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Studies on the Synthesis of 4-[1,8-Dioxygenated-9,10-dioxoanthracen(or anthracen)-2-yl]butanoic Acid Derivatives

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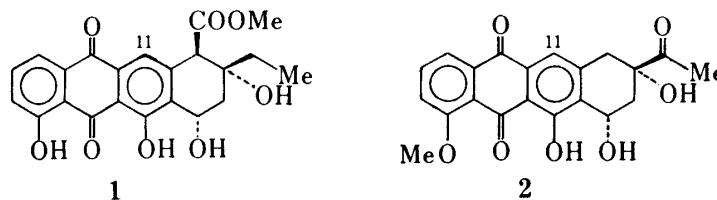
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The title compounds (**11**—**14**, **16**, **17**), which are expected to be valuable in the synthesis of 11-deoxyanthracyclines, were prepared from readily available 1,8-dihydroxyanthracene-9,10-dione (chrysazin) (**3**) by employing the Claisen rearrangement or Marschalk reaction as a key synthetic step.

Keywords—11-deoxyanthracyclines; 11-deoxyanthracyclones; 1,8-dioxygenated-9,10-dioxoanthracenes; 1,8-dioxygenated-anthracenes; anticancer agents; Claisen rearrangement; Marschalk reaction

The 11-deoxyanthracyclines are of current interest because they may provide better therapeutic indices in the treatment of human cancers than the ordinary 11-oxygenated anthracyclines.¹⁾ For this reason, many synthetic studies have been carried out on the 11-deoxyanthracyclines,²⁾ the aglycones of 11-deoxyanthracyclines, represented by aklavinone (**1**)³⁾ and 11-deoxydaunomycinone (**2**).⁴⁾



In connection with our synthetic approach to these 11-deoxyanthracyclines, an effective method which can readily provide 4-[1,8-dioxygenated-9,10-dioxoanthracen (or anthracen)-2-yl]butanoic acid derivatives was sought.⁵⁻⁸⁾ We have now found that the desired compounds can be elaborated from readily available 1,8-dihydroxyanthracene-9,10-dione(chrysazin)(**3**) by employing the Claisen rearrangement^{3f,9-12)} or Marschalk reaction^{2,13-16)} as a key step.

Thus, alkylation of 1-hydroxy-8-methoxyanthracene-9,10-dione(chrysazin monomethyl ether) (**4**),^{17,18)} readily obtainable from **3** on a large scale, with allyl bromide gave an 88% yield of the allyl ether (**5**). Claisen rearrangement of **5**⁹⁻¹²⁾ was effected by heating a solution of **5** in *N,N*-diethylaniline at 200°C, giving the 2-allylanthracene-9,10-dione derivative (**6**) in 57% yield¹⁹⁾ with concomitant formation of **4** in 20% yield. After methylation of **6** with dime-

	R ¹	R ²	R ³		
3 :	H	H	H	6 :	Me
4 :	Me	H	H	7 :	Me
5 :	Me	CH ₂ -CH=CH ₂	H	8 :	Me
				9 :	Me
				10 :	Me
				11 :	Me
				12 :	Me
				13 :	Me
				14 :	Me

thyl sulfate (87%), the methyl ether (7) was subjected to hydroboration followed by oxidation, to produce the alcohol (8) in 71% yield. Successive mesylation (97%) of **8**²⁰⁾ and substitution with cyanide (94%) gave the nitrile (10), which was transformed to the desired ethyl 4-(1,8-dimethoxy-9,10-dioxoanthracen-2-yl)butanoate (11) in 98% yield by way of the imino ether.²¹⁾ Alkaline hydrolysis of **11** yielded the acid (12) quantitatively.

