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Intramolecularly *Friedel-Crafts* Acylated Emodin Derivatives. An Access to the Cores of Angucyclinones, Anthracyclinones, and to Hypericin Analogues

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Summary. Intramolecularly emodin based *Friedel-Crafts* acylation provided a new route for the synthesis of the angucyclinone and anthracyclinone core as well as access to a new class of cyclopentanone condensed anthraquinones. In addition, the anthracyclinone may serve as a synthon for bathochromically shifted hypericin derivatives.

Keywords. Emodin; *Friedel-Crafts* acylation; Anthracyclinones; Angucyclinones.

Introduction

Hydroxylated anthraquinones and their derivatives are used in several fields, mainly as anticancer or antimicrobial drugs [1], but also as photosensitizers [2]. Emodin (1,3,8-trihydroxy-6-methyl-9,10-anthraquinone) is a naturally occurring anthraquinone, which is of particular interest as it can be used for the preparation of hypericin [3], a well known photosensitizer with broad anticancer and antiviral activity [4–6].

In our search for potential precursors for photodynamically active hypericin derivatives [7], we now investigated the synthesis of a new class of intramolecularly *Friedel-Crafts* acylated emodin derivatives. These compounds are interesting hypericin synthons, as the carbonyl group should exert a bathochromic effect as well as it should not interfere with the photosensitization processes. We herein report our efforts in the syntheses of intramolecularly 2- or 4-acylated emodin derivatives, starting from tri-*O*-methyl emodin aldehyde (**1**) [8].

In addition, benz[*a*]anthraquinone based angucyclinones and the naphthacene based anthracyclinones are highly interesting because of their outstanding

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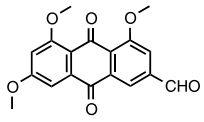

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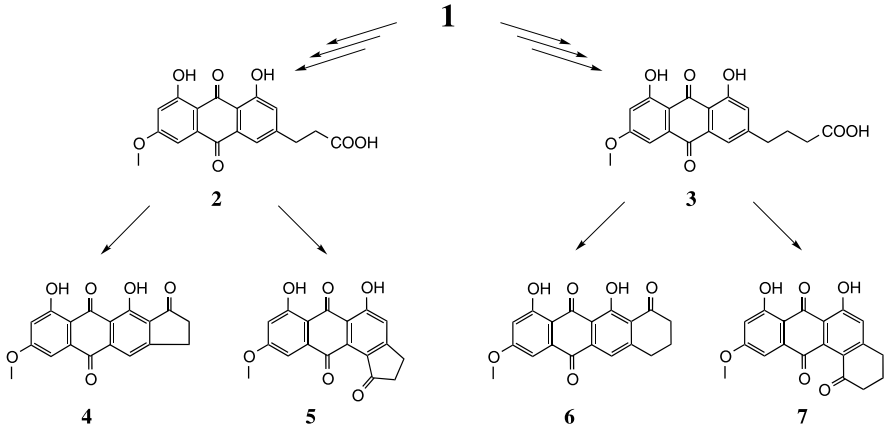
biological activities [9]. Strategies for the preparation of angucyclinones and anthracyclinonens include *Marschalk* type reactions [10], *Diels-Alder* reactions [11], biomimetic polyketide condensation [12], or direct orthometallation approaches [13]. However, to the best of our knowledge, no applications of intramolecular *Friedel-Crafts* acylations for the formation of the A ring of these systems have been reported so far. Therefore, the *Friedel-Crafts* strategy reported in this account is not only interesting for syntheses of new hypericin synthons, it also offers a novel, useful method to prepare the core of angucyclinones and anthracyclinones starting from the naturally occuring emodin.

Results and Discussions

Starting from **1**, easily prepared from emodin according to Ref. [8], we focused on the syntheses of five- and six-membered ring systems. There is only one example of an intramolecular *Friedel-Crafts* acylation of anthraquinones to be found in literature [14]. Moreover, to the best of our knowledge, no cyclopentanone condensed anthraquinones have been prepared by this way so far, which might be rationalized by the high deactivation of the aromatic system towards an electrophilic attack due to the electron withdrawing quinone system. Accordingly, the acylation turned out to be the key step in this work. The aim was to introduce the corresponding carboxylic acid in position 3 followed by an intramolecular *Friedel-Crafts* acylation as envisaged in Scheme 1. Of course, in this process a pair of cyclization products involving a five- or six-membered condensed ring, **4** and **5** or **6** and **7**, is possible in principle. The 2-acylated compounds **4** and **6** may be dimerized to the corresponding hypericin derivatives [3], or form the core of

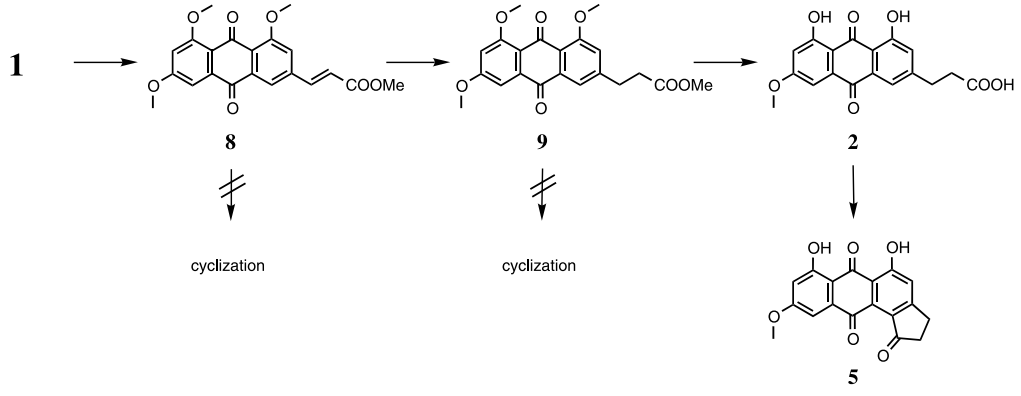


Scheme 1

anthracyclinones whereas the 4-acylated derivatives are core representatives of the angucyclinones. The ratio between **4** and **5** as well as between **6** and **7** was interesting, as it would certainly depend on the relative activations of the respective ring positions.

