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ANTHRACYCLINONE SYNTHESES USING STRONG BASE INDUCED CYCLOADDITION OF HOMOPHTHALIC ANHYDRIDES AND RELATED COMPOUNDS

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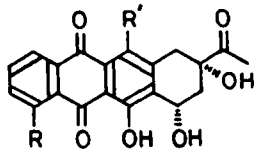
Abstract—The strong base induced cycloaddition of homophthalic anhydrides and related compounds to halo-1,4-naphthoquinone derivatives has been shown to provide short convergent syntheses of anthracyclinones, 4-demethoxydaunomycinone (**1**), daunomycinone (**2**), 11-deoxydaunomycinone (**3**), and 11-deoxycarminomycinone (**4**).

A. INTRODUCTION

The total synthesis of anthracyclines is believed to be among the most promising subjects for the development of new drugs for treatment of cancer[1] and has been studied intensively in the last several years. Synthetic approaches to the anthracycline antibiotics, especially efforts directed toward a regiospecific preparation of their aglycones (anthracyclinones) have been reviewed.[2] We have been much interested in convergent regiospecific assemblies[3,4] of *peri*-hydroxy polycyclic systems related to anthracyclinone syntheses. Very recently we have communicated[5,6] the brief and regiospecific syntheses of the late-stage intermediates to anthracyclinones, 4-demethoxydaunomycinone (**1**), daunomycinone (**2**), 11-deoxydaunomycinone (**3**) and 11-deoxycarminomycinone (**4**). In this report we wish to describe the combination of these synthetic methods, namely the strong-base-induced cycloaddition of homophthalic anhydrides and related compounds to halo-1,4-naphthoquinone derivatives. Before discussing the



1 R=H; R'=OH

2 R=OMe; R'=OH

3 R=OMe; R'=H

4 R=OH; R'=H

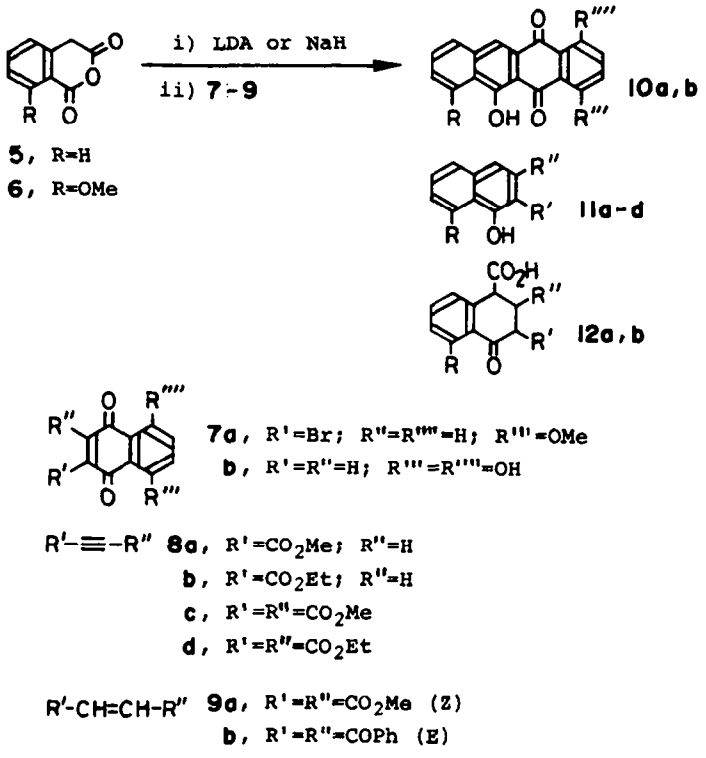
syntheses of these anthracyclinones, a brief explanation of the strong-base-induced cycloaddition of homophthalic anhydrides and related compounds is appropriate.

B. STRONG BASE INDUCED CYCLOADDITION OF HOMOPHTHALIC ANHYDRIDES AND RELATED COMPOUNDS

The deprotonation of the benzyl proton (C-4 proton) of homophthalic anhydrides (**5**, **6**) was efficiently effected by strong bases such as lithium diisopropylamide (LDA) or sodium hydride (NaH) under mild conditions to give the corresponding alkaline salts, which reacted smoothly with various types of carbon–carbon multiple bonds (**7–9**) to give the linearly condensed *peri*-hydroxy polycyclic compounds (**10–12**) in a single step[4] (Scheme 1). An attractive feature of these reactions is that cycloadducts were obtained regioselectively in high yields. Moreover, the present base induced cycloaddition of homophthalic anhydrides is widely applicable to a variety of other related systems, such as **13**, **14**, **15**, and **16**, which provide *peri*-hydroxy polycyclic cyclohexene,[6] indole,[7] benzofuran,[7] and thiophene compounds,[8] regioselectively. The route involving a Diels–Alder type reaction of anhydrides to dienophiles (route a) is more probable than another route involving a Michael addition of anhydrides to electron deficient olefins (route b) as exemplified in the reaction of the alkaline salt of **6** with **7a** leading to **10a** (Scheme 2),[4] although it is not rigorously defined.

C. REGIOCONTROLLED SYNTHESIS OF 4-DEMETHOXYDAUNOMYCINONE (1) AND DAUNOMYCINONE (2)

Our synthetic approach for the construction of the aglycones (**1**, **2**) entails the strong-base-induced cycloaddition of homophthalic anhydrides to the new quinone acetals (**17**, **18**) leading to the key tetracyclic ketones as illustrated in Scheme 3. However, the absence of the method for preparing quinone acetals (**17**, **18**) necessitated prior development of brief procedures for their preparation. The preparation of **17** and **18** was achieved in 65 and 56% overall yields from commercially available 2,6- (**19**) and 2,5-dichlorobenzoquinones (**20**), respectively by the three-step sequence shown in Scheme 4. Diels–Alder reaction of 2-[(trimethylsilyl)oxy]butadiene (**21**) with **19** led to the adduct, which was acetalized by the method of Larson[9] to give the chloro acetal. Dehydrochlorination of the acetal with triethylamine gave **17**. A series of reactions was readily performed in one pot within 10 hr if ether was used as a solvent. When the same sequence of reactions was carried out with **20** as the starting material, the isomeric quinone acetal **18** was obtained. The orientation of the Diels–Alder reaction of **21** with **19** and **20** was readily assigned by the fact that the

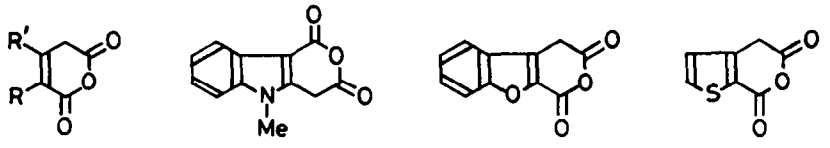


Scheme 1.

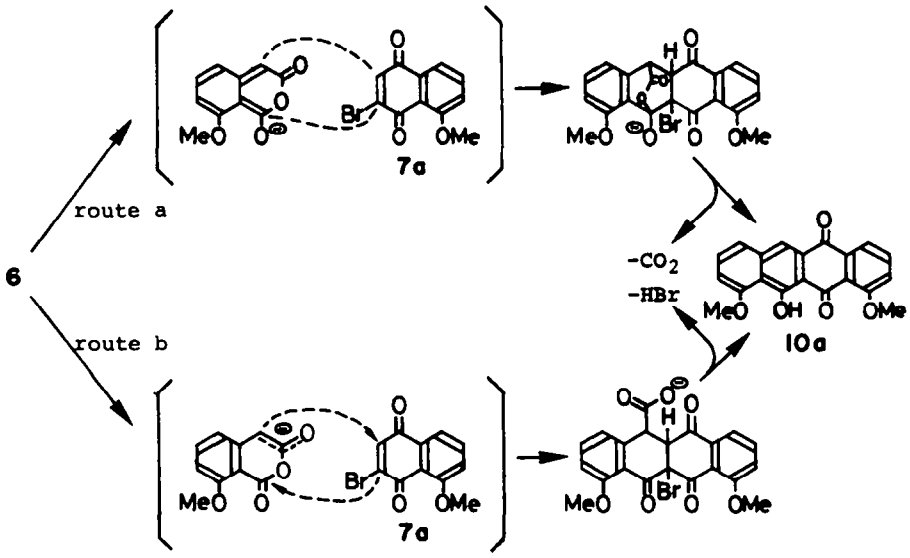
nucleophilic end of the diene systems selectively reacts at the unsubstituted olefinic site of the chlorobenzoquinones,[10] and confirmed by the conversion of **17** into the known[11] hydroxynaphthoquinone (**22**).

