aqueous mixture was extracted with CH_2Cl_2 (4 × 100 mL), and the combined extract was dried (Na_2SO_4) and evaporated to produce 2.7 g of an orange solid. Recrystallization of this material from hexane/CH_2Cl_2 and chromatography (DCLC) of the mother liquor on CC-4 silica, eluting with 20% EtOAc/hexane, gave 1.97 g (90%) of **50**, 39 mg of **42**, and 13 mg of a material whose spectrum was consistent with **52**.

50: mp 208–211 °C; IR 3680, 3580, 3300, 2940, 2860, 1630, 1600, 1580, 1460, 1440, 1400 1360, 1330, 1300, 1150, 1120, 1060 cm^{-1}; ^1H NMR ($CDCl_3$)[32] 0.12 (s, 9), 1.0–2.5 (m, 5), 2.58 (s, 1), 3.0–3.9 (m, 3), 4.02 (s, 3), 7.0–8.1 (m, 3), 13.46 (s, 1), 14.59 (s, 1); MS *m/e* (%) 439 (8), 438 (M^+, 27), 424 (21), 423 (69), 406 (26), 405 (87), 353 (10), 327 (13), 280 (14), 149 (22), 73 (100).

Anal. Calcd for $C_{24}H_{26}O_6Si$ (438.56): C, 65.73; H, 5.98. Found: C, 65.75; H, 6.27.

(±)-3-Ethynyl-1,2,3,4,4aβ,12aβ-hexahydro-3β,6,11-trihydroxy-7-methoxy-1α-(trimethylsilyl)-5,12-naphthacenedione (65). In a procedure identical with that described for the synthesis of **50**, 600 mg (1.45 mmol) of **64** in 30 mL of THF was added to a THF (30 mL) solution of the acetylide salt generated from condensed acetylene (~15 mL) and 1.8 mL (4.50 mmol) of EtMgBr. After workup of the reaction mixture, the resulting yellow-orange product solid was recrystallized from CH_2Cl_2/hexane to yield 303 mg (48%) of **65**: mp 263–267 °C; IR 3680, 3580, 3300, 2940, 2860, 2840, 1630, 1600, 1580, 1460, 1440, 1400, 1340, 1300, 1160, 1120, 1080, 1040 cm^{-1}; ^1H NMR 0.14 (s, 9), 1.0–2.5 (m, 5), 2.57 (s, 1), 3.0–3.9 (m, 3), 4.03 (s, 3), 7.0–8.1 (m, 3), 13.42 (s, 1), 14.68 (s, 1); MS *m/e* (%) 439 (13), 438 (M^+, 39), 424 (9), 423 (28), 406 (29), 405 (99), 387 (14), 353 (5), 327 (8), 280 (6), 73 (100).

Anal. Calcd for $C_{24}H_{26}O_6Si$ (438.56): C, 65.73; H, 5.98. Found: C, 65.52; H, 5.91.

(±)-3β-(Acetyloxy)-3-ethynyl-1,2,3,4,4aβ,12aβ-hexahydro-6,11-dihydroxy-10-methoxy-1α-(trimethylsilyl)-5,12-naphthacenedione (53). To 1.26 g (2.9 mmol) of **50** dissolved in 25 mL of freshly distilled isopropenyl acetate under an argon atmosphere was added 50 mg of *p*-toluenesulfonic acid monohydrate. After this mixture was stirred at room temperature for 3 days, the yellow crystalline product precipitated from solution. The acetate (**53**) was isolated by filtration and washed with a 3:1 mixture of hexane/Et_2O. The concentrated filtrate was chromatographed (DCLC) on CC-4 silica, eluting with 15% EtOAc/hexane, to give a combined yield of 1.19 g (86%) of **53**: mp 249–255 °C; IR 3680, 3300, 2940, 2900, 2860, 2840, 1740, 1630, 1600, 1580, 1460, 1440, 1400, 1370, 1320, 1300, 1160, 1130, 1060, 1020 cm^{-1}; ^1H NMR ($CDCl_3$)[31] 0.14 (s, 9), 1.0–2.9 (m, 5), 1.97 (s, 3), 2.72 (s, 1), 3.1–3.5 (m, 2), 4.02 (s, 3), 7.0–8.1 (m, 3), 13.41 (s, 1), 14.59 (s, 1); MS *m/e* (%) 481 (3), 480 (M^+, 12), 466 (10), 465 (26), 406 (30), 405 (100), 387 (7), 353 (7), 330 (13), 327 (11), 73 (88).

