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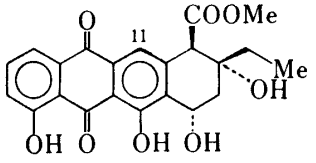
The title compounds (**11**—**14**, **16**, **17**), which are expected to be valuable in the synthesis of 11-deoxyanthracyclinones, were prepared from readily available 1,8-dihydroxyanthracene-9,10-dione (chrysazin) (**3**) by employing the Claisen rearrangement or Marschalk reaction as a key synthetic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

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

The 11-deoxyanthracyclinones 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-deoxyanthracyclinones,[2] the aglycones of 11-deoxyanthracyclines, represented by aklavinone (**1**)[3] and 11-deoxydaunomycinone (**2**).[4]



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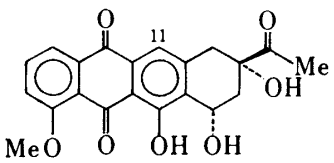

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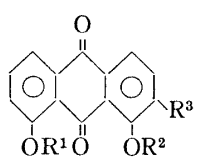
In connection with our synthetic approach to these 11-deoxyanthracyclinones, an effective method which can readily provide 4-[1,8-dioxygenated-9,10-dioxoanthracen (or anthracen)-2-yl]butanoic acid derivatives was sought.[5-8] We have now found that the desired compounds can be elaborated from readily 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% yield[19] with concomitant formation of **4** in 20% yield. After methylation of **6** with dime-



	R^1	R^2	R^3
3:	H	H	H
4:	Me	H	H
5:	Me	CH_2–CH=CH_2	H

	R^1	R^2	R^3
6:	Me	H	CH_2–CH=CH_2
7:	Me	Me	CH_2–CH_2=CH_2
8:	Me	Me	$CH_2CH_2CH_2OH$
9:	Me	Me	$CH_2CH_2CH_2OMs$
10:	Me	Me	$CH_2CH_2CH_2CN$
11:	Me	Me	$CH_2CH_2CH_2COOEt$
12:	Me	Me	$CH_2CH_2CH_2COOH$
13:	Me	H	$CH_2CH_2CH_2COOH$
14:	Me	H	$CH_2CH_2CH_2COOEt$

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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 anthracyclinones by Sutherland,[14] Brown,[15] and Krohn[16] in 1978, the Marschalk reaction has been anticipated to be one of the most versatile methods for elaborating various 11-oxygenated anthracyclinones from1,4-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.

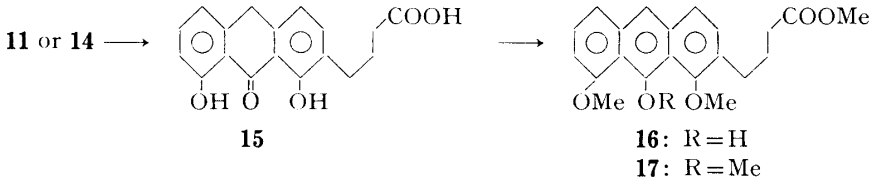

Chart 1

Reduction of **11** or **14** with stannous chloride in conc. hydrochloric acid[8] 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-deoxyanthracyclinones is in progress in this laboratory.

Experimental[24]

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 (C_6H_6–$CHCl_3$ 3: 2) followed by recrystallization from EtOH, giving pure **4** as orange needles, mp 200—201°C (lit.,[18] mp 198°C). IR ν_{max}^{Nujol} cm^{-1}: 1669, 1641 (quinone). NMR (in $CDCl_3$): 4.06 (3H, s, $OC\underline{H}_3$), 7.27 (1H, dd, $J_{6,7}=8.0$ Hz, $J_{5,7}=2.0$ Hz, C_7–$\underline{H}$), 7.35 (1H, dd, $J_{2,3}=8.0$ Hz, $J_{2,4}=2.0$ Hz, C_2–$\underline{H}$), 7.60 (2H, dd, $J_{2,3}=J_{3,4}=J_{5,6}=J_{6,7}=8.0$ Hz, C_3–$\underline{H}$ and C_6–$\underline{H}$), 7.79 (1H, dd, $J_{5,6}=8.0$ Hz, $J_{5,7}=2.0$ Hz, C_5–$\underline{H}$), 7.96 (1H, $J_{3,4}=8.0$ Hz, $J_{2,4}=2.0$ Hz, C_4–$\underline{H}$), 12.85 (1H, s, O$\underline{H}$).