The starting 8-methoxyhomophthalic anhydride (**6**) was prepared by the reported[12] or our improved method.[13] Unknown 5-methoxyhomophthalic anhydride (**27**) was synthesized from the aryloxazoline (**23**) in 37% overall yield using the *ortho*-lithiation developed by Meyers.[14] The reaction sequence is outlined in Scheme 5.

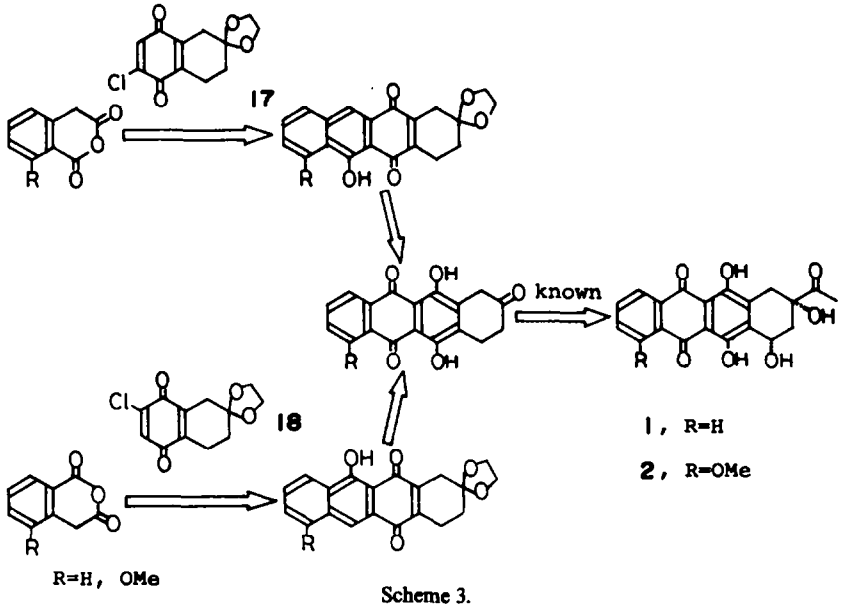
The cycloaddition of the alkaline salts of homophthalic anhydrides (**5**, **6**, **27**) to **17** and **18** was examined next. The cycloaddition chemistry of **5** was initially explored with **17**. Lithiation of **5** with lithium diisopropylamide (LDA) in dry tetrahydrofuran (THF) followed by treatment with **17** at −78°C for 20 min under nitrogen gave a nearly quantitative yield of the 6-hydroxynaphthacene (**28**), regiospecifically. A more general and practical preparation of **28** was performed by the reaction of **17** with the sodium salt generated from **5** and an equivalent amount of NaH in dry THF at 0° for 20 min and at room temperature for 30 min. On the other hand, the reaction of **18** with an equimolar amount of **5** under the same conditions using LDA or NaH gave the isomeric 11-hydroxynaphthacene (**29**). The isolated regioisomers **28** and **29** were distinguishable by the chemical shifts of the phenolic protons in their respective ^{1}H-NMR spectra. Our next attempt was to oxidize the *para*-position of **28** and **29**. However, all our attempts under various conditions such as O_2/hν or aq.NaOH, CrO_3/AcOH, *m*—CPBA/CH_2Cl_2, H_2O_2/aq.NaOH or $AlCl_3$—Cl CH_2CH_2Cl, MnO_2/CH_2Cl_2, H_5IO_6/DMF, PCC/CH_2Cl_2, and $BF_3 \cdot Et_2O/Ac_2O$ failed to give the desired oxidized naphthacenes. The oxidation of **28** and **29** proceeded poorly under a variety of conditions such as $Hg(OAc)_2$/AcOH—CH_2Cl_2, $Tl(NO_3)_3/CHCl_3$—MeOH, $Tl(OCOCF_3)_3$/AcOH—MeOH, and PhI $(OAc)_2/HClO_4$/AcOH—C_6H_6. Finally, it sufficiently proceeded by the use of $Pb(OAc)_4$. Treatment of **28** and **29** with $Pb(OAc)_4$ in AcOH—CH_2Cl_2 gave a considerable yield of the corresponding *para*-acetoxylated naphthacenes, **30** and **31**, respectively. Treatment of **30** and **31** with trifluoroacetic acid (CF_3CO_2H) caused deacetalization, deacetylation, and enol-keto isomerization in B/C rings at the same time to give the same naphthacene (**32**)[15,16] almost in the same yields (Scheme 6). Since the conversion of **32** to **1** has already been described,[16] our synthesis of **32**



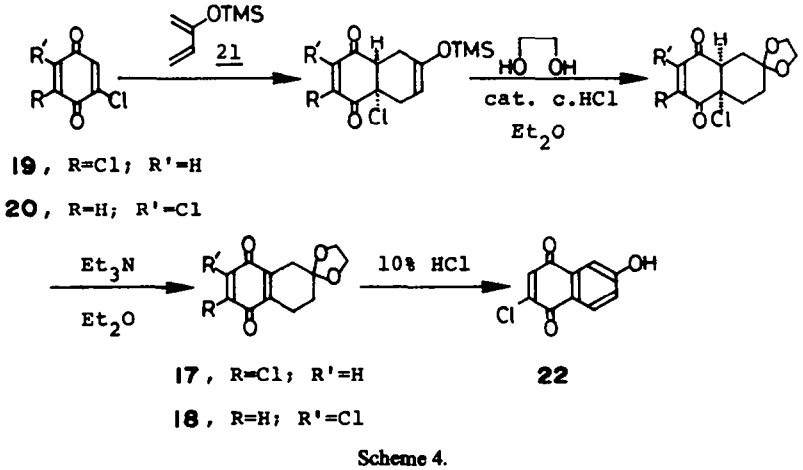
13 **14** **15** **16**



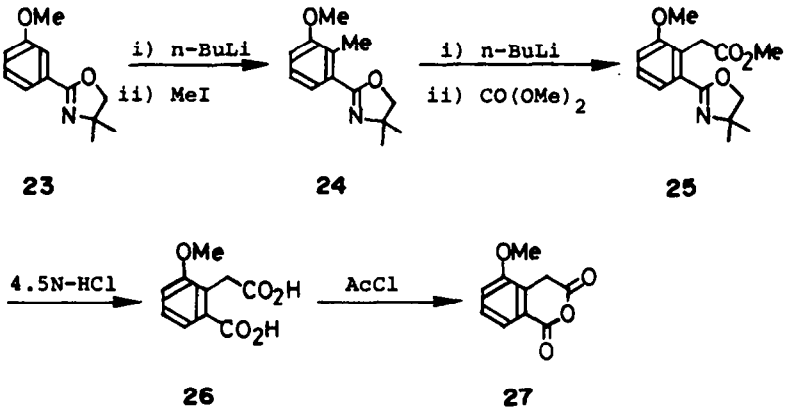
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

constitutes a new route to **1**. The synthetic sequences presented here furnished **32**, late-stage precursor to **1**, from **5** and **17** or **18** in three steps and high overall yields (76% or 70% overall yields, respectively).