Since the synthetic scheme exploited above is quite lengthy, direct introduction of a butanoic acid side chain into **4** was further examined by employing the Marschalk reaction.^{2,13-16)} After being introduced into the synthesis of anthracyclines by Sutherland,¹⁴⁾ Brown,¹⁵⁾ and Krohn¹⁶⁾ in 1978, the Marschalk reaction has been anticipated to be one of the most versatile methods for elaborating various 11-oxygenated anthracyclines from 1,4-dihydroxyanthracene-9,10-dione derivatives.^{6,13-16)}

After several preliminary experiments,²²⁾ we have found that reduction of **4** with sodium dithionite in aqueous alkaline solution, followed by reaction with 3-formylpropanoic acid generated *in situ* from methyl 3-formylpropanoate,²³⁾ reoxidation with air, and esterification of the acid (13), gives the ester (14) in 45% yield based on **4**. Methylation of **14** also yielded **11** in 93% yield. The two lots of **11** were shown to be identical by spectral comparisons and mixed melting point measurement.

Since preparation of the anthracene-9,10-dione derivatives such as **11** and **14** was completed as described above, conversion of these compounds into the anthracene derivatives was next attempted as shown in Chart 1.

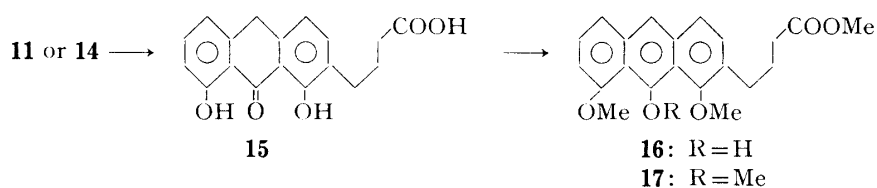


Chart 1

Reduction of **11** or **14** with stannous chloride in conc. hydrochloric acid⁸⁾ proceeded in 95% yield to give the anthrone (**15**), which, on methylation with dimethyl sulfate in acetone, yielded the dimethyl ether (**16**) in 50% yield. Further methylation of **16** with dimethyl sulfate in *N,N*-dimethylformamide afforded the trimethyl ether (**17**).

As exemplified above, it became possible to obtain 4-[1,8-dioxygenated-9,10-dioxoanthracen(or anthracen)-2-yl]butanoic acid derivatives (**11**—**14**, **16**, **17**) from the readily available compound **3**. On the basis of the numbers of synthetic steps, the latter route featuring the Marschalk reaction as a key step seems preferable.

Further elaboration of these butanoic acid derivatives to the 11-deoxyanthracyclines is in progress in this laboratory.

Experimental²⁴⁾

1-Hydroxy-8-methoxyanthracene-9,10-dione (Chrysazin Monomethyl Ether) (4)—The mono potassium salt (26.8 g, 0.096 mol) prepared from **3** and KOH in pyridine and MeOH according to the reported procedure,¹⁷⁾ was added to dimethyl sulfate (150 ml, 1.59 mol), and the mixture was stirred at 135°C for 4 h. Filtration followed by concentration *in vacuo* gave a mixture of **3**, **4**, and the dimethyl ether of **3** as an orange solid (24.4 g). The formation ratio of these compounds was determined as 16:74:10 from the NMR spectrum. Separation of **4** from the mixture was accomplished by column chromatography (C₆H₆–CHCl₃ 3:2) followed by recrystallization from EtOH, giving pure **4** as orange needles, mp 200–201°C (lit.,¹⁸⁾ mp 198°C). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1669, 1641 (quinone). NMR (in CDCl₃): 4.06 (3H, s, OCH₃), 7.27 (1H, dd, *J*_{6,7}=8.0 Hz, *J*_{5,7}=2.0 Hz, C₇-H), 7.35 (1H, dd, *J*_{2,3}=8.0 Hz, *J*_{2,4}=2.0 Hz, C₂-H), 7.60 (2H, dd, *J*_{2,3}=*J*_{3,4}=*J*_{5,6}=*J*_{6,7}=8.0 Hz, C₃-H and C₆-H), 7.79 (1H, dd, *J*_{5,6}=8.0 Hz, *J*_{5,7}=2.0 Hz, C₅-H), 7.96 (1H, *J*_{3,4}=8.0 Hz, *J*_{2,4}=2.0 Hz, C₄-H), 12.85 (1H, s, OH).