Five-Membered Ring Systems

In the first step, a *Wittig* reaction between the protected emodin aldehyde **1** and (carbomethoxymethyl)triphenylphosphonium bromide gave the cinnamate **8** in 71% yield (Scheme 2). Attempts to close the ring on the stage of the corresponding unsaturated acid with polyphosphoric acid (*PPA*) or trifluoroacetic anhydride (*TFAA*) under various conditions failed, which underscores the missing literature in the field of cinnamic acid based intramolecular *Friedel-Crafts* acylations. We then decided to carry out the ring closure on systems with a saturated side chain. Therefore, **8** was hydrogenated in presence of Pd/C yielding 91% of **9**. Unfortunately, again no ring closure of the corresponding acid could be achieved, which illustrates the high deactivation of this compound towards an electrophilic attack.



Scheme 2

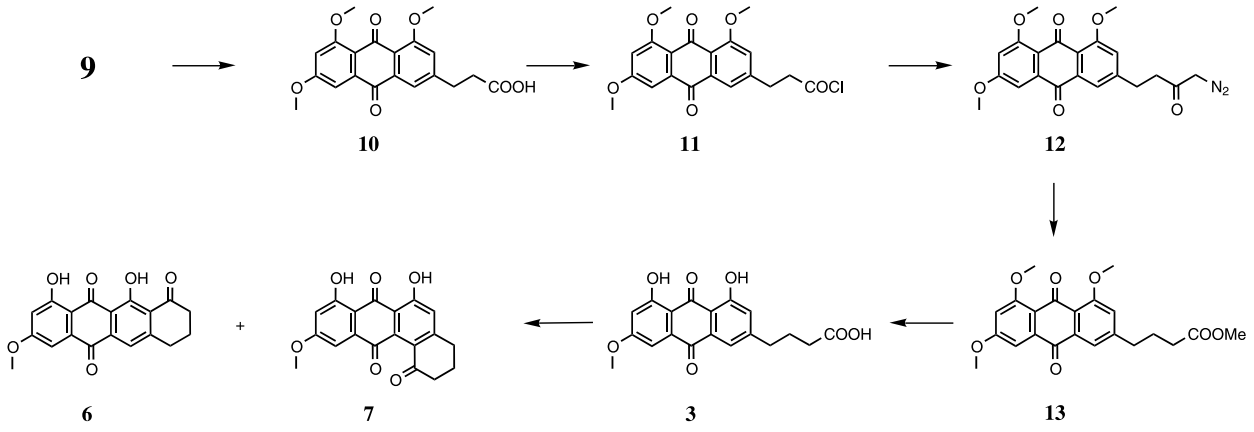
To enhance the reactivity of **9**, it was deprotected by means of HBr/*Ac*OH, giving the higher activated dihydroxy acid **2** in 66% yield. Heating of **2** with *PPA* at 60°C for 16 h gave the 4-acylated methoxy emodin **5** in 64% yield. As no formation of the potential hypericin precursor **4** could be observed also at an elevated temperature (90°C), position 4 of this compound turned out to be the favoured position for an electrophilic attack.

Compounds **2**, **5**, **8**, and **9** were fully characterized on basis of their IR, UV/Vis, MS, and NMR spectra, particularly by 2D NMR measurements including HSQC, HMBC, and N*O*ESY experiments.

In conclusion, a regioselective synthesis of **5** could be achieved in a four-step procedure starting from the readily available aldehyde **1** in an overall yield of 28%. This compound gives access to a new class of angular cyclopentanone condensed anthraquinones, which have not yet been described in literature. However, with respect to the potential hypericin synthon **4** this strategy was inconclusive.

Six-Membered Ring Systems

We first tried to prepare the butyrate **13** starting from **1** *via* a *Wittig* reaction with β-(carbomethoxyethyl)triphenylphosphonium bromide. However, also under a variety of conditions (NaH/*DMSO*, K_2CO_3/18-crown-6, different temperatures) formation of **13** could not be achieved. We therefore chose a different route, starting from the already prepared ester **9**, *via* an *Arndt-Eistert* chain elongation (Scheme 3).



Scheme 3

First, **9** was saponified to the corresponding acid **10** in 90% yield. Formation of the acid chloride **11** could be achieved by treatment of **10** with an excess of oxalyl chloride in benzene. It has to be mentioned, that formation of **11** with the commonly used $SOCl_2$ was not possible due to the instability of the methoxy groups under these reaction conditions. The rather unstable **11** had to be converted directly, without any further purification, to the α-diazoketone **12**, by means of reaction with an ethereal solution of CH_2N_2. Finally, reflux of **12** in *Me*OH in the presence of Ag_2O gave the desired **13** in 75% yield.

Due to the better reactivity of the hydroxy derivative **2** in intramolecular *Friedel-Crafts* acylation as observed before, we chose a similar way in the syntheses of the six-membered rings. HBr/*Ac*OH mediated deprotection of **13** gave **3** in 80% yield. Accordingly, **13** could be obtained from **1** in a seven-step synthesis in a total yield of 35%. Heating of **3** in *PPA* at 90°C for 2 h gave complete conversion yielding the angucyclinone **7** as the main product and about 20% of the hypericin synthon **6**. With respect to the synthesis of novel hypericin derivatives, the product ratio in dependence of the conditions was investigated. We found that a lower reaction temperature (60°C), but a therefore longer reaction time could provide **6** with nearly 40% selectivity.

The preference of the *Friedel-Crafts* cyclization into position 4 in the five- and six-membered rings is remarkable because position 2 should be the more activated one (*ortho* positioned to the hydroxy group), whereas position 4 would be deactivated by the *ortho* positioned quinone-carbonyl group. This effect could be due to a preferred complexation of the pre-transition state by the quinone-carbonyl group.