Anal. Calcd for $C_{26}H_{28}O_7Si$ (480.60): C, 64.98; H, 5.87. Found: C, 64.79; H, 5.87.

(±)-3β-(Acetyloxy)-3-ethynyl-1,2,3,4,4aβ,12aβ-hexahydro-6,11-dihydroxy-7-methoxy-1α-(trimethylsilyl)-5,12-naphthacenedione (66). By the procedure described in the previous experiment, 160 mg (0.36 mmol) of **65** dissolved in 20 mL of isopropenyl acetate was combined with 10 mg of *p*-toluenesulfonic acid monohydrate. The product (**66**) was isolated by filtration, and the concentrated filtrate was chromatographed (DCLC) to give 162 mg (93%) of **66**: mp 226–228 °C; IR 3680, 3300, 2950, 2900, 2860, 2840, 1750, 1630, 1610, 1580, 1460, 1440, 1400, 1370, 1340, 1300, 1150, 1130, 1110, 1080, 1040, 1020 cm^{-1}; ^1H NMR 0.16 (s, 9), 1.0–2.9 (m, 5), 1.98 (s, 3), 2.73 (s, 1), 3.1–3.5 (m, 2), 4.02 (s, 3), 6.9–8.1 (m, 3), 13.44 (s, 1), 14.64 (s, 1); MS *m/e* (%) 481 (12), 480 (M^+, 38), 465 (1), 406 (34), 405 (100), 387 (4), 353 (2), 330 (5), 327 (6), 73 (87).

Anal. Calcd for $C_{26}H_{28}O_7Si$ (480.60): C, 64.98; H, 5.87. Found: C, 65.29; H, 5.99.

(±)-3β-(Acetyloxy)-3-ethynyl-1,2,3,4,4aβ,12aβ-hexahydro-10-methoxy-1α-(trimethylsilyl)-5,6,11,12-naphthacenetetrone (54). Lead tetraacetate (1.04 g, 2.3 mmol) was added to a stirred CH_2Cl_2 (30 mL) solution of **53** (1.02 g, 2.1 mmol) under argon and immersed in an ice bath. An almost immediate color change (yellow to red) and precipitation of a white solid were noted. Within 10 min, the reaction was complete and the lead salts were removed by filtration. Concentrating the filtrate under reduced pressure gave the rust-brown quinone product (**54**), which was dissolved in CH_2Cl_2 (3 mL) and reprecipitated with hexanes. The product was isolated by filtration, washed with hexane, and dried to give 1.01 g (98%) of **54**: mp 158–162 °C; IR 3670, 3300, 2940, 2900, 2840, 1740, 1720, 1660, 1580, 1470, 1370, 1350, 1330, 1280, 1160, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) 0.15 (s, 9), 1.0–2.9 (m, 5), 1.99 (s, 3), 2.72 (s, 1), 3.3–3.7 (m, 2), 3.97 (s, 3), 7.1–7.9 (m, 3); MS *m/e* (%) 480 (M^+ + 2, 2), 465 (4), 419 (3), 405 (12), 75 (100).

Anal. Calcd for $C_{26}H_{26}O_7Si$ (478.59): C, 65.25; H, 5.48. Found: C, 65.01; H, 5.29.

(±)-3β-(Acetyloxy)-3-ethynyl-1,2,3,4,4aβ,12aβ-hexahydro-7-methoxy-1α-(trimethylsilyl)-5,6,11,12-naphthacenetetrone (67). In a reaction identical with that described above for the synthesis of **54**, 50 mg (0.10 mmol) of **66** was oxidized with $Pb(OAc)_4$ (55 mg, 0.12 mmol) to give 48 mg (96%) of **67**: mp 186–216 °C; IR 3680, 3300, 2940, 2840, 1750, 1720, 1670, 1590, 1480, 1450, 1370, 1280, 1120, 1070, 1020 cm^{-1}; ^1H NMR (CD_2Cl_2) 0.14 (s, 9), 1.1–2.8 (m, 5), 1.98 (s, 3), 2.80 (s, 1), 3.3–3.6 (m, 2), 3.98 (s, 3), 7.7–7.6 (m, 3); MS *m/e* (90), 480 (M^+ + 2, 3), 405 (11), 147 (5), 117 (30), 75 (100).