1-Allyloxy-8-methoxyanthracene-9,10-dione (5)—Allyl bromide (18 ml, 0.208 mol) was added to a mixture of **4** (7.00 g, 28 mmol) and powdered anhyd. K_2CO_3 (7.76 g, 56 mmol) in Me_2CO (750 ml), and the mixture was heated at reflux for 120 h with stirring. After reaction for 55 h, a further amount of allyl bromide (3.0 ml, 35 mmol) was added to the reaction mixture. Filtration and concentration *in vacuo* gave crude **5** as a pale yellow solid (9.79 g), which on recrystallization from EtOH afforded pure **5** as yellow leaflets (7.10 g, 88%), mp 174–175°C. IR ν_{max}^{KBr} cm^{-1} : 1665 (quinone), 1590 (aromatic ring). NMR (in $CDCl_3$): 3.98 (3H, s, OCH_3), 4.75 (2H, br d, $J=4.8$ Hz, $CH_2=CH-CH_2O$), 5.34 (1H, br dd, $J=9.6$ and 2.0 Hz, $E-CH_2C=C-H$), 5.56 (1H, br dd, $J=16.5$ and 2.0 Hz, $Z-CH_2C=C-H$), 6.17 (1H, ddt, $J=16.5$, 9.6, and 4.8 Hz, $CH_2=CHCH_2$), 7.26 (2H, br d, $J_{2,3}=J_{6,7}=7.5$ Hz, C_2-H and C_7-H), 7.58 (1H, dd, $J_{2,3}=J_{3,4}=7.5$ Hz or $J_{5,6}=J_{6,7}=7.5$ Hz, C_3-H or C_6-H), 7.60 (1H, dd, $J_{2,3}=J_{3,4}=7.5$ Hz or $J_{5,6}=J_{6,7}=7.5$ Hz, C_3-H or C_6-H), 7.81 (2H, dd, $J_{3,4}=J_{5,6}=7.5$ Hz, $J_{2,4}=J_{5,7}=2.0$ Hz, C_4-H and C_5-H). This compound was immediately subjected to the next rearrangement.

2-Allyl-1-hydroxy-8-methoxyanthracene-9,10-dione (6)—A mixture of **5** (1.00 g, 3.4 mmol) and 2,6-di-*tert*-butyl-phenol (30 mg) in *N,N*-diethylaniline (30 ml) was heated at 200°C for 4 h with stirring under an argon atmosphere. *N,N*-Diethylaniline was removed by concentration *in vacuo*, and the residue was dissolved in EtOAc (200 ml). The organic solution was washed with 10% HCl and satd. NaCl. Filtration and concentration *in vacuo* followed by column chromatography ($C_6H_6-CHCl_3$ 4: 1) afforded **6** as an orange solid (570 mg, 57%), mp 169°C, and **4** as a yellow solid (171 mg, 20%). Recrystallization of **6** from EtOAc gave an analytical sample of **6** as an orange powder, mp 171.5–172°C. IR ν_{max}^{KBr} cm^{-1} : 1657, 1627 (quinone), 1584 (aromatic ring). NMR (in $CDCl_3$): 3.51 (2H, d, $J=6.5$ Hz, $CH_2CH=CH_2$), 4.02 (3H, s, OCH_3), 4.95–5.25 (1H, m, $E-CH_2C=C-H$), 4.85–5.40 (1H, m, $Z-CH_2C=C-H$), 6.05 (1H, ddt, $J=17.0$, 9.0, and 6.5 Hz, $CH_2CH=CH_2$), 7.23 (1H, dd, $J_{6,7}=9.0$ Hz, $J_{5,7}=2.0$ Hz, C_7-H), 7.52 (1H, d, $J_{3,4}=7.0$ Hz, C_3-H), 7.60 (1H, dd, $J_{5,6}=J_{6,7}=9.0$ Hz, C_6-H), 7.76 (1H, d, $J_{3,4}=7.0$ Hz, C_4-H), 7.85 (1H, dd, $J_{5,6}=9.0$ Hz, $J_{5,7}=2.0$ Hz, C_5-H), 13.25 (1H, s, OH). Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found: C, 73.33; H, 4.85.

