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An Efficient, Regiospecific Synthesis of 4-Demethoxydaunomycinone and Daunomycinone

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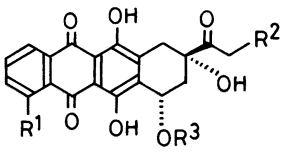
4-Methoxy and 4-acetoxyhomophthalic anhydrides were prepared by convenient oxidations of homophthalic acid derivatives followed by hydrolysis and dehydrative cyclization. Strong base-induced cycloaddition of these anhydrides to 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone gave the tetracyclic adducts, which were efficiently converted into 4-demethoxydaunomycinone and daunomycinone.

Keywords——anthracyclinone; 4-demethoxydaunomycinone; daunomycinone; cycloaddition; 4-methoxyhomophthalic anhydride; 4-acetoxyhomophthalic anhydride; ethynylcerium(III) 1,2-addition reagent

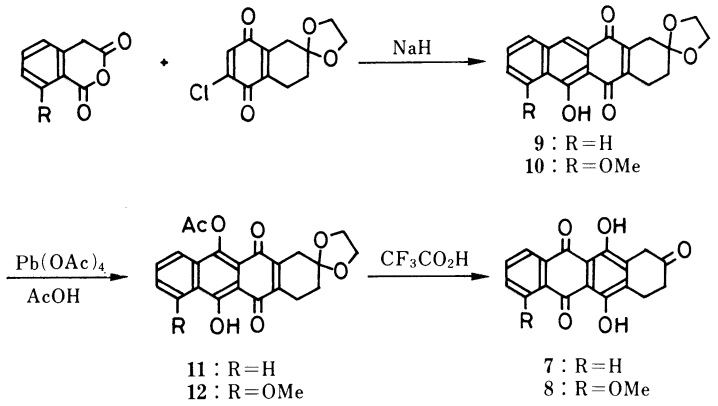
The anthracycline antibiotics, daunomycin (**1**), adriamycin (**2**), and 4-demethoxydaunomycin (**3**), are clinically significant drugs for the treatment of a broad spectrum of human cancers.[1] Efficient total synthesis of these anthracyclines, especially regiospecific preparation, has been the subject of intense study[2] due to the lack of an efficient biosynthetic process as well as the search for more active analogs with reduced cardiotoxicity. We have reported[3] a regiocontrolled synthesis of the late-stage intermediates (**7** and **8**) to the anthracyclinones (**4**—**6**) using a strong base-induced cycloaddition of homophthalic anhydrides to 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone as shown in Chart 1. Although this method is useful for the small-scale preparation of **7** and **8**, the oxidation step of the cycloadducts (**9** and **10**) to the *para*-acetoxylated products (**11** and **12**) with lead tetraacetate (LTA)/acetic acid–methylene chloride remains to be investigated since the yields are quite variable (25—79%) depending on the reaction conditions, especially the purity of the reagent itself, the reaction temperature, and the scale of the reaction. We have previously communicated[4] a greatly improved synthesis of **7** and **8** by using the previously C_4-acetoxylated homophthalic anhydrides (**14** and **15**) and an efficient conversion of **7** and **8** into **4** and **5**. We present here a full account of the work as well as a demonstration of the synthetic utility of C_4-oxygenated homophthalic anhydrides (**13**—**15**) for the preparation of key intermediates (**7** and **8**).

Results and Discussion

The requisite starting materials, 4-methoxy- (**13**) and 4-acetoxyhomophthalic anhydrides (**14** and **15**) were unknown in the literature. Since 2′-oxygenated homophthalic acids seemed to be favorable starting materials for **13**—**15**, we first tried the introduction of some oxygen functions at the $C_{2'}$-position of dimethyl homophthalate followed by hydrolysis of the esters. Dimethyl homophthalate was converted into the ketene silyl acetal intermediate (i) with



1 : R^1=OMe, R^2=H, R^3=daunosaminyl
2 : R^1=OMe, R^2=OH, R^3=daunosaminyl
3 : R^1=R^2=H, R^3=daunosaminyl
4 : R^1=R^2=R^3=H
5 : R^1=OMe, R^2=R^3=H
6 : R^1=OMe, R^2=OH, R^3=H