Anal. Calcd for $C_{26}H_{26}O_7Si$ (478.59): C, 65.25; H, 5.48. Found: C, 65.55; H, 5.72.

***trans*-(±)-8-(Acetyloxy)-8-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-10-(trimethylsilyl)-5,12-naphthacenedione (55).** A solution of **54** (960 mg, 2.0 mmol) in 25 mL of HOAc under an argon atmosphere was immersed in an oil bath maintained at 90 ± 3 °C. After the addition of 250 mg (2.5 mmol) of KOAc, the warmed mixture was stirred for 2.5 h before it was cooled to room temperature and allowed to stand for 19 h. The red crystalline product (**55**) was isolated by filtration, washed with a 1:1 mixture of Et_2O/hexane, and dried in vacuo (640 mg). The mother liquor and washes were combined with H_2O (150 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extract was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (DCLC) of the residue on CC-4 silica using 10% EtOAc/hexanes as eluent provided 74 mg of **54** and an additional 130 mg of **55** (yield = 770 mg, 87%): mp 156–241 °C dec; IR ($CHCl_3$) 3700, 3320, 2960, 2900, 2850, 1750, 1620, 1590, 1450, 1390, 1370, 1350, 1290, 1070, 1040, 990 cm^{-1}; ^1H NMR ($CDCl_3$)[32] 0.09 (s, 9), 1.8–3.3 (m, 4), 2.09 (s, 3), 2.41 (s, 1), 3.5–3.9 (m, 1), 4.05 (s, 3), 7.1–8.0 (m, 3), 13.46 (s, 1), 14.05 (s, 1); MS *m/e* (%) 479 (1), 478 (M^+, 2), 475 (5), 463 (16), 460 (20), 418 (18), 404 (36), 403 (100), 401 (16), 388 (7), 387 (10), 346 (13), 73 (20).

Anal. Calcd for $C_{26}H_{26}O_7Si$ (478.59): C, 65.25; H, 5.48. Found: C, 65.07; H, 5.48.

***trans*-(±)-9-(Acetyloxy)-9-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-7-(trimethylsilyl)-5,12-naphthacenedione (68).** By the procedure described for the synthesis of **55**, 48 mg (0.10 mmol) of **67** in 12.5 mL of HOAc was treated with 125 mg (1.3 mmol) of KOAc. After this mixture was stirred for 3 h under argon at 90 ± 4 °C, it was cooled to room temperature and poured into H_2O (50 mL). This mixture was extracted with CH_2Cl_2 (4 × 25 mL), and the combined organic extracts were washed with H_2O (25 mL), dried (Na_2SO_4), and concentrated to yield 43 mg (90%) of **68** after drying: mp 203–205 °C; IR 3320, 2960, 2940, 2860, 1750, 1620, 1590, 1450, 1290, 1070, 1020, 990 cm^{-1}; ^1H NMR ($CDCl_3$) 0.07 (s, 9), 1.8–3.1 (m, 4), 2.10 (s, 3), 2.38 (s, 1), 3.5–3.9 (m, 1), 4.07 (s, 3), 7.2–8.1 (m, 3), 13.62 (s, 1), 13.84 (s, 1); MS *m/e* (%) 479 (1), 478 (M^+, 4), 418 (37), 404 (26), 403 (100), 401 (22), 387 (27), 346 (11), 330 (12), 328 (11), 310 (11), 73 (99).

Anal. Calcd for $C_{26}H_{26}O_7Si$ (478.59): C, 65.25; H, 5.48. Found: C, 64.94; H, 5.89.

