Syntheses of Anthracenones. 3. Revised Preparative Route to 10-Benzoyl-1,8-dihydroxy-9(10*H*)-anthracenones

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The acylation of anthralin (1,8-dihydroxy-9(10*H*)-anthracenone) with acetylsalicylic acid chloride in toluene and collidine was found to give the *O*-acylated product, rather than 10-(acetylsalicyl)-anthralin. A procedure is described for benzoylation of anthralin in the 10-position which involves reaction of 1,8-diacetoxy-9(10*H*)-anthracenone with benzoyl chloride and sodium hydride in THF followed by hydrolysis of an intermediate enol ester. Furthermore, when benzoyl chloride and DMF were used for the acylation of anthralin, a Vilsmeier-type reaction was observed leading to a novel enamine derivative of anthralin which was hydrolyzed or benzoylated to an enol or enol ester, respectively.

Introduction

In our preceding papers,[1,2] we reported on selective syntheses of isomers and other derivatives of the antipsoriatic drug anthralin (**1**, 1,8-dihydroxy-9(10*H*)-anthracenone). However, its therapeutic use is accompanied by severe inflammation and staining of the skin. These side effects may be interpreted in terms of the efficacy of the anthracenones to generate oxygen radicals.[3,4] It is now well established that 1,8-dihydroxy-9(10*H*)-anthracenones easily undergo one-electron oxidation to produce radical intermediates, including anthracenon-9-yl radicals and secondary radicals.[5] Coincident with this process is the generation of reactive oxygen species. The methylene moiety at C-10 has been recognized as a key site of the formation of superoxide radical, which in turn can dismutate to produce hydrogen peroxide, and in the presence of iron, the highly reactive hydroxyl radical.[6] Data of ESR studies and molecular calculations are consistent with an anthracenone radical structure containing a carbon-centered radical at the bridging 10-carbon.[7] It was anticipated that appropriate chemical modification of anthralin might provide agents with diminished oxygen-radical formation.[8,9] In particular, substitution with an electron-withdrawing acyl group at the 10-position impairs the reduction power of anthracenones.[10] We have applied such rationale to the synthesis of 10-ω-phenylacyl derivatives with modulated redox properties.[8] The compounds were prepared by reaction of the appropriate acyl chlorides with anthralin in toluene and pyridine. Under these conditions acylation takes place at C-10 via the carbanion.

Structure−activity relationships revealed that the mere presence of an acyl substituent at C-10 of anthralin does not necessarily lead to enhanced activity, and it was demonstrated that a terminal phenyl ring is required.[8] However, a major obstacle encountered in this study has been the lack of a convenient and effective method for the preparation of 10-benzoyl derivatives of anthralin, the lowest homologs in this series. These compounds are of particular interest, since they lack methylene units linking the terminal phenyl and the carbonyl group at C-10. This suggests a strong impact on anthracenone radical formation and redox properties, depending on the nature of the substituents on the terminal phenyl ring.

Although the acylation with ω-phenyl terminated acyl chlorides proceeded smoothly, benzoyl chlorides, under identical reaction conditions, did not result in the anticipated 10-benzoyl derivatives, but exclusively gave a mixture of mono- and diesters of the 1- and 8-hydroxyl groups. On the basis of these observations and in search for an appropriate solution for this problem, we have developed an alternative preparative route to 10-benzoyl derivatives of anthralin.

Results and Discussion

The only study aimed at the synthesis of anthralin derivatives with free phenolic groups and a 10-benzoyl substituent which has so far appeared in the literature is by Berset al.[11] In this approach, the acid chloride of acetylsalicylic acid was reacted with **1** in toluene and collidine, and the structure of the obtained product was assigned to 10-(acetylsalicyl)anthralin (**2**, Scheme 1). On the basis of reported ^{1}H NMR and IR data the structure assignment of **2** is questionable, and the compound may be an oxygen acylated rather than a C-10 acylated derivative. This prompted us to reinvestigate the synthetic utility of this reaction. Attempts to prepare **2** using this method failed in our hands. Only the *O*-acylated 1-[(2-acetoxybenzoyl)oxy]-8-hydroxy-9(10*H*)-anthracenone (**3**) was isolated as a reaction product, as evidenced by the ^{1}H NMR spectrum. In fact, compound **3** prepared according to the method of Berset et al.[11] did not reveal the characteristic downfield shift for the C-10 proton of 10-acylated anthralin derivatives compared to

