Total Synthesis of Premithramycinone H and Related Anthrapyran Antibiotics

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Two approaches are described for the preparation of 2-(1′,3′-dioxoalkyl)-substituted 1-hydroxyanthraquinones **10a–d** and **20a–c**, which were cyclized in a biomimetic-type reaction to the anthra[1,2-*b*]pyran skeletons **11a–d** and **21a–c** of the heydamycin- or pluramycin-type antibiotics. Cleavage of the methyl ethers afforded the natural product premithramycinone H (**2**). The simple derivative **11b** showed inhibition of the A431 cell line in μmolar concentrations.

Introduction

The 4*H*-anthra[1,2-*b*]pyran antibiotics of the heydamycin or pluramycin types (for the basic structure **1** of the pluramycins see Scheme 1) are known for their antibacterial and antitumor activity. Their chemistry, biochemistry and biological activity was extensively reviewed some time ago.[1,2] More recently, the pluramycins have again attracted interest in biology as described in the account of Hansen and Hurley: "Pluramycins. Old Drugs Having Modern Friends in Structural Biology."[3] One reason for this renewed importance was the discovery of the highly specific intercalation into DNA,[4] resulting in a specific alkylation of guanine at N-7,[5] making the pluramycins valuable tools for the detailed investigation of the structure of DNA.

Our interest in the total synthesis was stimulated as a result of a recent report by Rohr and Salás et al., describing the remarkable antitumor activity of premithramycinone H (**2**), a metabolic shunt product discovered in the course of the biosynthetic investigations of the aureolic acid antibiotic mithramycin.[6] Another report described the interesting neuronal cell protecting properties of espicufolin (**3**), an anthrapyran isolated from a *Streptomyces* species.[7] Related naphthopyranones (TMC-256A1 and -C1) were found to be potent inhibitors of IL-4 signal transduction.[8] Interestingly however, only one major synthesis of the kidamycinone methyl ether (**4**) by Hauser and Rhee has been reported in the literature in which the selenium dioxide mediated cyclization of ring A in the hydroquinone methyl ether **5** was a key step (Scheme 1).[9]

Results and Discussion

We now report our work on the synthesis of premithramycinone H (**2**) and related, simpler anthrapyran antibiotics. Our goal was to make this class of compounds readily available and in substantial amounts for biological testing and for the investigation of the structural requirements for antitumor activity. To this end, three approaches were employed. The key steps in the first two approaches included a Marschalk alkylation reaction of hydroxylated anthraquinones[10,11] followed by a Baker−Venkataraman[12,13] or aldol-type chain elongation and then an acid-catalyzed cyclization of ring A as shown by the disconnections **A** in Scheme 2. In the third approach, we used the methodology of Harris[14] and Yamaguchi[15] to construct anthraquinones with ester and acyl side chains such as **19**, followed by a Baker−Venkataraman rearrangement and a cyclization to the 4*H*-anthra[1,2-*b*]pyrans as shown by the disconnections **B** in Scheme 2. The procedure culminated with the total synthesis of premithramycinone H (**2**) (Scheme 5).

In the original version of the Marschalk reaction,[10] phenolic dihydroanthraquinones are alkylated in the position *ortho* to the phenolic hydroxy group by heating to reflux with aldehydes under basic conditions. At low temperatures, however, the originally introduced hydroxyalkyl group may be preserved if the intermediate hydroquinones are rapidly re-oxidized to the quinones using hydrogen peroxide in an alkaline reaction medium.[11] This reaction was used to introduce hydroxyethyl side chains into the three initially selected hydroxyanthraquinones **6a−c** to form the hydroxyethyl compounds **7a−c** (Scheme 3). The reaction temperatures had to be adjusted for the different reactivities of the corresponding hydroquinones of the hydroxyanthraquinones **6a−c** and were varied between 5 and 20 °C. At 20 °C, reduction occurred to some extent to the corresponding ethyl anthraquinones, which were easily removed by chro-

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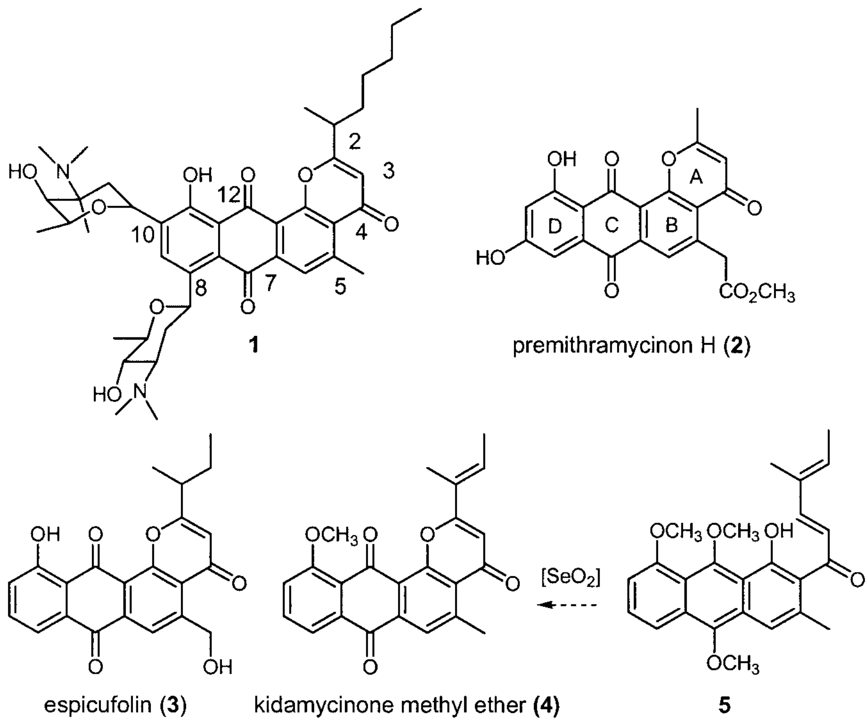
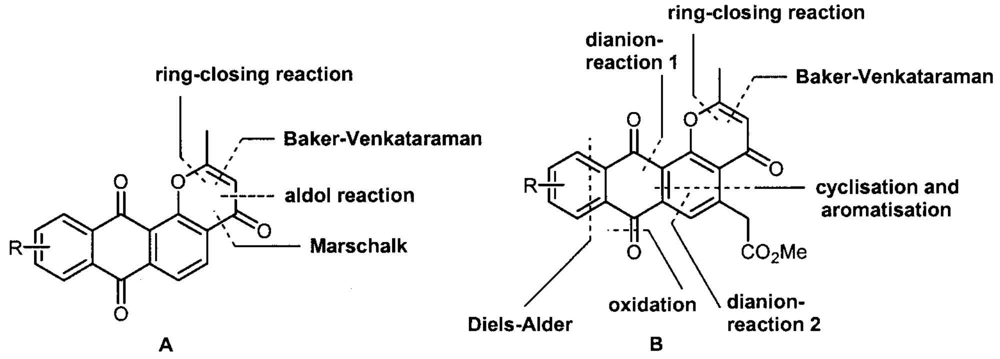


Scheme 1. Structure of some 4*H*-anthra[1,2-*b*]pyran antibiotics and synthesis of the kidamycinone methyl ether (**4**)

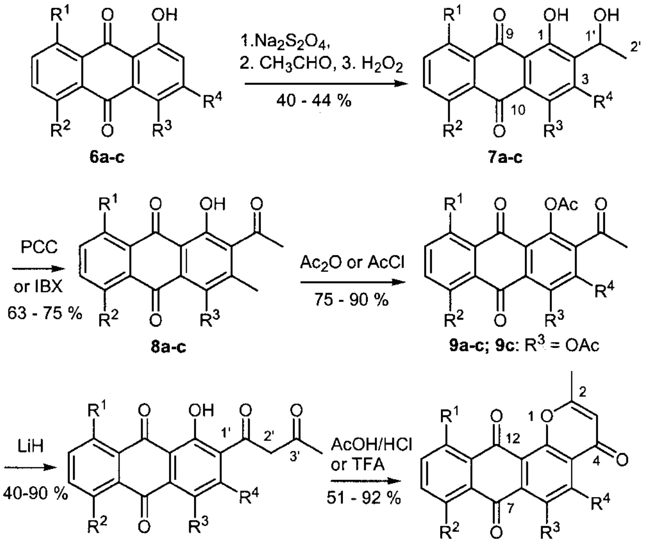


Scheme 2. Disconnections used in the construction of the 4*H*-anthra[1,2-*b*]pyran skeleton

matography or crystallization. The subsequent PCC oxidations[16] to the ketones **8a−c** were uneventful as were the subsequent acetylations to the acetates **9a−c**. Several bases were used to initiate the subsequent intramolecular acylation (Baker−Venkataraman reaction). In our hands, lithium hydride in boiling THF[17] gave the best results and the corresponding β-diketones **10a−c** were isolated in yields of between 40 and 95 %.