***cis*-(±)-8,10-Bis(acetyloxy)-8-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-5,12-naphthacenedione (58). A.** To 694 mg (1.45 mmol) of **55** dissolved in 25 mL of HOAc were added 500 mg (5.1 mmol) of KOAc and 770 mg (1.74 mmol) of $Pb(OAc)_4$. This mixture was stirred at room temperature and under argon for 3 days. The red crystalline product (**58**) that had precipitated from solution was isolated by filtration, washed with 30 mL of HOAc, washed with 3 × 50 mL of a 1:1 mixture of Et_2O/hexane, and dried (0.50 g, 74%). The red mother liquor,

following dilution with 100 mL of H_2O, was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts after drying (Na_2SO_4) and removing all solvent gave an additional 160 mg of **58** (total yield = 660 mg, 98%): mp stable 300 °C; IR 3680, 3520, 3300, 2970, 2940, 2820, 1750, 1620, 1580, 1370, 1280, 1140, 1120, 1070, 1050, 1030, 990 cm^{-1}; ^1H NMR ($CDCl_3$)[33] 1.8–4.1 (m, 4), 1.97 (s, 3), 2.02 (s, 3), 2.65 (s, 1), 4.06 (s, 3), 6.2–6.4 (m, 1), 7.1–8.1 (m, 3), 13.17 (s, 1), 13.55 (s, 1); MS *m/e* (%) 464 (M^+, 1), 404 (3), 362 (11), 346 (11), 345 (29), 344 (100), 327 (16), 326 (43), 325 (17), 314 (7), 298 (15).

Anal. Calcd for $C_{25}H_{20}O_9$ (464.43): C, 64.65; H, 4.34. Found: C, 64.80; H, 4.35.

B. Direct Synthesis of 58 from 53. To a stirred HOAc (25 mL) solution of **53** (500 mg, 1.05 mmol) under argon were added 450 mg (4.6 mmol) of KOAc and 560 mg (1.26 mmol) of $Pb(OAc)_4$. Within 5 min the yellowish mixture had turned red and after 30 min, TLC (30% EtOAc/toluene) indicated the conversion to **54** was complete. The flask was immersed in an oil bath maintained at 90 ± 3 °C for 1.75 h and then cooled to room temperature (1 h). TLC indicated that the generation of **55** was complete and a small amount of **58** was produced. An additional 510 mg (1.15 mmol) of $Pb(OAc)_4$ was added. After 2 days of slow stirring, the red crystalline product (**58**) was isolated by filtration, washed with HOAc (20 mL), washed with 2 × 50 mL of a 1:1 mixture of Et_2O/hexane, and dried in vacuo (202 mg, 42%). The combined mother liquor and washes were diluted with H_2O (150 mL) and 100 mL of CH_2Cl_2. After the CH_2Cl_2 phase was separated, the aqueous phase was extracted with 2 × 50 mL of CH_2Cl_2. The combined extract was dried (Na_2SO_4) and concentrated to yield an additional 242 mg of **58**, which was identical with the material whose preparation is described above (total yield = 444 mg, 91%).

Direct Synthesis of *cis*-(±)-7,9-Bis(acetyloxy)-9-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-5,12-naphthacenedione (69) from (±)-3β-(Acetyloxy)-3-ethynyl-1,2,3,4,4aβ,12aβ-hexahydro-6,11-dihydroxy-7-methoxy-1α-(trimethylsilyl)-5,12-naphthacenedione (66). By the procedure described above for the synthesis of **58**, 790 mg (1.64 mmol) of **66**, 20 mL of HOAc, 700 mg (7.1 mmol) of KOAc, and 874 mg (2.0 mmol) of $Pb(OAc)_4$ were combined and stirred under argon at room temperature for 30 min. The mixture was heated at 92 ± 3 °C for 1.45 h, cooled to room temperature (1 h), charged with $Pb(OAc)_4$ (800 mg, 1.80 mmol), and stirred slowly for 2 days. The red-orange crystalline product (**69**) was isolated by filtration and washed liberally with a 1:1 mixture of Et_2O/hexane (480 mg). After the combined mother liquor and washes were worked up, the residue was chromatographed (DCLC) on CC-4 silica, eluting with 10% EtOAc/toluene, to yield an additional 87 mg (combined yield 75%) of **69**: mp >300 °C; IR 3680, 3320, 2930, 2840, 1750, 1620, 1590, 1420, 1380, 1290, 1140, 1130, 1100, 1060, 1050 cm^{-1}; ^1H NMR (CD_2Cl_2) 1.8–4.0 (m, 4), 1.93 (s, 3), 1.99 (s, 3), 2.68 (s, 1), 4.03 (s, 3), 2.68 (s, 1), 4.03 (s, 3), 6.1–6.5 (m, 1), 7.2–8.1 (m, 3), 13.20 (s, 1), 13.70 (s, 1); MS *m/e* (%) 465 (1), 464 (M^+, 3), 405 (7), 393 (3), 362 (6), 344 (100), 326 (29).