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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, $OC\underline{H}_3$), 4.75 (2H, br d, J=4.8 Hz, CH_2=CH-$C\underline{H}_2O$), 5.34 (1H, br dd, J=9.6 and 2.0 Hz, E-CH_2C=C-$\underline{H}$), 5.56 (1H, br dd, J=16.5 and 2.0 Hz, Z-CH_2C=C-$\underline{H}$), 6.17 (1H, ddt, J=16.5, 9.6, and 4.8 Hz, CH_2=$C\underline{H}CH_2$), 7.26 (2H, br d, $J_{2,3}=J_{6,7}$=7.5 Hz, C_2-$\underline{H}$ and C_7-$\underline{H}$), 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-$\underline{H}$ or C_6-$\underline{H}$), 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-$\underline{H}$ or C_6-$\underline{H}$), 7.81 (2H, dd, $J_{3,4}=J_{5,6}$=7.5 Hz, $J_{2,4}=J_{5,7}$=2.0 Hz, C_4-$\underline{H}$ and C_5-$\underline{H}$). 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, $C\underline{H}_2CH$=CH_2), 4.02 (3H, s, $OC\underline{H}_3$), 4.95—5.25 (1H, m, E-CH_2C=C-$\underline{H}$), 4.85—5.40 (1H, m, Z-CH_2C=C-$\underline{H}$), 6.05 (1H, ddt, J=17.0, 9.0, and 6.5 Hz, $CH_2C\underline{H}$=CH_2), 7.23 (1H, dd, $J_{6,7}$=9.0 Hz, $J_{5,7}$=2.0 Hz, C_7-$\underline{H}$), 7.52 (1H, d, $J_{3,4}$=7.0 Hz, C_3-$\underline{H}$), 7.60 (1H, dd, $J_{5,6}=J_{6,7}$=9.0 Hz, C_6-$\underline{H}$), 7.76 (1H, d, $J_{3,4}$=7.0 Hz, C_4-$\underline{H}$), 7.85 (1H, dd, $J_{5,6}$=9.0 Hz, $J_{5,7}$=2.0 Hz, C_5-$\underline{H}$), 13.25 (1H, s, O$\underline{H}$). *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, $C\underline{H}_2CH$=CH_2), 3.95, 4.00 (6H, two s, $OC\underline{H}_3\times2$), 4.90—5.40 (2H, m, CH_2CH=$C\underline{H}_2$), 5.97 (1H, ddt, J=12.4, 8.0, and 6.2 Hz, $CH_2C\underline{H}$=CH_2), 7.26 (1H, dd, $J_{6,7}$=7.5 Hz, $J_{5,7}$=2.0 Hz, C_7-$\underline{H}$), 7.49 (1H, d, $J_{3,4}$=8.0 Hz, C_3-$\underline{H}$), 7.60 (1H, dd, $J_{5,6}=J_{6,7}$=7.5 Hz, C_6-$\underline{H}$), 7.84 (1H, dd, $J_{5,6}$=7.5 Hz, $J_{5,7}$=2.0 Hz, C_5-$\underline{H}$), 7.93 (1H, d, $J_{3,4}$=8.0 Hz, C_4-$\underline{H}$). *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, $CH_2C\underline{H}_2CH_2OH$), 2.43 (1H, br s, O$\underline{H}$), 2.87 (2H, dd, J=8.0 and 7.0 Hz, $C\underline{H}_2$ CH_2CH_2OH), 3.67 (2H, dd, J=7.0 and 5.0 Hz, $C\underline{H}_2OH$), 3.95, 3.99 (6H, two s, $OC\underline{H}_3\times2$). 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, $CH_2C\underline{H}_2CH_2$), 2.92 (2H, t, J=7.5 Hz, $C\underline{H}_2CH_2CH_2O$), 3.02 (3H, s, $SO_2C\underline{H}_3$), 3.95, 3.99 (6H, two s, $OC\underline{H}_3\times2$), 4.25 (2H, t, J=6.0 Hz, $C\underline{H}_2O$). 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, $CH_2C\underline{H}_2CH_2$), 2.2—2.62 (2H, m, $C\underline{H}_2CN$), 2.92 (2H, t, J=7.0 Hz, $C\underline{H}_2CH_2CH_2CN$), 3.97, 4.00 (6H, two s, $OC\underline{H}_3\times2$). Signals due to the aromatic ring were similar to those of **7**. *Anal.* Calcd for $C_{21}H_{17}O_4N$: C,