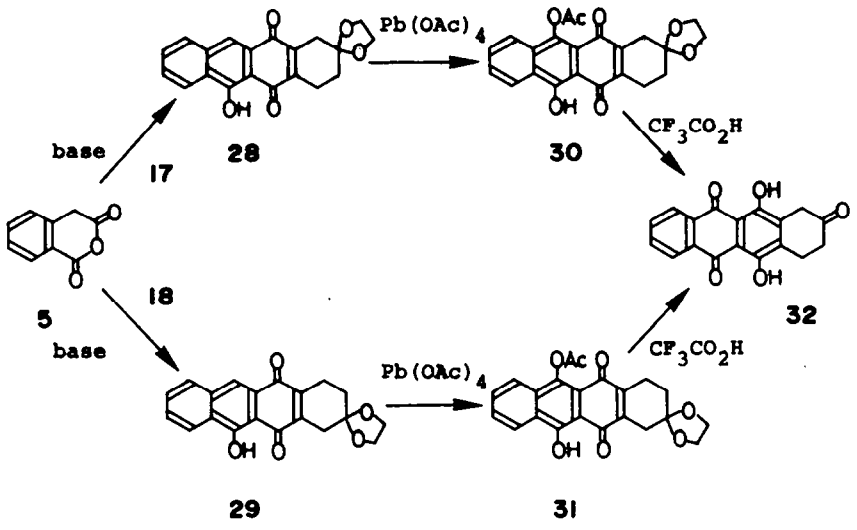
As for the mechanism of the oxidation of **28** or **29** to **30** or **31**, there are two possible routes (route a and b) as shown in Scheme 7: (a) involving a ligand exchange of $Pb(OAc)_4$ between the phenolic hydroxyl group and acetoxyl group and subsequent oxidation of the *para*-position of the aromatic ring with concomitant reduction of lead (IV) to lead (II) and (b) direct substitution of $Pb(OAc)_4$ at the *para*-position of phenolic hydroxyl group and subsequent nucleophilic displacement of the lead substituent from the intermediate by acetoxyl anion. We have examined the oxidation of O-methyl- and O-acetylhydroxynaphthacenes (**33**, **34**) with $Pb(OAc)_4$. Since treatment of **33** or **34** with $Pb(OAc)_4$ in $AcOH—CH_2Cl_2$ for a long period did not give the oxidized products at all, the former ligand exchange route (route a) in Scheme 7 seems to be plausible for the mechanism.

For the synthesis of daunomycinone (**2**), two different routes were established by starting from the anhydrides, **6** and **27** as outlined in Scheme 8. The alkaline salt of **6** was reacted with **17** to give the adduct **35** in high yield, regiospecifically. The conversion of **35** to the desired ketone **37** was accomplished by the same method as described for the conversion of **28** or **29** to **32**. Oxidation of **35** using $Pb(OAc)_4$ gave the acetoxynaphthacene **36**, which underwent acid hydrolysis of both acetal and acetoxy groups followed by enol-keto isomerization *in situ* with CF_3CO_2H to give **37**,[17,18] which was in all respects identical with authentic samples generously provided by Prof. F. M. Hauser and Prof. A. S. Kende. We have separately prepared a series of unknown regioisomers (**38**–**40**) by the reaction of **6** with **18** as shown in Scheme 8 and confirmed that our method gave only the desired tetracyclic compounds, regiospecifically: Regioisomer (**38**) was not contained in the crude product of the reaction of **6** and **17** (checked by tlc and the phenolic protons in their ^{1}H-NMR). An alternative sequence to the ketone **37** was accomplished by the reaction of the sodio anion of **27** with **18** and oxidation of the cycloadduct followed by acid treatment. The produced **37** was shown to be identical with an authentic sample prepared above. Both routes are not so different in the reaction steps and overall yields except that the oxidation step using $Pb(OAc)_4$ in the latter route proceeds more readily than the former one. Since **37** has been converted to **2**,[19] our routes comprise a brief and regiospecific synthesis of **2**. The synthetic sequences presented here furnished **37**, late-stage precursor to **2**, from the anhydrides **6** and **27** in three steps and high overall yields (38% and 37% overall yields, respectively).

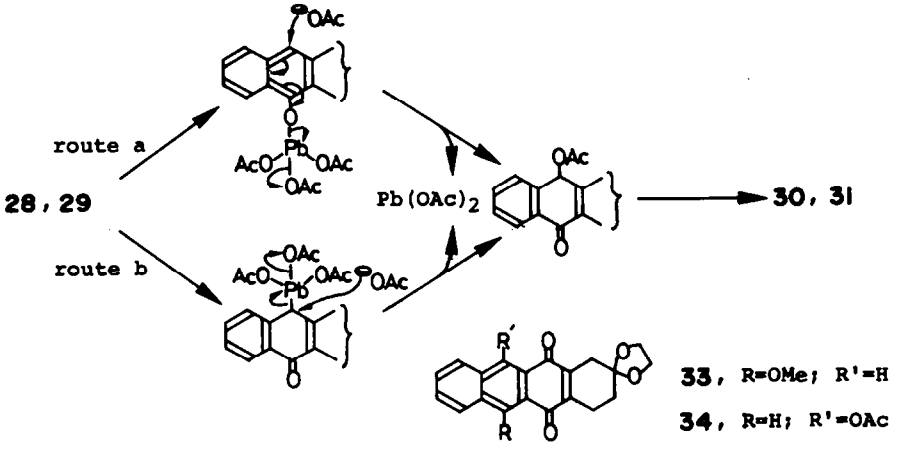
D. REGIOCONTROLLED SYNTHESIS OF 11-DEOXYDAUNOMYCINONE (3) AND 11-DEOXYCARMINOMYCINONE (4)

Anthracylines both of synthetic and natural origin show great potential as substitutes for the first-generation anthracycline drugs. In the past few years, several potentially useful 11-deoxyanthracyclines have been isolated. The 11-deoxyanthracyclines are of current interest due to the less toxicity and there have very recently been several reports on their total syntheses[20] or other related approaches.[21–27] Our synthetic route to **3** and **4** focuses upon a preparation of the key tetracyclic ketone **43**,[21–27] which is thought to be a common intermediate toward all 11-deoxyanthracyclinones. We can now apply our previous method[5] for **1** and **2** to a facile synthesis of **3** and **4**. Our synthetic strategy to **3** and **4**, which is outlined in Scheme 9, centers on the one-step construction of a linear tetracycles having anthraquinone moiety through oxyanion assisted-cycloaddition of appropriately functionalized anhydride **44** to **7a**.