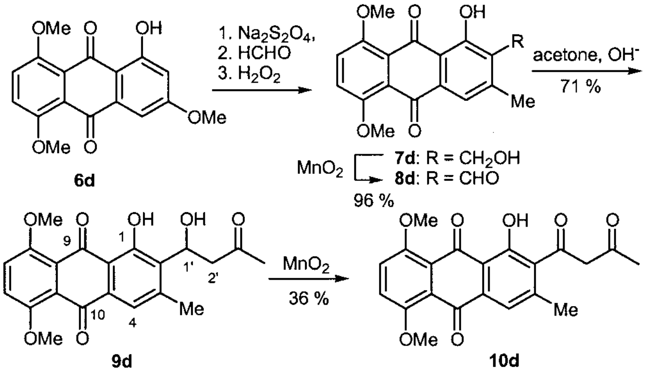
Alternatively, the required side chain could also be introduced with a comparable overall yield by attachment of the C_1 and C_3 units as exemplified by the phenolic anthraquinone **6d**.[18] The anthraquinone **6d** was thus reduced to the dihydro form and hydroxymethylated with formaldehyde to **7d**, after oxidation with H_2O_2. The latter was oxidized with active manganese dioxide to the aldehyde **8d**.[19] The chain was then extended by an aldol reaction with acetone to yield the alcohol **9d** which was oxidized to the diketone **10d** by repetition of the MnO_2 oxidation procedure (Scheme 4).

We experienced no problems with the unsaturated side chains as encountered by Hauser and Rhee in their synthesis of kidamycinone methyl ether (**4**),[9] so that the acid-catalyzed cyclization of the diketones **10a−d** was attempted next. Mechanistically, the reaction can be easily understood as a reversible hemiketal formation involving the phenolic group and the 3′-oxo group, followed by irreversible water elimination to form the pyranone ring. We found that hydrochloric acid in acetic acid[20] gave varying yields and that simply dissolving the phenolic β-diketones in trifluoroacetic acid induced cyclization to the corresponding 4*H*-anthra[1,2-*b*]pyrans **11a−d** in nearly quantitative yields.



	R^1	R^2	R^3	R^4
a:	H	H	H	H
b:	OMe	H	H	H
c:	H	H	OH	H

Scheme 3. Synthesis of anthra[1,2-*b*]pyrans by the Marschalk alkylation followed by a Baker−Venkataraman chain elongation and an acid catalyzed cyclization

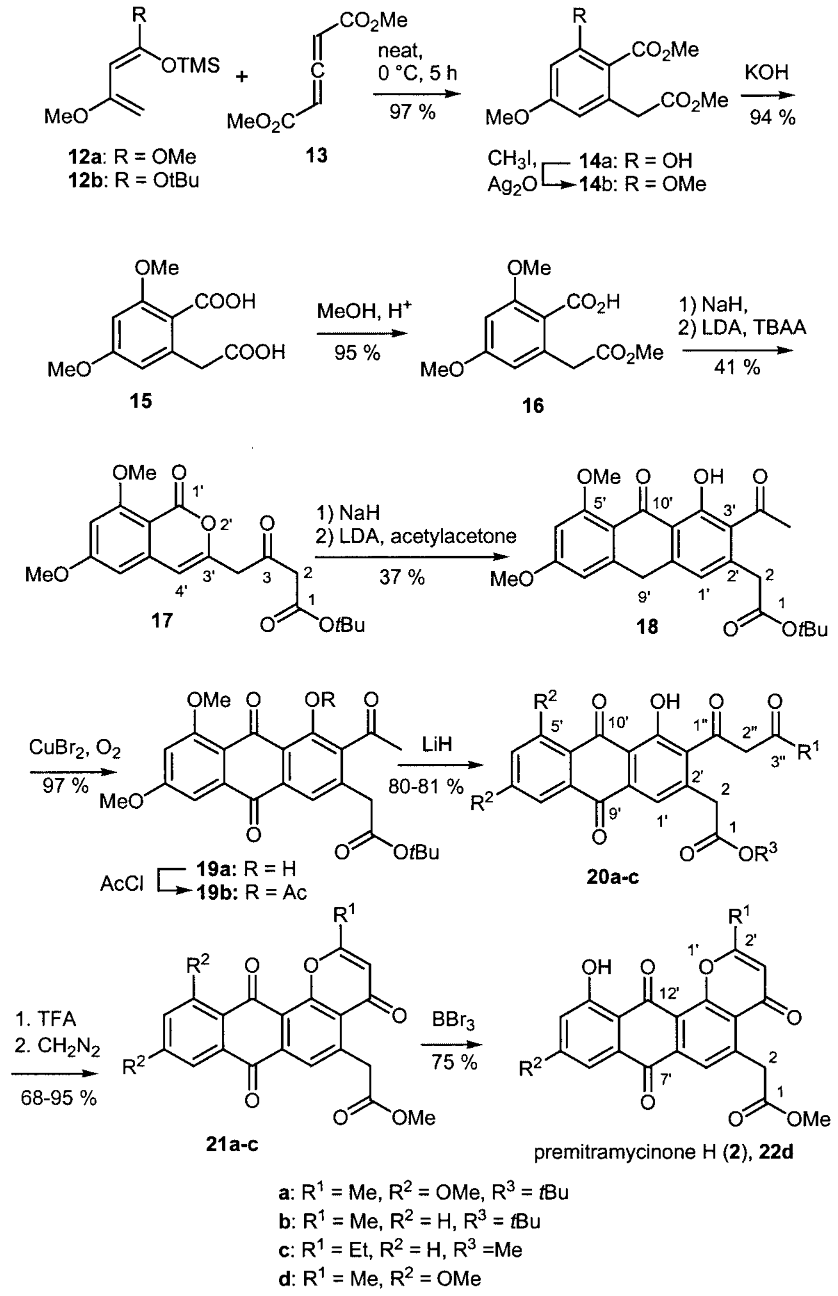


Scheme 4. Synthesis of **10d** by sequential attachment of C_1 and C_3 units

Having achieved the synthesis of the simple 4*H*-anthra[1,2-*b*]pyrans which are interesting models for structure−activity studies of antitumor activity (see below), we turned our attention to the synthesis of premithramycinone H (**2**) and other derivatives with acetic ester side chains on the anthraquinone core (Scheme 5). Fortunately, in this context, we profited from our previous studies on aklanonic acid which is a presumed late intermediate in anthracycline biosynthesis.[17] The synthesis of the oxo ester precursors such as **18** or **19** (Scheme 5) was achieved using successive condensations of the monoester **16** with the dianions of acetoacetate and 2,4-pentanedione by the procedure pioneered by Harris[21] and later by Yamaguchi.[15] The Baker−Venkataraman reaction can again be used successfully for chain elongation. Interestingly, the same or similar intermediate decaketides are biosynthetically used for both groups of natural products: the anthracyclines in constructing the carbocyclic ring in an aldol-type reaction[22] and the 4*H*-anthra[1,2-*b*]pyran antibiotics in the formation of the heterocyclic pyranone ring.[9] The requisite monoacid **16** for premithramycinone H (**2**) was first prepared by Kjaer[23] and Henderson[24] by a different route. A method more appropriate for larger scale preparation, however, was the Diels−Alder reaction of the 3-methoxyketene acetals **12a** or **12b** with the allene diester **13**, a reaction which proceeds with remarkable regioselectivity.[25] In the reaction of diene **12a** with the ketene **13**, however, a mixture of phenol **14a** and the dimethyl ether **14b** was produced. The monophenol can be methylated to the dimethyl ether **14b** using methyl iodide and silver oxide (basic conditions lead to *C*-methylation of the benzylic position). The exclusive formation of the required monomethoxy diester **14a** was achieved when the corresponding mixed *tert*-butoxy-OTMS ketene acetal was used in the Diels−Alder reaction, as previously observed in related reactions.[26] Silylketene acetals are very often used in Diels−Alder reactions.[27] The use of the *tert*-butoxy-OTMS ethers such as **12b** for selective synthesis of phenols (instead of mixtures with methyl ethers) is therefore of general importance for Diels−Alder reactions with ketene acetals.

The best way to produce the desired monoester **16** was by saponification of the diester **14b** to the diacid **15**, followed by efficient monoesterification of the phenylacetic acid moiety. The regioselectivity of the reaction was confirmed by comparison of the spectroscopic data of **16** with those of an authentic sample[23,24] and independently by selective BH_3 reduction of the acid in the presence of the ester.[28]

The subsequent construction of the benzopyranone **17** was achieved by selective deprotonation of the monoacid **16** using sodium hydride and subsequent ester condensation with the dianion of *tert*-butyl acetoacetate (TBAA). The pyranone ring was probably formed by hemiketal formation followed by the β-elimination of water. In the next reaction, the electrophilicity of the β-oxo ester side chain was reduced by deprotonation to form the stabilized enolate, and the dianion of acetylacetone only attacked the pyranone carbonyl group. The intermediate oligoketide then underwent cyclization to the anthrone **18** (for mechanistic considerations and intermediates see ref.[17]) Oxidation to the anthraquinone **19a** was best achieved by copper-catalyzed air oxidation,[29] followed by acetylation to **19b**. A Baker−Venkataraman rearrangement to produce **20a** was then induced by treatment of the acetate **19b** with lithium hydride. At this stage, two more compounds, **20b** (R^1 = Me; R^2 = H) and **20c** (R^1 = Et; R^2 = H), prepared earlier in connection with aklanonic acid synthesis[17] were ready for acid-catalyzed cyclization to 4*H*-anthra[1,2-*b*]pyrans. In fact, treatment with trifluoroacetic acid induced cyclization as well as cleavage of the *tert*-butyl ester. The intermediate anthraquinoneacetic acids were prone to decarboxylation[17] and were therefore immediately esterified by treatment with diazomethane to afford the esters **21a−c**. The structure of the chloroform-soluble dimethyl ether **21a** was elucidated by extensive NMR experiments, including



Scheme 5. Synthesis of premithramycinone (**2**) using the dianion approach followed by chain elongation and TFA-catalyzed cyclization

an assignment of all hydrogen and carbon atoms (see Exp. Sect.) which was supported by 2D spectra. Cleavage to afford the fermentation product premithramycinone H (**2**) was then achieved by treatment of the corresponding dimethyl ether **21a** with boron tribromide, yielding the monophenol **22d** as an isolable intermediate. The published NMR spectroscopic data (DMSO/1 % TFA solution)[6] are in good agreement with those of the synthetic product.