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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 H_2O (50 ml), and extracted with Et_2O. The combined ethereal extracts were washed with satd. $NaHCO_3$ 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 Et_2O yielded pure **11** as yellow needles, mp 70—74°C. IR ν_{max}^{KBr} cm^{-1}: 1729 (COOEt), 1673 (quinone), 1585 (aromatic ring). NMR (in $CDCl_3$): 1.23 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.65—2.28 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.15—2.65 (2H, m, $C\underline{H}_2COOEt$), 2.80 (2H, t, J=7.0 Hz, $C\underline{H}_2CH_2CH_2COOEt$), 3.96, 4.00 (6H, two s, $OC\underline{H}_3\times2$), 4.15 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 7.24 (1H, dd, $J_{6,7}$=8.0 Hz, $J_{5,7}$=2.5 Hz, C_7–$\underline{H}$), 7.47 (1H, d, $J_{3,4}$=8.0 Hz, C_3–$\underline{H}$), 7.56 (1H, dd, $J_{5,6}$=$J_{6,7}$=8.0 Hz, C_6–$\underline{H}$), 7.79 (1H, dd, $J_{5,6}$=8.0 Hz, $J_{5,7}$=2.5 Hz, C_5–$\underline{H}$), 7.91 (1H, d, $J_{3,4}$=8.0 Hz, C_4–$\underline{H}$). MS *m/e*: 382 [M^+], 367 [M^+-CH_3]. *Anal.* Calcd for $C_{22}H_{22}O_6$: 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 (C_6H_6–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 ν_{max}^{KBr} cm^{-1}: 1688 (COOH), 1667 (quinone), 1578 (aromatic ring). NMR (in $CDCl_3$): 1.75—2.35 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.25—2.70 (2H, m, $C\underline{H}_2COOH$), 2.89 (2H, t, J=7.5 Hz, $C\underline{H}_2CH_2CH_2COOH$), 3.98, 4.02 (6H, two s, $OC\underline{H}_3\times2$), 10.23 (1H, br s, $COO\underline{H}$). Signals due to the aromatic ring were similar to those of **11**. MS *m/e*: 354 [M^+], 339 [M^+-CH_3]. *Anal.* Calcd for $C_{20}H_{18}O_6\cdot1/6H_2O$: 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. Na_2CO_3, and then used for the next reaction.