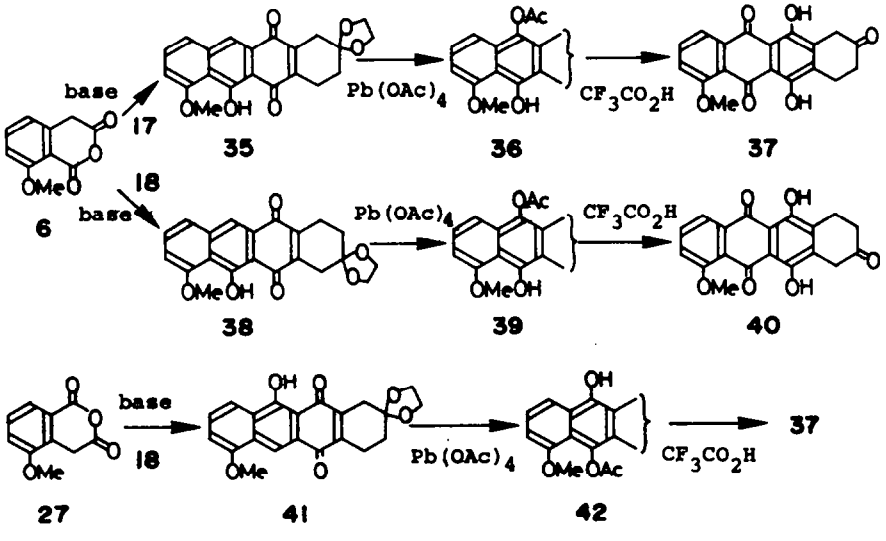
The requisite anhydride **44** was prepared from the readily available diethyl allenedicarboxylate in six steps with a 38% overall yield according to Scheme 10. Diels–Alder reaction of the allenedicarboxylate with **21** in CH_3CN followed by acid hydrolysis gave the ketoester **45**. Acetalization of **45** with ethylene glycol and pyridinium *p*-toluenesulfonate in refluxing benzene gave a 1:4 mixture of *exo* and *endo* olefin acetals. Heating of the mixture in $Et_3N—THF$ (1:1) gave the *endo* olefin acetal **46**. Hydrolysis of **46** with aq. KOH in refluxing EtOH followed by acidification with 10% HCl gave the diacid **47**, which was cyclized with trimethylsilylethoxyacetylene[28] to give the desired



Scheme 6.



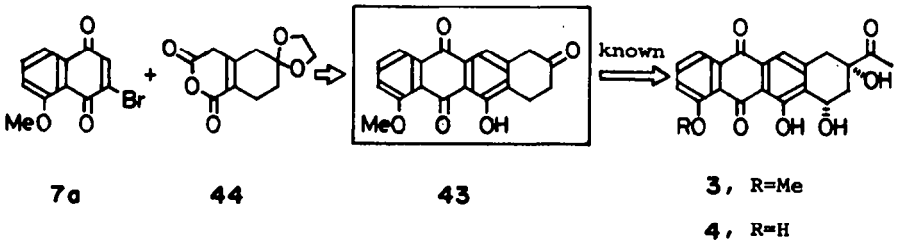
Scheme 7.



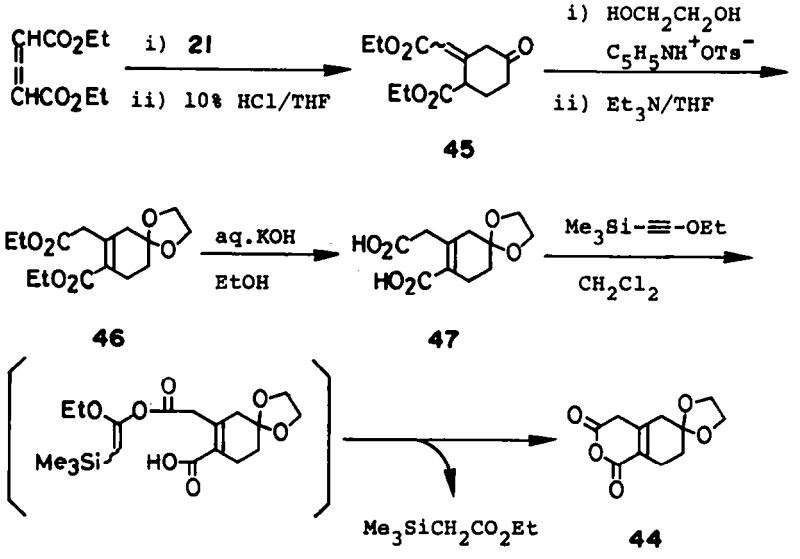
Scheme 8.

anhydride **44**. Another starting material **7a** was prepared from 3-bromojuglone by methylation with MeI and Ag_2O.

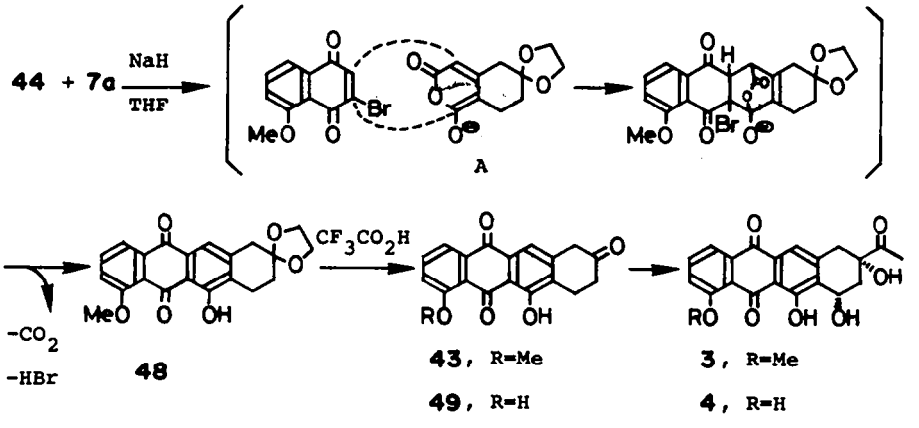
The synthesis of **3** and **4** was established by starting from the anhydride **44** as outlined in Scheme 11. Treatment of sodio anion of **44** with **7a** gave a 78% yield of the tetracyclic quinone acetal **48** as the sole product. A plausible pathway is the strong-base-induced cycloaddition[4] of the active diene moiety (A) to **7a** regiospecifically, followed by spontaneous loss of CO_2 and HBr, giving **48**. Deacetalization of **48** with CF_3CO_2H in water gave the key tetracyclic ketone **43** in quantitative yield, which was in all respects identical with an authentic sample generously provided by Prof.



Scheme 9.



Scheme 10.



Scheme 11.

J. P. Gesson. Since the conversion of **43** to **3** has already been described,[26] our synthesis of **43** constitutes a brief and regiospecific route to **3**. For the synthesis of **4**, the ketone **43** was demethylated with $AlCl_3$ in refluxing CH_2Cl_2 to give the ketone **49**. Since **49** has been converted to **4**,[27] our synthesis of **49** constitutes a new efficient synthesis of **4**. The present strong-base-induced cycloaddition of homophthalic anhydrides and related compounds provides a potentially useful convergent synthesis of a variety of anthracyclinone analogues.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrophotometer using $CHCl_3$ as a solvent (unless otherwise noted). ^{1}H-NMR spectra were recorded on a Hitachi R-22 (90 MHz) spectrometer using $CDCl_3$ as a solvent (unless otherwise noted) with TMS as an internal standard, and MS on a JEOL D-300 mass spectrometer. Column chromatography was carried out using silica gel 60 (E. Merck).

The following were prepared by the literature method quoted: compounds **6**,[13] **7a**,[3,29] **21**,[30] **23**,[31] and diethyl allenedicarboxylate.[32]

A. SYNTHESIS OF 4-DEMETHOXYDAUNOMYCINONE (1) AND DAUNOMYCINONE (2)

2-Chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone **17**

A stirred mixture of **19** (700 mg, 3.95 mmol) and **21**[30] (600 mg, 4.22 mmol) in C_6H_6 (7 ml) was heated at 50° for 4 hr under argon. The soln was concentrated *in vacuo*. To the stirred soln of the residue in dry Et_2O (10 ml), $HOCH_2CH_2OH$ (400 mg, 6 mmol) and a catalytic amount (two drops) of c. HCl were added at 0° and the mixture was stirred at room temp for 5 hr, diluted with Et_2O (20 ml), treated with Et_3N (400 mg, 4 mmol) at room temp for 3 hr, poured into water (20 ml), and extracted with C_6H_6 (2 × 30 ml). The combined extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude **17** as a solid, which was purified by column chromatography (C_6H_6 : AcOEt = 19 : 1) to give a 65% overall yield (653 mg) of **17**; m.p. 149–150° (C_6H_6—n·hexane); IR 1670, 1655, 1595, 1125 cm^{-1}; ^{1}H-NMR δ 1.86 (t, 2H, J = 7 Hz), 2.55–2.90 (m, 4H), 4.00 (s, 4H), 6.82 (s, 1H); MS *m/e* 254 (M^+). (Found: C, 56.60; H, 4.27; Cl, 14.08. Calc for $C_{12}H_{11}O_4Cl$: C, 56.60; H, 4.35; Cl, 13.92%.)

