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Highly Substituted Anthraquinones by Anionic Cyclization Reactions

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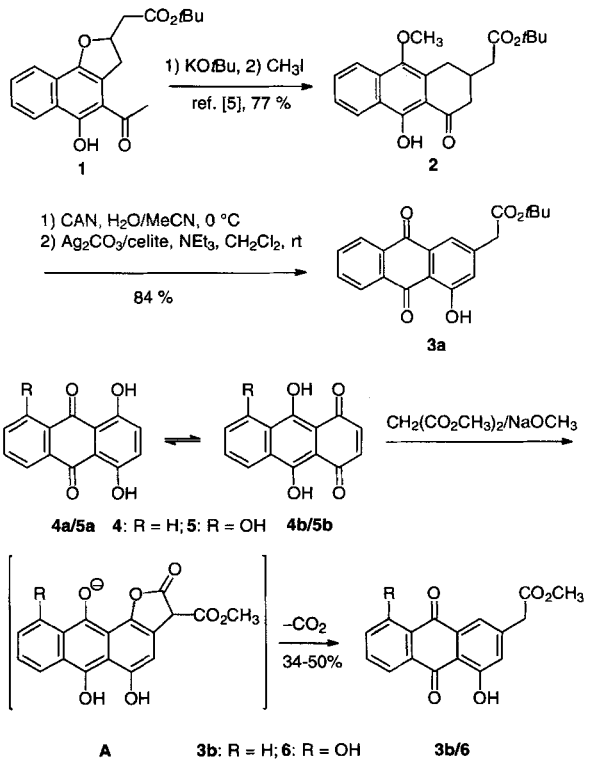
Abstract. Highly substituted anthraquinone esters (**3a/b**, **6**, **20**) and acids (**12**, **21**) are synthesized by base induced anionic cyclizations starting from bisalkylated naphthalenes (e.g. **10**) or monoalkylated naphthoquinones (e.g. **19**).

Anthraquinones can easily be prepared using Friedel-Crafts (a recent variation see [1]) or the Diels-Alder reactions (review [2]). However, the relatively harsh conditions of the Lewis acid-catalyzed reactions and the electronic requirements of the [2+4] cycloaddition [3] often impose restrictions on the substitution pattern of highly functionalized derivatives.

In connection with ongoing investigations on anthracycline precursors [4, 5], synthetic angucycline antibiotics [6, 7], and the search for biologically active compounds in the field of osteoarthritis [8, 9] we developed a series of short routes to highly substituted anthraquinone derivatives based on mild base induced cyclizations. In this context we have exploited the property of the 1,4-naphthoquinone and also of the 1,4-dihydroxyanthraquinone moieties as Michael acceptors. The scope of the methodology is very broad and depends primarily on the nature and substitution pattern of the side chain(s).

In the first part, we made use of an observation in connection with a synthesis of 4-deoxyaklanonic acid where the acetyl naphthofuran **1** could be cyclisized in high yield by treatment with *t*-BuOK and MeI to the tetrahydroanthracenone **2** [5]. In the context of this investigation we wanted to explore an operationally easy way for the conversion of **2** to the 4-deoxyakalvinone precursor **3a** [10, 11] (Scheme 1). After some experimentation we found a good solution for the desired transformation (methylether cleavage and several dehydrogenation steps) in the combination of ceriumammonium nitrate (CAN) and Fetizon's reagent (Ag_2CO_3/celite) which was recently used by Hauser et al. [12] for the dehydrogenation of partially hydrogenated anthraquinones.

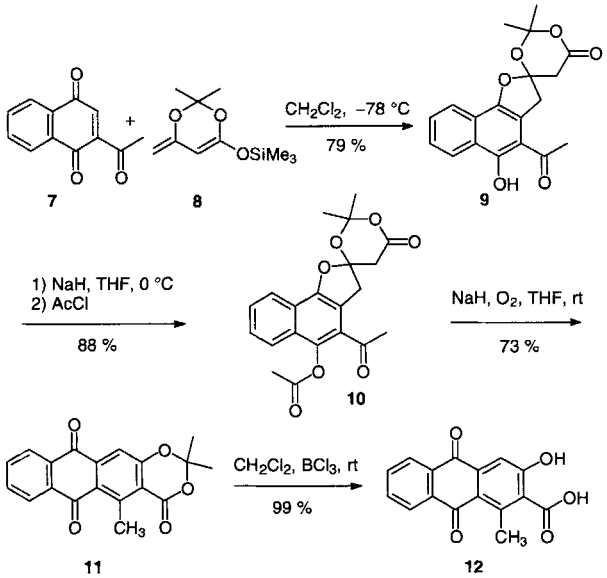
In addition, we have found an alternative and mechanistically interesting pathway to **3b** as a valuable starting material for aklavinon synthesis [10, 11] and also to the corresponding 8-hydroxy derivative **6**. We observed that quinizarine (**4**) and also 5-hydroxyquinizarine (**5**) reacted with the sodium salt of dimethyl malonate in refluxing methanol to yield the deoxygenated anthraquinone acetic esters **3b** and **6**. A related



Scheme 1

observation with **4** and acetoacetate was previously made by Sutherland et al. [13]. The reaction probably involved Michael addition of the malonate to the tautomeric quinizarine forms **4b/5b**, cyclization to the γ-lactone intermediate **A**, followed by retro Michael reaction with regeneration of the anthraquinoide system and decarboxylation to **3b** and **6** (Scheme 1). Interestingly, the regioisomer **6** was the only product isolated in the reaction of **5**.