9 : R=H
10 : R=OMe

11 : R=H
12 : R=OMe

7 : R=H
8 : R=OMe

Chart 1

lithium diisopropylamide (LDA)/trimethylsilyl chloride, and (i) was oxidized with LTA[5] or *m*-chloroperbenzoic acid (*m*-CPBA)[6] to give dimethyl 2′-acetoxy- (**16**) or 2′-hydroxyhomophthalate (**17**) in 83% or 44% yield, respectively. 2′-Methoxylation was accomplished by the treatment of dimethyl homophthalate with $PhI(OAc)_2$ [phenyl iodosyl diacetate, PIDA] in methanolic sodium methoxide to give a 50% yield of dimethyl 2′-methoxyhomophthalate (**18**).[7] Although hydrolysis of the ester (**18**) gave the desired 2′-methoxyhomophthalic acid (**19**), other esters (**16** and **17**) gave an unwanted product, phthalide-3-carboxylic acid (**20**) selectively on alkaline hydrolysis followed by careful acidification. After several unsuccessful attempts,[8] the 2′-acetoxyhomophthalic acids (**21** and **22**) were successfully obtained from the homophthalic acids themselves by the most straightforward method: the homophthalic acids were treated with 3.2 eq of LDA in tetrahydrofuran (THF) and quenched with trimethylsilyl chloride to give the ketene silyl acetal intermediates (ii), which were oxidized with LTA in benzene to give quantitatively the corresponding 2′-acetoxyhomophthalic acids. These acids (**19**, **21**, and **22**) were treated with 1.3 eq of trimethylsilylethoxyacetylene[9] in methylene chloride to give, in quantitative yields, the 4-methoxy-(**13**) and 4-acetoxyhomophthalic anhydrides (**14** and **15**), respectively.

Conversion of the anhydrides (**13**—**15**) to the tetracyclic adducts (**23**—**25**) was carried out by our strong base-induced cycloaddition method.[3] Treatment of the sodium salts generated from these anhydrides and 1.0—1.1 eq of NaH in THF with 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone at room temperature gave the regiospecific naphthacenediones (**23**—**25**) in 65%, 72%, and 62% yields, respectively. The latter two adducts (**24** and **25**) were identical with authentic samples prepared earlier by us [3b] and were readily hydrolyzed quantitatively to **7** and **8** with 80% trifluoroacetic acid. The former adduct was assigned as **23** on the basis of spectral evidence and the following chemical