Anal. Calcd for $C_{25}H_{20}O_9$ (464.43): C, 64.65; H, 4.34. Found: C, 64.36; H, 4.27.

***cis*-(±)-8-Acetyl-8,10-bis(acetyloxy)-7,8,9,10-tetrahydro-6,11-dihydroxy-1-methoxy-5,12-naphthacenedione (59).** To a solution of 300 mg (0.65 mmol) of **58** in 40 mL of CH_2Cl_2 were added 0.5 mL of H_2O and 385 mg (1.40 mmol) of $HgCl_2$. This mixture was stirred 17 h under argon and then diluted with 100 mL each of 10% HCl and CH_2Cl_2. The CH_2Cl_2 phase was separated and the aqueous phase extracted with 50 mL of CH_2Cl_2. The combined organic extract was washed with 2 × 100 mL of 10% HCl and 150 mL of H_2O, dried (Na_2SO_4), and evaporated to provide 297 mg (95%) of **59**. Only traces of **63** were detected in this product. A sample of **59** was chromatographed (DCLC) on CC-7 silica, eluting with 35% EtOAc/toluene containing 0.5 mL of HOAc/L: mp >300 °C; IR 3670, 2960, 2920, 2850, 1740, 1720, 1610, 1380, 1370, 1280, 1120, 1040, 980 cm^{-1}; ^1H NMR ($CDCl_3$) 1.8–3.8 (m, 4), 2.02 (s, 3), 2.05 (s, 3), 2.25 (s, 3), 4.08 (s, 3), 6.4–6.5 (m, 1), 7.1–8.1 (m, 3), 13.30 (s, 1), 13.68 (s, 1); MS *m/e* (%) 482 (M^+, 1), 422 (1), 380 (2), 362 (52), 344 (8), 337 (6), 319 (7), 301 (8), 43 (100).

Anal. Calcd for $C_{25}H_{22}O_{10}$ (482.45): C, 62.24; H, 4.60. Found: C, 62.05; H, 4.52.

***cis*-(±)-8-Ethynyl-7,8,9,10-tetrahydro-6,8,10,11-tetrahydroxy-1-methoxy-5,12-naphthacenedione (63).** A mixture of **58** (100 mg, 0.22 mmol) in 60 mL of THF, 5 mL of H_2O, and 5 mL of concentrated HCl was refluxed under argon for 72 h, cooled to room temperature, and stirred slowly for another 48 h. The red crystalline product (**63**) was isolated by filtration, washed with THF (100 mL), and dried in vacuo (63 mg). On concentrating the filtrate, 15 mg of a second crop of **63** was obtained, raising the total yield to 78 mg (95%): mp >300 °C; IR 3700, 3620, 3280, 2960, 2930, 1620, 1580, 1480, 1380, 1080, 1060, 1020 cm^{-1}; ^1H NMR (DMSO-d_6) 1.8–2.5 (m, 4), 3.00 (s, 1), 3.98 (s, 3), 6.16 (bs, 1), 7.4–8.0 (m, 3), 10.58 (s, 1), 11.14 (s, 1); MS *m/e* (%) 381 (19), 380 (M^+, 65), 363 (30), 362 (100), 345 (26), 344 (40), 334 (24), 326 (22), 319 (26), 309 (35), 295 (27).

Anal. Calcd for $C_{21}H_{16}O_7$ (380.36): C, 66.31; H, 4.24. Found: C, 66.50; H, 4.16.