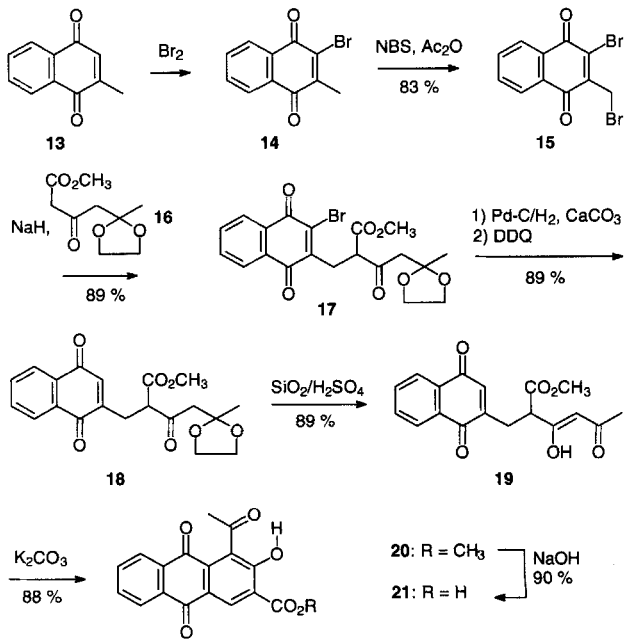
In connection with a biomimetic type synthesis of the anthracycline intermediate aklanonic acid [14] we have observed the facile addition of the 1,3-diene **8** to 2-acetyl-1,4-naphthoquinone (**7**) to afford the spiroanellated naphthofuran **9** in 79% yield [5]. We wondered if **9** could undergo base-catalyzed cyclization reactions to yield potentially interesting anthraquinones. Various reaction pathways were possible. Base-catalyzed β-elimination with opening of the spiro system ultimately led to aklanonic acid type compounds [5]. However, a different route was followed after blocking the phenolic hydroxyl as an acetate **10**. The ester dienolate attacked the acetyl carbonyl followed by elimination, saponification of the phenolic acetate, and a series of oxidation steps to the anthraquinone **11**. The overall yield of 73% for this reaction cascade involving at least five consecutive steps is surprisingly high. The acetonide protecting group remains unchanged during the cyclization, but can be cleaved quantitatively with BCl_3 to afford the phenolic acid **12** (Scheme 2).



Scheme 2

The crucial cyclization step from **10** to **11** involved the reaction of two side chains attached to the naphthalene nucleus. Products with different substitution patterns were obtained by the intramolecular addition of nucleophilic centers in *mono*alkylated 1,4-naphthoquinones to the electrophilic naphthoquinone double bond.

A very priceworthy and generally applicable starting material for this reaction type is 2-methyl-1,4-naphthoquinone **13**. The required dibromide **15** was obtained in one operation by reaction of **13** with a large excess of NBS [15], but the two step procedure via the monobromide **14** (Scheme 3) followed by NBS bromination was more economic. Nucleophilic displacement of the reactive quasi benzylic bromine with the β-ketoesters such as **16** [16] proceeded at mild conditions and in high yield (89%) to afford the adduct **17**. The protection of the quinoide vinylic position at C-2 by bromine was absolutely necessary to prevent competitive Michael additions and also unwanted premature cyclizations. The bromine in adduct **17** was easily removed by catalytic hydrogenation followed by addition of dichlorodicyano benzoquinone (DDQ) for the reoxidation of the intermediate naphthohydroquinone to the quinone **18**.



Scheme 3

The acetal protection group of **18** was cleaved quantitatively using a variation [17] of the method described by Huet et al. [18] (silica gel, 15% H_2SO_4) to yield the β-diketone **19**. The highly stabilized carbanion of **19** cyclized under very mild conditions (K_2CO_3/THF) to afford the anthraquinone **20** in 88% yield. The initial tetrahydroanthraquinone formed immediately after the Michael addition easily oxidizes to the quinone under the basic conditions used. Interestingly, no reaction of the nucleophilic side chain with the C-1 quinone carbonyl was observed. The methyl ester **20** can be saponified to the acid **21** with sodium hydroxide.

Experimental

For general methods and instrumentation see ref. [19]

(4-Hydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-acetic acid tert-butyl ester (**3a**)

An ice-cold solution of tetrahydroanthracenone **1** [5] (0.50 g, 1.4 mmol) in MeCN (40 ml) was treated dropwise with a solution of CAN (1.79 g, 3.22 mmol) in water (8 ml). After 30 min the reaction mixture was quenched with CH_2Cl_2/brine (20 ml/20 ml), the organic phase was separated, washed three times with brine (each 10 ml), dried (Na_2SO_4), and the solvent was removed at reduced pressure. The residue was dissolved in dry CH_2Cl_2 (10 ml) and the solution was treated under N_2 with Fetizon's reagent [20] (1.58 g, 1 mmol Ag_2CO_3 in 0.57 g) and one drop of triethylamine. After stirring for 15 min the mixture was filtered through celite and evaporated at reduced pressure. The residue was filtered through a short column of silica gel (ethylacetate/petroleum ether 2:8) to afford anthraquinone **3a** (0.34 g, 84%; m.p. 123 °C).