2-Allyl-1,8-dimethoxyanthracene-9,10-dione (7)—A mixture of **6** (4.56 g, 15.5 mmol), dimethyl sulfate (6.0 ml, 63.4 mmol), and anhyd. K_2CO_3 (5.01 g, 36.2 mmol) in Me_2CO (800 ml) was heated at reflux for 21 h with stirring, then cooled. Filtration and concentration *in vacuo* gave a brownish-yellow solid (6.07 g), which was recrystallized from EtOH to give pure **7** as yellow needles (4.15 g, 87%), mp 132–132.5°C. An analytical sample was prepared by further recrystallization from EtOH, yellow needles, mp 135–135.5°C. IR ν_{max}^{KBr} cm^{-1} : 1677 (quinone), 1584 (aromatic ring). NMR (in $CDCl_3$): 3.55 (2H, d, $J=6.2$ Hz, $CH_2CH=CH_2$), 3.95, 4.00 (6H, two s, $OCH_3 \times 2$), 4.90–5.40 (2H, m, $CH_2CH=CH_2$), 5.97 (1H, ddt, $J=12.4$, 8.0, and 6.2 Hz, $CH_2CH=CH_2$), 7.26 (1H, dd, $J_{6,7}=7.5$ Hz, $J_{5,7}=2.0$ Hz, C_7-H), 7.49 (1H, d, $J_{3,4}=8.0$ Hz, C_3-H), 7.60 (1H, dd, $J_{5,6}=J_{6,7}=7.5$ Hz, C_6-H), 7.84 (1H, dd, $J_{5,6}=7.5$ Hz, $J_{5,7}=2.0$ Hz, C_5-H), 7.93 (1H, d, $J_{3,4}=8.0$ Hz, C_4-H). Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.78; H, 5.13.

3-(1,8-Dimethoxy-9,10-dioxoanthracen-2-yl)propan-1-ol (8)—A solution of diborane-THF complex (1 M solution in THF) (5.55 ml, 5.55 mmol) was added to a solution of **7** (566 mg, 1.84 mmol) in THF (18 ml). After being kept at room temperature for 23 h, the reaction mixture was diluted with H_2O (5 ml), 3 N NaOH (2 ml, 6.0 mmol), and 30% H_2O_2 (2 ml), and the whole was stirred at 50°C for 5 h. This mixture was diluted with Et_2O and H_2O , and the upper organic phase was separated and washed with H_2O and satd. NaCl. Filtration and concentration *in vacuo* gave a yellow solid. Purification by column chromatography ($C_6H_6-EtOAc$ 4: 1) gave **8** as a yellow solid (423 mg, 71%), mp 81°C. Repeated recrystallizations from EtOAc yielded pure **8** as yellow needles, mp 94–97°C. IR ν_{max}^{KBr} cm^{-1} : 3400 (OH), 1665 (quinone), 1580 (aromatic ring). NMR (in $CDCl_3$): 1.60–2.23 (2H, m, $CH_2CH_2CH_2OH$), 2.43 (1H, br s, OH), 2.87 (2H, dd, $J=8.0$ and 7.0 Hz, $CH_2CH_2CH_2OH$), 3.67 (2H, dd, $J=7.0$ and 5.0 Hz, CH_2OH), 3.95, 3.99 (6H, two s, $OCH_3 \times 2$). Signals due to the aromatic ring protons were similar to those of **7**. Anal. Calcd for $C_{19}H_{18}O_5-1/3H_2O$: C, 68.66; H, 5.66. Found: C, 68.63; H, 5.50.