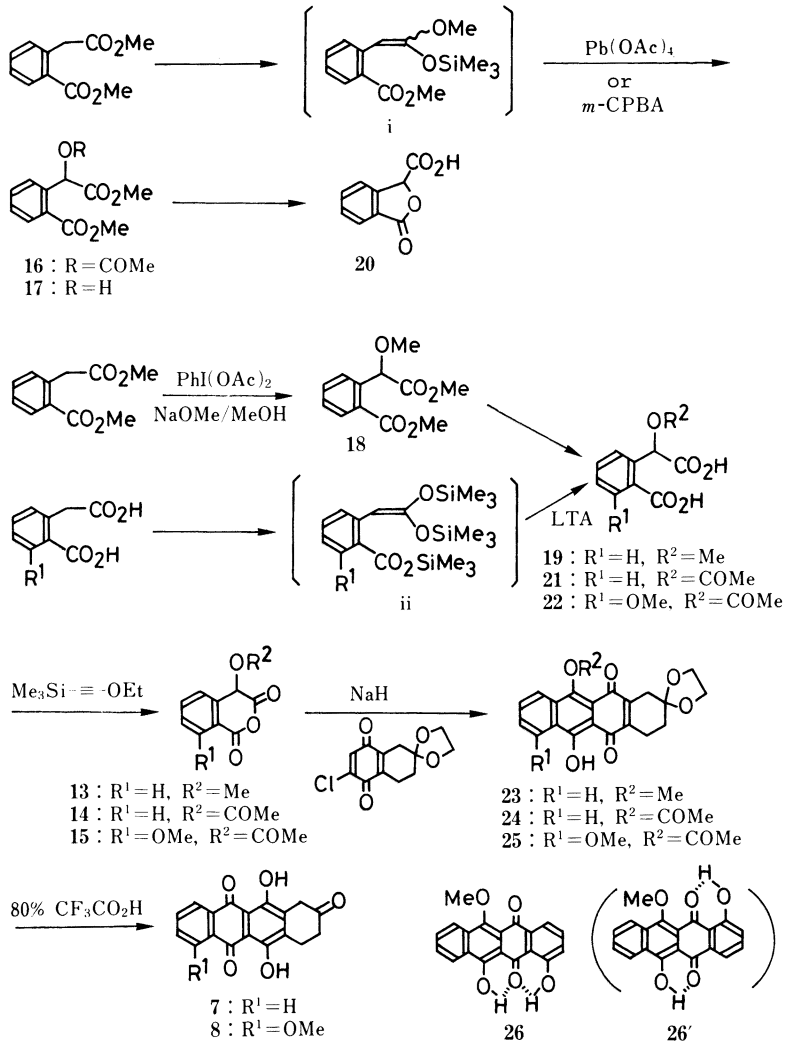


Chart 2

behavior: hydrolysis of **23** with 80% trifluoroacetic acid gave a quantitative yield of **7** and the regiochemistry of the cycloaddition of 4-methoxyhomophthalic anhydride (**13**) was shown to have the same orientation as that of the 4-acetoxyhomophthalic anhydrides (**14** and **15**) in the reaction with 3-bromo-5-hydroxy-1,4-naphthoquinone, giving the single adduct (**26**) [not the regioisomer **26'**].[10] As shown above, the use of C_4-acetoxyhomophthalic anhydrides (**14** and **15**) instead of homophthalic anhydrides was found to be the best method for the preparation of **7** and **8**.

As for the side-chain elaboration of the 9-keto group of these tetracyclic ketones (**7** and **8**), there remains the need for some improvements since the reported side-chain elaboration of the 9-keto group by using ethynylmagnesium bromide gives inadequate yields.[11] All other existing methodologies for the homologation of **7** and **8** using acyl anion equivalents were tried but did not give satisfactory results, probably due to the ready base-catalyzed enolization of the 9-keto group. Recently, we have found[12] that trimethylsilylethynylcerium (III) reagent is quite useful for the conversion of an enolizable ketone into a hydroxyacetone moiety and we

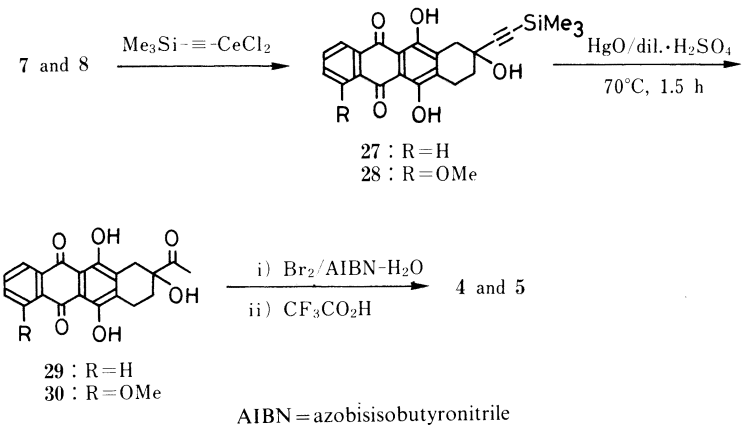


Chart 3

successfully applied this method for the conversion of **7** and **8** to the 9-hydroxyacetone compounds.[13,14] Trimethylsilylethynylation of the tetracyclic ketones (**7** and **8**) with 20 eq of trimethylsilylethynylcerium (III) chloride [prepared from trimethylsilylethynyllithium and cerium (III) chloride in THF] at −78 °C for 3 h gave the 9-trimethylsilylethynyl alcohols (**27** and **28**) in 77% and 69% yields, respectively. Direct transformation of a 2-trimethylsilylethynyl group into a methyl ketone was readily accomplished by a standard method using mercury (II) ion: treatment of the trimethylsilylethynyl alcohols (**27** and **28**) with HgO/dil. H_2SO_4 in refluxing THF gave the 9-hydroxyacetone compounds (**29** and **30**) in 87% and 86% yields, respectively. As conversion of **29** or **30** into **4** or **5** by convenient methods has already been described,[11,15] our approach constitutes a highly convergent synthesis of **4** and **5**.

Experimental

All melting points are uncorrected. Infrared (IR) absorption spectra were recorded on a JASCO HPIR-102 spectrometer and proton nuclear magnetic resonance (^{1}H-NMR) spectra on a Hitachi R-20A (60 MHz), a Hitachi R-22 (90 MHz), or a JEOL JNM-FX 90Q (90 MHz) spectrometer (with tetramethylsilane as an internal standard). Low- and high-resolution mass spectra (MS) were obtained with a JEOL JMS D-300 instrument, with a direct inlet system at 70 eV. Column chromatography was carried out on Merck Silica gel 60.