$C_{20}H_{18}O_5$ (338.4) Calcd. C 71.00 H 5.36
Found C 71.12 H 5.48

IR (KBr, cm^{-1}): ν = 2984 , 1729 (C=O, ester), 1674 (C=O, quinone), 1636, 1275, 1136. – UV (methanol): λ_{max} (lg ε) = 223 nm (4.28), 253 (4.46), 328 (3.48), 402 (3.75). – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, $OC(CH_3)_3$], 3.64 (s, 2 H, CH_2), 7.23 (s, 1 H, 3'-H), 7.75 (s, 1' H, 1-H), 7.79–7,83 (m, 2 H, 6'-H, 7'-H), 8.28–8.33 (m, 2 H, 5'-H, 8'-H), 12.56 (s, 1 H, OH). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.8 [q, $OC(CH_3)_3$], 42.7 (t, CH_2), 81.6 [s, $OC(CH_3)_3$], 114.8 (s), 120.6 (d, C-3'), 124.5 (d, C-1), 126.7 (d), 127.2 (d), 133.0 (s), 133.2 (s), 133.4 (s), 134.0 (d), 134.4 (d), 144.3 (s, C-1'), 162.5 (s, C-4'), 168.9 [s, $CO_2C(CH_3)_3$], 182.2 (s, CO quinone), 188.0 (s, CO quinone). – MS (EI, 70 eV): *m/z* (%) = 338 (12) [M^+], 282 (100) [M^+–CH_2=$C(CH_3)_2$], 265 (18) [M^+– $C(CH_3)_3$– OH], 209 (16), 181 (8), 152 (24).

(4-Hydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-acetic acid methyl ester (**3b**)

A solution of sodium methyl malonate [prepared from sodium (2.3 g, 100 mmol), methyl malonate (8.5 ml, 75 mmol), and dry methanol (20 ml)] was added under nitrogen to a solution of quinizarine (**4**) (5 g, 20 mmol) in methanol (250 ml). The mixture was refluxed for 3 d, then carefully neutralized by addition of acetic acid (6.2 ml, 100 mmol), and evaporated at reduced pressure to a volume of ca. 50 ml. Dichloromethane (100 ml) was added, the mixture was filtered, the filtrate washed three times with water, dried (Na_2SO_4), filtered, and the filtrate was evaporated to dryness at reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to afford from the fraction of medium polarity methyl ester **3b** (2.85 g, 50%); m.p. 146 °C.

$C_{17}H_{12}O_5$ (296.3) Calcd. C 68.92 H 4.08
Found C 68.76 H 3.85

IR (KBr, cm^{-1}): ν = 3400 (OH), 2969 (CH), 1730, 1639, 1591 (CO), 1343, 1278, 1206 (OH, CH). – UV (MeOH): λ_{max} (lg ε) = 206 (4.23), 223 (4.23), 253 (4.38), 328 (3.47), 403 (3.73) nm. – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.71 (s, 3 H, OCH_3), 3.71 (s, 2 H, CH_2), 7.20 (d, 1 H, *J* = 1.5 Hz, 3'-H), 7.70 (d, 1 H, *J* = 1.5 Hz, 1'-H), 7.78 (m, 2 H, 5'-H, 8'-H), 8.25 (m, 2 H, 6'-H, 7'-H), 12.52 (s, 1 H, OH). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 41.77 (t, CH_2), 52.84 (q, OCH_3), 121.15 (d), 125.14 (d), 127.30 (d), 127.86 (d), 133.57 (2 C, s), 133.92 (2 C, s), 134.64 (d), 135.07 (d), 144.05 (s, C-2'), 163.12 (s, C-4'), 170.74 (s, $COOCH_3$), 182.65 (s, CO), 188.64 (s, CO). – MS (EI, 70 eV): *m/z* (%) = 296 (100) [M^+], 237 (56), 209 (51), 152 (42).

(4,8-Dihydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)-acetic acid methyl ester (**6**)

Ester **6** was obtained as described for **3b** from methyl malonate (14.4 ml, 64 mmol) and 1,4,5-trihydroxyanthraquinone (**5**) (2.048 g, 8 mmol); yield 0.849 g (34%); m.p. 162 °C.

$C_{17}H_{12}O_6$ (312.3) Calcd. C 65.27 H 3.87
Found C 65.19 H 3.78

IR (KBr, cm^{-1}): ν = 3443 (OH), 2973 (CH), 1728, 1635, 1612 (CO), 1342, 1290 (OH,CH). – UV (MeOH): λ_{max} (lg) = 221 nm (4.23), 253 (4.18), 388 (3.56), 4.16 (2.54). – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 3.78 (s, 2 H, CH_2), 7.32 (m, 2 H, 3'-H, 7'-H), 7.82 (m, 3 H, 1'-H, 5'-H, 6'-H), 12.61 (s, 1 H, OH), 12.62 (s, 1 H, OH). – ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 41.73 (t, CH_2), 52.91 (q, OCH_3), 119.78 (d), 120.97 (d), 125.41 (d), 125.76 (d), 133.56 (2 C, s), 133.66 (2 C, s), 137.27 (d), 144.13 (s, C-2'), 163.22 (s), 163.33 (s), 170.66 (s, $COOCH_3$), 187.92 (s, CO), 188.16 (s, CO). – MS (EI/302 °C): *m/z* (%) = 312 (100) [M^+], 253 (48), 225 (57), 197 (18).