***cis*-(±)-9-Ethynyl-7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-1-methoxy-5,12-naphthacenedione (70).** A solution of **69** (220 mg, 0.47 mmol) in 100 mL of THF, and 10 mL each of concentrated HCl and H_2O was refluxed for 60 h, cooled to room temperature, and diluted with water (125 mL) and CH_2Cl_2 (100 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. The product residue (**70**), whose TLC indicated a single anthracycline product, was washed extensively with Et_2O to remove THF decomposition residue. These washes were concentrated and the residue was chromatographed (DCLC) on CC-4 silica, eluting with 10–40% EtOAc/toluene to give **70** in a combined yield of 173 mg (96%): mp 242–243 °C; IR 3700, 3620, 3320, 2940, 2860, 1620, 1590, 1380, 1350, 1290, 1070, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) 1.9–3.7 (m, 5), 2.55 (s, 1), 4.07 (s, 3), 7.4–8.1 (m, 3), 13.56 (s, 1), 13.66 (s, 1); MS *m/e* calcd for $C_{21}H_{16}O_7$ 380.089; found 380.089.

(±)-Daunomycinone (5). To the red solution of **63** (8 mg, 0.021 mmol) in a mixture of H_2O (1 mL), HOAc (1 mL), MeOH (2 mL), and THF (4 mL) was added 40 mg of Dowex 50W-X8/Hg^{2+}.[28] This mixture was stirred at room temperature under argon for 17 h before TLC indicated that the reaction was complete, with **5** as the only discernible product. The mixture was filtered and the resin washed with CH_2Cl_2. The filtrate was washed with H_2O, dried (Na_2SO_4), and evaporated to give 5 mg (60%) of **5** that was identical in all respects with an authentic sample.[29]

Synthesis of 59 from (±)-Daunomycinone (5). A single crystal of *p*-toluenesulfonic acid monohydrate was added to an authentic sample (10 mg, 0.025 mmol) of (±)-daunomycinone (**5**)[29] dissolved in 5 mL of freshly distilled isopropenyl acetate. This mixture was stirred at room temperature under argon for 10 days before TLC (50% EtOAc/toluene HOAc) indicated the reaction was nearly complete. After the mixture was diluted with 100 mL of CH_2Cl_2, it was washed 3 × 75 mL of H_2O, dried (Na_2SO_4), and evaporated. The red residue was chromatographed (DCLC) on CC-7 silica, eluting with 35% EtOAc/toluene containing 0.5 mL of HOAc/L to yield 9 mg (75%) of **59** that was identical with the material prepared from **58**.

(±)-Isodaunomycinone (6). Dowex 50W-X8 Hg^{2+} (400 mg) was added to **70** (100 mg, 0.26 mmol) dissolved in a mixture of H_2O (10 mL), HOAc (10 mL), MeOH (20 mL), and THF (40 mL). After the mixture was stirred at room temperature under argon for 48 h, the resin was filtered and washed with CH_2Cl_2, MeOH, and finally acetone. The filtrate was washed with 3 × 75 mL of H_2O, dried, and concentrated. The red residue was chromatographed (DCLC) on CC-4 silica, eluting with 20% EtOAc/toluene containing 0.5 mL of HOAc/L, to generate 103 mg (99%) of dark red (±)-isodaunomycinone (**6**): mp 225–231 °C (lit.[34] mp 237 °C); IR 3690, 3610, 3510, 3440, 2930, 2860, 1725, 1620, 1590, 1290 cm^{-1}; ^1H NMR (CD_2Cl_2) 1.9–3.9 (m, 5), 2.37 (s, 3), 4.02 (s, 3), 7.5–8.0 (m, 3), 13.40 (s, 1), 13.67 (s, 1); MS *m/e* (%) 399 (6), 398 (M^+, 29), 380 (6), 362 (51), 344 (28), 339 (21), 337 (68), 323 (12), 322 (16), 309 (23), 301 (20), 217 (25), 91 (28), 43 (100).

Anal. Calcd for $C_{21}H_{18}O_8$ (398.37): C, 63.22; H, 4.55. Found: C, 63.04; H, 4.67.