3-(1,8-Dimethoxy-9,10-dioxoanthracene-2-yl)propyl Methanesulfonate (9)—A mixture of **8** (376 mg, 1.15 mmol) and methanesulfonyl chloride (305 mg, 2.65 mmol) in pyridine (2 ml) was stirred at room temperature for 1.5 h. The reaction mixture was poured into ice-water (10 g), and extracted with EtOAc. The combined organic extracts were washed successively with satd. $CuSO_4$ and satd. NaCl. Filtration and concentration *in vacuo* gave **9** as a yellow oil (450 mg, 97%). IR ν_{max}^{film} cm^{-1} : 1670 (quinone), 1590 (aromatic ring), 1350, 1325, 1170 (SO_3). NMR (in $CDCl_3$): 1.75–2.40 (2H, m, $CH_2CH_2CH_2$), 2.92 (2H, t, $J=7.5$ Hz, $CH_2CH_2CH_2O$), 3.02 (3H, s, SO_2CH_3), 3.95, 3.99 (6H, two s, $OCH_3 \times 2$), 4.25 (2H, t, $J=6.0$ Hz, CH_2O). Signals due to the aromatic protons were similar to those of **7**. The methanesulfonate (**9**) which solidified on standing overnight at room temperature, mp 104.5–108°C (dec.), was used immediately for the next reaction.

4-(1,8-Dimethoxy-9,10-dioxoanthracen-2-yl)butanenitrile (10)—A mixture of **9** (443 mg, 1.09 mmol) and NaCN (177 mg, 3.61 mmol) in DMSO (5 ml) was stirred at 60°C for 2.5 h, then poured into ice-water (30 g). The aqueous mixture was extracted with EtOAc. The combined organic extracts were washed with H_2O and satd. NaCl. Filtration and concentration *in vacuo* gave **10** as a yellow solid (346 mg, 94%), mp 116–123°C. Recrystallization from EtOAc-hexane (8: 3) yielded pure **10** as orange needles, mp 122.5–123°C. IR ν_{max}^{KBr} cm^{-1} : 2240 (CN), 1666 (quinone), 1583 (aromatic ring). NMR (in $CDCl_3$): 1.67–2.34 (2H, m, $CH_2CH_2CH_2$), 2.2–2.62 (2H, m, CH_2CN), 2.92 (2H, t, $J=7.0$ Hz, $CH_2CH_2CH_2CN$), 3.97, 4.00 (6H, two s, $OCH_3 \times 2$). Signals due to the aromatic ring were similar to those of **7**. Anal. Calcd for $C_{21}H_{17}O_4N$: C,

71.63; H, 5.11; N, 4.18. Found: C, 71.51; H, 5.10; N, 4.25.

Ethyl 4-(1,8-Dimethoxy-9,10-dioxoanthracen-2-yl)butanoate (11)—a) **11** from **10**: Conc. sulfuric acid (353 mg, 3.45 mmol) was added to a solution of **10** (206 mg, 0.61 mmol) in 95% EtOH (3 ml), and the mixture was heated at reflux for 8 h with stirring. The reaction mixture was poured into H₂O (50 ml), and extracted with Et₂O. The combined ethereal extracts were washed with satd. NaHCO₃ and satd. NaCl. Filtration and concentration *in vacuo* gave crude **11**, contaminated with a small amount of the demethylated compound (TLC analysis), as a brown oil (248 mg). Methylation of this sample in a manner similar to that described for the preparation of **7** from **6** gave crude **11** as a brown soft solid (229 mg, 98% based on **10**), mp 58–63°C. Recrystallization from Et₂O yielded pure **11** as yellow needles, mp 70–74°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1729 (COOEt), 1673 (quinone), 1585 (aromatic ring). NMR (in CDCl₃): 1.23 (3H, t, $J=7.5$ Hz, CH₂CH₃), 1.65–2.28 (2H, m, CH₂CH₂CH₂), 2.15–2.65 (2H, m, CH₂COOEt), 2.80 (2H, t, $J=7.0$ Hz, CH₂CH₂CH₂COOEt), 3.96, 4.00 (6H, two s, OCH₃ × 2), 4.15 (2H, q, $J=7.5$ Hz, CH₂CH₃), 7.24 (1H, dd, $J_{6,7}=8.0$ Hz, $J_{5,7}=2.5$ Hz, C₇-H), 7.47 (1H, d, $J_{3,4}=8.0$ Hz, C₃-H), 7.56 (1H, dd, $J_{5,6}=J_{6,7}=8.0$ Hz, C₆-H), 7.79 (1H, dd, $J_{5,6}=8.0$ Hz, $J_{5,7}=2.5$ Hz, C₅-H), 7.91 (1H, d, $J_{3,4}=8.0$ Hz, C₄-H). MS m/e : 382 [M⁺], 367 [M⁺–CH₃]. Anal. Calcd for C₂₂H₂₂O₆: C, 69.10; H, 5.80. Found: C, 69.05; H, 5.80.