3-Chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (**18**)

This was similarly prepared from **20** (300 mg, 1.70 mmol) and **21** (300 mg, 2.11 mmol) in C_6H_6 (3 ml) in 56% overall yield (241 mg); m.p. 98–98.5° (C_6H_6—n·hexane); IR 1650, 1600, 1120 cm^{-1}; ^{1}H-NMR δ 1.82 (t, 2H, J = 7 Hz), 2.55–2.80 (m, 2H), 2.70 (s, 2H), 4.00 (s, 4H), 6.89 (s, 1H); MS *m/e* 254 (M^+). (Found: C, 56.61; H, 4.27; Cl, 14.09. Calc for $C_{12}H_{11}O_4Cl$: C, 56.60; H, 4.35; Cl, 13.92%.)

2-Chloro-6-hydroxy-1,4,-naphthoquinone (**22**)

A soln of **17** (40 mg, 0.16 mmol) in 10% HCl (0.5 ml) and acetone (8 ml) was heated at reflux for 15 min. The mixture was concentrated *in vacuo* and extracted with C_6H_6 (2 × 10 ml), washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a solid, which was chromatographed (CH_2Cl_2) to give a 49% yield (16 mg) of **22**; m.p. 228–231° (1,2-dichlorobenzene) (lit.[11] m.p. 229–230°); IR (KCl) 3410, 1665, 1585, 1575 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 7.09 (dd, 1H, J = 8 and 2.5 Hz), 7.20 (d, 1H, J = 2.5 Hz), 7.26 (s, 1H), 7.87 (d, 1H, J = 8 Hz).

2-(2-Methyl-3-methoxyphenyl)-4,4-dimethyl-2-oxazoline (**24**)

A soln of **23**[31] (1.5 g, 7.3 mmol) in anhyd THF (15 ml) was treated with a soln of n-BuLi (1.6 M, 7ml, 11.2 mmol) in hexane at −45° (CH_3CN-dry ice bath) under N_2. The soln was stirred for 1.5 hr under the same conditions and MeI (2.4 ml, 38.5 mmol) was added. The mixture was allowed to warm to room temp, poured into water (20 ml), and extracted with CH_2Cl_2 (2 × 30 ml). The combined extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude **24**, which was purified by column chromatography (CH_2Cl_2) to give a 91% yield (1.453 g) of **24** as a yellow oil; IR 1665, 1645, 1640, 1595, 1580 cm^{-1}; ^{1}H-NMR δ 1.39 (s, 6H), 2.40 (s, 3H), 3.81 (s, 3H), 4.03 (s, 2H), 6.85 (dd, 1H, J = 7.5 and 3 Hz), 7.12 (t, 1H, J = 7.5 Hz), 7.27 (dd, 1H, J = 7.5 and 3 Hz); MS *m/e* 219 (M^+). (Found: C, 71.29; H, 7.91; N, 6.37. Calc for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39%.)

2-(2-Carbomethoxymethyl-3-methoxyphenyl)-4,4-dimethyl-2-oxazoline (**25**)

A soln of **24** (220 mg, 1 mmol) in anhyd THF (5 ml) was treated with a soln of n-BuLi (1.5 M, 0.8 ml, 1.2 mmol) in hexane at 0° under N_2. The soln was stirred for 1 hr under the same conditions and dimethyl carbonate (0.5 ml, 5.9 mmol) was added dropwise at −78°. The mixture was allowed to warm to room temp, stirred for 1 hr, quenched with water (3 ml), and extracted with CH_2Cl_2 (2 × 15 ml). The combined extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude **25**, which was purified by column chromatography (CH_2Cl_2) to give a 48% yield (133 mg) of **25** as a syrup; IR 1735, 1725, 1655, 1645, 1640, 1595, 1580 cm^{-1}; ^{1}H-NMR δ 1.33 (s, 6H), 3.65 (s, 3H), 3.81 (s, 3H), 4.01 (s, 2H), 4.18 (s, 2H), 6.95 (dd, 1H, J = 7.5 and 2 Hz), 7.23 (t, 1H, J = 7.5 Hz), 7.43 (dd, 1H, J = 7.5 and 2 Hz); MS *m/e* 277 (M^+). (Found: C, 65.14; H, 7.14; N, 5.06. Calc for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05%.)

6-Methoxyhomophthalic acid (**26**)

A soln of **25** (140 mg, 0.51 mmol) in 4.5 N—HCl (10 ml) was heated at reflux for 1 day. After cooling, the soln was extracted with Et_2O (2 × 15 ml), washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give an 85% yield (91 mg) of **26** as colorless crystals; m.p. 189.5–190.5° (AcOEt); IR (KCl) 3200–2700, 2700–2575, 2570–2500, 1720, 1710, 1685, 1675, 1595, 1585 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.78 (s, 3H), 3.93 (s, 2H), 7.12 (dd, 1H, J = 8 and 2 Hz), 7.27 (t, 1H, J = 8 Hz), 7.42 (dd, 1H, J = 8 and 2 Hz); MS *m/e* 210 (M^+). (Found: C, 56.98; H, 4.82. Calc for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80%.)

5-Methoxyhomophthalic anhydride (**27**)

To a soln of acetyl chloride (0.2 ml) in anhyd acetone (0.5 ml) was added **26** (160 mg, 0.76 mmol) portionwise. The mixture was stirred at room temp for 30 min and concentrated *in vacuo* to give a quantitative yield (145 mg) of **27** as colorless crystals; m.p. 156.5–157.5° (C_6H_6-n·hexane); IR 1800, 1750, 1600 cm^{-1}; ^{1}H-NMR δ 3.90 (s, 3H), 3.98 (s, 2H), 7.12 (bd, 1H, J = 8 Hz), 7.39 (t, 1H, J = 8 Hz), 7.74 (bd, 1H, J = 8 Hz); MS *m/e* 192 (M^+). (Found: C, 62.55; H, 4.12. Calc for $C_{10}H_8O_4$: C, 62.50; H, 4.20%.)

General procedure for the strong base induced cycloaddition of homophthalic anhydrides (**5**, **6**, **27** *or* **44**)

Procedure A. A soln of n-BuLi (1.6 M, 0.68 ml, 1.1 mmol) was added under N_2 at 0° to a stirred soln of dry diisopropylamine (110 mg, 1.1 mmol) in anhyd THF (4 ml) and cooled to −78°. The mixture was stirred for 0.5 hr under the same conditions and then used as a THF soln of LDA. A soln of homophthalic anhydride (**5** or **6**, 1 mmol) in anhyd THF (4 ml) was added dropwise to the soln of LDA over a few minutes and a soln of haloquinone (**17** or **18**, 1 mmol) in anhyd THF (5 ml) was then added to the mixture. The whole was stirred at −78° for 20 min, allowed to warm to room temp, and stirred for 20 min. The mixture was quenched with sat aq. NH_4Cl (5 ml) and then partitioned between 5% HCl (5 ml) and CH_2Cl_2 (50 ml). The organic layer was washed with brine (10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was subjected to column chromatography using C_6H_6, C_6H_6—Et_2O,

C_6H_6—AcOEt, and/or $CHCl_3$—AcOEt as eluting solvents to give the corresponding adduct (**28**, **29**, **35**, or **38**).