Unfortunately, reactions in *PPA* are limited by its high viscosity, which requires an enhanced reaction temperature. In an experiment carried out at 40°C homogenization of the reaction mixture

was hardly possible. It resulted in a conversion of less than 75% (20 h) and no improvement of the ratio. Using the commonly used *PPA* alternative $P_2O_5/MeSO_3H$ [15], which allows the reaction at lower temperatures, gave no reaction, as well as reaction in *TFAA*. *Smyth et al.* recently reported the use of *TFAA*/phosphoric acid (*PA*) mixtures for *Friedel-Crafts* acylations [16]. Using this method we observed quite similar product distributions as in the case of *PPA*. After 30 min reflux (60°C), **6** was obtained with about 35% selectivity, the same ratio which was also obtained after 2 h at 25°C. Thus this method gives no improvement (concerning the ratio) in comparison to the *PPA* mediated ring closure. Furthermore, conversion was always limited to about 75%, due to the already mentioned formation of precipitate in the case of rather deactivated compounds [16].

Compounds **3**, **6**, **7**, **10**, and **13** were fully characterized on basis of their IR, UV/Vis, MS, and NMR spectra, particularly by 2D NMR measurements including HSQC, HMBC, and N*O*ESY experiments.

In conclusion, we found that ring closure of **3** is possible with good conversion rate, which gives access to the angucyclinone and anthracyclinone core *via* a novel route starting from the naturally occurring emodin. In contrast to the five-membered rings, where no acylation in position 2 occurred, a better activation of position 2 of the six-membered ring systems towards an attack by the acylating reagent was observed. The ratio between **6** and **7** could slightly be influenced by variation of the reaction conditions, but always giving **7** as the main product. With respect to the syntheses of new bathochromically shifted hypericin derivatives, we found that **6** has a bathochromically shifted absorption maximum of about 10 nm (in comparison to the unsubstituted 1,8-dihydroxy-6-methoxy-3-methyl-9,10-anthraquinone), which makes it a promising precursor for hypericin derivatives with photodynamic therapy potential. Compound **6** might serve as an entrance to the anthracyclinones as well as **7** could be used as a key synthon of angucyclinonens.

Experimental

Solvents were of *p.a.* quality unless otherwise stated. Melting points were measured on a *Kofler* melting point microscope (Reichert, Vienna). NMR spectra were recorded on a Bruker Avance DRX 500 MHz spectrometer using a TXI cryoprobe with *z*-gradient coil and on a Bruker Avance DPX 200 MHz spectrometer. 2D NMR experiments were performed on the 500 MHz spectrometer using standard pulse sequences as provided by the manufacturer. Typical 90° hard pulse durations were 8.2 µs (^{1}H) and 16.6 µs (^{13}C), 90° pulses in decoupling experiments were set to 67 µs. HSQC and HMBC experiments were optimized for coupling constants of 145 Hz for single quantum correlations and 10 Hz for multi-bond correlations. The N*O*ESY mixing time was set to 400 ms. IR, UV/Vis, and mass spectra were recorded using the Bruker Tensor 27, Varian Cary 100 Bio UV/Vis, and Hewlett Packard 59987 quadrupole instrument.

(E)-Methyl 3-(1,6,8-trimethoxy-9,10-anthraquinon-3-yl)acrylate (**8**, $C_{21}H_{18}O_7$)

(Carbomethoxymethyl)triphenylphosphonium bromide (1.27 g, 3.06 mmol, prepared according to Ref. [17]), 0.83 g of dried K_2CO_3 (6.1 mmol), and 0.6 g of 18-crown-6 (2.27 mmol) were dissolved in 100 cm^3 absolute CH_2Cl_2 and refluxed for 30 min. Then 1 g **1** (3.06 mmol), dissolved in 100 cm^3 CH_2Cl_2 was added dropwise over a period of 30 min. The reaction solution was refluxed for 5 h, cooled, and extracted with H_2O_{deion} three times. The organic layer was evaporated to dryness and the residue washed with ice cold Et_2O several times, giving 0.835 g (2.18 mmol) of a mixture of **8** (over 90% selectivity) and the corresponding (*Z*)-isomer (71%). Mp 218–223°C; TLC: $R_f = 0.71$ ($CHCl_3$:*Me*OH = 20:1); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C): $\delta = 3.85$ (s, COO–CH_3), 3.97 (s, 6-OCH_3),

3.98 (s, 8-OCH_3), 4.04 (s, 1-OCH_3), 6.63 (d, $J = 16.0$ Hz, =CH–COO–), 6.80 (d, $J = 2.38$ Hz, ar-H7), 7.35 (d, $J = 2.38$ Hz, ar-H5), 7.37 (d, $J = 1.47$ Hz, ar-H2), 7.72 (d, $J = 16.0$ Hz, ar–CH=), 8.01 (d, $J = 1.47$ Hz, ar-H4) ppm; N*O*ESY ($CDCl_3$): 6-OCH_3 ↔ ar-H5 and ar-H7, 8-OCH_3 ↔ ar-H7, 1-OCH_3 ↔ ar-H2, ar-H2 ↔ =CH–COO– and ar–CH=, ar-H4 ↔ =CH–COO– and ar–CH=; ^{13}C NMR (125 MHz, $CDCl_3$, 30°C): $\delta = 52.2$ (COO–*C*H_3), 56.2 (6-OCH_3), 56.7 (8-OCH_3), 56.9 (1-OCH_3), 102.4 (C5), 105.7 (C7), 117.2 (C2), 118.5 (C4), 118.6 (C8a), 121.7 (–*C*H_2–COO–), 124.9 (C9a), 135.4 (C4a), 136.5 (C10a), 139.5 (C3), 143.0 (3-CH_2–), 160.3 (C1), 162.1 (C8), 164.3 (C6), 166.9 (–COO–), 181.4 (C9), 183.9 (C10) ppm; HMBC ($CDCl_3$): C1 ↔ 1-OCH_3 and ar-H2, C3 ↔ ar-H2, ar-H4, and ar–CH=, C4a ↔ ar-H4, C6 ↔ ar-H5, ar-H7, and 6-OCH_3, C8 ↔ ar-H7 and 8-OCH_3, C8a ↔ ar-H7 and ar-H5, C9a ↔ ar-H2 and ar-H4, C10 ↔ ar-H4 and ar-H5, C10a ↔ ar-H5, –COO– ↔ =CH–COO– and COO–CH_3; HSQC data were according to structure; ESI-MS ($CH_3OH + 1$ vol-% HCOOH, $\gamma \sim 1$ mg cm^{-3}, positive ion mode): $m/z = 383$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3006$, 2945, 2842, 1705, 1666, 1598, 1562, 1459, 1439, 1351, 1327, 1282, 1246, 1165, 1131, 1072, 1054, 1026, 981, 946, 876, 849, 756, 561 cm^{-1}; UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 246 (86), 290 (100), 410 (24) nm (%).