b) **11** from **14**: Treatments of **14** (93.1 mg, 0.25 mmol) similar to those described for the preparation of **7** from **6** gave **11** as a yellow solid (95.2 mg) after filtration and concentration *in vacuo*. Purification by preparative TLC (C₆H₆–EtOAc 1:1) gave pure **11** as a yellow solid (89.4 mg, 93%), mp 71–77°C. This sample showed no melting point depression, mp 70.5–76°C, on mixed melting point measurement with **11** prepared in a). Spectral (IR and NMR) properties of this sample were identical with those given in a).

4-(1,8-Dimethoxy-9,10-dioxoanthracen-2-yl)butanoic Acid (12)—A mixture of **11** (667 mg, 1.74 mmol) and 2.5% NaOH (6 ml, 3.75 mmol) in EtOH (10 ml) was stirred at room temperature for 4 h. The reaction mixture was concentrated *in vacuo*, acidified with conc. HCl (pH=2), then extracted with EtOAc. The combined organic extracts were washed with satd. NaCl. Filtration and concentration *in vacuo* gave **12** as a yellow solid (621 mg, 100%), mp 142°C. Recrystallization from EtOAc gave pure **12** as yellow needles, mp 142–142.5°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1688 (COOH), 1667 (quinone), 1578 (aromatic ring). NMR (in CDCl₃): 1.75–2.35 (2H, m, CH₂CH₂CH₂), 2.25–2.70 (2H, m, CH₂COOH), 2.89 (2H, t, $J=7.5$ Hz, CH₂CH₂CH₂COOH), 3.98, 4.02 (6H, two s, OCH₃ × 2), 10.23 (1H, br s, COOH). Signals due to the aromatic ring were similar to those of **11**. MS m/e : 354 [M⁺], 339 [M⁺–CH₃]. Anal. Calcd for C₂₀H₁₈O₆·1/6H₂O: C, 67.22; H, 5.16. Found: C, 67.24; H, 5.18.

Methyl 3-Formylpropanoate—Prepared from succinic anhydride according to the reported method.²³⁾ Colorless oil, bp 94–98.5°C (45 mmHg) (lit.,^{23b)} bp 69–70°C (14 mmHg).

Ethyl 4-(1-Hydroxy-8-methoxy-9,10-dioxoanthracen-2-yl)butanoate (14)—A heterogeneous mixture of methyl 3-formylpropanoate (5.00 g, 43 mmol) and 0.1 N HCl (100 ml, 10 mmol) was stirred at 85–90°C for 40 min, giving a clear solution of 3-formylpropanoic acid. After cooling, the acidic solution was neutralized (pH=7) by the addition of solid anhyd. Na₂CO₃, and then used for the next reaction.

A solution of NaOH (97%) (7.00 g, 0.17 mol) in H₂O (400 ml) was added to a mixture of **4** (7.00 g, 27.5 mmol) and Na₂S₂O₄ (6.00 g, 34.5 mmol), and the whole was stirred at 105°C for 0.5 h under an argon atmosphere. Since the reduction of **4** to its *leuco* form was incomplete, further Na₂S₂O₄ (2.00 g, 11.4 mmol) was added to the aqueous mixture, giving a pale red solution of the *leuco* form of **4**.