Antitumor Activity

The antitumor activity of premithramycinone H (**2**) against four different cell lines was reported by Rohr et al.[6] The three anthra[1,2-*b*]pyrans **11b**, **11d**, and **21b** were selected for antitumor activity in our tests.[30] The compounds were tested on human A 431 cells/P-glycoprotein (3 d expo-

Table 1. Antitumor activity of compounds **11b**,**d** (Scheme 3) and **21b** (Scheme 5)

Compound	A431 IC_{50}	MaTu/Adr IC_{50}	MTT inhibition
11b	8.8 μM	21 μM	20 %
11d	> 30 μM	–	20 %
21b	> 30 μM	–	–

sure) and with overexpressed MaTu/Adr cells (3 d exposure). In addition, the activity against mitochondria was tested (MTT assay, 4 h exposure). Whereas **11d** and **21d** showed low activity (IC_{50} > 30 µm), the growth of A 431 cells was significantly inhibited by derivative **11b** (IC_{50} = 8.8 µm) (Table 1).

Conclusion

In a biomimetic-type reaction, several 2-(1′,3′-dioxoalkyl)-substituted 1-hydroxyanthraquinones **10a−d** and **20a−c** were cyclized to the anthra[1,2-*b*]pyran skeleton of the heydamycin- or pluramycin-type antibiotics including the naturally occurring premithramycinone H (**2**). Of the compounds tested for antitumor activity, the simple derivative **11b** showed IC_{50} in µmolar concentrations.

Experimental Section

General: For general methods and instrumentation see ref.[31] NMR: "E" indicates "enol" tautomer and "K" the "keto" tautomer.

Hydroxyethylation of Anthraquinone Monophenols 6a−c. General Procedure: Using a modification[11] of the Marschalk[10] reaction, a solution of the hydroxyanthraquinones **6a−c** (6.7 mmol) [**6a** and **6c** are commercially available, for 1-hydroxy-8-methoxyanthraquinone (**6b**) see refs.[32,33]] in methanol (40 mL) was first treated at 0 °C with an aqueous NaOH solution (10 mL, 1 M) and then under nitrogen with a solution of sodium dithionite (20 mL, 0.5 M). The color changed from purple-red to brownish-yellow after the dithionite reduction. Acetaldehyde (35.4 mmol, 2 mL) was then added and stirring at 5 °C (**7a**, **7b** at 20 °C) was continued until the starting material was almost (ca. 90 %) consumed (TLC control, ca. 2 h). The solution was diluted with water and hydrogen peroxide (3 %, ca. 10 mmol) was added for re-oxidation of the hydroanthraquinones to the anthraquinones. The solution was acidified with HCl (10 mL, 1 N), the precipitate collected by filtration and the aqueous phase extracted with dichloromethane (10 mL). The dried precipitate and the residue from the extraction were combined and purified by column chromatography on silica gel (30 g; CH_2Cl_2) or by crystallization to afford the (hydroxyethyl)anthraquinones **7a−c**.

1-Hydroxy-2-(1-hydroxyethyl)anthraquinone (7a): Starting material **6a** (1.0 g, 6.7 mmol), product **7a**, yellow crystals (0.53 g, 44 %, m.p. 293−294 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.61 (d, $J_{1',2'}$ = 6.50 Hz, 3 H, 2′-H), 5.30 (q, $J_{1',2'}$ = 6.50 Hz, 1 H, 1′-H), 7.75−7.96 (m, 4 H), 8.29−8.35 (m, 2 H), 13.07 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 23.65 (q, C-2′), 51.84 (d, C-1′), 116.02 (s, C-9a), 119.06 (d, C-4), 127.01 (d, C-8), 127.25 (d, C-5), 132.46 (s, C-2), 133.55 (s, C-4a), 133.89 (s, C-8a), 134.43 (d, C-6), 134.90 (d, C-7), 135.58 (s, C-10a), 135.99 (d, C-3), 160.48 (s, C-1), 182.85 (s, C-10), 189.00 (s, C-9) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3556, 3417, 3097, 1674, 1633, 1589, 1435, 1362, 1313, 1298, 1201, 1184, 1157, 1030, 1016, 787, 729, 679, 598, 499. UV (CH_3CN): λ_{max} (lg ε) = 271 (4.52), 414 (2.05) nm. MS (EI, 70 eV): *m/z* (%) = 268 (8) [M^+], 250 (15), 237 (15), 222 (10), 207 (10), 192 (26), 163, 18), 149 (30), 109 (32), 83 (52), 57 (50), 43 (40), 28 (100). HRMS (EI, 70 eV, $C_{16}H_{12}O_4$): calcd. 268.07356, found 268.07281.

1-Hydroxy-2-(1-hydroxyethyl)-8-methoxyanthraquinone (7b): Starting material 1-hydroxy-8-methoxyanthraquinone (**6b**) (3.0 g, 11.8 mmol), product **7b**, yellow crystals (1.4 g, 40 %; m.p. 69−71 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.60 (d, $J_{1',2'}$ = 6.50 Hz, 3 H, CH_3, 2′-H), 4.12 (s, 3 H, OCH_3), 5.30 (q, $J_{1',2'}$ = 6.50 Hz, 1 H, 1′-H), 7.40 (d, $J_{6,7}$ = 8.40 Hz, 1 H, 7-H), 7.79 (m, 3 H, 3-H, 4-H, 6-H), 8.00 (d, $J_{5,6}$ = 7.66 Hz, 1 H, 5-H), 13.51 (s, 1 H, OH) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3450 (OH), 2975 (CH), 2929 (CH), 2841 (OCH_3), 1672 (CO), 1631 (CO), 1589 (aryl), 1429, 1274, 1233. MS (EI, 80 eV): *m/z* (%) = 298 (86) [M^+], 283 (100) [$M^+ - CH_3$], 265 (25) [$M^+ - CH_3OH$], 255 (80), 240 (38), 237 (10), 223 (4), 212 (5), 193 (5), 165 (12), 149 (18), 139 (15), 97 (16), 84 (22), 49 (42), 43 (24). $C_{17}H_{14}O_5$ (298.29): calcd. C 68.45, H 4.73; found C 68.15, H 4.43.

1,4-Dihydroxy-2-(1-hydroxyethyl)anthraquinone (7c):[34] Dihydroquinizarin (leucoquinizarin) (10 g, 46 mmol) afforded orange crystals (6.5 g, 54 %, m.p. 133−135 °C, ref.[35] 136−137 °C, ref.[34] 105 °C). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.1 (q, C-2′), 65.8 (d, C-1′), 125.5 (d, C-3), 127.4 (d), 133.7 (s), 133.9 (s), 134.8 (d), 134.9 (d), 147.3 (s), 155.8 (s, C-1), 158.4 (s, C-4), 186.7 (s, C-9), 187.6 (s, C-10) ppm.

Oxidation of (Hydroxyethyl)anthraquinones 7a,b with PCC. General Procedure: Solutions of the (hydroxyethyl)anthraquinones **7a**,**b** (1.53 mmol) in dry dichloromethane (100 mL) were treated with PCC (2.09 mmol) and stirred at room temperature until the starting materials had been converted (ca. 2 h, TLC control). The solids were removed by filtration and the organic phases were concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (6 g, CH_2Cl_2) to afford the 2-acetylanthraquinones **8a**,**b**.

2-Acetyl-1-hydroxyanthraquinone (8a):[36] Starting material **7a** (410 mg, 1.53 mmol), product **8a** (300 mg, 1.13 mmol, 73 %, m.p. 181 °C, ref.[36] 166 °C), yellow solid. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.79 (s, 3 H, 2′-H), 7.81−7.90 (m, 3 H, 4-H, 6-H, 7-H), 8.17 (d, $J_{3,4}$ = 7.99 Hz, 1 H, 3-H), 8.26−8.35 (m, 2 H, 5-H, 8-H), 13.64 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.3 (q, C-2′), 117.5 (s, C-9a), 119.0 (d, C-4), 127.5 (d, C-8), 127.9 (d, C-5), 132.4 (s, C-2), 133.4 (s, C-10a), 133.6 (s, C-8a), 134.9 (d, C-6), 135.5 (d, C-5), 136.4 (s, C-4a), 138.2 (d, C-3), 162.7 (s, C-1), 182.3 (s, C-10), 189.3 (s, C-9), 198.2 (s, C-1′) ppm.