Methyl 2-Acetoxy-2-(2-methoxycarbonylphenyl)acetate (16)——A solution of *n*-BuLi (1.6 N, 0.75 ml, 1.2 mmol) was added dropwise under nitrogen to a stirred solution of dry diisopropylamine (0.17 ml, 1.2 mmol) in anhydrous THF (3 ml) at 0 °C. The mixture was stirred for a few minutes under the same conditions and then used as a THF solution of LDA. A solution of dimethyl homophthalate (208 mg, 1.0 mmol) in anhydrous THF (3 ml) was added dropwise to the solution of LDA over a few minutes at −78 °C and Me_3SiCl (0.25 ml, 2.0 mmol) was added to the mixture. The whole was stirred at −78 °C for 2 h, allowed to warm to room temperature, and stirred for 30 min. The reaction mixture was concentrated under reduced pressure and pentane (6 ml) was added to the residue. The mixture was filtered rapidly and the filtrate was concentrated *in vacuo* to give the ketene silyl acetal intermediate (i) (282 mg, approximately 100%), which was used in the next oxidation reaction without purification. A solution of the ketene silyl acetal (i) (140 mg, approximately 0.5 mmol) in dry benzene (2 ml) was added to a stirred suspension of LTA (247 mg, 0.5 mmol) in dry benzene (3 ml) at room temperature under nitrogen. The resulting slurry was stirred for 2 h under the same conditions and filtered to remove lead (II) acetate. The filtrate was poured into 5% HCl (15 ml), and extracted with ether (15 ml × 2). The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a residue, which was subjected to column chromatography on silica gel with hexane : ethyl acetate = 5 : 1 as the eluting solvent to give an 83% yield of **16** (110 mg): colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1720. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 2.17 (s, 3H, OCOMe), 3.72 (s, 3H, CO_2Me), 3.91 (s, 3H, CO_2Me), 7.07 (s, 1H, $-CHCO_2Me$), 7.5—7.55 (m, 3H, ArH), 7.9—7.95 (m, 1H, ArH). *Anal.* Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.81; H, 5.04.

Methyl 2-Hydroxy-2-(2-methoxycarbonylphenyl)acetate (17)——A solution of the ketene silyl acetal (i) (840 mg, approximately 3 mmol), prepared by the procedure described above, in dry hexane (10 ml) was added to a stirred suspension of *m*-CPBA (80%, 647 mg, 3.0 mmol) in dry hexane (10 ml) at 0 °C under nitrogen. The resulting slurry was stirred at room temperature for 30 min and filtered. The filtrate was worked up in the same manner as described

for the preparation of **16** to give a 44% yield of **17** (296 mg): colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 3.48 (s, 3H, CO_2Me), 3.71 (s, 3H, CO_2Me), 5.97 (s, 1H, C<u>H</u>CO_2Me), 7.1—7.8 (m, 4H, ArH). The 2-hydroxy ester (**17**) was acetylated with Ac_2O–pyridine to give the acetate (**16**), which was identical with a sample obtained from dimethyl homophthalate.

Methyl 2-Methoxy-2-(2-methoxycarbonylphenyl)acetate (18)——Dimethyl homophthalate (208 mg, 1.0 mmol) was added to a stirred solution of Na (76 mg, 3.3 mmol) in dry MeOH (3 ml) at room temperature under nitrogen. The mixture was stirred for a few minutes under the same conditions and $C_6H_5I(OAc)_2$ (483 mg, 1.5 mmol) was added. The resulting slurry was stirred at room temperature for 4 d, poured into 10% hydrochloric acid, made neutral, and extracted with CH_2Cl_2 (10 ml × 3). The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel with hexane : ethyl acetate = 10 : 1 as the eluting solvent to give a 50% yield of **18** (118 mg): colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 2950, 2830, 1740, 1720, 1600, 1580. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 3.47 (s, 3H, OMe), 3.70 (s, 3H, CO_2Me), 3.90 (s, 3H, CO_2Me), 5.80 (s, 1H, –C<u>H</u>CO_2Me), 7.3—7.6 (m, 3H, ArH) 7.8—8.0 (m, 1H, ArH). Exact MS Calcd for $C_{12}H_{14}O_5$: 238.0841. Found: 238.0846.