A solution of NaOH (97%) (7.00 g, 0.17 mol) in H_2O (400 ml) was added to a mixture of **4** (7.00 g, 27.5 mmol) and $Na_2S_2O_4$ (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 $Na_2S_2O_4$ (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 $Na_2S_2O_4$ (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. H_2SO_4 (1 ml) in EtOH (700 ml), and the mixture was refluxed for 6 h with stirring, then cooled. Satd. $NaHCO_3$ (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% $NaHCO_3$ and satd. NaCl. Filtration and concentration *in vacuo* gave crude **14** as a brown solid (8.46 g). Purification by column chromatography (C_6H_6–CH_2Cl_2 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 ν_{max}^{KBr} cm^{-1}: 1720 (ester), 1660, 1629 (quinone), 1585 (aromatic ring). NMR (in $CDCl_3$): 1.33 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.70—2.30 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.10—2.65 (2H, m, $C\underline{H}_2COOEt$), 2.83 (2H, t, J=7.0 Hz, $C\underline{H}_2CH_2CH_2COO$), 4.06 (3H, s, $OC\underline{H}_3$), 4.16 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 7.36 (1H, dd, $J_{6,7}$=8.0 Hz, $J_{5,7}$=2.0 Hz, C_7–$\underline{H}$), 7.60 (1H, d, $J_{3,4}$=6.5 Hz, C_3–$\underline{H}$), 7.73 (1H, dd, $J_{5,6}$=$J_{6,7}$=8.0 Hz, C_6–$\underline{H}$), 7.86 (1H, d, $J_{3,4}$=6.5 Hz, C_4–$\underline{H}$), 7.94 (1H, dd, $J_{5,6}$=8.0 Hz, $J_{5,7}$=2.0 Hz, C_5–$\underline{H}$), 13.29 (1H, s, $O\underline{H}$). MS *m/e*: 368 [M^+], 323 [$M^+-OC_2H_5$], 295 [$M^+-COOC_2H_5$], 281 [$M^+-CH_2COOC_2H_5$], 267 [$M^+-CH_2CH_2COOC_2H_5$]. *Anal.* Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.30; H, 5.45.

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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 ν_{max}^{KBr} cm^{-1}: 1689 (COOH), 1620 (ketone), 1600 (aromatic ring). NMR (in DMSO-d_6): 1.55—2.15 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.05—2.55 (2H, m, $C\underline{H}_2COOH$), 2.40—2.90 (2H, m, $C\underline{H}_2CH_2CH_2COOH$), 4.28 (2H, s, C_{10}–$\underline{H}$), 6.60—7.80 (5H, m, aromatic protons), 12.03, 12.40 (2H, two s, $O\underline{H}\times2$). MS *m/e*: 312 [M^+], 267 [M^+-COOH], 253 [M^+-CH_2COOH]. *Anal.* Calcd for $C_{18}H_{16}O_5\cdot1/2H_2O$: 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 (C_6H_6–$CHCl_3$ 1: 1) gave pure **16** as a brown caramel (52.3 mg, 50%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1729 (ester), 1623, 1557 (aromatic ring). NMR (in $CDCl_3$): 1.70—2.30 (3H, m, $CH_2C\underline{H}_2CH_2$), 2.10—2.65 (2H, m, $C\underline{H}_2COOMe$), 2.90 (2H, t, $J=7.0$ Hz, $C\underline{H}_2CH_2CH_2COO$), 3.67 (3H, s, $COOC\underline{H}_3$), 4.00, 4.03 (6H, two s, $OC\underline{H}_3\times2$), 6.72 (1H, dd, $J=7.0$ and 2.0 Hz, C_7–$\underline{H}$), 7.10—7.97 (4H, m, other aromatic protons), 8.06 (1H, s, C_{10}–$\underline{H}$), 10.34 (1H, s, $O\underline{H}$). 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 (C_6H_6–$CHCl_3$ 2: 1), gave pure **17** as an orange viscous oil (12.7 mg, 24%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester), 1625, 1557 (aromatic ring). NMR (in $CDCl_3$): 1.70 (2H, m, CH_2-$C\underline{H}_2CH_2$), 2.20—2.65 (2H, m, $C\underline{H}_2COOMe$), 2.87 (2H, t, $J=7.0$ Hz, $C\underline{H}_2CH_2CH_2COO$), 3.58 (3H, s, $COOC\underline{H}_3$), 3.86, 3.90, 3.92 (9H, three s, $OC\underline{H}_3\times3$), 6.66 (1H, dd, $J=7.0$ and 1.5 Hz, C_7–$\underline{H}$), 6.85—7.85 (4H, m, other aromatic protons), 7.98 (1H, s, C_{10}–$\underline{H}$). MS *m/e*: 368 [M^+].

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