4'-Acetyl-5'-hydroxy-2,2-dimethylspiro[1,3-dioxane-4,2'(3'H)-naphtho[1,2-b]furan]-6'-one (**9**)

A solution of quinone **7** [21] (700 mg, 3.5 mmol) in dry CH_2Cl_2 (50 ml) was treated dropwise at 78 °C with silylether **8** [22] (901 mg, 4.2 mmol). After stirring for 30 min the mixture was allowed to warm to 20 °C (1 h) and stirring was continued for 1.5 h. The solution was then quenched with sat. NH_4Cl solution (20 ml), the organic phase was separated, and the aqueous phase was washed twice with CH_2Cl_2 (each 10 ml). The combined organic phases were treated with brine (20 ml), dried (Na_2SO_4), filtered, and the solvent was removed at reduced pressure. Crystallization of the resulting oil from ether (10 ml) afforded the spiro compound **9** (950 mg, 79%, m.p. 122 °C).

$C_{19}H_{18}O_6$ (342.5) Calcd. C 66.66 H 5.30
Found C 66.59 H 5.20

IR (KBr, cm^{-1}): ν = 3414 (OH), 3009, 2923, 1746 (C=O), 1618 (C=C), 1387, 1359, 1279. – UV (methanol): λ_{max} (lg ε) = 221 nm (4.28), 252 (4.08), 278 (4.04), 418 (3.57). – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.62 and 1.83 [2 s, 6 H, $C(CH_3)_2$], 2.63 (s, 3 H, $COCH_3$), 3.21 (AB signal, J_{AB} = 17.6 Hz, 2 H), 3.70 (AB signal, J_{AB} = 16.5 Hz, 2 H), 7.54 (m, 1 H, Ar-H), 7.66 (m, 1 H, Ar-H), 7.83 (d, *J* = 8.2 Hz, 1 H, Ar-H), 8.47 (d, *J* = 8.4 Hz, 1 H, Ar-H), 14.31 (s, 1 H, OH). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.4 and 29.8 [q, $C(CH_3)_2$], 30.5 (q, $COCH_3$), 38.7 (t), 47.8 (t), 106.6 (s, C-2'), 107.4 (s), 110.6 (s), 112.9 (s), 120.7 (d), 124.4 (s), 125.0 (d), 125.3 (s), 126.1 (d), 130.4 (d), 144.5 (s), 159.5 (s), 170.0 (s, C-6'), 203.5 (s, $COCH_3$). – MS (70 eV): *m/z* (%) = 342 (1) [M^+], 284 (3) [M^+ – $(CH_3)_2CO$], 240 (100) [M^+–$(CH_3)_2CO$ – CH_3CO], 225 (54), 222 (55), 197 (13).

5'-Acetoxy-4'-acetyl-2,2-dimethylspiro[1,3-dioxane-4,2'(3'H)-naphtho[1,2-b]furan]-6'-one (**10**)

A solution of the phenol **9** (550 mg, 1.65 mmol) in dry THF (15 ml) was treated at 0 °C with NaH (77 mg of a 60 % suspension in oil, 1.98 mmol). After stirring for 1 h freshly distilled acetyl chloride (0.14 ml, 1.98 mmol) was added and stirring was continued for 30 min at 22 °C. CH_2Cl_2 (30 ml) was added at 0 °C, the mixture was hydrolyzed by addition of water (5 ml), and acidified with 2 N HCl (10 ml). The organic phase was separated, washed twice with water (10 ml) and then with brine (10 ml), dried (Na_2SO_4), and filtered. The solvent was removed at reduced pressure and the acetate **10** (560 mg, 88%) was crystallized from ether/petroleum ether (5 ml/5 ml); m.p. 113 °C decomp.).

$C_{21}H_{20}O_7$ (384.4) Calcd. C 65.62 H 5.24
Found C 65.78 H 5.46

IR (KBr, cm^{-1}): ν = 1748 (C=O ester), 1694 (C=O ketone), 1372 ($OCOCH_3$), 1306, 1202. – UV (methanol): λ_{max} (lg ε) = 220 nm (4.39), 238 (4.34), 252 (4.28), 301 (3.56), 350 (3.49). – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.61 and 1.81 [2 s, 6 H, $C(CH_3)_2$], 2.52 (s, 3 H, $OCOCH_3$), 2.61 (s, 3 H, $COCH_3$), 3.17 (AB signal, J_{AB} = 17.7 Hz, 2 H), 3.67 (AB signal, J_{AB} = 17.6 Hz, 2 H), 7.53–7.62 (m, 2 H, 7'-H, 8'-H), 7.77–7.84 (m, 1 H, Ar-H), 7.92–7.94 (m, 1 H, Ar-H). – ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.9 (q, $OCOCH_3$), 28.6 and 29.7 [q, $C(CH_3)_2$], 31.0 (q, $COCH_3$), 38.6 (t), 40.0 (t), 106.6 (s, C-2'), 109.0 (s, spiro-C), 116.2 (s), 121.4 (d), 122.0 (s), 122.7 (d), 125.7 (s), 127.0 (s), 127.3 (d), 128.2 (d), 140.5 (s), 150.7 (s), 165.0 (s, $OCOCH_3$), 169.5(s, C-4), 197.9 (s, $COCH_3$). – MS (CI, NH_3, neg.): *m/z* (%) = 384 (44) [M^+], 341 (58) [$M^+ - CH_3CO$], 322 (31), 283 (19), 282 (51), 240 (45), 239 (100), 147 (53), 121 (21).