Methyl 3-(1,6,8-trimethoxy-9,10-anthraquinon-3-yl)propionate (**9**, $C_{21}H_{20}O_7$)

A solution of 0.380 g of **8** (0.99 mmol) and 0.07 g of Pd/C (10%) in 500 cm^3 *Me*OH and 50 cm^3 $CHCl_3$ was Ar-flushed three times and then stirred under H_2 for 50 h. Afterwards the catalyst was filtered off, the solvent evaporated, and the resulting red solid dried over P_2O_5 giving 0.348 g (0.90 mmol) of **9** (91%). Mp 153–158°C; TLC: $R_f = 0.25$ ($CHCl_3$:*Et*O*Ac* = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C): $\delta = 2.71$ (t, $J = 7.58$ Hz, –CH_2–COO–), 3.05 (t, $J = 7.58$ Hz, ar–CH_2–), 3.69 (s, –COO–CH_3), 3.95 (s, 6-OCH_3), 3.96 (s, 8-OCH_3), 3.98 (s, 1-OCH_3), 6.76 (d, $J = 2.20$ Hz, ar-H7), 7.14 (s, ar-H2), 7.33 (d, $J = 2.20$ Hz, ar-H5), 7.66 (s, ar-H4) ppm; N*O*ESY ($CDCl_3$): 6-OCH_3 ↔ ar-H5 and ar-H7, 8-OCH_3 ↔ ar-H7, 1-OCH_3 ↔ ar-H2, ar–CH_2– ↔ ar-H2, ar-H4, and –CH_2–COO–; ^{13}C NMR (125 MHz, $CDCl_3$, 30°C): $\delta = 31.4$ (ar–CH_2–), 35.0 (–CH_2–COO–), 52.0 (–COO–*C*H_3), 56.1 (6-OCH_3), 56.7 (8-OCH_3), 56.8 (1-OCH_3), 102.2 (C5), 105.6 (C7), 118.6 (C8a), 118.7 (C2), 118.8 (C4), 122.5 (C9a), 135.0 (C4a), 136.6 (C10a), 147.2 (C3), 160.2 (C1), 162.0 (C8), 164.0 (C6), 172.9 (–COO–), 181.8 (C9), 184.4 (C10) ppm; HMBC ($CDCl_3$): C1 ↔ 1-OCH_3 and ar-H2, C3 ↔ ar-H2, ar-H4, and ar–CH_2–, C4a ↔ ar-H4, C6 ↔ ar-H5, ar-H7, and 6-OCH_3, C8 ↔ ar-H7 and 8-OCH_3, C8a ↔ ar-H7 and ar-H5, C9a ↔ ar-H2 and ar-H4, C10 ↔ ar-H4 and ar-H5, C10a ↔ ar-H5, ar-CH_2 ↔ –CH_2–COO–, –COO– ↔ –CH_2–COO– and COO–CH_3; HSQC data were according to structure; ESI-MS ($CH_3OH + 1$ vol-% HCOOH, $\gamma \sim 1$ mg cm^{-3}, positive ion mode): $m/z = 385$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3004$, 2947, 2840, 1734, 1663, 1599, 1561, 1458, 1444, 1426, 1351, 1324, 1275, 1244, 1206, 1188, 1162, 1130, 1071, 1020, 957, 945, 874, 838, 752 cm^{-1}; UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 276 (100), 401 (24) nm (%).

3-(1,8-Dihydroxy-6-methoxy-9,10-anthraquinon-3-yl)propionic acid (**2**, $C_{18}H_{14}O_7$)

A solution of 46 mg of **9** (0.119 mmol) in 10 cm^3 glacial *Ac*OH was heated to reflux. Then 6 cm^3 HBr (47%) were added dropwise over a period of 30 min and it was refluxed for further 60 min. The reaction was controlled *via* TLC. The solution was poured on ice/H_2O, extracted with $CHCl_3$, and evaporated. The crude product (34 mg) was purified by column chromatography ($CHCl_3$:*Me*OH = 20:1) giving 27 mg (0.079 mmol) of **2** (66%). Mp 210–216°C; TLC: $R_f = 0.18$ ($CHCl_3$:*Me*OH = 20:1); ^{1}H NMR (500 MHz, *DMSO*-d_6, 30°C): $\delta = 2.63$ (t, $J = 7.32$ Hz, –CH_2–COO–), 2.94 (t, $J = 7.32$ Hz, ar–CH_2–), 3.94 (s, 6-OCH_3), 6.87 (d, $J = 2.14$ Hz, ar-H7), 7.19 (d, $J = 2.14$ Hz, ar-H5), 7.25 (s, ar-H2), 7.59 (s, ar-H4), 11.96 (s, 8-OH), 12.15 (s, 1-OH), 12.19 (s, –COOH) ppm; N*O*ESY (*DMSO*-d_6): 6-OCH_3 ↔ ar-H5 and ar-H7, ar–CH_2– ↔ ar-H2, ar-H4, and –CH_2–COO–; ^{13}C NMR (125 MHz, *DMSO*-d_6, 30°C): $\delta = 30.4$ (ar–CH_2–), 33.9 (–*C*H_2–COOH),

56.3 (6-OCH_3), 106.5 (C7), 107.7 (C5), 109.8 (C8a), 113.9 (C9a), 119.9 (C4), 123.7 (C2), 133.0 (C4a), 134.8 (C10a), 151.4 (C3), 161.4 (C1), 164.4 (C8), 166.1 (C6), 173.3 (–COOH), 181.1 (C10), 189.9 (C9) ppm; HMBC (*DMSO*-d_6): C1 ↔ ar-H2, C3 ↔ ar-H2, ar-H4, and ar–CH_2–, C6 ↔ ar-H5, ar-H7, and 6-OCH_3, C8 ↔ ar-H7, C8a ↔ ar-H7 and ar-H5, C9a ↔ ar-H2 and ar-H4, C10 ↔ ar-H4 and ar-H5, C10a ↔ ar-H5, ar–CH_2 ↔ –CH_2–COO–, –COO– ↔ –CH_2–COO–; HSQC data were according to structure; ESI-MS (CH_3OH + 1 vol-% NH_3, $\gamma \sim 1\,mg\,cm^{-3}$, negative ion mode): $m/z = 341$ ($[M-H]^-$); IR (KBr): $\bar{\nu} = 3448, 2925, 2854, 1706, 1671, 1629, 1561, 1480, 1388, 1262, 1218, 1161, 1099, 990, 911, 761\,cm^{-1}$; UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 267 (100), 286 (96), 438 (42) nm (%).