The aqueous solution of sodium 3-formylpropanoate prepared above was gradually added to the solution of the *leuco* form of **4** over 1 h with stirring. When one-third of the original volume had been added, further Na₂S₂O₄ (1.00 g, 5.7 mmol) was added to the reaction mixture to reduce the formed keto form of **4** or the reaction product (**13**). After the total amount of sodium 3-formylpropanoate had been added, the whole was heated at reflux for 6 h with stirring. After cooling of the mixture, air was bubbled through it to reoxidize the reaction product. Acidification of the oxidized reaction mixture with conc. HCl, followed by concentration *in vacuo*, gave a residue, which was extracted with MeOH. The methanolic solution was filtered and concentrated *in vacuo* to give crude **13** as a brown solid (8.7 g).

Crude **13** (8.7 g) was directly added to a mixture of conc. H₂SO₄ (1 ml) in EtOH (700 ml), and the mixture was refluxed for 6 h with stirring, then cooled. Satd. NaHCO₃ (150 ml) was added to the ethanolic solution. The whole mixture was concentrated *in vacuo* to ca. 200 ml, then extracted with EtOAc (300 ml). The lower aqueous phase was saturated with NaCl, and further extracted with EtOAc. The combined organic extracts were washed with 10% NaHCO₃ and satd. NaCl. Filtration and concentration *in vacuo* gave crude **14** as a brown solid (8.46 g). Purification by column chromatography (C₆H₆–CH₂Cl₂ 1:1) afforded **14** as an orange solid (4.52 g, 45%), mp 102–107°C, and **4** as an orange solid (155 mg, 2% recovery). An analytical sample of **14** was prepared by repeated recrystallizations from EtOAc–hexane. Colorless needles, mp 106–106.5°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1720 (ester), 1660, 1629 (quinone), 1585 (aromatic ring). NMR (in CDCl₃): 1.33 (3H, t, $J=7.0$ Hz, CH₂CH₃), 1.70–2.30 (2H, m, CH₂CH₂CH₂), 2.10–2.65 (2H, m, CH₂COOEt), 2.83 (2H, t, $J=7.0$ Hz, CH₂CH₂CH₂COO), 4.06 (3H, s, OCH₃), 4.16 (2H, q, $J=7.0$ Hz, CH₂CH₃), 7.36 (1H, dd, $J_{6,7}=8.0$ Hz, $J_{5,7}=2.0$ Hz, C₇-H), 7.60 (1H, d, $J_{3,4}=6.5$ Hz, C₃-H), 7.73 (1H, dd, $J_{5,6}=J_{6,7}=8.0$ Hz, C₆-H), 7.86 (1H, d, $J_{3,4}=6.5$ Hz, C₄-H), 7.94 (1H, dd, $J_{5,6}=8.0$ Hz, $J_{5,7}=2.0$ Hz, C₅-H), 13.29 (1H, s, OH). MS m/e : 368 [M⁺], 323 [M⁺–OC₂H₅], 295 [M⁺–COOC₂H₅], 281 [M⁺–CH₂COOC₂H₅], 267 [M⁺–CH₂CH₂COOC₂H₅]. Anal. Calcd for C₂₁H₂₀O₆: C, 68.47; H, 5.47. Found: C, 68.30; H, 5.45.

4-(1,8-Dihydroxy-9-oxo-10H-anthracen-2-yl)butanoic Acid (15)—Conc. hydrochloric acid (2.5 ml) was added to a mixture of **14** (504 mg, 1.37 mmol) and SnCl_2 (751 mg, 3.76 mmol) in AcOH (10 ml), and the whole was heated at reflux for 1.25 h. After being cooled, the reaction mixture was diluted with H_2O (10 ml). The precipitated yellow solid was collected by filtration, washed thoroughly with H_2O , and dried *in vacuo*, giving crude **15** as yellow crystals (408 mg, 95%), mp 187–192°C. Recrystallization from AcOH– H_2O gave pure **15** as yellow leaflets, mp 185–188°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1689 (COOH), 1620 (ketone), 1600 (aromatic ring). NMR (in $\text{DMSO}-d_6$): 1.55–2.15 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.05–2.55 (2H, m, CH_2COOH), 2.40–2.90 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$), 4.28 (2H, s, $\text{C}_{10}\text{-H}$), 6.60–7.80 (5H, m, aromatic protons), 12.03, 12.40 (2H, two s, OH $\times$ 2). MS m/e : 312 [M^+], 267 [$\text{M}^+ - \text{COOH}$], 253 [$\text{M}^+ - \text{CH}_2\text{COOH}$]. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_5 \cdot 1/2\text{H}_2\text{O}$: C, 67.28; H, 5.33. Found: C, 67.38; H, 5.27.