2,2,5-Trimethyl-1,3-dioxanaphthacen-4,6,11-trione (**11**)

A solution of the acetate **10** (250 mg, 0.65 mmol) in THF (15 ml) was treated at 0 °C under an atmosphere of oxygen with NaH (132 mg, 3.25 mmol of a 60% dispersion in oil). After warming to room temperature stirring was continued for 3 h and the reaction mixture was diluted with CH_2Cl_2 (30 ml). The excess of NaH was hydrolyzed at 0 °C by addition of water (20 ml), the mixture was acidified with 2 N HCl (5 ml), the organic phase was separated, washed with water (15 ml) and brine (15 ml), dried (Na_2SO_4), and filtered. The filtrate was evaporated at reduced pressure and the residue chromatographed (silica gel, CH_2Cl_2) to yield pure trione **11** (154 mg, 73%) as a yellow solid; m.p. 188 °C.

$C_{19}H_{14}O_5$ (322.3) Calcd. C 70.80 H 4.38
Found C 70.80 H 4.71

IR (KBr, cm^{-1}): ν = 2931, 1740 (C=O), 1678 (quinone), 1661, 1586, 1327, 1262. – UV (methanol): λ_{max} (lg ε) = 231 nm (4.14), 246 (4.16), 274 (4.24), 460 (2.77). – ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.80 [s, 6 H, $C(CH_3)_2$], 3.23 (s, 3 H, $ArCH_3$), 7.73–7.88 (m, 2 H, 8-H, 9-H), 7.80 (s, 1 H, 12-H), 8.20–8.28 (m, 2 H, 7-H, 10-H). – ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 19.9 (q, $ArCH_3$), 26.1 [q, $C(CH_3)_2$], 106.4 (s, C-2), 115.0 (d, C-12), 118.5 (s), 127.1 (d), 128.0 (d), 132.5 (s), 133.9 (d), 135.3 (d), 135.9 (s), 140.4 (s), 150.8 (s), 159.4 (s), 160.2 (s), 182.7 and 183.9 (2 s, quinone). – MS (EI, 70 eV): *m/z* (%) = 322 (11) [M^+], 264 (100) [$M^+ - C_3H_6O$], 236 (32) [$M^+ - C_3H_6O$ - CO], 208 (14) [$M^+ - C_3H_6O - 2$ CO], 180 (13) [$M^+ - C_3H_6O - 3$ CO], 152 (14) [$M^+ - C_3H_6O - 4$ CO].

3-Hydroxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (**12**)

A solution of acetonide **11** (135 mg, 0.42 mmol) in dry CH_2Cl_2 (8 ml) was treated at 22 °C with a 1 M solution of BCl_3 [compare ref. 23] in CH_2Cl_2 (2.16 ml). After stirring for 10 min the mixture was diluted with ethyl acetate (30 ml) and quenched with water (15 ml). The aqueous phase was saturated with NaCl, the organic phase was separated, washed twice with brine (each 10 ml), dried (Na_2SO_4), and filtered. The filtrate was evaporated at reduced pressure to afford pure carboxylic acid **12** (118 mg, 99%); m.p. 245 °C (decomp.).

$C_{16}H_{10}O_5$ (282.3) Calcd. C 68.09 H 3.57
Found C 67.91 H 3.73

IR (KBr, cm^{-1}): ν = 3372 (OH), 2924, 1707 (C=O acid), 1671 (quinone), 1570, 1306, 1273, 1254. – ^{1}H-NMR (300 MHz, MeOH): δ = 1.99 (s, 3 H, CH_3), 6.83 (s, 1 H, 4-H), 6.96–7.06 (m, 2 H, 6-H, 7-H), 7.36 (m, 2 H, 5-H, 8-H). – ^{13}C-NMR (75 MHz, MeOH): δ = 20.0 (q, CH_3), 112.8 (d, C-4), 125.0 (s), 127.3 (d), 128.0 (d), 131.7 (s), 133.6 (s), 134.3 (d), 135.4 (d), 136.3 (s), 138.2 (s), 142.3 (s), 159.5 (s), 171.2 (s, CO_2H), 184.1 and 184.5 (2 s, quinone). – MS (EI, 70 eV): *m/z* (%) = 282 (72) [M^+], 264 (100) [$M^+ - H_2O$], 236 (42) [$M^+ - H_2O$ – CO], 208 (26) [$M^+ - H_2O - 2$ CO], 180 (24), 152 (33), 76 (16).

2-Bromo-3-bromomethyl-1,4-naphthoquinone (**15**)

A solution of 2-bromo-3-methyl-1,4-naphthoquinone (10.0 g, 39.8 mmol), obtained by bromination of 3-methyl-1,4-naphthoquinone [15]) in acetic acid anhydride (160 ml) was treated with NBS (8.00 g, 44.9 mmol) and AIBN (0.50 g, 3.0 mmol). The mixture was heated to 130–140 °C for 45 min, the cold solution (20 °C) was poured into ice-water (1 l), the precipitate was collected by filtration, washed with water, and dissolved in CH_2Cl_2 (200 ml). The solution was dried (Na_2SO_4), filtered, and the volume of the filtrate was reduced at reduced pressure to ca. 50 ml. The dibromide **15** was crystallized by addition of petroleum ether to afford 10.9 g (83%); m.p. 121.2 °C, ref. [24] m.p. 119–120 °C.

– ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 4.62 (s, 2 H, CH_2Br), 7.73–7.85 (m, 2 H, 6-H, 7-H), 8.11–8.21 (m, 2 H, 5-H, 8-H). – ^{13}C-NMR ($CDCl_3$, 200 MHz): δ = 26.03 (t, CH_2Br), 127.84 (d, C-5, C-8), 128.20 (d, C-5, C-8), 131.52 (s, C-4a, C-8a), 131.64 (s, C-4a, C-8a), 134.78 (d, C-6, C-7), 135.01 (d, C-6, C-7), 141.42 (s, C-2), 146.70 (s, C-3), 177.76 (s, C-1, C-4), 180.03 (s, C-1, C-4).

2-(3-Bromo-1,4-dioxo-1,4-dihydronaphthalen-2-ylmethyl)-4-(2-methyl-[1,3]dioxolan-2-yl)-3-oxobutanoic acid methyl ester (**17**)

A solution of dibromonaphthoquinone **15** (2.00 g, 6.1 mmol) in THF (50 ml) was treated at –15 °C under argon with a solution of the sodium salt of β-ketoester **16** [prepared from a solution of **16** (2.44 g, 12.1 mmol) in THF (30 ml) and NaH (290 mg, 12.1 mmol)]. After stirring for 30 min at this temperature the mixture was allowed to warm to 20 °C, diethyl ether (100 ml) was added, the organic phase was washed with

saturated aqueous solution of NH_4Cl (20 ml), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/2% CH_3OH) to afford **17** (2.36 g, 89%); m.p. 99 °C (petroleum ether).

$C_{20}H_{19}O_7Br$ (451.3) Calcd. C 53.23 H 4.24
Found C 53.12 H 4.18

IR (KBr, cm^{-1}): ν = 2953 (C–H), 2890 (C–H), 1730 (ester CO), 1674 (CO), 1659 (quinone), 1591 (arom. C=C), 1281 (C–Br). – UV (methanol): λ_{max} (lg ε) = 206 nm (4.12), 246 (4.08), 252 (4.08), 282 (4.06), 335 (3.36). – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 1.35 (s, 3 H, dioxolane-CH_3), AB system (δ_A = 2.82), δ_B = 3.02, $^2J_{AB}$ = 13.8 Hz, 2 H, 4-H), AMX system [δ_A = 4.16 (dd, $^3J_{AM}$ = 8.4 Hz, $^3J_{AX}$ = 6.6 Hz, 1 H, 2-H), δ_M = 3.48 (dd, $^3J_{AM}$ = 8.4 Hz, $^2J_{MX}$ = 13.4 Hz, 1 H, quinone-CH_2), δ_X = 3.42 (dd, $^3J_{AX}$ = 6.6 Hz, $^2J_{MX}$ =13.4 Hz, 1 H, quinone-CH_2)], 3.67 (s, 3 H, OCH_3), 3.82–3.98 (m, 4 H, OCH_2CH_2O), 7.73–7.79 (m, 2 H, 6'-H, 7'-H), 8.09–8.16 (m, 2 H, 5'-H, 8'-H). – ^{13}C-NMR ($CDCl_3$, 60 MHz): δ = 24.24 (q, CH_3), 29.75 (t, CH_2), 50.69 (t, C-4), 52.80 (q, OCH_3), 56.70 (d, C-2), 64.33 and 64.58 (2 × t, OCH_2CH_2O), 107.71 (s, dioxolane OCO), 126.99 (d, C-5', C-8'), 127.44 (d, C-5', C-8'), 130.84 (s, C-4a', C-8a'), 131.29 (s, C-4a', C-8a'), 133.92 (d, C-6', C-7'), 134.15 (d, C-6'-, C-7'), 140.03 (s, C-2', C-3'), 148.60 (s, C-2', C-3'), 168.95 (s, C-1), 177,18 (s, C-1', C-4'), 181.35 (s, C-1', C-4'), 199.97 (s, C-3). – MS (EI/100 C): *m/z* (%) = 438/436 (0.6, isotope peaks), 437/435 (1.4) [M^+–CH_3], 406/404 (<0.1), 403/405 (0.5), 319 /317 (2.6), 87 (100) [$CH_3C(OCH_2CH_2O)^+$], 43 (23).

2-(1,4-Dioxo-1,4-dihydronaphthalen-2-ylmethyl)-4-(2-methyl-[1,3]dioxolan-2-yl)-3-oxobutanoic acid methyl ester (**18**)

A suspension of bromonaphthoquinone **17** (3.0 g, 6.65 mmol) and $CaCO_3$ (6.6 g, 66 mmol) in dry methanol (100 ml) was hydrogenated at 22 °C and 1 atm over palladium/charcoal. After 5 h the calculated amount of hydrogen was consumed. The suspension was filtered under nitrogen, DDQ (1.66 g, 7.3 mmol) was added, the solution was stirred for 10 min, and the solvent was removed at reduced pressure. The residue was dissolved in CH_2Cl_2 (100 ml), washed with saturated aqueous solution of NH_4Cl, dried ($MgSO_4$), filtered, and purified by flash chromatography on silica gel (CH_2Cl_2) to afford **18** (2.2 g, 89%, oil).