Procedure B. A mixture of homophthalic anhydride (**5**, **27**, or **44**, 1 mmol) and NaH (60% in mineral oil, 1 mmol) in anhyd THF (20 ml) was stirred at 0° for 3 min. A soln of haloquinone (**17**, **18**, or **7a**, 1 mmol) in anhyd THF (5 ml) was added to the mixture. The whole was stirred at 0° for 20 min, allowed to warm to room temp, and stirred for 30 min. The reaction mixture was worked up as in procedure A to give the corresponding adduct (**28**, **29**, **41**, or **48**).

2,2-Ethylenedioxy-6-hydroxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**28**)

(i) This was prepared from **5** (81 mg, 0.5 mmol) and **17** (127 mg, 0.5 mmol) by procedure A in 95% yield (161 mg); m.p. 264–265° ($CHCl_3$) (lit.[5] 229–230.5°); IR 1655, 1630, 1605 cm^{-1}; ^{1}H-NMR δ 1.92 (t, 2H, J = 6.5 Hz), 2.8–3.1 (m, 4H), 4.02 (s, 4H), 7.5–7.95 (m, 3H), 8.01 (s, 1H), 8.35–8.55 (m, 1H), 13.93 (s, 1H); MS *m/e* 336 (M^+). (Found: C, 71.00; H, 4.73. Calc for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80%.)

(ii) This was prepared from **5** (41 mg, 0.25 mmol) and **17** (63 mg, 0.25 mmol) by procedure B in 82% yield (69 mg). Recrystallization of the crude product gave pure **28**, which was identical with an authentic sample obtained from i in all respects.

2,2-Ethylenedioxy-11-hydroxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**29**)

(i) This was prepared from **5** (42 mg, 0.26 mmol) and **18** (63 mg, 0.25 mmol) by procedure A in 90% yield (76 mg); m.p. 235–238° ($CHCl_3$) (lit.[5] 214–216°); IR 1655, 1630, 1605 cm^{-1}; ^{1}H-NMR δ 1.92 (t, 2H, J = 6.5 Hz), 2.8–3.1 (m, 4H), 4.02 (s, 4H), 7.5–8.0 (m, 3H), 8.01 (s, 1H), 8.3–8.6 (m, 1H), 13.85 (s, 1H); MS *m/e* 336 (M^+). (Found: C, 71.36; H, 4.68. Calc for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80%.)

(ii) This was prepared from **5** (41 mg, 0.25 mmol) and **18** (63 mg, 0.25 mmol) by procedure B in 92% yield (77 mg). Recrystallization of the crude product gave pure **29**, which was identical with an authentic sample obtained from (i) in all respects.

11-Acetoxy-2,2-ethylenedioxy-6-hydroxy-1,2,3,4,-tetrahydronaphthacene-5,12-dione (**30**)

A soln of **28** (22 mg, 0.06 mmol) in AcOH (3 ml) and CH_2Cl_2 (1.5 ml) was treated with $Pb(OAc)_4$ (60 mg, 0.13 mmol) at room temp for 16 hr. The mixture was concentrated *in vacuo* and partitioned between water and $CHCl_3$ (50 ml). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to column chromatography ($CHCl_3$: AcOEt = 30:1) to give a 70% yield of **30**; m.p. 215–217° (MeOH); IR 1760, 1655, 1630 cm^{-1}; ^{1}H-NMR δ 1.95 (t, 2H, J = 7 Hz), 2.47 (s, 3H), 2.83 (s, 2H), 3.02 (t, 2H, J = 7 Hz), 3.98 (s, 4H), 7.4–7.7 (m, 2H), 7.9–8.2 (m, 2H), 13.50 (s, 1H). (Exact mass calc for $C_{22}H_{18}O_7$, 394.1050; found, 394.1047.)

6-Acetoxy-2,2-ethylenedioxy-11-hydroxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**31**)

This was similarly prepared from **29** (42 mg, 0.13 mmol) and $Pb(OAc)_4$ (110 mg, 0.25 mmol) in 79% yield; m.p. 226–228° (MeOH); IR 1760, 1655, 1630 cm^{-1}; ^{1}H-NMR δ 1.93 (t, 2H, J = 7.5 Hz), 2.48 (s, 3H), 2.81 (t, 2H, J = 7.5 Hz), 3.00 (s, 2H), 4.02 (bs, 4H), 7.5–7.8 (m, 2H), 8.0–8.4 (m, 2H), 13.47 (s, 1H). (Exact mass calc for $C_{22}H_{18}O_7$, 394.1050; found, 394.1050.)

6,11-Dihydroxy-7,8-dihydronaphthacene-5,9(10H),12-trione (**32**)

(i) *From* **30**. A soln of **30** (10 mg, 0.025 mmol) in CF_3CO_2H (1 ml) and water (0.5 ml) was heated at 50° for 3 hr, concentrated *in vacuo*, and partitioned between water and $CHCl_3$ (20 ml). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed ($CHCl_3$: AcOEt = 9:1) to give a 95% yield of **32**; m.p. 296–298° (MeOH) (lit.[16] 300°); IR 1710, 1610, 1580 cm^{-1}; ^{1}H-NMR δ 2.64 (t, 2H, J = 7.5 Hz), 3.40 (t, 2H, J = 7.5 Hz), 3.76 (s, 2H), 7.6–7.9 (m, 2H), 8.2–8.4 (m, 2H), 13.32 (s, 1H), 13.42 (s, 1H).

(ii) *From* **31**. This was similarly prepared from **31** (10 mg, 0.025 mmol) with CF_3CO_2H (1 ml) and water (0.5 ml) in 80% yield. Recrystallization of the crude product gave **32**, which was identical with an authentic sample obtained from (i) in all respects.

2,2-Ethylenedioxy-6-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**33**)

A suspension of **28** (100 mg, 0.298 mmol) in $CHCl_3$ (3 ml) was shaken vigorously with Ag_2O (100 mg, 0.43 mmol) and MeI (1 ml, 16 mmol) for 1 hr. Two further additions of Ag_2O (50 mg) and MeI (1 ml) were made at intervals of 1 hr with shaking. Stirring was continued at room temp for 36 hr, then the mixture was filtered, and the residue was extracted with $CHCl_3$ (20 ml). The extract was concentrated *in vacuo* and the residue was chromatographed (CH_2Cl_2: Et_2O = 10:1) to give an 80% yield (83 mg) of **33**; m.p. 195–196° (C_6H_6); IR 3050–2850, 1660, 1630, 1615 cm^{-1}; ^{1}H-NMR δ 1.88 (t, 2H, J = 6.5 Hz), 2.75–3.05 (m, 4H), 4.04 (s, 3H), 4.07 (s, 4H), 7.45–7.65 (m, 2H), 7.8–8.0 (m, 1H), 8.2–8.35 (m, 1H), 8.31 (s, 1H); MS *m/e* 350 (M^+). (Found: C, 71.95; H, 5.13. Calc for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18%.)

6-Acetoxy-3,3-ethylenedioxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**34**)

A soln of **29** (35 mg, 0.104 mmol) in Ac_2O (2 ml) and pyridine (2 ml) was allowed to stand at room temp overnight. The mixture was concentrated *in vacuo* and the residue was chromatographed (C_6H_6: Et_2O = 20:1) to give a 97% yield (38 mg) of **34**; m.p. 232–237° ($CHCl_3$—n·hexane); IR 1770, 1660, 1615 cm^{-1}; ^{1}H-NMR δ 1,8–2.15 (m, 2H), 2.59 (s, 3H), 2.7–3.1 (m, 4H), 4.03 (s, 4H), 7.4–7.75 (m, 2H), 7.9–8.3 (m, 2H), 8.56 (s, 1H); MS *m/e* 378 (M^+). (Found: C, 69.50; H, 4.63. Calc for $C_{22}H_{18}O_6$: C, 69.83; H, 4.80%.)