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Registry No. (±)-**5**, 59367-20-3; (±)-**6**, 72521-93-8; **12**, 14963-96-3; **13**, 150-78-7; **14**, 52541-76-1; (±)-**16**, 115514-87-9; (±)-**17**, 115514-88-0; **18**, 115514-89-1; **19**, 115514-90-4; **20**, 115514-91-5; **28**, 2961-04-8; **29**, 59326-07-7; **30**, 64831-67-0; **31**, 70071-71-5; (±)-**32**, 115514-92-6; (±)-**33**, 115514-93-7; (±)-**34**, 115514-94-8; (±)-**35**, 115514-95-9; (±)-**36**, 115514-96-0; (±)-**37**, 115514-97-1; (±)-**42**, 71571-58-9; (±)-**45**, 115514-98-2; (±)-**50**, 115533-09-0; (±)-**53**, 115515-02-1; (±)-**54**, 84938-46-5; (±)-**55**, 71571-60-3; (±)-**58**, 115515-06-5; (±)-**59**, 115515-08-7; (±)-**63**, 115515-09-8; (±)-**64**, 115514-99-3; (±)-**65**, 115515-01-0; (±)-**66**, 115515-03-2; (±)-**67**, 115515-04-3; (±)-**68**, 115515-05-4; (±)-**69**, 115515-07-6; (±)-**70**, 115515-10-1; (±)-**71**, 115515-00-9; C_2H_2, 74-86-2.

New Synthetic Approaches to Cyclopenta[*a*]phenanthrenes and Their Carcinogenic Derivatives

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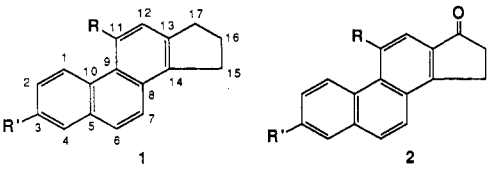
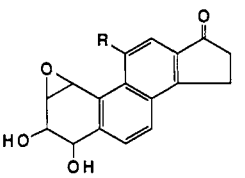
A new general synthetic approach to cyclopenta[*a*]phenanthrenes including their carcinogenic 11-methyl (**1b**) and 17-keto (**2d** and **2b**) derivatives is reported. The simplest example entails alkylation of the bromomagnesium salt of an enamine derivative of cyclopentanone with 2-(1-naphthyl)ethyl iodide followed by acidic hydrolysis, acid-catalyzed cyclization of the alkylated cyclopentanone, and dehydrogenation of the product over a Pd catalyst. Although reaction of the resulting cyclopenta[*a*]phenanthrenes with DDQ in acetic acid affords a mixture of ketones formed by oxidation at both benzylic sites, regiospecific oxidation at the 17-position may be achieved by prior hydrogenation of the 6,7-bond. These synthetic methods provide good overall yields of cyclopenta[*a*]phenanthrenes in relatively few steps. The method is potentially adaptable to the synthesis of the biologically active diol epoxide metabolites.

Although the carcinogenic properties of cyclopenta[*a*]phenanthrene derivatives have been known for many years, compounds in this class have attracted relatively little attention. However, renewed interest has been generated by the finding that cyclopenta[*a*]phenanthrenes are widely distributed in petroleum, mineral oils, coal, lake sediments, and other natural environments[1-4] where they are thought to arise from sterols by microbiological dehydrogenation.[3,4] There is also evidence that cyclopenta[*a*]phenanthrenes may be formed by pyrolysis of the sterols present in edible oils during cooking.[4] The chemistry and biological properties of the cyclopenta[*a*]phenanthrenes have been extensively reviewed in the excellent recent monograph by Coombs and Bhatt.[4] While the parent hydrocarbon 16,17-dihydro-15*H*-cyclopenta[*a*]phenanthrene (**1a**) and its 17-keto analogue **2a** are inactive, the 11-methyl-17-keto derivative **2b** is a relatively potent carcinogen on mouse skin, comparable in activity to benzo[*a*]pyrene.[4-7] There is also now substantial evidence that the active carcinogenic forms of the cyclopenta[*a*]phenanthrenes are diol epoxide metabolites, such as **3**.[4,8,9] However, the synthesis of these active metabolites has not been accomplished.



1 **2**

a: R ◻ R' = H; b: R = CH_3, R' = H; c: R ◻ H, R' = OCH_3



3a: R = H; b: R = CH_3

One of the principal bottlenecks to investigations of the cyclopenta[*a*]phenanthrenes has been their unavailability except through tedious multistep syntheses.[4] Accordingly, we have sought to devise more convenient synthetic approaches in order to make molecules of this class more accessible for studies of their biological properties and mechanism of action. We now report a new general synthesis of cyclopenta[*a*]phenanthrenes which provides good yields in relatively few steps. The method is potentially adaptable to the preparation of the biologically active diol epoxide intermediates.

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