$C_{20}H_{20}O_7$ (372.4) Calcd. C 64.51 H 5.41
Found C 64.55 H 5.24

UV(methanol): λ_{max} (lg ε) = 203 nm (3.95), 252 (4.11), 331 (3.24). – IR (KBr, cm^{-1}): ν = 2975 (C–H), 1746 (ester CO), 1717 (CO), 1663 (quinone), 1595 (arom. C=C), 1049. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 1.33 (s, 3H, dioxolane-CH_3), AB system (δ_A = 2.84, δ_B = 3.04, $^2J_{AB}$ = 13.4 Hz, 2 H, 4-H), AMX system [δ_A = 4.19 (dd, $^3J_{AM}$ = 7.3 Hz, 1 H, 2-H), δ_M = 3.08 (dd, $^3J_{AM}$ = 7.3 Hz, $^2J_{MX}$ = 13.4 Hz, 1 H, quinone-CH_2), δ_X = 3.11 (dd, $^3J_{AX}$ = 6.6 Hz, $^2J_{MX}$ = 13.4 Hz, 1 H, quinone-CH_2)], 3.73 (s, 3 H, OCH_3), 3.90 (m, 4 H, OCH_2CH_2O), 6.84 (s, 1 H, 3-H), 7.84 (m, 2 H, 6-,7-H), 8.20 (m, 2 H, 5-,8-H). – ^{13}C ($CDCl_3$, 200 MHz): δ = 24.32 (q, dioxolane CH_3), 28.35 (t, C-2 CH_2), 51.01 (t, 4-C), 52.67 (q, OCH_3), 57.68 (t, C-2), 64.50 (t, OCH_2CH_2O), 107.92 (s, dioxolane OCO), 126.12 (d, C-5', C-8'), 126.47 (d, C-5', C-8'), 132.02 (s, C-4a', C-8a'), 132.13 (s, C-4a', C-8a'), 133.73 (d, C-6', C-7'), 133.77 (d, C-6', C-7'), 136.91 (d, C-3') 147.78 (s, C-2'), 168.71(s, C-1), 184,69 (s, C-1', C-4'), 184.88 (s, C-1', C-4'), 200.46 (s, C-3). – MS (EI, 80 °C): *m/z* (%) = 358 (0.6) [M^+ + 1], 357 (3.2) [M^+], 342 (0.3) [M^+ + 1 – OCH_3], 325 (1.5), 283 (2.5), 239 (12), 113 (10), 99 (8), 87 (100).

2-(1,4-Dioxo-1,4-dihydronaphthalene-2-ylmethyl)-3,5-dioxohexanoic acid methyl ester (**19**)

A suspension of silica gel (19 g) in CH_2Cl_2 (50 ml) was treated with 15% sulfuric acid (1.2 ml) and the suspension was stirred for 10 min. A solution of dioxolane **18** (1.0 g, 2.7 mmol) in CH_2Cl_2 (50 ml) was then added and stirring was continued for 1 h at 22 °C (tlc control). The suspension was filtered, the silica gel rinsed with CH_2Cl_2/2% CH_3OH (100 ml), the combined organic phases were washed with water (100 ml), dried, ($MgSO_4$), filtered, and purified by crystallization from diethyl ether to afford **19** (0.78 g, 89%); p. 65 °C.

$C_{18}H_{16}O_6$ (328.3) Calcd. C 65.85 H 4.91
Found C 66.57 H 4.42

IR (KBr, cm^{-1}): ν = 3432 (chelat. OH), 3067 (C–H), 2957 (C–H), 1748 (ester CO), 1709 (CO), 1665 (quinone), 1593 (arom.C=C), 1327, 1300.– UV (methanol): λ_{max} (lg) = 206 nm (4.27), 248 (4.33). – ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.05 (s, 3 H, 6-H), 3.13 (m, 1 H, CH_2), 3.73 (d, ^3J = 7.2 Hz, 1 H, 2-H), 3.73 (s, 3 H, OCH_3), 5.62 (s, 1 H, 4-H), 6.84 (s, 1 H, 3'-H), 7.70–7.82 (m, 6'-H, 7'-H), 8.02–8.87 (m, 5'-H, 8'-H), 14.98 (s, 1 H, chelat.-OH). – ^{13}C-NMR ($CDCl_3$, 60 MHz): δ = 23.68 (q, C-6), 29.16 (t, C-2 CH_2), 52.61 (q, OCH_3), 53.33 (d, C-2), 99.64 (d, C-4), 126.00 (d, C-5', C-8'), 126.43 (d, C-5', C-8'), 131.83 (s, C-4a' and C-8a'), 133.61 (d, C-6', C-7'), 133.75 (d, C-6', C-7'), 136.69 (d, C-3'), 147.17 (s, C-2'), 169.23 (s, C-1), 184.47 (s, C-1', C-4'), 184.70 (s, C-1', C-4'), 188.75 (s, C-3, C-5), 190.08 (s, C-3, C-5). – MS (EI, 75 C): *m/z* (%) = 328 (18) [M^+], 310 (46) [M^+ – H_2O], 296 (44) [M^+ – CH_3OH], 286 (62), 268 (28), 254 (46), 239 (76), 226 (43), 212 (86), 184 (100), 85 (80) [$CH_3COCH_2CO^+$], 43 (90) [CH_3CO^+].