2-Acetyl-1-hydroxy-8-methoxyanthraquinone (8b): Starting material **7b** (80 mg, 0.27 mmol), product **8b** (50 mg, 0.17 mmol, 63 %, m.p. 212−213 °C), yellow solid. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.80 (s, 3 H, CH_3), 4.13 (s, 3 H, OCH_3), 7.43 (d, $J_{6,7}$ = 8.05 Hz, 1 H, 7-H), 7.83−8.15 (m, 4 H, 3-H, 4-H, 5-H, 6-H), 14.00 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.3 (q, C-2′), 57.2 (q, C-1′′), 118.3 (d, C-7), 118.9 (d, C-6), 120.7 (d, C-4), 120.9 (s, C-8a, C-9a), 133.0 (s, C-2), 135.6 (s, C-10a), 135.8 (s, C-4a), 136.7 (d, C-5), 137.2 (d, C-3), 161.5 (s, C-1), 162.8 (s, C-8), 182.8 (s, C-10), 189.6 (s, C-9), 198.8 (s, C-1′) ppm. MS (EI, 70 eV): *m/z* (%) = 296 (199) [M^+], 281 (68) [$M^+ - CH_3$], 250 (18), 238 (10), 210 (5), 152 (7), 126 (20), 115 (5), 77 (4), 63 (12), 43 (29). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3450 (OH), 3100 (CH), 3002 (CH), 2940 (CH), 2842 (OCH_3), 1667 (CO), 1631 (CO), 1600 (aryl), 1584 (aryl), 1486, 1269, 1228, 1191. UV (CH_3CN): λ_{max} (lg ε) = 269 (2.25) nm. $C_{17}H_{12}O_5$ (296.28): calcd. C 68.92, H 4.08; found C 68.74, H 3.80.

2-Acetyl-1,4-dihydroxyanthraquinone (8c):[37] A solution of **7c** (200 mg, 0.70 mmol) in dry THF (20 mL) was treated with IBX {1-hydroxy-1-oxo-1*H*-1λ^5-benzo[*d*][1,2]iodoxol-3-one} in DMSO (0.14 mol/L, 5 mL) and stirred at 50−60 °C (45 min, TLC control). The solution was filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (4 g, CH_2Cl_2) to afford **8c** as an orange solid (148 mg, 0.53 mmol, 75 %, m.p. 199−201 °C, ref.[37] 200−202 °C). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.1 (q, C-2′), 114.5 (s, C-9a), 115.8 (d, C-3), 127.7 (s, C-4a), 127.7 (d, C-8), 130.1 (d, C-5), 133.6 (s, C-2), 133.8 (s, C-10a), 135.3 (d, C-7, C-6), 137.7 (s, C-8a), 156.8 (s, C-4), 157.1 (s, C-1), 187.5 (s, C-9), 187.8 (s, C-10), 197.8 (s, C-1′) ppm.

1-Hydroxy-5,8-dimethoxy-3-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (8d):[19] A solution of **7d** (0.500 g, 1.52 mmol) in CH_2Cl_2 (150 mL) was treated with activated MnO_2 (2.65 g, 30.48 mmol) and stirred at 22 °C (overnight, TLC control). Silica gel (5 g) was added and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (20 g, CH_2Cl_2) to afford **8d** as an orange solid (0.480 g, 1.46 mmol, 96 %, m.p. 210−213 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71 (s, 3 H, CH_3), 4.02 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 7.42 (s, 2 H, 6-H, 7-H), 7.51 (s, 1 H, 4-H), 10.76 (s, 1 H, CHO), 13.58 (s, 1 H, OH) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1695, 1675, 1640, 1605, 1590, 1570, 1495, 1440, 1410, 1350, 1285, 1255, 1235, 1195, 1130, 1095, 1065, 1010, 985, 880, 825. UV (CH_2Cl_2): λ_{max} (lg ε) = 225 (4.57), 251 (4.25), 450 (3.99) nm. MS (EI, 70 eV): *m/z* (%) = 326 (62) [M^+], 298 (100), 268 (9), 255 (17), 237 (9), 223 (4), 209 (6), 181 (6), 165 (5), 152 (6), 127 (7), 97 (7), 83 (7), 71 (9), 57 (13), 43 (11). HRMS (EI, 70 eV, $C_{18}H_{14}O_6$): calcd. 326.0790, found 326.0790. $C_{18}H_{14}O_6$ (326.30): calcd. C 66.25, H 4.32; found C 65.90, H 4.23.

Acetylation of the Phenols 8a−c. General Procedures. Method A: A suspension of the phenol (10 mmol) in acetic anhydride (30 mL) was treated with three drops of pyridine and the solution stirred at 80 °C for 2 h. The mixture was then poured into ice-cold water, stirred for 20 min, and then extracted with dichloromethane (80 mL). The organic phase was washed with water (4 × 10 mL), dried with $MgSO_4$ and the solvent removed under reduced pressure. The crude product was isolated as a red solid, which was purified as detailed below. **Method B:** To a solution of the phenol (10 mmol) in dry dichloromethane (40 mL), pyridine (4.0 mL), acetyl chloride (3.5 mL, 50 mmol) and DMAP (3 mol %) were added successively. The solution was stirred at 20 °C for approximately 2 h (TLC control). The solution was then diluted with dichloromethane (100 mL) and poured into ice-cold HCl (2 mol/L, 100 mL). The phases were separated and the organic phase was first washed with dilute aqueous $NaHCO_3$ solution (2 × 40 mL) and then with brine (50 mL). The organic phase was dried with $MgSO_4$, the solvent removed under reduced pressure and the resultant crude product purified as described below.

2-Acetyl-9,10-dioxo-9,10-dihydroanthracen-1-yl Acetate (9a):[36] Prepared according to method B. Starting material **8a** (365 mg, 1.37 mmol) afforded red crystals of **9a** (372 mg, 1.21 mmol, 88 %, m.p. 165 °C, ref.[36] 167−168 °C) after crystallization from chloroform/petroleum ether. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, 2′′-H), 2.65 (s, 3 H, 2-H), 7.74−7.86 (m, 2 H), 8.10 (d, J = 8.13 Hz, 1 H), 8.17−8.34 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (q, C-2′′), 30.9 (q, C-2), 125.8 (d, C-8′), 127.4 (d, C-5′), 127.8 (d, C-4′), 132.8 (s, C-9a′), 134.6 (d, C-6′), 134.9 (d, C-7′), 135.1 (d, C-3′), 137.4 (s, C-2′, C-10a′), 138.6 (s, C-4a′, C-8a′), 149.0 (s, C-1′), 169.6 (s, C-1), 181.8 (s, C-9′), 182.3 (s, C-10′), 197.7 (s, C-1′′) ppm.

2-Acetyl-8-methoxy-9,10-dioxo-9,10-dihydroanthracen-1-yl Acetate (9b): Prepared according to method A. **8b** (50 mg) afforded orange crystals of **9b** (42 mg, 75 %, m.p. 172−173 °C) after crystallization from dichloromethane/diethyl ether. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, CH_3, 2-H), 2.64 (s, 3 H, CH_3, 2′′-H), 4.04 (s, 3 H, OCH_3), 7.36 (d, $J_{6',7'}$ = 8.29, 1 H, 7′-H), 7.71 (dd, $J_{6',7'}$ = 8.29, $J_{5',6'}$ = 7.55 Hz, 1 H, 6′-H), 7.89 (d, $J_{5',6'}$ = 7.55 Hz, 1 H, 5′-H), 8.03 (d, $J_{3',4'}$ = 8.01 Hz, 1 H, 4′-H), 8.23 (d, $J_{3',4'}$ = 8.01 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.9 (q, C-2), 30.8 (q, C-2′′), 57.2 (q, OCH_3), 119.0 (d, C-7′), 119.8 (d, C-6′), 123.2 (s, C-8a′), 125.2 (d, C-5′), 127.8 (s, C-9a′), 133.8 (d, C-4′), 135.0 (s, C-2′), 135.4 (d, C-3′), 136.5 (s, C-10a′), 138.8 (s, C-4a′), 148.5 (s, C-1′), 160.5 (s, C-8′), 169.8 (s, C-1′), 181.5 (s, C-10′), 182.9 (s, C-9′), 198.0 (s, C-1′′) ppm. MS (EI, 70 eV): *m/z* (%) = 338 (20) [M^+], 296 (100) [$M^+ - C_2H_2O$], 281 (95), 251 (80), 238 (60), 210 (18), 182 (12), 153 (14), 139 (42), 76 (12), 43 (6). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3095 (CH), 2924 (CH), 2857 (OCH_3), 1760 (CO), 1703 (CO), 1678 (CO), 1584 (Aryl.), 1481, 1455, 1378. UV (CH_3CN): λ_{max} (lg ε) = 275 (3.51), 327 (3.22), 384 (3.11) nm. $C_{19}H_{14}O_6$ (338.31): calcd. C 67.45, H 4.17; found C 67.03, H 3.99.