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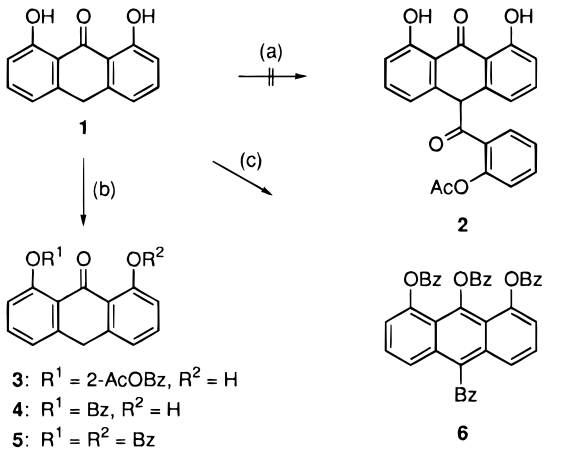
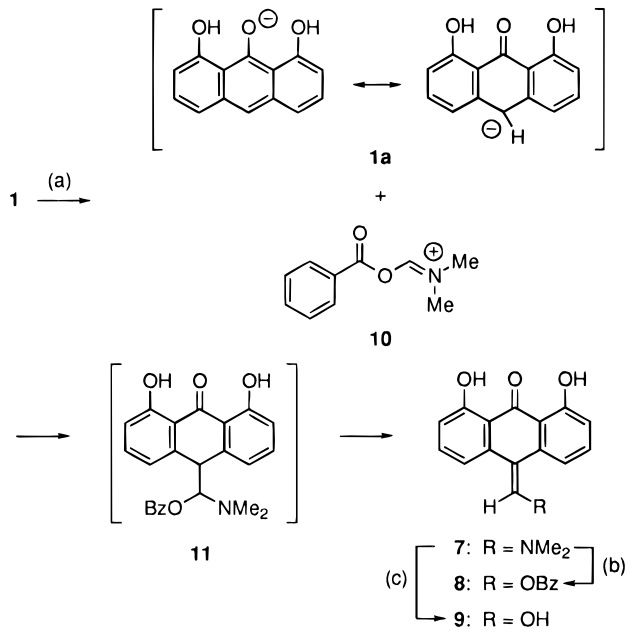
Scheme 1[a]



[a] Reagents: (a) acetylsalicylic acid chloride, collidine or pyridine, toluene; (b) benzoyl chloride, pyridine or hexamethylphosphoric triamide; (c) benzoyl chloride, NaH, THF.

Scheme 2[a]



[a] Reagents: (a) benzoyl chloride, DMF; (b) H_2O, benzoyl chloride; (c) HCl, H_2O.

the signal of C-10 unsubstituted anthralin. Integration of the peak area confirmed the presence of *two* protons at C-10. Hence, an alternative preparative route was required.

Attempted modifications of the standard method for the preparation of 10-acyl anthralin derivatives were unsuccessful; in spite of varying the base, the base-to-anthrone-ratio, the solvent, the order of additions, and the time and temperature, only the *O*-benzoylated compounds **4** and **5** were obtained from the reaction of **1** and benzoyl chloride. In addition, when sodium hydride was used as a base in THF, benzoylation of **1** gave a tetrabenzoylated compound **6** (Scheme 1).