5,7-Dihydroxy-9-methoxy-6,11-dioxonaphto[f]indanone (**5**, $C_{18}H_{12}O_6$)

A suspension of 15 mg of **2** (0.044 mmol) in 3 cm^3 *PPA* was heated to 60°C and stirred for 16 h. The solution was poured on ice/H_2O and extracted with $CHCl_3$. The combined organic layers were washed with a $NaHCO_3$ solution and evaporated. The crude product (12 mg) was purified by preparative TLC ($CHCl_3$/silica gel) giving 9 mg (0.028 mmol) of **5** (64%). Mp decomp. ≥200°C; TLC: $R_f = 0.4$ ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C): $\delta = 2.81$ (t, $J = 6.41$ Hz, –CH_2–CO–), 3.17 (t, $J = 6.14$ Hz, ar–CH_2–), 3.95 (s, 6-OCH_3), 6.69 (d, $J = 2.40$ Hz, ar-H7), 7.25 (s, ar-H2), 7.39 (d, $J = 2.40$ Hz, ar-H5), 11.90 (s, 8-OH), 12.87 (s, 1-OH) ppm; N*O*ESY ($CDCl_3$): 6-OCH_3 ↔ ar-H5 and ar-H7, 8-OH ↔ ar-H7, 1-OH ↔ ar-H2, ar–CH2– ↔ –CH_2–CO– and ar-H2; ^{13}C NMR (125 MHz, $CDCl_3$, 30°C): $\delta = 26.2$ (ar–CH_2–), 37.6 (–CH_2–CO–), 56.4 (6-OCH_3), 106.9 (C7), 108.8 (C5), 109.7 (C8a), 117.4 (C9a), 120.5 (C2), 129.3 (C4), 135.0 (C4a or C10a), 136.7 (C10a or C4a), 163.6 (C3), 165.2 (C8), 166.1 (C1), 167.6 (C6), 181.0 (C10), 191.5 (C9), 200.7 (ar–CO–) ppm; HMBC ($CDCl_3$): C1 ↔ 1-OH and ar-H2, C3 ↔ ar-H2 and ar–CH_2–, C6 ↔ ar-H5, ar-H7, and 6-OCH_3, C8 ↔ ar-H7 and 8-OH, C8a ↔ ar-H7 and ar-H5, C9a ↔ ar-H2, C10 ↔ ar-H5, ar–CH_2 ↔ –CH_2–CO–, ar–CO– ↔ CH_2–CO–; HSQC data were according to structure; ESI-MS (CH_3OH + 1 vol-% HCOOH, $\gamma \sim 1\,mg\,cm^{-3}$, positive ion mode): $m/z = 325$ ($[M+H]^+$); IR (KBr): $\bar{\nu} = 2960, 2925, 2853, 1709, 1622, 1560, 1488, 1441, 1394, 1363, 1262, 1235, 1159, 1131, 1075, 799, 640\,cm^{-1}$; UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 239 (65), 273 (100), 447 (26) nm (%).

3-(1,6,8-Trimethoxy-9,10-anthraquinon-3-yl)propionic acid (**10**, $C_{20}H_{18}O_7$)

The ester **9** (0.348 g, 0.90 mmol) was suspended in 130 cm^3 2 *N* NaOH and refluxed for 90 min. The solution was washed with $CHCl_3$ three times and then acidified with HCl (3%) until the product precipitated. This suspension was then extracted with $CHCl_3$ and the combined organic layers were evaporated to dryness giving 0.301 g (0.81 mmol) of **10** (90%). Mp 125–136°C; TLC: $R_f = 0.20$ ($CHCl_3$:*Me*OH = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C): $\delta = 2.77$ (t, $J = 7.58$ Hz, –CH_2–COO–), 3.06 (t, $J = 7.58$ Hz, ar–CH_2–), 3.95 (s, 6-OCH_3), 3.96 (s, 8-OCH_3), 3.98 (s, 1-OCH_3), 6.76 (d, $J = 1.96$ Hz, ar-H7), 7.16 (s, ar-H2), 7.32 (d, $J = 1.96$ Hz, ar-H5), 7.68 (s, ar-H4) ppm; N*O*ESY ($CDCl_3$): 6-OCH_3 ↔ ar-H5 and ar-H7, 8-OCH_3 ↔ ar-H7, 1-OCH_3 ↔ ar-H2, ar–CH_2– ↔ –CH_2–CO–, ar-H2, and ar-H4; ^{13}C NMR (125 MHz, $CDCl_3$, 30°C): $\delta = 31.1$ (–CH_2–COO–), 34.5 (ar–CH_2–), 56.1 (6-OCH_3), 56.7 (8-OCH_3), 56.9 (1-OCH_3), 102.3 (C5), 105.6 (C7), 118.6 (C8a), 118.7 (C4), 118.8 (C2), 122.6 (C9a), 135.1 (C4a), 136.6 (C10a), 146.8 (C3), 160.2 (C1), 162.0 (C8), 164.1 (C6), 175.8 (–COOH), 181.8 (C9), 184.4 (C10) ppm; HMBC ($CDCl_3$): C1 ↔ 1-OCH_3 and ar-H2, C3 ↔ ar-H2, ar-H4, and ar–CH_2–, C4a ↔ ar-H4, C6 ↔ ar-H5, ar-H7, and 6-OCH_3, C8 ↔ ar-H7 and 8-OCH_3, C8a ↔ ar-H7 and ar-H5, C9a ↔ ar-H2 and ar-H4, C10 ↔ ar-H4 and ar-H5, C10a ↔ ar-H5, ar–CH_2 ↔ –C*H*$_2$–COOH, –COOH ↔ –CH_2–COOH; HSQC data were according to structure; ESI-MS (CH_3OH + 1 vol-% HCOOH, $\gamma \sim 1\,mg\,cm^{-3}$, positive ion mode): $m/z = 370$ ($[M]^+$); IR (KBr): $\bar{\nu} = 3481, 2942, 2843, 1717, 1655, 1598, 1563, 1459, 1429, 1331, 1256, 1205, 1162, 1131, 1068, 1017, 945, 874, 754, 659, 564\,cm^{-1}$; UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 279 (100), 401 (22) nm (%).