2-Methoxy-2-(2-carboxyphenyl)acetic Acid (19)——A solution of **18** (150 mg, 0.63 mmol) in 7% aqueous KOH (4 ml) and MeOH (2 ml) was heated at reflux for 3 h. The mixture was concentrated *in vacuo* and partitioned between ether (15 ml) and water (5 ml). The solution was adjusted to pH 1 by addition of conc. HCl and extracted with ether. The aqueous layer was saturated with NaCl and extracted with ether (30 ml × 3). The combined extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an 89% yield of **19** (117 mg). Recrystallization from ethyl acetate gave a pure sample as colorless crystals; mp 148—149 °C. *Anal.* Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 56.95; H, 4.75.

3-Phthalidecarboxylic Acid (20)——1) From **16**: A solution of **16** (180 mg, 0.68 mmol) in 30% aqueous NaOH (3 ml) and MeOH (3 ml) was heated at reflux for 2 h. The reaction mixture was worked up as described for the preparation of **19** to give a quantitative yield (120 mg) of **20**. Recrystallization from ethyl acetate gave a pure sample: mp 151—153 °C (lit.[16] 149—150 °C). IR ν_{max}^{KCl} cm^{-1}: 2850, 1770, 1710. ^{1}H-NMR (acetone-d_6) δ: 6.11 (s, 1H, CH), 7.75—7.85 (m, 4H, ArH).

2) From **17**: The ester (**17**) (152 mg, 0.68 mmol) was treated with 30% aqueous NaOH under the conditions described above (1) to give a 96% yield (115 mg) of **20**, which was identical with an authentic sample obtained from **16**.

2-Acetoxy-2-(2-carboxyphenyl)acetic Acid (21)——A solution of homophthalic acid (180 mg, 1.0 mmol) in dry THF (3 ml) was added dropwise to a solution of LDA (3.2 mmol) in THF over a few minutes at −78 °C under nitrogen and the mixture was stirred for 30 min under the same conditions. After addition of Me_3SiCl (0.75 ml, 5.9 mmol), the reaction mixture was stirred at −78 °C for 1.5 h, allowed to warm to room temperature, and stirred for an additional 30 min. Work-up in the same manner as described for the preparation of **16** gave the ketene silyl acetal intermediate (ii), which was used in the next oxidation reaction without purification. A solution of the ketene silyl acetal (ii) in dry benzene (4 ml) was added to a stirred suspension of LTA (550 mg, 1.12 mmol) in dry benzene (3 ml) at room temperature under nitrogen. The resulting slurry was worked up in the same manner as described for the preparation of **16** to give a quantitative yield (238 mg) of **21**. Recrystallization from ethyl acetate–hexane gave a pure sample; mp 148—150 °C. IR ν_{max}^{KCl} cm^{-1}: 3070 sh, 3020 sh, 2920, 2850, 2630, 1755, 1720, 1675, 1600, 1580. ^{1}H-NMR (acetone-d_6) δ: 2.12 (s, 3H, OCOMe), 6.80 (br s, 2H, CO_2H × 2), 7.18 (s, 1H, –C<u>H</u>CO_2H), 7.2—7.8 (m, 3H, ArH), 7.9—8.15 (m, 1H, ArH). *Anal.* Calcd for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.39; H, 4.29.

2-Acetoxy-2-(2-carboxy-3-methoxyphenyl)acetic Acid (22)——According to the same procedure as described for the preparation of **21**, a 97% yield (261 mg) of **22** was obtained from 2-carboxy-3-methoxyphenylacetic acid (210 mg, 1.0 mmol). The product was used in the next reaction without purification: colorless syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300—2800, 1760—1710. ^{1}H-NMR (acetone-d_6) δ: 2.09 (s, 3H, OCOMe), 3.87 (s, 3H, OMe), 6.21 (s, 1H, –C<u>H</u>CO_2H), 6.30 (br s, 2H, CO_2H × 2), 6.95—7.55 (m, 3H, ArH). Exact MS Calcd for $C_{12}H_{12}O_7$: 268.0580. Found: 268.0574.