Interestingly, when DMF was used as solvent, the *O*-benzoyl derivatives were not obtained, but rather a novel enamine derivative **7** of anthralin was isolated, along with the enol ester **8** (Scheme 2), which may be formed from the enamine **7** as a consequence of aqueous reaction workup. We subjected the enamine **7** to hydrolysis and obtained 10-formylanthralin as the enol tautomer **9**. The absence of an aldehyde absorption in the IR spectrum confirmed that no tautomerization to the 10-formyl derivative took place. In further support of this, the ^{1}H NMR spectrum, recorded in DMSO-d_6, displayed no signal for an aldehydic proton, but a resonance at δ 8.47 corresponding to the proton at the enol carbon. As in compounds **7** and **8**, this signal is clearly distinguished from the aromatic protons. A possible mechanism for the formation of **9** is given in Scheme 2. In nonpolar aprotic solvents anthralin exists as the anthracenone tautomer exclusively,[12−14] whereas the 1,8,9-trihydroxyanthracene could only be identified in hexamethylphosphoric triamide.[12] When bases are added or when anthralin is dissolved in polar aprotic solvents it is partially converted to its anion **1a**,[14−16] which is the predominant form in basic solutions and in DMF.[14,17] On the basis of computational studies, the ionization site for anthralin was predicted to be at the 10-position.[18] The formation of **7** is without precedence but can be rationalized in a straightforward manner as a process involving electrophilic substitution at the 10-position of the quite electron-rich, nucleophilic polyhydroxyanthracene anion **1a** of anthralin thus formed in DMF. In such a Vilsmeier-type reaction, the disubstituted formamide will be activated by benzoyl chloride, in place of the more common $POCl_3$, and the attacking species is **10**, which has already been described as the reactive intermediate in the preparation of formamidinium salts using benzoyl chloride and DMF in the presence of a carboxamide.[19] The intermediate **11** may eliminate benzoic acid to give the enamine **7** or hydrolyze to **9**. Modified Vilsmeier reactions using benzoyl chloride in place of $POCl_3$ have also been described for the formylation of other substrates.[20,21]

In further attempts to obtain the desired 10-benzoylanthralin, we envisaged protection of the free phenolic groups of **1** in order to prevent *O*-acylation. To this end, a versatile protecting group is required which is introducable with respect to the C-10 reactivity of **1** and selectively removable under conditions that would not affect the C-10 benzoyl substituent. At the beginning of our studies a promising preparative procedure involved reaction of the 1,8,9-tris(trimethylsilyl) ether[22] of **1** with benzoyl chloride. Unfortunately, Friedel-Crafts conditions (aluminum chloride, carbon disulfide, argon) which convert the trimethylsilyl ether of 9-anthracenol and benzoyl chloride to 10-benzoyl-9(10*H*)-anthracenone,[23] gave only **1** when 1,8,9-tris[(trimethylsilyl)oxy]anthracene was used.

Furthermore, use of the recently described 1,8-dimethoxy-9-hydroxyanthracene[2] (**12**) was studied. Friedel−Crafts reaction with benzoyl chloride gave the expected

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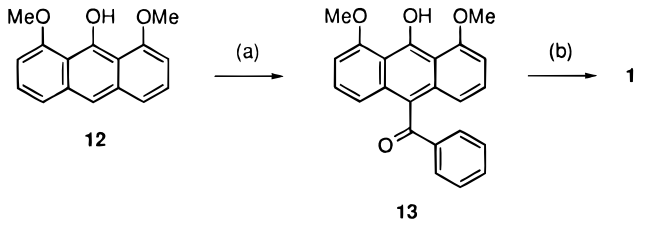
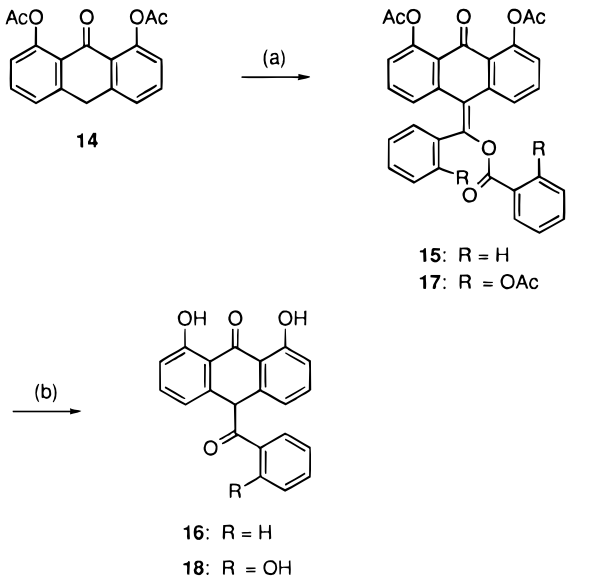
Scheme 3[a]



[a] Reagents: (a) benzoyl chloride, $AlCl_3$, 1,2-dichloroethane, 0−5 °C; (b) BBr_3, CH_2Cl_2, −78 °C.