Methyl 3-(1,6,8-trimethoxy-9,10-anthraquinon-3-yl)butyrate (**13**, $C_{22}H_{22}O_7$)

To a solution of 0.360 g of **10** (0.973 mmol) in 60 cm^3 absolute benzene 1 cm^3 oxalyl chloride (5.5 mmol) was added, and it was refluxed for 3 h. After evaporation of the solvent NMR spectra showed ≥95% conversion to 3-(1,6,8-trimethoxy-9,10-anthraquinone-3-yl)propionyl chloride (**11**). ^{1}H NMR (200 MHz, $CDCl_3$, 30°C): $\delta = 3.10$ (t, $J = 7.0$ Hz, –CH_2–), 3.29 (t, $J = 7.0$ Hz, –CH_2–), 3.95 (s, 6H, –OCH_3), 3.99 (s, 3H, –OCH_3), 6.77 (d, $J = 1.8$ Hz, ar-H7), 7.12 (s, ar-H2), 7.31 (d, $J = 1.8$ Hz, ar-H5), 7.65 (s, ar-H4) ppm. Due to its instability, crude **11** was directly dissolved in 50 cm^3 of absolute CH_2Cl_2 and added dropwise to a stirred ice/NaCl cooled ethereal solution of CH_2N_2 (obtained from 1.5 g of *N*-methyl-*N*-nitrosourea (14 mmol) [18]). The solution was kept below 0°C for 3 h, then stirred for further 60 min until room temperature was reached, and evaporated to dryness giving the crude 1-diazo-4-(1,6,8-trimethoxy-9,10-anthraquinone-3-yl)butan-2-one (**12**). TLC: $R_f = 0.11$ ($CHCl_3$:*EtOAc* = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$, 30°C): $\delta = 2.70$ (t, $J = 7.2$ Hz, –CH_2–), 3.05 (t, $J = 7.2$ Hz, –CH_2–), 3.95 (s, 6H, –OCH_3), 3.97 (s, 3H, –OCH_3), 5.25 (s, –CH–N_2), 6.76 (d, $J = 1.9$ Hz, ar-H7), 7.14 (s, ar-H2), 7.31 (d, $J = 1.9$ Hz, ar-H5), 7.63 (s, ar-H4) ppm. Crude **12** was dissolved in 250 cm^3 of *Me*OH and 20 cm^3 of $CHCl_3$ without further purification. After addition of 60 mg of Ag_2O the solution was refluxed for 2 h. The reaction was controlled *via* TLC. After filtration of the catalyst, the solvent was evaporated and the red residue dissolved in CH_2Cl_2 and extracted with H_2O. The organic layer was dried over Na_2SO_4, evaporated to dryness, and the residue dried over P_2O_5 in vacuum giving 0.289 g (0.743 mmol) of **13** (overall yield: 75%); Mp 130–135°C; TLC: $R_f = 0.25$ ($CHCl_3$:*EtOAc* = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C): $\delta = 2.02$ (tt, $J = 7.69$, 7.27 Hz, –CH_2–C*H*$_2$–CH_2–), 2.37 (t, $J = 7.27$ Hz, –CH_2–COO–), 2.76 (t, $J = 7.69$ Hz, ar–CH_2–), 3.68 (s, COO–CH_3), 3.95 (s, 6-OCH_3), 3.96 (s, 8-OCH_3), 3.98 (s, 1-OCH_3), 6.76 (d, $J = 2.35$ Hz, ar-H7), 7.10 (d, $J = 1.28$ Hz, ar-H2), 7.32 (d, $J = 2.35$ Hz, ar-H5), 7.65 (d, $J = 1.28$ Hz, ar-H4) ppm; N*O*ESY ($CDCl_3$): 6-OCH_3 ↔ ar-H5 and ar-H7, 8-OCH_3 ↔ ar-H7, 1-OCH_3 ↔ ar-H2, ar–CH_2– ↔ –CH_2–C*H*$_2$–CH_2–, ar-H2, and ar-H4, –CH_2–COO ↔ –CH_2–C*H*$_2$–CH_2–; ^{13}C NMR (125 MHz, $CDCl_3$, 30°C): $\delta = 26.1$ (–CH_2*C*–H_2–CH_2–), 33.4 (–CH_2–COO), 35.7 (ar–CH_2–), 51.8 (COO–*C*H_3), 56.1 (6-OCH_3), 56.7 (8-OCH_3), 56.8 (8-OCH_3), 102.1 (C5), 105.5 (C7), 118.6 (C2), 118.7 (C4), 119.1 (C8a), 122.3 (C9a), 134.9 (C4a), 136.7 (C10a), 148.2 (C3), 160.2 (C1), 161.9 (C8), 164.0 (C6), 173.7 (–COO–), 181.9 (C9), 184.5 (C10) ppm; HMBC ($CDCl_3$): C1 ↔ 1-OCH_3 and ar-H2, C3 ↔ ar-H2, ar-H4, and ar–CH_2–, C4a ↔ ar-H4, C6 ↔ ar-H5, ar-H7, and 6-OCH_3, C8 ↔ ar-H7 and 8-OCH_3, C8a ↔ ar-H7 and ar-H5, C9a ↔ ar-H2 and ar-H4, C10 ↔ ar-H4 and ar-H5, C10a ↔ ar-H5, ar–CH_2 ↔ –CH_2–C*H*$_2$–CH_2–, –COO– ↔ –CH_2–COO– and COO–CH_3; HSQC data were according to structure; ESI-MS (CH_3OH + 1 vol-% HCOOH, $\gamma \sim 1$ mg cm^{-3}, positive ion mode): $m/z = 399$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 2935$, 2843, 1733, 1668, 1597, 1457, 1434, 1330, 1249, 1204, 1162, 1131, 1068, 1018, 946, 846, 754, 697 cm^{-1}; UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 278 (100), 405 (24) nm (%).