Treatments of **11** (2.85 g, 7.74 mmol) similar to those described for **14** gave crude **15** (2.33 g, 100%) as a yellow powder, mp 189–193°C. This sample was identical with **15** obtained from **14** on the basis of spectral (IR and NMR) comparisons.

Methyl 4-(9-Hydroxy-1,8-dimethyl-anthracen-2-yl)butanoate (16)—A mixture of **15** (92.1 mg, 0.29 mmol) and powdered anhyd. K_2CO_3 (300 mg, 2.17 mmol) in Me_2CO (15 ml) was heated at reflux for 0.5 h with stirring. Dimethyl sulfate (0.20 ml, 2.11 mmol) was added to the reaction mixture, then the whole was refluxed for 2.5 h with stirring. After cooling of the reaction mixture, filtration and concentration *in vacuo* gave a brown oil (127 mg), which was dissolved in CH_2Cl_2 (50 ml). The organic solution was washed with 10% NaHCO_3 and H_2O . Filtration and concentration *in vacuo* gave crude **16** as a yellow viscous oil (103 mg). Purification by column chromatography ($\text{C}_6\text{H}_6\text{-CHCl}_3$ 1:1) gave pure **16** as a brown caramel (52.3 mg, 50%). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3300 (OH), 1729 (ester), 1623, 1557 (aromatic ring). NMR (in CDCl_3): 1.70–2.30 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.10–2.65 (2H, m, CH_2COOMe), 2.90 (2H, t, $J = 7.0$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{COO}$), 3.67 (3H, s, COOCH_3), 4.00, 4.03 (6H, two s, $\text{OCH}_3 \times 2$), 6.72 (1H, dd, $J = 7.0$ and 2.0 Hz, $\text{C}_7\text{-H}$), 7.10–7.97 (4H, m, other aromatic protons), 8.06 (1H, s, $\text{C}_{10}\text{-H}$), 10.34 (1H, s, OH). MS m/e : 354 [M^+].

Methyl 4-(1,8,9-Trimethoxy-anthracen-2-yl)butanoate (17)—A mixture of **16** (50.8 mg, 0.14 mmol) and NaOMe (9.0 mg, 0.17 mmol) in DMF (1.0 ml) was stirred at 70°C for 15 min. Dimethyl sulfate (0.1 ml, 1.05 mmol) was added to the reaction mixture, and the whole was stirred at 70°C for 1.5 h. After being cooled and diluted with H_2O (20 ml) and 1 N HCl (20 ml), the whole mixture was extracted with CH_2Cl_2 . The organic extracts were combined, and washed with H_2O . Filtration and concentration *in vacuo*, followed by purification with column chromatography ($\text{C}_6\text{H}_6\text{-CHCl}_3$ 2:1), gave pure **17** as an orange viscous oil (12.7 mg, 24%). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1730 (ester), 1625, 1557 (aromatic ring). NMR (in CDCl_3): 1.70 (2H, m, $\text{CH}_2\text{-CH}_2\text{CH}_2$), 2.20–2.65 (2H, m, CH_2COOMe), 2.87 (2H, t, $J = 7.0$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{COO}$), 3.58 (3H, s, COOCH_3), 3.86, 3.90, 3.92 (9H, three s, $\text{OCH}_3 \times 3$), 6.66 (1H, dd, $J = 7.0$ and 1.5 Hz, $\text{C}_7\text{-H}$), 6.85–7.85 (4H, m, other aromatic protons), 7.98 (1H, s, $\text{C}_{10}\text{-H}$). MS m/e : 368 [M^+].

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