Scheme 4[a]



[a] Reagents: (a) benzoyl chloride or acetylsalicylic acid chloride, NaH, THF, room temperature, N_2; (b) 9% NaOH, ethanol, room temperature, N_2.

10-benzoylated 9-hydroxyanthracene **13** (Scheme 3). The 10-hydroxy proton chemical shift at δ 11.32 supports the presence of this tautomeric form. However, deprotection of both methyl ethers of **13** with boron tribromide resulted also in loss of the benzoyl function at C-10, yielding **1** as the sole product.

Finally, use of the more readily removable acetyl group was studied. Thus, anthralin diacetate **14**[24] was treated with benzoyl chloride and sodium hydride in THF, but did not afford the expected 10-benzoylated product. Alternatively, the enol ester **15** was isolated (Scheme 4). Nonetheless, hydrolysis of **15** yielded the desired 10-benzoylanthralin (**16**). Thus, debenzoylation of **15** produces an intermediate enol which is further deacetylated (or *vice versa*) and tautomerizes to **16**. Our hydrolytic conditions use 9% aqueous sodium hydroxide and require continuous TLC controls to avoid degradation to **1**. Characterization of **16** by ^{1}H NMR spectroscopy revealed a large 1.8 ppm downfield shift for the C-10 proton compared to that of **1**,[13] even larger than the shifts (0.8 ppm) observed for the 10-ω-phenylacyl analogs.[8] Thus, this proton is located in the 10-benzoyl phenyl ring's shielding region.

Similarly, enol ester **17** was produced in 64% yield from the reaction of acetylsalicylic acid chloride and **14**, which was readily hydrolyzed to 10-salicylanthralin (**18**). Berset et al.[11] envisaged the synthesis of this derivative as their initial goal, since they expected a greater impact on the therapeutic need by combination of anthralin and the keratolytic activity of salicylic acid within one molecule. However, hydrolysis of their putative 10-(acetylsalicyl)anthralin failed to give **18**,[11] since the correct structure of their compound is the phenol ester **3**, which can only be hydrolyzed to **1**.

In conclusion, 10-benzoyl- and 10-salicylanthralin have both been synthesized for the first time from anthralin using a three-step route applicable to the synthesis of novel anthracenones substituted on the benzoyl moiety, which forms the basis of ongoing studies. Furthermore, our results of the attempted benzoylation of anthralin in DMF seem to be consistent with a Vilsmeier-type reaction having occurred to produce an enamine which was then hydrolyzed or benzoylated to an enol or enol ester, respectively.

Experimental Section

General. For analytical instruments and methods, see ref 8. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian EM 390 (90 MHz) or a Bruker WM 250 (250 MHz), using tetramethylsilane as an internal standard. Fourier-transform IR spectra (KBr) were recorded on a Nicolet 510M FTIR spectrometer. Mass spectra were obtained on a Varian MAT 112S, EI-MS (70 eV); relative intensities are given in parentheses. Thin layer chromatography (TLC) was conducted on Merck Kieselgel 60 F_{254} precoated silica gel plates. Column chromatography was performed on Merck silica gel (70−230 mesh) with CH_2Cl_2 as eluant, unless otherwise stated. Elemental analyses were determined by the Microanalytical Laboratories at the University of Regensburg.

1-(2-Acetoxybenzoyl)-8-hydroxy-9(10*H*)-anthracenone (3). Following the method of Berset,[11] **1** (2.26 g, 10 mmol) was dissolved in dry toluene (40 mL) and cooled to 0 °C. Collidine (1.82 g, 15 mmol) was added under N_2 and then acetylsalicylic acid chloride (1.99 g, 10 mmol) dropwise within 30 min, and the mixture was brought to room temperature in the course of 6 h. Then it was filtered by suction and evaporated. Purification by column chromatography afforded yellow needles: 28% yield; mp 168 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 12.62 (s, 1 H), 8.38−6.84 (m, 10 H), 4.38 (s, 2 H), 2.31 (s, 3 H). Anal. Calcd for $C_{23}H_{16}O_6$: C, 71.13; H, 4.15. Found: C, 71.07; H, 4.17. The analytical data are identical with those of an authentic sample of Berset's[11] compound.