3-(1,8-Dihydroxy-6-methoxy-9,10-anthraquinon-3-yl)butyric acid (**3**, $C_{19}H_{16}O_7$)

A solution of 0.119 g **13** (0.298 mmol) in 45 cm^3 glacial *Ac*OH was heated to reflux. After dropwise addition of 15 cm^3 HBr (47%) over a period of 30 min the mixture was refluxed for further 60 min. The reaction was controlled *via* TLC. The solution was poured on ice/H_2O, extracted with $CHCl_3$, and evaporated. The crude product (0.129 g) was purified by column chromatography ($CHCl_3$:*Me*OH = 20:1) giving 0.085 g (0.238 mmol) of **3** (80%). Mp 202–205°C; TLC: $R_f = 0.12$ ($CHCl_3$:*Me*OH = 20:1); ^{1}H NMR (200 MHz, $CDCl_3$, 30°C): $\delta = 2.02$ (m, –CH_2–), 2.40 (t, $J = 7.14$ Hz, –CH_2–COOH), 2.77 (t, $J = 7.63$ Hz, ar–CH_2) 3.95 (s, 6-OCH_3), 6.69 (d, $J = 1.27$ Hz, ar-H7), 7.11 (s, ar-H2), 7.38 (d, $J = 1.27$ Hz, ar-H5), 7.65 (s, ar-H4), 12.13 (s, –OH), 12.29 (s, –OH) ppm; ^{1}H NMR (500 MHz, *DMSO*-d_6, 30°C): $\delta = 1.85$ (tt, $J = 7.32$, 7.63 Hz, –CH_2–C*H*$_2$–CH_2–), 2.26 (t, $J = 7.32$ Hz, –CH_2–COOH), 2.73 (t, $J = 7.63$ Hz, ar–CH_2–), 3.94 (s, 6-OCH_3), 6.88 (d, $J =$ 2.14 Hz, ar-H7), 7.20 (s, ar-H2), 7.21 (d, $J = 2.14$ Hz, ar-H5), 7.56 (s, ar-H4), 12.08 (bs, 3H, –OH, –COOH) ppm; N*O*ESY (*DMSO*-d_6): 6-OCH_3 ↔ ar-H5 and ar-H7, ar–CH_2– ↔ ar-H2, ar-H4,

and –CH_2–C*H*$_2$–CH_2–, –C*H*$_2$–COOH ↔ –CH_2–C*H*$_2$–CH_2–; ^{13}C NMR (125 MHz, *DMSO*-d_6, 30°C): $\delta = 26.1$ (–CH_2–*C*H_2–CH_2–), 33.6 (–CH_2–COOH), 35.2 (ar–CH_2–), 57.1 (6-OCH_3), 107.3 (C7), 108.4 (C2), 110.6 (C8a), 114.6 (C9a), 120.5 (C4), 124.4 (C5), 133.8 (C4a), 135.6 (C10a), 152.9 (C3), 162.3 (C1), 165.2 (C8), 166.9 (C6), 174.7 (–COOH), 181.9 (C10), 190.7 (C9) ppm; HMBC (*DMSO*-d_6): C1 ↔ ar-H2, C3 ↔ ar-H2, ar-H4, and ar–CH_2–, C6 ↔ ar-H5, ar-H7, and 6-OCH_3, C8 ↔ ar-H7, C8a ↔ ar-H7 and ar-H5, C9a ↔ ar-H2 and ar-H4, C10 ↔ ar-H4 and ar-H5, C10a ↔ ar-H5, ar–CH_2 ↔ –CH_2–C*H*$_2$–CH_2–, –COO– ↔ –CH_2–COO–; HSQC data were according to structure; ESI-MS (CH_3OH + 1 vol-% NH_3, $\gamma \sim 1$ mg cm^{-3}, negative ion mode): $m/z = 355$ ($[M-H]^-$); IR (KBr): $\bar{\nu} = 3272$, 2924, 2853, 1736, 1701, 1623, 1605, 1559, 1476, 1434, 1391, 1308, 1256, 1212, 1161, 1095, 1028, 992, 915, 783, 666, 637 cm^{-1}; UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 267 (100), 290 (97), 440 (58) nm (%).

Friedel-Crafts Acylation of ***3***

Polyphosphoric Acid (PPA): In a typical experiment 15 mg of **3** (=0.042 mmol) were suspended in 3 cm^3 *PPA*, heated to a certain temperature, and after total dissolution stirred for a certain time. The solution was then poured on ice/H_2O and extracted with $CHCl_3$. The combined organic layers were washed with a $NaHCO_3$ solution and evaporated. Products **6** and **7** were separated by preparative TLC ($CHCl_3$/silica gel). Conditions: a) 90°C, 2 h, 100% conv, 20% **6**, 80% **7**; b) 60°C, 3 h, 80% conv, ≤40% **6**, ≥60% **7**; c) 40°C, 20 h, ≤75% conv, 35% **6**, ≥60% **7**.

Trifluoroacetic Anhydride (TFAA)/Phosphoric Acid (PA): In a typical experiment 15 mg of **3** (=0.042 mmol) were suspended in 5 cm^3 *TFAA*, cooled to 10°C, and 1 cm^3 of *PA* was added. After dissolution the solution was heated to a certain temperature and stirred for a certain time. In each experiment a precipitate was formed about 5 min after total homogenisation of the reaction mixture. The solution was then poured on ice/H_2O and extracted with $CHCl_3$. The combined organic layers were washed with a $NaHCO_3$ solution and evaporated. Products **6** and **7** were separated by preparative TLC ($CHCl_3$/silica gel). Conditions: a) 60°C, 30 min, 75% conv, 30% **6**, 70% **7**; b) 25°C, 2 h, 70% conv, ≤35% **6**, ≥65% **7**.