4-Acetyl-3-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid methyl ester (**20**)

A suspension of K_2CO_3 (1.0 g, 7.2 mmol) and 18-crown-6 (30 mg) in THF (20 ml) was treated with a solution of **19** (300 mg, 0.914 mmol) (the color changes first to black and then to red). After 5 min 0.5 N HCl (40 ml) was added and the aqueous phase was extracted three times with CH_2Cl_2 (each 100 ml). The combined organic phases were dried (Na_2SO_4), filtered, and the filtrate was evaporated to dryness. The residue was crystallized from diethyl ether to afford **20** (260 mg, 88%, yellow needles); m.p. 243 °C.

$C_{18}H_{12}O_6$ (324.3) Calcd. C 66.67 H 3.73
Found C 66.63 H 3.65

UV(methanol): λ_{max} (lg ε) = 207 nm (4.27), 255 (4.43), 269 (4.40), 472 (3.62). – IR (KBr, cm^{-1}): ν = 3432 (chelat. OH) , 3073 (C–H), 2959 (C–H), 1711 (aliph. CO), 1676 (quinone), 1292. – ^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 2.67 (s, 3 H, CH_3CO), 4.08 (s, 3 H, OCH_3), 7.76–7.84 (m, 2 H, 6-H, 7-H), 8.20–8.24 (m, 1 H, 5-H, 8-H), 8.28–8.32 (m, 1 H, 5-H, 8-H), 8.87 (s, 1 H, 1-H), 11.56 (s, 1 H, chelat.-OH). – ^{13}C-NMR ($CDCl_3$, 50 MHz): δ = 31.35 (q, CH_3CO), 53.83 (q, OCH_3),

117.30 (s, C-4a), 125.67 (s, C-9a), 127.84 (d, C-5, C-8), 128.03 (d, C-5, C-8), 131.51 (d, C-1), 132.89 (s, C-2, C-8a, C-10a), 133.56 (s, C-2, C-8a, C-10a), 133.59 (s, C-2, C-8a, C-10a), 134.74 (d, C-6, C-7), 135.31 (d, C-6, C-7), 135.39 (s, C-4), 161.90 (s, C-3), 169.69 (s, CO_2CH_3), 181.34 (s, C-9, C-10), 183.15 (s, C-9, C-10), 202.12 (s, CH_3CO). – MS (EI, 100 °C): *m/z* (%) = 325 (2), 324 (8) [M^+], 310 (16), 309 (16) [M^+–CH_3], 293 (8), 278 (20), 277 (100) [M^+–CH_3–CH_3OH], 249 (20), 193 (8), 165 (18), 137 (29).

4-Acetyl-3-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (**21**)

A solution of ester **20** (110 mg, 0.34 mmol) in a mixture of CH_3OH (50 ml) and CH_2Cl_2 (10 ml) was treated under nitrogen with 2 N NaOH (0.7 ml) and the mixture was stirred for 24 h at 22 °C. The solution was acidified by addition of 1 N HCl (2 ml), the solvent was removed at reduced pressure, and the residue was redissolved in CH_2Cl_2 (100 ml, 5% CH_3OH). The solution was dried (Na_2SO_4), filtered, and evaporated at reduced pressure to afford acid **21** (95 mg, 90%); m.p. 248 °C (decomp.).

$C_{17}H_{10}O_6$ (310.3) Calcd. C 65.81 H 3.25
Found C 65.36 H 3.43

UV (methanol): λ_{max} (lg ε) = 207 nm (4.19), 251 (4.29), 278 (4.31). – IR (KBr, cm^{-1}): ν = 3410 (OH), 1707 (acid CO), 1676 (quinone), 1590 (arom. C=C), 1572, 1335, 1298, 1136. – ^{1}H-NMR ([D_6]-DMSO, 200 MHz): δ = 2.49 (s, 3 H, CH_3CO), 7.87–7.99 (m, 2 H, 6-H, 7-H), 8.11–8.23 (m, 2 H, 5-H, 8-H), 8.61 (s, 1 H, 1-H). – ^{13}C-NMR ([D_6]-DMSO, 50 MHz): δ = 31.63 (q, CH_3CO), 120.86 (s, C-4a, C-9a), 122.78 (s, C-4a, C-9a), 127.54 (d, C-5, C-8) 127.73 (d, C-5, C-8), 131.15 (d, C-1), 133.03 (s, C-2, C-4, C-8a, C-10a), 133.81 (s, C-2, C-4, C-8a, C-10a), 134.01 (s, C-2, C-4, C-8a, C-10a), 134.16 (s, C-2, C-4, C-8a, C-10a), 134.99 (d, C-6, C-7), 135.77 (d, C-6, C-7), 166.07 (s, C-3), 170.57 (s, CO_2H), 181.45 (s, C-9, C-10), 183.92 (s, C-9, C-10), 202.82 (s, CH_3CO). – MS (EI, 100 °C): *m/z* (%) = 309 (2), [M^+ – 1], 295 (2) [M^+ – CH_3], 278 (22), 277 (100) [M^+–1–CH_3OH], 249 (18), 235 (8), 193 (10), 165 (20), 137 (22), 87 (76), 43 (45) [CH_3CO^+].

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