1-(Benzoyloxy)-8-hydroxy-9(10*H*)-anthracenone (4). To a solution of **1** (0.45 g, 2 mmol) in HMPTA (15 mL) was added benzoyl chloride (0.84 g, 6 mmol), and the solution was stirred for 12 h at room temperature. Then the mixture was poured into water (500 mL) and extracted with ether (2 × 50 mL). The combined organic phase was washed with water (3 × 50 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography afforded a pale yellow powder: 43% yield; mp 173 °C; FTIR 1733, 1631 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 12.72 (s, 1 H), 8.37−6.78 (m, 11 H), 4.38 (s, 2 H); MS m/z = 330 (32, M^+). Anal. Calcd for $C_{21}H_{14}O_4$: C, 76.34; H, 4.27. Found: C, 76.23; H, 4.56.

1,8-Bis(benzoyloxy)-9(10*H*)-anthracenone (5) was prepared as described for **4**, but pyridine was used instead of HMPTA. After the reaction was complete, the mixture was poured into 3.5% HCl (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL): 64% yield; mp 210 °C (lit.[25] mp 214−216 °C).

1,8,9-Tris(benzoyloxy)-10-benzoylanthracene (6). To a suspension of **1** (0.50 g, 2.21 mmol) in absolute THF (20 mL) was added NaH (0.50 g) under N_2 and then benzoyl chloride (1.86 g, 13.26 mmol) dropwise. After the reaction was complete, the mixture was stirred for 1 h. Then the mixture was

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poured into ice−water (300 g) and 37% HCl (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with water (3 × 100 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography afforded a pale yellow powder: 58% yield; mp 260 °C; FTIR 1740, 1661 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.17−6.42 (m, 26 H); MS m/z = 642 (8, M^+). Anal. Calcd for $C_{42}H_{26}O_7$: C, 78.50; H, 4.08. Found: C, 78.07; H, 4.34.

1,8-Dihydroxy-10-[(*N*,*N*-dimethylamino)methylene]-9(10*H*)-anthracenone (7). To a solution of **1** (1.00 g, 4.42 mmol) in dry DMF (20 mL) was added benzoyl chloride (0.62 g, 4.42 mmol) in one portion under N_2, and the solution was stirred until the reaction was complete (TLC control). Then the mixture was poured into ice−water (500 g) and extracted with ether (3 × 100 mL). The combined organic phase was washed with water (4 × 100 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography (ether) afforded dark-red crystals: 51% yield; mp 131 °C; FTIR 1607 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 13.98 (s, 2 H), 8.02 (s, 1 H), 7.52−6.52 (m, 6 H), 3.02 (s, 6 H); MS m/z = 281 (100, M^+). Anal. Calcd for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.45; H, 5.38; N, 5.00.

1,8-Dihydroxy-10-[(benzoyloxy)methylene]-9(10*H*)-anthracenone (8) was obtained from the reaction above, along with **7**, as a yellow powder: 15% yield; mp 190 °C; FTIR 1748, 1638 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 12.53 (s, 1 H), 12.42 (s, 1 H), 8.52 (s, 1 H), 8.30−6.92 (m, 11 H). Anal. Calcd for $C_{22}H_{14}O_5$: C, 73.74; H, 3.94. Found: C, 73.61; H, 4.10.

1,8-Dihydroxy-10-(hydroxymethylene)-9(10*H*)-anthracenone (9). A suspension of **7** (0.3 g, 1.07 mmol) in HOAc (10 mL), 37% HCl (5 mL), and water (15 mL) was stirred at room temperature under N_2, until the reaction was complete (TLC control). Water (20 mL) was added, and the mixture was filtered by suction, washed with water (50 mL), and dried. Recrystallization from CH_2Cl_2−methanol (9 + 1) afforded an orange powder: 64% yield; mp 173 °C dec; ^1H NMR (90 MHz, DMSO-d_6) δ 12.82 (s, 2 H), 8.47 (s, 1 H), 7.95−6.73 (m, 6 H), the enolic OH-signal was absent; MS m/z = 254 (28, M^+). Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96. Found: C, 70.43; H, 4.33.