2,2-Ethylenedioxy-6-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**35**)

This was prepared from **6** (48 mg, 0.25 mmol) and **17** (64 mg, 0.25 mmol) by procedure A in 62% yield (57 mg); m.p. 252–254° (CH_2Cl_2—MeOH); IR 1650, 1630, 1600, 1575 cm^{-1}; ^{1}H-NMR δ 1.89 (t, 2H, J = 6.5 Hz), 2.75–3.0 (m, 4H), 4.00 (bs, 7H), 7.00 (dd, 1H, J = 8 and 1.5 Hz), 7.2–7.6 (m, 2H), 7.93 (s, 1H), 15.01 (s, 1H); MS *m/e* 366 (M^+). (Found: C, 68.61; H, 4.86. Calc for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95%.)

11-Acetoxy-2,2-ethylenedioxy-6-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**36**)

This was obtained from **35** (28 mg, 0.076 mg) and $Pb(OAc)_4$ (85 mg, 0.19 mmol) in 61% yield (20 mg) by the same procedure as described for the conversion of **28** to **30**; m.p. 244.5–246° (CH_2Cl_2—EtOH); IR 1760, 1660, 1630, 1590 cm^{-1}; ^{1}H-NMR δ 1.93 (t, 2H, J = 6.5 Hz), 2.46 (s, 3H), 2.84 (bs, 2H), 3.04 (t, 2H, J = 6.5 Hz), 4.03 (s, 4H), 4.04 (s, 3H), 7.23 (dd, 1H, J = 8 and 1.5 Hz), 7.62 (t, 1H, J = 8 Hz), 7.81 (dd, 1H, J = 8 and 1.5 Hz), 13.76 (s, 1H); MS *m/e* 424 (M^+). (Found: C, 65.07; H, 4.59. Calc for $C_{23}H_{20}O_8$: C, 65.09; H, 4.75%.)

6,11-Dihydroxy-4-methoxy-7,8-dihydronaphthacene-5,9(10H),12-trione (**37**)

(i) The compound **36** (40 mg, 0.094 mmol) was hydrolyzed by the same procedure as described for the conversion of **30** to **32** to give a 95% yield of **37**; m.p. 252–256° (AcOH) (lit.[17] 248–250°, 252–256°); IR 1715, 1615, 1590 cm^{-1}; ^{1}H-NMR δ 2.63 (t, 2H, J = 6.5 Hz), 3.26 (t, 2H, J = 6.5 Hz), 3.60 (s, 2H), 4.07 (s, 3H), 7.34 (dd, 1H, J = 8 and 1.5 Hz), 7.74 (t, 1H, J = 8 Hz), 8.02 (dd, 1H, J = 8 and 1.5 Hz), 13.27 (s, 1H), 13.78 (s, 1H); MS *m/e* 338 (M^+).

(ii) The compound **42** (20 mg, 0.047 mmol) was similarly hydrolyzed with CF_3CO_2H (2 ml) and water (1 ml) at 55° for 15 hr. There was obtained a quantitative yield of **37**, which was identical with an authentic sample obtained from (i) in all respects.

2,2-Ethylenedioxy-11-hydroxy-10-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**38**)

This was prepared from **6** (96 mg, 0.5 mmol) and **18** (127 mg, 0.5 mmol) by procedure A in 73% yield (135 mg); m.p. 223–226° (AcOH); IR 1660, 1630, 1600, 1580 cm^{-1}; ^{1}H-NMR δ 1.89 (t, 2H, J = 6.5 Hz), 2.7–3.0 (m, 4H), 4.03 (bs, 7H), 6.96 (dd, 1H, J = 8 and 1.5 Hz), 7.3–7.7 (m, 2H), 14.91 (s, 1H); MS *m/e* 366 (M^+). (Found: C, 68.81; H, 4.89. Calc for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95%.)

6-Acetoxy-2,2-ethylenedioxy-11-hydroxy-10-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**39**)

This was obtained from **38** (40 mg, 0.11 mmol) and $Pb(OAc)_4$ (120 mg, 0.27 mmol) in 43% yield by the same procedure as described for the conversion of **28** to **30**; m.p. 231.5–233.5° (CH_2Cl_2—MeOH); IR 1765, 1665, 1630, 1590 cm^{-1}; ^{1}H-NMR δ 1.92 (t, 2H, J = 6.5 Hz), 2.44 (s, 3H), 2.87 (t, 2H, J = 6.5 Hz), 2.98 (bs, 2H), 4.02 (s, 7H), 7.22 (dd, 1H, J = 8 and 1.5 Hz), 7.60 (t, 1H, J = 8 Hz), 7.79 (dd, 1H, J = 8 and 1.5 Hz), 13.70 (s, 1H); MS *m/e* 424 (M^+). (Found: C, 64.80; H, 4.65. Calc for $C_{23}H_{20}O_8$: C, 65.09; H, 4.75%.)

6,11-Dihydroxy-1-methoxy-7,8-dihydronaphthacene-5,9(10H),12-trione (**40**)

The compound **39** (32 mg, 0.075 mmol) was hydrolyzed by the same procedure as described for the conversion of **30** to **32** to give a 90% yield (23 mg) of **40**; m.p. 228–233° decomp (AcOH); IR 1720, 1610, 1580 cm^{-1}; ^{1}H-NMR δ 2.60 (t, 2H, J = 6.5 Hz), 3.17 (t, 2H, J = 6.5 Hz), 3.58 (s, 2H), 4.04 (s, 3H), 7.28 (dd, 1H, J = 8 and 1.5 Hz), 7.67 (t, 1H, J = 8 Hz), 7.92 (dd, 1H, J = 8 and 1.5 Hz), 13.29 (s, 1H), 13.60 (s, 1H). (Exact mass calc for $C_{19}H_{14}O_6$, 338.0791; found, 338.0793.)

2,2-Ethylenedioxy-11-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**41**)

This was prepared from **27** (48 mg, 0.25 mmol) and **18** (63 mg, 0.25 mmol) by procedure B in 77% yield (70 mg); m.p. 231–234° (CH_2Cl_2—MeOH); IR 1655, 1630, 1600, 1575 cm^{-1}; ^{1}H-NMR δ 1.89 (t, 2H, J = 6.5 Hz), 2.8–3.0 (m, 4H), 4.00 (s, 3H), 4.02 (s, 4H), 6.97 (bd, 1H, J = 8 Hz), 7.49 (t, 1H, J = 8 Hz), 7.92 (bd, 1H, J = 8 Hz), 8.42 (s, 1H), 13.76 (s, 1H); MS *m/e* 366 (M^+). (Found: C, 69.05; H, 4.90. Calc for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95%.)

6-Acetoxy-2,2-ethylenedioxy-11-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (**42**)

This was obtained from **41** (30 mg, 0.082 mmol) and $Pb(OAc)_4$ (80 mg, 0.18 mmol) in 49% yield (17 mg) by the same procedure as described for the conversion of **28** to **30**; m.p. 233–236° (CH_2Cl_2—MeOH); IR 1765, 1665, 1630, 1585 cm^{-1}; ^{1}H-NMR δ 1.93 (t, 2H, J = 6.5 Hz), 2.46 (s, 3H), 2.89 (t, 2H, J = 6.5 Hz), 2.97 (bs, 2H), 3.96 (s, 3H), 4.00 (s, 4H), 7.22 (dd, 1H, J = 8 and 1.5 Hz), 7.58 (t, 1H, J = 8 Hz), 7.83 (dd, 1H, J = 8 and 1.5 Hz), 13.21 (s, 1H); MS *m/e* 424 (M^+). (Found: C, 65.03; H, 4.74. Calc for $C_{23}H_{20}O_8$: C, 65.09; H, 4.75%.)