4-Methoxyhomophthalic Anhydride (13)——A solution of **19** (115 mg, 0.55 mmol) and trimethylsilylethoxyacetylene (116 mg, 0.82 mmol) in dry CH_2Cl_2 (2 ml) was stirred at 40 °C for 3.5 h. After removal of insoluble material by filtration, the filtrate was concentrated *in vacuo* to give a 92% yield (97 mg) of **13**. Recrystallization from CH_2Cl_2–hexane gave a pure sample as colorless crystals; mp 122—125 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1805, 1765, 1605. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 3.76 (s, 3H, OMe), 5.17 (s, 1H, CH), 7.5—7.85 (m, 3H, ArH), 8.05—8.25 (s, 1H, ArH). *Anal.* Calcd for $C_{10}H_8O_4 \cdot H_2O$; C, 57.14; H, 4.80. Found: C, 57.17; H, 4.78.

4-Acetoxyhomophthalic Anhydride (14)——A solution of **21** (80 mg, 0.34 mmol) and trimethylsilylethoxyacetylene (65 mg, 0.46 mmol) in dry CH_2Cl_2 (1.5 ml) was stirred at room temperature for 4 h. Concentration of the reaction mixture *in vacuo* gave a quantitative yield (74 mg) of **14**: colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1805, 1765, 1600. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 2.31 (s, 3H, OCOMe), 6.53 (s, 1H, CH), 7.3—7.9 (m, 3H, ArH), 8.05—8.3 (m, 1H, ArH), MS *m/z*: 220 (M^+). Exact MS Calcd for $C_{11}H_8O_5$: 220.0369. Found: 220.0351.

4-Acetoxy-8-methoxyhomophthalic Anhydride (15)——A solution of **22** (80 mg, 0.30 mmol) and trimethylsilylethoxyacetylene (65 mg, 0.46 mmol) in dry CH_2Cl_2 (1.5 ml) was stirred at room temperature for 4 h. Concentration of the reaction mixture *in vacuo* gave a quantitative yield (74 mg) of **15**. Recrystallization from benzene–hexane gave a

pure sample: mp 162—164 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1815, 1765, 1600. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 2.32 (s, 3H, OCOMe), 4.00 (s, 3H, OMe), 6.51 (s, 1H, CH), 6.9—7.2 (m, 2H, ArH), 7.70 (t, 1H, J=7.5 Hz, ArH), MS m/z: 250 (M^+). *Anal.* Calcd for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03. Found: C, 57.27; H, 4.01.

General Procedure for the Cycloaddition of Homophthalic Anhydrides (13—15) to 2-Chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone Leading to Cycloadducts (23—25)——A mixture of the anhydride (0.5 mmol) and NaH (60% in mineral oil, 0.55 mmol) in anhydrous THF (2 ml) was stirred at room temperature for several minutes under nitrogen, then a solution of the quinone (0.5 mmol) in anhydrous THF (4 ml) was added. The reaction mixture was stirred at room temperature for a suitable period (checked by thin layer chromatography (TLC)), then quenched with saturated aqueous NH_4Cl (20 ml) and extracted with CH_2Cl_2 (20 ml × 3). The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel with $CHCl_3$: ether = 30 : 1 as the eluting solvent to give the corresponding adduct.

2,2-Ethylenedioxy-6-hydroxy-11-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (23)——This was prepared from **13** (45 mg, 0.23 mmol) and 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (59 mg, 0.23 mmol) at room temperature for 3 h in a 65% yield (55 mg). Recrystallization from benzene gave a pure sample: mp 238—240 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2925, 2875, 2850 sh, 1650 sh, 1645 sh, 1635, 1600, 1575. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.91 (t, 2H, J=7 Hz, CH_2), 2.7—3.1 (m, 4H, CH_2 × 2), 4.00 (s, 4H, OCH_2CH_2O), 4.05 (s, 3H OMe), 7.6—7.9 (m, 2H, ArH), 8.2—8.6 (m, 2H, ArH), 14.80 (s, 1H, OH). *Anal.* Calcd for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 68.94; H, 4.80.

11-Acetoxy-2,2-ethylenedioxy-6-hydroxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (24)——This was prepared from **14** (74 mg, 0.34 mmol) and 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (86 mg, 0.34 mmol) at room temperature for 18 h in a 75% yield (99 mg). Recrystallization from CH_2Cl_2–MeOH gave a pure sample: mp 225—228 °C (lit.[3b] 215—217 °C). This was identical with an authentic sample.