10-Benzoyl-1,8-dimethoxy-9-hydroxyanthracene (13). A suspension of anhydrous $AlCl_3$ (0.8 g, 6 mmol) in 1,2-dichloroethane (20 mL) was cooled to 0 °C. Benzoyl chloride (1.21 g, 8.60 mmol) was added, and the solution was stirred for 20 min. To this mixture was added a solution of **12**[2] (0.31 g, 1.20 mmol) dropwise at 0 °C under N_2, and the mixture was stirred at 0−5 °C for 3 h. Then it was poured into ice−water (300 g) and 37% HCl (10 mL), and the mixture was thoroughly shaken and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with water (3 × 100 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography (ether) afforded a yellow powder: 64% yield; mp 175 °C dec; FTIR 3315, 1667 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 11.32 (s, 1 H), 7.90−6.60 (m, 11 H), 4.10 (s, 6 H). Anal. Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 76.81; H, 5.01.

Ether Cleavage of 13. A solution of **13** (0.20 g, 0.56 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of BBr_3 (0.70 g, 2.80 mmol) in CH_2Cl_2 (25 mL) at −78 °C under N_2. The solution was allowed to warm to room temperature, stirred for 24 h, poured into water (200 mL), and stirred for an additional 15 min, and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was washed with water (2 × 40 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography afforded **1** as the sole product.

1,8-Diacetoxy-10-[1-(benzoyloxy)-1-phenylmethylene]-9(10*H*)-anthracenone (15). To a suspension of NaH (0.30 g) in absolute THF (25 mL) was added **14**[26] (0.31 g, 1 mmol) under N_2, and the mixture was stirred at room temperature for 15 min. Benzoyl chloride (0.84 g, 6 mmol) was added in one portion, and the mixture was stirred for 1 h. After the reaction was complete, the mixture was stirred once more for 1 h. It was then poured into water (200 mL) and 37% HCl (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with water (3 × 50 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography afforded a pale yellow powder: 53% yield; mp 169 °C; FTIR 1771, 1746, 1671 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.93−7.00 (m, 16 H), 1.72 (s, 6 H); MS m/z = 518 (2, M^+). Anal. Calcd for $C_{32}H_{22}O_7$: C, 74.12; H, 4.28. Found: C, 74.28; H, 4.48.

1,8-Dihydroxy-10-benzoyl-9(10*H*)-anthracenone (16). To a solution of **15** (0.20 g, 0.39 mmol) in 99% ethanol (20 mL) was added dropwise a solution of 9% aqueous NaOH (5 mL). The mixture was stirred at room temperature until the reaction was complete (TLC control). It was then poured into water (100 mL) and 37% HCl (15 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was washed with water (3 × 50 mL), dried over Na_2SO_4, and evaporated. Purification by column chromatography afforded yellow needles: 53% yield; mp 230 °C; FTIR 1681, 1615 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 12.32 (s, 2 H), 7.86−6.79 (m, 11 H), 6.05 (s, 1 H). Anal. Calcd for $C_{21}H_{14}O_4$: C, 76.36; H, 4.27. Found: C, 76.28; H, 4.27.

1,8-Diacetoxy-10-[1-[(2-acetoxybenzoyl)oxy]-1-(2-acetoxyphenyl)methylene]-9(10*H*)-anthracenone (17) was prepared from **14**[26] (0.50 g, 1.15 mmol) and acetylsalicylic acid chloride (1.19 g, 6 mmol) as described for **15** and afforded a pale yellow powder: 64% yield; mp 125 °C; FTIR 1769, 1671 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.83−7.03 (m, 14 H), 2.23 (s, 3 H), 2.10 (s, 3 H), 1.77 (s, 6 H). Anal. Calcd for $C_{36}H_{26}O_{11}$: C, 68.14; H, 4.13. Found: C, 68.28; H, 4.30.

1,8-Dihydroxy-10-(2-hydroxybenzoyl)-9(10*H*)-anthracenone (18) was prepared from **17** (0.12 g, 0.19 mmol) as described for **16** and afforded yellow crystals: 59% yield; mp 210 °C; FTIR 1688, 1636 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 12.57 (s, 1 H), 11.90 (s, 1 H), 10.40 (s, 1 H), 7.68−6.77 (m, 10 H), 6.27 (s, 1 H). Anal. Calcd for $C_{21}H_{14}O_5$: C, 72.83; H, 4.07. Found: C, 72.56; H, 3.99.

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