B. SYNTHESIS OF 11-DEOXYDAUNOMYCINONE (3) AND 11-DEOXYCARMINOMYCINONE (4)

Ethyl 2-carboethoxy-5-oxo-1-cyclohexylideneacetate (**45**)

A soln of diethyl allenedicarboxylate[32] (1.6 g, 8.6 mmol) and **21**[30] (4.4 g, 30 mmol) in CH_3CN (16 ml) was heated at reflux for 6 hr under N_2 and concentrated *in vacuo*. To a cooled soln of the residue in THF (150 ml), 10% HCl (30 ml) was added dropwise. The mixture was stirred at 0° for 1 hr, neutralized with 10% aq. NaOH, and extracted with C_6H_6 (3 × 50 ml). The combined extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude **45**, which was purified by column chromatography (n·hexane: AcOEt = 3:1) to give a 50% yield (1.1 g) of **45**; IR 1735, 1730, 1675 cm^{-1}; ^{1}H-NMR δ 1.29 (t, 6H, J = 7 Hz), 2.2–2.6 (m, 4H), 3.36 (bs, 2H), 3.45–3.65 (m, 1H), 4.15 (q, 2H, J = 7 Hz), 4.18 (q, 2H, J = 7 Hz), 5.98 (bs, 1H). (Exact mass calc for $C_{13}H_{18}O_5$, 254.1155; found, 254.1176.)

Ethyl 2-(2-carboethoxy-5,5-ethylenedioxycyclohex-1-enyl)-acetate (**46**)

A mixture of **45** (1.01 g, 4 mmol), $HOCH_2CH_2OH$ (0.34 ml, 6.0 mmol), and pyridinium *p*-toluenesulfonate (0.25 g, 1.0 mmol) in C_6H_6 (30 ml) was refluxed for 4 hr with azeotropic removal of the water formed using Dean–Stark apparatus. After cooling, the mixture was diluted with C_6H_6 (30 ml) and washed with d. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. To a soln of the residue in THF (50 ml), Et_3N (50 ml) was added. The mixture was heated at reflux for 17 hr, concentrated *in vacuo* and partitioned between C_6H_6 (100 ml) and water (20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude **46**, which was purified by column chromatography (n·hexane: AcOEt = 3:1) to give an 81% yield (0.96 g) of **46**; IR 1735, 1730, 1710 cm^{-1}; ^{1}H-NMR δ 1.28 (t, 6H, J = 7 Hz), 1.65–1.95 (m, 2H), 2.4–2.75 (m, 4H), 3.46 (bs, 2H), 3.97 (s, 4H), 4.13 (q, 2H, J = 7 Hz), 4.16 (q, 2H, J = 7 Hz); MS *m/e* 298 (M^+). (Found: C, 60.50; H, 7.42. Calc for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43%.)

2-(2-Carboxy-5,5-ethylenedioxycyclohex-1-enyl)acetic acid (**47**)

A soln of **46** (330 mg, 1.1 mmol) and KOH (220 mg, 4 mmol) in EtOH (10 ml) and water (3 ml) was heated at reflux for 2 hr. The mixture was concentrated *in vacuo* to 3 ml, diluted with ether (30 ml), acidified to pH 3–4 with 10% HCl, saturated with NaCl, and extracted with Et_2O (2 × 50 ml). The organic layer was dried ($MgSO_4$), concentrated, and washed with a small amount of Et_2O to give a 93% yield (246 mg) of **47**, which was not purified; m.p. 137.5–138.5°; IR (KCl) 3200–2500, 1720, 1710, 1680, 1625 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 1.6–1.9 (m, 2H), 2.4–2.7 (m, 4H), 3.51 (bs, 2H), 3.93 (s, 4H). (Exact mass calc for $C_{11}H_{14}O_6$, 242.0789; found, 242.0789.)

6,6-Ethylenedioxy-5,6,7,8-tetrahydrohomophthalic anhydride (**44**)

A suspension of **47** (142 mg, 0.59 mmol) and trimethylsilylethoxyacetylene[33] (125 mg, 0.88 mmol) in CH_2Cl_2 (3 ml) was stirred at room temp for 3 hr. After filtration of a small amount of insoluble material, the filtrate was concentrated *in vacuo* to give a quantitative yield (134 mg) of **44**; m.p. 181–184° (THF); IR 1810, 1790, 1755, 1745, 1675 cm^{-1}; ^{1}H-NMR δ 1.7–2.05 (m, 2H), 2.4–2.85 (m, 4H), 3.3–3.5 (m, 2H), 4.00 (s, 4H); MS *m/e* 224 (M^+). (Found: C, 58.78; H, 5.35. Calc for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40%.)

9,9-Ethylenedioxy-6-hydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (**48**)

This was prepared from **44** (45 mg, 0.20 mmol) and **7a** (59 mg, 0.22 mmol) by procedure B described for the strong-base-induced cycloaddition of homophthalic anhydrides in 78% yield (57 mg); m.p. 221–223° (n·hexane—C_6H_6) (lit.[22] 220–222°); IR 1670, 1625, 1590 cm^{-1}; ^{1}H-NMR δ 1.98 (bt, 2H, J = 7 Hz), 3.00 (bt, 2H, J = 7 Hz), 3.02 (bs, 2H), 4.00 (s, 4H), 4.02 (s, 3H), 7.25 (dd, 1H, J = 8 and 2 Hz), 7.40 (s, 1H), 7.64 (t, 1H, J = 8 Hz), 7.88 (dd, 1H, J = 8 and 2 Hz), 13.29 (s, 1H).

6-Hydroxy-4-methoxy-7,8-dihydronaphthacene-5,9(10H),12-trione (**43**)

A soln of **48** (165 mg, 0.45 mmol) in CF_3CO_2H (10 ml) and water (5 ml) was stirred at room temp for 14 hr. The mixture was worked up by the same procedure as described for the conversion of **30** to **32** to give a quantitative yield (145 mg) of **43**; m.p. 256–257° decomp (THF) (lit.[23] 258–259°, lit.[24] 256–258°, lit.[25] 241–243° decomp); IR (KCl) 1710, 1670, 1625, 1580 cm^{-1}; ^{1}H-NMR δ 2.58 (t, 2H, J = 7 Hz), 3.22 (t, 2H, J = 7 Hz), 3.66 (s, 2H), 4.04 (s, 3H), 7.28 (dd, 1H, J = 8 and 2 Hz), 7.46 (bs, 1H), 7.68 (t, 1H, J = 8 Hz), 7.90 (dd, 1H, J = 8 and 2 Hz), 13.36 (s, 1H).

4,6-Dihydroxy-7,8-dihydronaphthacene-5,9(10H), 12-trione (**49**)

To a soln of **43** (35 mg, 0.11 mmol) in CH_2Cl_2 (35 ml), $AlCl_3$ (160 mg, 1.2 mmol) was added and the mixture was heated at reflux for 3 hr. The reaction mixture was poured into a mixture of sat. aq. $(CO_2H)_2$ (50 ml) and Et_2O (50 ml), stirred at room temp for 1 hr, and extracted with Et_2O (50 ml). The extract was washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (CH_2Cl_2 : MeOH = 100 : 1) to give an 85% yield (29 mg) of **49**; m.p. 242–244° ($CHCl_3$) (lit.[23] 241–242°, lit.[27] 242° decomp); IR (KCl) 1725, 1665, 1610, 1600 cm^{-1}; ^{1}H-NMR δ 2.60 (bt, 2H, J = 7 Hz); 3.22 (bt, 2H, J = 7 Hz), 3.67 (s, 2H), 7.23 (dd, 1H, J = 8 and 2 Hz), 7.53 (s, 1H), 7.61 (t, 1H, J = 8 Hz), 7.77 (dd, 1H, J = 8 and 2 Hz), 12.00 (s, 1H), 12.45 (s, 1H).

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