4-Acetoxy-2-acetyl-9,10-dioxo-9,10-dihydroanthracen-1-yl Acetate (9c): Prepared according to method B. Starting material **8c** (288 mg, 1.02 mmol) afforded red crystals of **9c** (338 mg, 0.92 mmol, 90 %, m.p. 161 °C) after crystallization from chloroform/petroleum ether. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 2.63 (s, 3 H, CH_3), 7.74 (s, 1 H, 3′-H), 7.75−7.81 (m, 2 H, 5′-H, 8′-H), 8.13−8.21 (m, 2 H, 6′-H, 7′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (q, CH_3), 21.7 (q, CH_3), 30.8 (q, C-2′′), 127.3 (d, C-3′), 127.5 (d, C-8′), 128.7 (s, C-4a′, C-9a′), 131.0 (d, C-5′), 133.5 (s, C-2′), 133.9 (s, C-10a′), 134.7 (d, C-6′), 134.8 (d, C-7′), 139.4 (s, C-8a′), 146.7 (s, C-1′), 148.2 (s, C-4′), 169.5 (s, C-1), 169.8 (s, C-1′′′), 181.5 (s, C-9′), 181.7 (s, C-10′), 196.3 (s, C-1′′) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3070, 3028, 2927, 2854, 1766, 1709, 1674, 1589, 1431, 1396, 1365, 1319, 1254, 1176, 1157, 1080, 1011. UV (CH_3CN): λ_{max} (lg ε) = 267 (4.91), 383 (4.30) nm. MS (CI, 120 eV): *m/z* (%) = 367 (10) [$M^+ + 1$], 351 (6), 325 (100), 282 (18), 267 (4), 57 (88), 43 (26). $C_{20}H_{14}O_7$ (366.33): calcd. C 65.57, H 3.85; found C 65.73, H 3.69.

1-Hydroxy-2-(1-hydroxy-3-oxobutyl)-5,8-dimethoxy-3-methylanthraquinone (9d):[19] A solution of **8d** (500 mg, 1.53 mmol) in THF (150 mL) was treated with an NaOH solution (1 mol/L, 20 mL) and water (50 mL) and cooled to 0 °C. Acetone (25 mL) was added and the solution was stirred at 0−5 °C under argon (7 h, TLC control). The solution was poured into ice-cold water (100 mL), acidified to pH = 5, extracted with CH_2Cl_2 (3 × 60 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by column chromatography on silica gel (20 g, CH_2Cl_2/MeOH, 98:2) to afford **9d** as an orange solid (418 mg, 1.09 mmol, 71 %, m.p. 184 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, $COCH_3$), 2.54 (s, 3 H, CH_3), 2.92 (dd, J_{gem} = 16.5, J_{vic} = 5 Hz, 1 H, 2′-H), 3.33 (dd, J_{gem} = 16.5, J_{vic} = 8.5 Hz, 1 H, 2′-H), 3.96 (d, J = 10 Hz, 1 H, 1′-OH), 4.00 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 5.51 (ddd, $J_{H,OH}$ = 10, J_{vic} = 8.5, J_{vic} = 5 Hz, 1 H, 1′-H), AB-signal (δ_A = 7.37, δ_B = 7.41, J = 9 Hz, 2 H, 6-H, 7-H), 7.51 (s, 1 H, 4-H), 13.64 (s, 1 H, OH) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3500, 2945, 1720, 1665, 1630, 1565, 1495, 1405, 1275, 1245, 1235, 1195, 1130, 1100, 1055, 1005. UV (CH_2Cl_2): λ_{max} (lg ε) = 231 (4.65), 260 (4.30), 451 (4.06). MS (EI, 70 eV): *m/z* (%) = 384 (10) [M^+], 327 (85), 298 (100), 267 (7), 255 (13), 237 (7), 139 (5), 58 (5), 43 (18). $C_{21}H_{20}O_7$ (384.38): calcd. C 65.62, H 5.24; found C 65.47, H 5.21.

Baker−Venkataraman Rearrangement of 9a−c. General Procedure: LiH (10 mmol) was added at 0 °C to a solution of **9a−c** (3 mmol) in dry THF (300 mL) and the suspension was heated to reflux under argon for ca. 20 h (TLC control). After cooling to 20 °C, the solution was neutralized at 0 °C by addition of HCl (2 N, 6 mL). The solvent was removed under reduced pressure, the residue redissolved in dichloromethane (100 mL), the organic phase washed with HCl (2 N, 2 × 20 mL) and water (2 × 20 mL), dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product was purified as described below.

1-Hydroxy-2-(3-oxobutyryl)anthraquinone (10a): Starting material **9a** (350 mg, 1.14 mmol), product **10a** pale yellow crystals (274 mg, 0.90 mmol, 74 %, m.p. 189−191 °C) after crystallization from dichloromethane/diethyl ether. ^{1}H NMR (200 MHz, $CDCl_3$) (enol): δ = 2.31 (s, 3 H, 4′-H), 6.85 (s, 1 H, 2′-H), 7.86−7.95 (m, 3 H, 4-H, 6-H, 7-H), 8.32−8.42 (m, 3 H, 3-H, 5-H, 8-H), 13.97 (s, 1 H, OH), 16.06 (br. s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) (enol): δ = 27.4 (q, C-4′), 103.2 (d, C-2′), 116.9 (s, C-9a), 119.3 (d, C-4), 127.6 (d, C-8), 127.9 (d, C-5), 129.2 (s, C-2), 133.4 (s, C-10a), 133.8 (s, C-4a, C-8a), 134.9 (d, C-6), 135.5 (d, C-7), 137.7 (d, C-3), 162.3 (s, C-1), 176.4 (s, C-3′), 182.3 (s, C-10), 189.7 (s, C-9), 197.9 (s, C-1′) ppm. IR (KBr, cm^{-1}): ṽ = 3444, 3093, 3062, 2924, 1670, 1635, 1589, 1547, 1477, 1419, 1350, 1331, 1304, 1265, 1107, 1045, 1022. UV (CH_3CN): λ_{max} (lg ε) = 270 (3.80), 406 (3.15) nm. MS (EI, 70 eV): *m/z* (%) = 308 (4) [M$^+$], 266 (40), 251 (100), 223 (5), 197 (2), 181 (2), 167 (20), 139 (30), 111 (12), 97 (18), 71 (24), 57 (36), 43 (28), 28 (50). $C_{18}H_{12}O_5$ (308.28): calcd. C 70.13, H 3.92; found C 69.30, H 3.54.

1-Hydroxy-8-methoxy-2-(3-oxobutyryl)anthraquinone (10b): The starting material **9b** (100 mg, 0.30 mmol) afforded a crude product (50 mg) which was purified by PTLC to yield **10b** as yellow crystals (40 mg, 0.12 mmol, 40 %, m.p. 218.5−219.5 °C). ^{1}H NMR (200 MHz, $CDCl_3$) (enol): δ = 2.30 (s, 3 H, 4′-H), 4.13 (s, 3 H, OCH_3), 6.83 (s, 1 H, 2′-H), 7.43 (d, $J_{6,7}$ = 8.21 Hz, 1 H, 7-H), 7.84 (m, 2 H, 4-H, 6-H), 8.00 (d, $J_{5,6}$ = 7.49 Hz, 1 H, 5-H), 8.33 (d, $J_{3,4}$ = 8.11 Hz, 1 H, 3-H), 14.31 (s, 1 H, OH), 16.09 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) (enol): δ = 27.4 (q, CH_3), 57.2 (q, OCH_3), 103.2 (d, C-2′), 118.4 (d, C-7), 118.9 (d, C-6), 120.7 (d, C-4), 129.5 (s, C-2, C-8a, C-9a), 135.8 (s, C-4a, C-10a), 136.7 (d, C-5), 136.8 (d, C-3), 161.5 (s, C-1), 162.4 (s, C-8), 176.8 (s, C-3′), 182.7 (s, C-10), 189.7 (s, C-9), 197.9 (s, C-1′) ppm. UV (CH_3CN): λ_{max} (lg ε) = 274 (4.52), 422 (4.04) nm. MS (EI, 70 eV): *m/z* (%) = 338 (36) [M$^+$], 295 (100), 281 (70), 252 (12), 238 (20), 210 (10), 182 (8), 154 (8), 139 (22), 76 (5), 63 (5), 43 (38). HRMS (EI, 70 eV, $C_{19}H_{14}O_6$): calcd. 338.0790, found 338.0849. $C_{19}H_{14}O_6$ (338.20): calcd. C 67.45, H 4.17; found C 66.92, H 3.76.