11-Acetoxy-2,2-ethylenedioxy-6-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (25)——This was prepared from **15** (86 mg, 0.34 mmol) and 2-chloro-6,6-ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (87 mg, 0.34 mmol) at room temperature for 15 h in a 62% yield (90 mg). Recrystallization from CH_2Cl_2–EtOH gave a pure sample: mp 244.5—246 °C (lit.[3b] 244.5—246 °C). This was identical with an authentic sample.

1,11-Dihydroxy-6-methoxynaphthacene-5,12-dione (26)——A solution of 3-bromo-5-hydroxy-1,4-naphthoquinone (16 mg, 0.06 mmol) in anhydrous THF (1 ml) was added to a stirred suspension of **13** (13 mg, 0.07 mmol) and NaH (60% in mineral oil, 8 mg, 0.20 mmol) in anhydrous THF (2 ml) at room temperature under nitrogen. The reaction mixture was stirred for 2 h under the same conditions, then quenched with saturated aqueous NH_4Cl (10 ml). The aqueous layer was adjusted to pH 2 by addition of 1 N HCl and extracted with CH_2Cl_2 (15 ml × 3). The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to preparative TLC on silica gel with benzene : hexane = 4 : 1 as the developing solvent to give a 77% yield (16 mg) of **26**. Recrystallization from benzene gave a pure sample: mp 234—236 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660, 1620, 1600, 1580. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 4.07 (s, 3H, OMe), 7.25 (dd, 1H, J=8, 1.5 Hz, ArH), 7.55—8.0 (m, 4H, ArH), 8.3—8.6 (m, 2H, ArH), 12.22 (s, 1H, OH), 14.40 (s, 1H, OH). Exact MS Calcd for $C_{19}H_{12}O_5$: 320.0683. Found: 320.0665.

6,11-Dihydroxy-7,8-dihydronaphthacene-5,9(10*H*),12-trione (7)——1) From **23**: A solution of **23** (20 mg, 0.055 mmol) in CF_3CO_2H (4 ml) and water (1 ml) was heated at 50 °C for 2 h, then concentrated *in vacuo*, and the residue was partitioned between CH_2Cl_2 (10 ml) and water. The aqueous layer was extracted with CH_2Cl_2 (20 ml × 2). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel with $CHCl_3$: ethyl acetate = 20 : 1 as the eluting solvent to give a quantitative yield (17 mg) of **7**. Recrystallization from CH_2Cl_2–MeOH gave a pure sample: mp over 300 °C, (lit.[3b] 296—298 °C, lit.[17] 300 °C). This was identical with an authentic sample.

2) From **24**: The experimental details were as reported.[3b]

6,11-Dihydroxy-4-methoxy-7,8-dihydronaphthacene-5,9(10*H*),12-trione (8)——The experimental details were as reported.[3b]

6,9,11-Trihydroxy-9-(2-trimethylsilylethynyl)-7,8,9,10-tetrahydronaphthacene-5,12-dione (27)——The $CeCl_3$–Me_3Si–≡–Li reagent system was used with a modification of the reported method.[18] Anhydrous cerium chloride ($CeCl_3$, 370 mg, 1.5 mmol) was placed in a two-necked flask, heated *in vacuo* (0.1 mmHg) at 140 °C for 2 h and then cooled. Dry THF (3 ml) was added under nitrogen, stirring was continued for 1 h, and the flask was cooled to −78 °C. Then lithium trimethylsilylacetylide [prepared from trimethylsilylacetylene (0.21 ml, 1.5 mmol) and *n*-BuLi (1.6 N, 0.61 ml, 0.97 mmol) in dry THF (2 ml) at −40 °C for 30 min] was added to the cooled suspension with stirring. The mixture was stirred at −78 °C for 1 h and then used as a THF solution of trimethylsilylethynylcerium (III) chloride. To this solution was added a solution of **7** (20 mg, 0.065 mmol) in dry THF (3 ml) at −78 °C under nitrogen. The mixture was stirred for 2 h under the same conditions and then quenched with water (15 ml), made acidic by addition of dil. HCl, and extracted with CH_2Cl_2 (30 ml × 2). The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$: ethyl acetate = 100 : 1 as the eluting solvent to give a 77% yield (21 mg) of **27** as a red solid. Recrystallization from $CHCl_3$–hexane gave a pure sample: mp 193—195 °C (lit.[14b] 190—191 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1590. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 0.17 (s, 9H, $SiMe_3$), 2.12 (br t, 2H, J=6.0 Hz, CH_2), 2.29 (br s, 1H, OH), 2.97 (br t, 2H,

J=6.0 Hz, CH_2), 3.13 (br s, 2H, CH_2), 7.7—7.9 (m, 2H, ArH), 8.2—8.35 (m, 2H, ArH), 13.35 (s, 1H, OH), 13.36 (s, 1H, OH). Exact MS Calcd for $C_{23}H_{22}O_5Si$: 406.1234. Found: 406.1218.