10,12-Dihydroxy-8-methoxy-1,2,3,4-tetrahydronaphtacene-1,6,11-trione (**6**, $C_{19}H_{14}O_6$)

Mp decomp. ≥195°C; TLC: $R_f = 0.50$ ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C): $\delta = 2.19$ (tt, $J = 5.80$, 6.41 Hz, –CH_2–C*H*$_2$–CH_2–), 2.79 (t, $J = 6.41$ Hz, –CH_2–CO–), 3.10 (t, $J = 5.80$ Hz, ar–CH_2–), 3.93 (s, 6-OCH_3), 6.74 (d, $J = 2.14$ Hz, ar-H7), 7.33 (d, $J = 2.14$ Hz, ar-H5), 7.68 (s, ar-H4), 12.88 (s, 8-OH), 13.94 (s, 1-OH) ppm; N*O*ESY ($CDCl_3$): 6-OCH_3 ↔ ar-H5 and ar-H7, ar-H4 ↔ ar–CH_2–, –CH_2–C*H*$_2$–CH_2– ↔ –CH_2–CO– and ar–CH_2–; ^{13}C NMR (125 MHz, $CDCl_3$, 30°C): $\delta = 22.4$ (–CH_2–*C*H_2–CH_2–), 31.0 (ar–CH_2–), 39.7 (–CH_2–CO–), 56.3 (6-OCH_3), 107.6 (C5), 107.7 (C7), 111.3 (C8a), 117.7 (C9a), 118.5 (C4), 122.9 (C2), 128.9 (C4a), 134.3 (C10a), 153.4 (C3), 164.8 (C1), 165.6 (C8), 166.1 (C6), 182.2 (C10), 187.9 (C9), 202.8 (ar–*C*O–CH_2–) ppm; HMBC ($CDCl_3$): C1 ↔ 1-OH, C2 ↔ 1-OH and ar–CH_2–, C3 ↔ ar-H4, and ar–CH_2–, C4a ↔ ar-H4, C6 ↔ ar-H5, ar-H7, and 6-OCH_3, C8 ↔ ar-H7, C8a ↔ ar-H7 and ar-H5, C9a ↔ ar-H4, C10 ↔ ar-H4 and ar-H5, C10a ↔ ar-H5, ar–CH_2 ↔ –CH_2–C*H*$_2$–CH_2–, –CO– ↔ –CH_2–CO–; HSQC data were according to structure; ESI-MS (CH_3OH + 1 vol-% HCOOH, $\gamma \sim 1$ mg cm^{-3}, positive ion mode): $m/z = 339$ ($[M+H]^+$); IR (KBr): $\bar{\nu} = 2956$, 2925, 2854, 1736, 1713, 1646, 1622, 1592, 1458, 1447, 1387, 1291, 1261, 1228, 1165, 1099, 1034, 999, 961, 803, 546 cm^{-1}; UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 243 (100), 283 (79), 449 (29) nm (%).

10,12-Dihydroxy-8-methoxy-1-oxo-1,2,3,4-tetrahydrobenz(a)anthraquinone (**7**, $C_{19}H_{14}O_6$)

Mp decomp. ≥200°C; TLC: $R_f = 0.51$ ($CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C): $\delta = 2.17$ (m, 2H, –CH_2–C*H*$_2$–CH_2–), 2.84 (m, 4H, –CH_2–CO, ar–CH_2–), 3.93 (s, 6-OCH_3), 6.66 (d, $J = 2.20$ Hz,

ar-H7), 6.99 (s, ar-H2), 7.24 (d, $J = 2.20$ Hz, ar-H5), 11.89 (s, 8-OH), 12.45 (s, 1-OH) ppm; N*O*ESY ($CDCl_3$): 6-$OCH_3 \leftrightarrow$ ar-H5 and ar-H7, 1-OH $\leftrightarrow$ ar-H2, ar-H2 $\leftrightarrow$ ar–CH_2–; ^{13}C NMR (125 MHz, $CDCl_3$, 30°C): $\delta = 22.2$ (–CH_2–*C*H_2–CH_2–), 30.4 (ar–CH_2–), 39.4 (–CH_2–CO–), 56.4 (6-OCH_3), 106.7 (C7), 108.5 (C5), 109.7 (C8a), 117.0 (C9a), 121.2 (C2), 121.6 (C4), 130.5 (C4a), 137.3 (C10a), 153.7 (C3), 163.5 (C1), 165.1 (C8), 167.4 (C6), 183.3 (C10), 191.3 (C9), 198.5 (ar–*C*O–CH_2–) ppm; HMBC ($CDCl_3$): C1 $\leftrightarrow$ 1-OH and ar-H2, C3 $\leftrightarrow$ ar-H2, and ar–CH_2–, C6 $\leftrightarrow$ ar-H5, ar-H7, and 6-OCH_3, C8 $\leftrightarrow$ ar-H7 and 8-OH, C8a $\leftrightarrow$ ar-H7 and ar-H5, C9a $\leftrightarrow$ ar-H2, C10 $\leftrightarrow$ ar-H5, C10a $\leftrightarrow$ ar-H5, ar–$CH_2 \leftrightarrow$ –CH_2–C*H*$_2$–CH_2–, –CO– $\leftrightarrow$ –CH_2–CO–; HSQC data were according to structure; ESI-MS (CH_3OH + 1 vol-% HCOOH, $\gamma \sim 1$ mg cm^{-3}, positive ion mode): $m/z = 339$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 2956, 2924, 2854, 1734, 1702, 1673, 1630, 1606, 1455, 1389, 1302, 1261, 1243, 1211, 1174, 1158, 1102, 1030, 1015, 990, 923, 858, 801, 779, 750, 639, 561$ cm^{-1}. UV-Vis ($CHCl_3$): λ_{max} (rel. int.) = 240 (63), 276 (100), 442 (33) nm (%).

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