1,4-Dihydroxy-2-(3-oxobutyryl)anthraquinone (10c): The starting material **9c** (338 mg, 0.92 mmol) afforded a crude product (304 mg) which was purified by crystallization from dichloromethane/diethyl ether to yield **10c** as yellow crystals (286 mg, 0.88 mmol, 95 %, m.p. 156−159 °C). ^{1}H NMR (200 MHz, $CDCl_3$) (enol): δ = 2.52 (s, 3 H, CH_3), 6.14 (s, 1 H, 2′-H), 8.08 (s, 1 H, 3-H), 8.24−8.29 (m, 2 H, 5-H, 8-H), 8.34−8.39 (m, 2 H, 6-H, 7-H), 14.10 (s, 1 H, OH), 14.20 (s, 1 H, OH) ppm. IR (KBr, cm^{-1}): ṽ = 3433, 2924, 1770, 1674, 1635, 1589, 1431, 1354, 1277, 1246, 1196, 1161, 1084, 1011, 945, 829, 798, 725, 420. MS (CI, isobutane, 200 eV): *m/z* (%) = 325 (5) [M$^+$ + 1], 225 (3), 113 (8), 57 (100), 39 (6).

1-Hydroxy-5,8-dimethoxy-3-methyl-2-(3-oxobutyryl)anthraquinone (10d): A solution of **9d** (150 mg, 0.39 mmol) in CH_2Cl_2 (40 mL) was treated with activated MnO_2 (1.70 g, 19.50 mmol) and stirred at room temp. (24 h, TLC control). Silica gel (5 g) was added and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (5 g, CH_2Cl_2/diethyl ether, 95:5) to afford **10d** as an orange solid (54 mg, 0.14 mmol, 36 %, m.p. 184 °C). ^{1}H NMR (200 MHz, $CDCl_3$) (enol): δ = 2.23 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 4.05 (s, 3 H, OCH_3), 4.07 (s, 3 H, OCH_3), 5.86 (s, 1 H, 2′-H), 7.43 (br. s, 2 H, 6-H, 7-H), 7.59 (s, 1 H, 4-H), 13.12 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) (enol): δ = 21.1 (q, C-1′′), 25.8 (q, C-4), 57.7 (q, OCH_3), 57.7 (q, OCH_3), 104.2 (d, C-3′), 116.6 (s, C-9a), 116.7 (s, C-8a), 116.9 (s, C-10a), 120.5 (d, C-7), 121.5 (d, C-6), 122.4 (d, C-4), 135.1 (s, C-2, C-4a), 146.1 (s, C-3), 155.3 (s, C-5), 155.9 (s, C-8), 159.9 (s, C-1), 186.2 (s, C-1′), 189.3 (s, C-9, C-10), 193.1 (s, C-3′) ppm. IR (KBr, cm^{-1}): ṽ = 1670, 1630, 1580, 1565, 1490, 1405, 1345, 1275, 1230, 1185, 1135, 1065, 980, 875, 820. UV (CH_2Cl_2): λ_{max} (lg ε) = 228 (4.56), 272 (4.39), 454 (4.07) nm. MS (EI, 70 eV): *m/z* (%) = 382 (52) [M$^+$], 367 (16), 339 (100), 325 (33), 267 (5), 191 (6), 97 (10), 69 (12), 57 (18). $C_{21}H_{18}O_7$ (382.36): calcd. C 65.96, H 4.74; found C 64.75, H 4.74.

Acid-Catalyzed Ring Closure of β-Diketones 10a−d to Anthrapyranones. General Procedure. Method A: Concd. HCl (0.2 mL) was added to a solution of **10a−c** (3 mmol) in acetic acid (15 mL). The solution was stirred at 100−110 °C for ca. 6 h (TLC control). After cooling to 20 °C, ethyl acetate (200 mL) was added and the solution was washed successively with water (3 × 30 mL) and a dilute aqueous $NaHCO_3$ solution (3 × 30 mL). The organic phase was dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified as described below. **Method B:** The β-diketone **10d** (0.2 mmol) was dissolved at 0 °C in trifluoroacetic acid (1.5 mL). After 20 min, the solution was warmed to 20 °C for 10 min. Dichloromethane (10 mL) was then added and the solvent removed under reduced pressure. The procedure was repeated twice to remove traces of trifluoroacetic acid. The crude product was purified as described below.

2-Methyl-1-oxabenzo[*a*]anthracene-4,7,12-trione (11a):[36] Preparation according to method A. **10a** (252 mg, 0.82 mmol) afforded pale yellow crystals of **11a** after crystallization from dichloromethane/diethyl ether (120 mg, 0.42 mmol, 51 %, m.p. 288−290 °C, ref.[36] 293 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.57 (s, 3 H, 1′-H), 6.34 (s, 1 H, 3-H), 7.81−7.85 (m, 2 H, 9-H, 10-H), 8.26−8.35 (m, 3 H, 6-H, 8-H, 11-H), 8.57 (d, $J_{5,6}$ = 8.24 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2 (q, CH_3), 111.6 (d, C-3), 122.8 (s, C-12a), 123.5 (d, C-6), 127.5 (d, C-11), 127.7 (d, C-8), 128.1 (s, C-4a), 132.2 (d, C-5), 132.5 (s, C-7a), 134.6 (d, C-9), 134.7 (s, C-11a), 135.3 (d, C-10), 138.1 (s, C-6a), 155.2 (s, C-12b), 169.2 (s, C-2), 177.5 (s, C-4), 181.85 (s, C-7), 182.8 (s, C-12) ppm.

11-Methoxy-2-methyl-1-oxabenzo[*a*]anthracene-4,7,12-trione (11b): Preparation according to method A. Starting material **10b** (40 mg, 0.12 mmol) afforded a crude product which was purified by PTLC (silica gel, CH_2Cl_2/MeOH, 98:2) to yield **11b** as yellow crystals (35 mg, 0.11 mmol, 92 %, m.p. 263−264 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 4.09 (s, 3 H, OCH_3), 6.32 (s, 1 H, 3-H), 7.40 (d, $J_{9,10}$ = 8.31 Hz, 1 H, 10-H), 7.74 (dd, $J_{8,9}$ = 7.74, $J_{9,10}$ = 8.31, 1 H, 9-H), 7.91 (dd, $J_{8,9}$ = 7.74, $J_{8,10}$ = 1.05 Hz, 1 H, 8-H), 8.22 (d, $J_{5,6}$ = 8.24 Hz, 1 H, 6-H), 8.53 (d, $J_{5,6}$ = 8.24 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4 (q, CH_3), 57.1 (q, OCH_3), 111.7 (d, C-3), 118.9 (d, C-10), 119.8 (d, C-9), 122.7 (d, C-8), 123.3 (s, C-11a), 124.8 (s, C-12a), 128.4 (s, C-2′), 131.2 (d, C-6), 134.8 (s, C-7a), 135.2 (d, C-5), 137.0 (s, C-6a), 154.7 (s, C-1′), 160.2 (s, C-11), 168.7 (s, C-2), 177.2 (s, C-4), 181.3 (s, C-7), 183.3 (s, C-12) ppm. IR (KBr, cm^{-1}): ṽ = 3089 (CH), 2929 (CH), 2841 (CH), 1693 (CO), 1651, 1585, 1470, 1388, 1320, 1295, 1222. UV (CH_2Cl_2): λ_{max} (lg ε) = 278 (4.5), 375 (2.5) nm. MS (EI, 80 eV): *m/z* (%) = 320 (100) [M$^+$], 291 (16), 274 (22), 251 (22), 234 (8), 206 (8), 163 (6), 138 (26), 125 (8), 63 (12), 39 (38). $C_{19}H_{12}O_5$ (320.07): calcd. C 71.25, H 3.78; found C 69.65, H 3.45.

6-Hydroxy-2-methyl-1-oxabenzo[*a*]anthracene-4,7,12-trione (11c): Preparation according to method A. Starting material **10c** (192 mg, 0.59 mmol) afforded pale yellow crystals of **11c** after crystallization from CH_2Cl_2/diethyl ether (144 mg, 0.47 mmol, 79 %, m.p. 237−240 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 6.28 (s, 1 H, 3-H), 7.85−7.98 (m, 2 H, 9-H, 10-H), 8.05 (s, 1 H, 5-H), 8.27−8.37 (m, 2 H, 8-H, 11-H), 12.68 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0 (q, CH_3), 110.1 (d, C-3), 120.0 (s, C-12a), 120.74 (d, C-5), 122.1 (s, C-4a), 127.2 (d, C-8/C-11), 127.6 (d, C-8/C-11), 130.9 (s, C-6a), 132.3 (s, C-7a/C-11a), 134.6 (s, C-7a/C-11a), 134.7 (d, C-9/C-10), 136.0 (d, C-9/C-10), 148.6 (s, C-12b), 158.2 (s, C-6), 169.9 (s, C-2), 176.9 (s, C-7/C-12), 181.2 (s, C-7/C-12), 189.5 (s, C-4) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1763, 1670, 1647, 1589, 1562, 1431, 1392, 1350, 1292, 1246, 1223, 1200, 1173, 1149, 1022. UV (CH_3CN): λ_{max} (lg ε) = 270 (2.75) nm. MS (EI, 70 eV): *m*/*z* (%) = 306 (80) [M^+], 282 (82), 267 (80), 239 (20), 211 (10), 182 (12), 167 (14), 149 (20), 111 (18), 84 (34), 57 (70), 43 (100). HRMS (EI, 70 eV, $C_{18}H_{10}O_5$): calcd. 306.0528, found 306.0525. $C_{18}H_{10}O_5$ (306.27): calcd. C 70.59, H 3.29; found C 69.84, H 2.82.