6,9,11-Trihydroxy-4-methoxy-9-(2-trimethylsilylethynyl)-7,8,9,10-tetrahydronaphthacene-5,12-dione (28)——According to the same procedure as described for the preparation of **27**, a 69% yield (19.5 mg) of **28** was obtained from trimethylsilylacetylene (0.21 ml, 1.5 mmol), *n*-BuLi (1.6 N, 0.61 ml, 0.97 mmol), anhydrous $CeCl_3$ (370 mg, 1.5 mmol) and **8** (22 mg, 0.065 mmol) as a red solid. Recrystallization from $CHCl_3$ gave a pure sample: mp 262—264.5 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1605, 1580. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 0.19 (s, 9H, $SiMe_3$), 2.0—2.2 (m, 3H, CH_2 and OH), 3.02 (br t, 2H, J=6.0 Hz, CH_2), 3.15 (br s, 2H, CH_2), 4.10 (s, 3H, OMe), 7.37 (dd, 1H, J=8.5, 1.0 Hz, ArH), 7.76 (t, 1H, J=8.5 Hz, ArH), 8.04 (dd, 1H, J=8.5, 1.0 Hz, ArH), 13.48 (s, 1H, OH), 13.85 (s, 1H, OH). Exact MS Calcd for $C_{24}H_{24}O_6Si$: 436.1339. Found: 436.1322.

9-Acetyl-6,9,11-trihydroxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (4-Demethoxy-7-deoxydaunomycinone) (29)——A solution of **27** (13 mg, 0.032 mmol), HgO (21 mg, 0.097 mmol), and 20% H_2SO_4 (0.5 ml) in THF (2 ml) was heated at reflux for 1.5 h and then cooled to room temperature. The reaction mixture was diluted with 0.5% HCl (10 ml) and extracted with CH_2Cl_2 (15 ml × 3). The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$: ethyl acetate = 50 : 1 as the eluting solvent to give an 87% yield (9.8 mg) of **29** as a red solid. Recrystallization from CH_2Cl_2–*n*-hexane gave a pure sample: mp 211—213.5 °C (lit.[14a] 212.5—214.5 °C, lit.[11b] 160—162 °C, lit.[19a] 210—212 °C, lit.[15a] 216—218 °C, lit.[19b] 210—211 °C, lit.[19c] 202—203 °C, lit.[19d] 214—216 °C, lit.[19e] 213—215 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705, 1615, 1585. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.85—2.1 (m, 2H, CH_2), 2.40 (s, 3H, COMe), 2.9—3.15 (m, 4H, CH_2 × 2), 3.79 (s, 1H, OH), 7.75—7.9 (m, 2H, ArH), 8.2—8.45 (m, 2H, ArH), 13.43 (s, 2H, OH × 2). MS *m/z*: 352 (M^+).

9-Acetyl-6,9,11-trihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (7-Deoxydaunomycinone) (30)——According to the same procedure as described for the preparation of **29**, an 86% yield (6.6 mg) of **30** was obtained from **28** (8.8 mg, 0.02 mmol), HgO (13 mg, 0.06 mmol), and 20% H_2SO_4 (0.3 ml) as a red solid. Recrystallization from ethyl acetate–THF gave a pure sample: mp 229—233.5 °C (lit.[20a] 229—231 °C, lit.[15b] 230—232 °C, lit.[15c] 228—230 °C, lit.[20b] 228—229 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705, 1605, 1580. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.85—2.1 (m, 2H, CH_2), 2.38 (s, 3H, COMe), 2.8—3.2 (m, 4H, CH_2 × 2), 3.78 (s, 1H, OH), 4.08 (s, 3H, OMe), 7.36 (br d, 1H, J=8.0 Hz, ArH), 7.74 (t, 1H, J=8.0 Hz, ArH), 8.02 (br d, 1H, J=8.0 Hz, ArH), 13.43 (s, 1H, OH), 13.87 (s, 1H, OH). MS *m/z*: 382 (M^+).

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