8,11-Dimethoxy-2,5-dimethyl-1-oxabenzo[*a*]anthracene-4,7,12-trione (11d): Preparation according to method B. Starting material **10d** (17 mg, 0.044 mmol) afforded a crude product which was purified by flash chromatography (silica gel; CH_2Cl_2/MeOH, 98:2) to afford **11d** as yellow crystals (14 mg, 0.038 mg, 85 %, m.p. 300−302 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 2.94 (s, 2 H, CH_3), 4.03 (s, 6 H, 2 × OCH_3), 6.23 (s, 1 H, 3-H), 7.32 (d, $J_{9,10}$ = 9.34 Hz, 1 H), 7.39 (d, $J_{9,10}$ = 9.34 Hz, 1 H), 7.87 (s, 1 H, 6-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8 (q, C-1′), 24.4 (q, C-1′′), 57.3 (q, OCH_3), 57.5 (q, OCH_3), 113.1 (d, C-3), 119.2 (d, C-10), 121.0 (d, C-9), 122.4 (s, C-12a), 124.9 (d, C-6), 125.5 (s, C-7a, C-11a), 125.9 (s, C-4a), 137.4 (s, C-6a), 147.6 (s, C-5), 153.3 (s, C-8), 153.9 (s, C-12b), 155.6 (s, C-11), 166.3 (s, C-2), 179.8 (s, C-12), 181.8 (s, C-7), 183.1 (s, C-4) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2924, 2846, 1678, 1651, 1631, 1585, 1566, 1466, 1385, 1335, 1265, 1227, 1188, 1111, 1061, 980, 841, 825. UV (CH_3CN): λ_{max} (lg ε) = 273 (4.23), 366 (1.15), 428 (1.43) nm. MS (EI, 70 eV): *m*/*z* (%) = 364 (85) [M^+], 335 (35), 307 (28), 278 (24), 265 (26), 240 (62), 199 (12), 183 (100), 155 (26), 139 (12), 105 (12), 76 (35), 57 (50), 43 (96). HRMS (EI, 70 eV, $C_{21}H_{16}O_6$): calcd. 364.0947, found 364.0920.

Preparation of the Ketene Acetals 12a,b. General Procedure:[38] A solution of the unsaturated ester (100 mmol) in dry THF (30 mL) was added at −80 °C over a period of 30 min to a solution of LDA (105 mmol) in dry THF (100 mL). After 30 min, chlorotrimethylsilane (120 mmol) in THF (15 mL) was added and the temperature was raised to 20 °C over 90 min. The solution was then concentrated under reduced pressure and cold hexane was added to form a white precipitate. The suspension was filtered through a fritted glass funnel and the solvent was removed under reduced pressure to give the ketene acetal which was used without further purification.

(1,3-Dimethoxybuta-1,3-dienyloxy)trimethylsilane [1,3-Dimethoxy-1-(trimethylsilyloxy)buta-1,3-diene] (12a):[39] Starting material methyl 3-methoxybut-2-enoate (10.0 g, 77 mmol) afforded **12a** (12.9 g, 65 mmol, 85 %, b.p. 54 °C/0.7 mbar, ref.[39] 57−62 °C/1.0 mbar) as a colorless oil. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.7 (q, 3 × CH_3), 54.5 (q, OCH_3), 55.4 (q, OCH_3), 76.0 (d, C-2), 79.0 (t, C-4), 159.1 (s, C-1, C-3) ppm.

1-*tert*-Butoxy-3-methoxy-1-(trimethylsilyloxy)buta-1,3-diene (12b):[40] Starting material *tert*-butyl 3-methoxybut-2-enoate (13.0 g, 75.6 mmol) afforded **12b** (17.9 g, 73.3 mmol, 97 %) as a colorless oil. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 0.9 (q, 3 × CH_3), 28.8 (q, 3 × CH_3), 54.5 (q, OCH_3), 80.1 (s, C-1′), 80.2 (t, C-4), 87.7 (d, C-2), 154.0 (s, C-3), 159.2 (s, C-1) ppm.

Dimethyl Penta-2,3-dienedioate (13):[41] Triethylamine (22 mL, 0.16 mol) was added slowly (over 10 min) to a solution of dimethyl 3-chloropent-2-enedioate[42] (28.34 g, 0.15 mol) in dry THF (100 mL). The solution was stirred at 0−5 °C for 18 h and the precipitate which formed was filtered and washed with diethyl ether (3 × 75 mL). The ethereal phases were combined and extracted successively with HCl (1 N, 3 × 75 mL) and brine (3 × 75 mL). The organic phase was dried with $MgSO_4$ and the solvent was removed under reduced pressure to give **13** as a colorless viscous oil (22.69 g, 0.14 mol, 97 %, b.p. 65 °C/0.10 mbar, ref.[41] 58 °C/0.03 mbar). ^1H NMR (200 MHz, $CDCl_3$): δ = 3.76 (s, 6 H, 2 × CH_3), 6.04 (s, 2 H, 2-H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 53.0 (q, 2 × CH_3), 92.5 (d, C-2, C-4), 164.1 (s, C-1, C-5), 220.1 (s, C-3) ppm.

Diels−Alder Reaction between the Allene 13 and the Ketene Acetals 12a,b. General Procedure:[25] The ketene acetals **12a**,**b** (120 mmol) were added at 0 °C to the allene **13** (100 mmol) and the mixtures were stirred at this temperature for 5 h. For aromatisation of the intermediate adducts, methanolic HCl (1.54 mmol/mL) was added slowly and addition was stopped when the color changed to light yellow. The solvents were then removed under reduced pressure and the crude products were purified by column chromatography on silica gel (CH_2Cl_2). **Method A:** The allene **13** (8.0 g, 51.3 mmol) and the ketene acetal **12a** (14.0 g, 69 mmol) afforded **14a** and **14b** as a mixture which was separated by chromatography (**14a**: 5.2 g, 20.5 mmol, m.p. 77−80 °C, ref.[43] 75−77 °C; **14b**: 4.6 g, 17.2 mmol, colorless oil; overall yield: 74 %). **Method B:** The allene **13** (8.0 g, 51.3 mmol) and the ketene acetal **12b** (17.9 g, 69 mmol) afforded **14a** (10.5 g, 41.3 mmol, 80 %, m.p. 77−80 °C, ref.[43] 75−77 °C) as colorless crystals.

Methylation of 14a:[43] MeI (2 mL) and Ag_2O (0.54 g, 2.33 mmol) were added to a solution of **14a** (1.69 g, 6.65 mmol) in dry acetone (20 mL) and the reaction was monitored by TLC. The solution was filtered and the solvent evaporated under reduced pressure. Flash chromatography on silica gel (20 g, CH_2Cl_2) afforded **14b** (1.73 g, 6.46 mmol, 97 %) as a colorless oil.

Methyl 2-Hydroxy-4-methoxy-6-(methoxycarbonylmethyl)benzoate (14a):[43] ^1H NMR (200 MHz, $CDCl_3$): δ = 3.70 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.84 (s, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 6.31 (d, $J_{3,5}$ = 2.55 Hz, 1 H, 3-H), 6.44 (d, $J_{3,5}$ = 2.55 Hz, 1 H, 5-H), 11.67 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.2 (t, C-1′′), 52.2 (q, OCH_3), 52.4 (q, OCH_3), 55.8 (q, OCH_3), 100.5 (d, C-3), 105.3 (d, C-5), 113.3 (s, C-1), 138.4 (s, C-6), 164.5 (s, C-2), 166.5 (s, C-4), 171.4 (s, C-1′), 172.3 (s, C-2′′) ppm.

Methyl 2,4-Dimethoxy-6-(methoxycarbonylmethyl)benzoate (14b):[44] ^1H NMR (200 MHz, $CDCl_3$): δ = 3.68 (s, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.41 (d, $J_{3,5}$ = 2.23 Hz, 1 H, 3-H), 6.44 (d, $J_{3,5}$ = 2.23 Hz, 1 H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.1 (t, C-1′′), 52.5 (q, OCH_3), 52.5 (q, OCH_3), 55.9 (q, OCH_3), 56.4 (q, OCH_3), 98.2 (d, C-3), 108.0 (d, C-5), 116.2 (s, C-1), 135.6 (s, C-6), 159.5 (s, C-2), 162.2 (s, C-4), 168.2 (s, C-1′), 171.7 (s, C-2′′) ppm.

2-(Carboxymethyl)-4,6-dimethoxybenzoic Acid (15):[44] KOH (2 g) was added to a solution of **14b** (1.64 g, 4.7 mmol) in ethanol (20 mL) and water (20 mL). The solution was heated to reflux for 8 h. After cooling, the solution was neutralized with dilute HCl (1 N) and the ethanol was removed under reduced pressure. The precipitate was purified by recrystallization from ethanol to give **15** as colorless crystals (1.06 g, 4.4 mmol, 94 %, m.p. 172−173 °C, ref.[45] 172−173 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.47 (br. s, 2

H, 3-H, 5-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 40.7$ (t, CH_2), 55.6 (q, OCH_3), 56.3 (s, OCH_3), 98.0 (d, C-5), 108.9 (d, C-3), 114.6 (s, C-1), 137.5 (s, C-2), 159.6 (s, C-6), 162.4 (s, C-4), 169.4 (s, C-1′), 173.7 (s, C-2′′) ppm.

2,4-Dimethoxy-6-(methoxycarbonylmethyl)benzoic Acid (16):[23] *p*-Toluenesulfonic acid (10 mg) was added to a solution of **15** (1.06 g, 4.4 mmol) in dichloromethane (30 mL) and methanol (5 mL) and the solution was stirred at reflux for 2 h. The dichloromethane was removed under reduced pressure and methanol (8 mL) was added. The solution was heated for 0.5 h to complete the esterification. The solvents were removed under reduced pressure and the crude product was crystallized from dichloromethane/petroleum ether (2 mL/5 mL) to afford **16** as white crystals (1.08 g, 4.2 mmol, 95 %, m.p. 122 °C, ref.[23] 128−129 °C). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 42.2$ (t, CH_2), 52.4 (q, OCH_3), 56.0 (q, OCH_3), 57.3 (q, OCH_3), 98.6 (d, C-3), 111.3 (s, C-1), 111.6 (d, C-5), 141.8 (s, C-6), 160.6 (s, C-2), 163.4 (s, C-4), 166.3 (s, C-1′), 172.2 (s, C-2′′) ppm.

***tert*-Butyl 4-(6,8-Dimethoxy-1-oxo-1*H*-isochromen-3-yl)-3-oxobutanoate (17):** A suspension of the sodium salt prepared from the monoester **16** (720 mg, 2.82 mmol) in dry THF (40 mL) was added slowly at −80 °C under argon to a solution of the *tert*-butyl acetoacetate dianion prepared from *tert*-butyl acetoacetate (1.10 mL, 6.63 mmol) and LDA (14 mmol) in dry THF (60 mL). The mixture was warmed to 20 °C over 1.5 h, acetic acid (1.5 mL) was then added dropwise at −10 °C and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (60 mL) and extracted with HCl (1 N, 2 × 40 mL). The organic phase was dried with $MgSO_4$, concentrated under reduced pressure and the residue treated with acetic anhydride (10 mL) at 0 °C for 16 h. The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol at −20 °C to afford **17** as pale yellow crystals (420 mg, 1.16 mmol, 41 %, m.p. 117−118 °C). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.50$ (s, 9 H, 3 × CH_3), 3.53 (s, 2 H, 4-H), 3.72 (s, 2 H, 2-H), 3.92 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 6.30 (s, 1 H, 4′-H), 6.38 (d, $J_{5',7'} = 2.09$ Hz, 1 H, 7′-H), 6.50 (d, $J_{5',7'} = 2.09$ Hz, 1 H, 5′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.4$ (q, 3 × CH_3), 47.3 (t, C-2), 50.6 (t, C-4), 56.1 (q, OCH_3), 56.7 (q, OCH_3), 82.9 [s, $C(CH_3)_3$], 99.3 (d, C-7′), 100.6 (d, C-4′), 103.5 (s, C-8a′), 107.2 (d, C-5′), 141.9 (s, C-4a′), 151.1 (s, C-3′), 159.3 (s, C-1′), 163.7 (s, C-8′), 166.0 (s, C-6′), 166.4 (s, C-1), 197.9 (s, C-3) ppm. MS (CI, isobutane, 120 eV): *m/z* (%) = 363 (66) [M$^+$], 307 (34), 263 (28), 113 (4), 57 (100), 43 (18). IR (KBr, cm^{-1}): $\tilde{\nu} = 3421$, 2976, 2940, 2910, 2848, 1749, 1735, 1712, 1670, 1599, 1569, 1458, 1429, 1375, 1352, 1271, 1213, 1167, 1115, 1066. UV (CH_3CN): λ_{max} (lg ε) = 270 (2.60), 322 (1.96) nm. $C_{19}H_{22}O_7$ (362.37): calcd. C 62.97, H 6.12; found C 62.87, H 5.67.

***tert*-Butyl (3-Acetyl-4-hydroxy-5,7-dimethoxy-10-oxo-9,10-dihydroanthracen-2-yl)acetate (18):** A suspension of the sodium salt of oxo ester **17** (2.2 mmol, 800 mg), and NaH (60 %, 4.6 mmol, 184 mg) in dry THF (50 mL) was added slowly at −80 °C under argon by means of a syringe pump to a solution of the acetylacetonate dianion, prepared from acetylacetone (12 mmol, 1.25 mL) and LDA (30 mmol) in THF (60 mL). The mixture was warmed to 20 °C and was stirred at this temperature for 1 h. The mixture was acidified with HCl (2 N, 60 mL) at −10 °C and extracted with ethyl acetate (2 × 60 mL). The organic phase was washed with brine (50 mL) and the solvent was removed under reduced pressure. The residue was redissolved in methanol (40 mL) and calcium acetate (12 g) was added. This suspension was heated at 45 °C under argon for 10 min. After cooling, HCl (2 N) was added to neutralize the mixture. The mixture was extracted with ethyl acetate (2 × 40 mL) and dichloromethane (40 mL). The combined organic phases were dried with $MgSO_4$ and the solvents were removed under reduced pressure. Crystallization from ethanol afforded **18** (351 mg, 0.8 mmol, 37 %, m.p. 177 °C) as pale yellow crystals. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.49$ (s, 9 H, 3 × CH_3), 2.64 (s, 3 H, CH_3), 3.68 (s, 2 H, 2-H), 3.95 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.33 (s, 2 H, 9′-H), 6.52 (d, $J_{6',8'} = 2.22$ Hz, 1 H, 8′-H), 6.56 (d, $J_{6',8'} = 2.22$ Hz, 1 H, 6′-H), 6.75 (s, 1 H, 1′-H), 14.20 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.2$ (q, 3 × CH_3), 32.2 (q, CH_3), 34.1 (t, C-9′), 40.7 (t, C-2), 56.1 (q, OCH_3), 56.4 (q, OCH_3), 81.4 [s, $C(CH_3)_3$], 98.1 (d, C-8′), 104.8 (d, C-6′), 114.5 (s, C-10a′), 116.9 (s, C-4a′), 120.7 (d, C-1′), 128.2 (s, C-3′), 139.7 (s,C-2′), 142.3 (s, C-8a′), 146.2 (s, C-9a′), 161.6 (s, C-4′), 163.9 (s, C-5′), 165.2 (s, C-7′), 170.3 (s, C-1), 188.9 (s, C-10′), 203.9 (s, C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 426 (60) [M$^+$], 370 (90), 353 (58), 311 (85), 281 (20), 267 (15), 239 (10), 211 (8), 181 (8), 163 (14), 139 (10), 85 (4), 57 (88), 43 (100), 28 (16). IR (KBr, cm^{-1}): $\tilde{\nu} = 3442$, 2978, 2933, 2850, 1734, 1684, 1610, 1569, 1500, 1458, 1419, 1412, 1400, 1367, 1354, 1331, 1254, 1221, 1157, 1092, 964, 837, 602. UV (CH_3CN): λ_{max} (lg ε) = 269 (2.11), 343 (1.89) nm. $C_{24}H_{26}O_7$ (426.46): calcd. C 67.59, H 6.15; found C 66.87, H 5.76.

***tert*-Butyl (3-Acetyl-4-hydroxy-5,7-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)acetate (19a):** A solution of the anthrone **18** (286 mg, 0.68 mmol) in THF (50 mL) was treated with $CuBr_2$ (80 mg), and then water (5 mL) was added. The resultant suspension was stirred at 20 °C under oxygen for 3 h. The solvent was removed under reduced pressure and the residue dissolved in a mixture of dichloromethane (20 mL) and H_2O (10 mL). The organic phase was washed with H_2O (3 × 10 mL) to remove the copper salts. The organic phase was dried with $MgSO_4$, filtered, concentrated under reduced pressure and the residue was crystallized from ethanol to afford **19a** (288 mg, 0.67 mmol, 97 %, m.p. 189 °C) as orange crystals. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.49$ (s, 9 H, 3 × CH_3), 2.69 (s, 3 H, CH_3), 3.78 (s, 2 H, CH_2), 4.03 (s, 3 H, OCH_3), 4.07 (s, 3 H, OCH_3), 6.83 (d, $J_{6',8'} = 2.47$ Hz, 1 H, 6′-H), 7.49 (d, $J_{6',8'} = 2.47$ Hz, 1 H, 8′-H), 7.63 (s, 1 H, 1′-H), 13.64 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.4$ (q, 3 × CH_3), 32.2 (q, CH_3), 40.5 (t, CH_2), 56.6 (q, OCH_3), 57.1 (q, OCH_3), 82.3 [s, $C(CH_3)_3$], 104.7 (d, C-8′), 105.3 (d, C-6′), 116.5 (s, C-10a′), 121.5 (d, C-1′), 132.9 (s, C-4a′), 136.8 (s, C-3′), 137.8 (s, C-2′), 140.6 (s, C-8a′, C-9a′), 160.7 (s, C-4′), 163.6 (s, C-5′), 166.1 (s, C-7′), 169.9 (s, C-1), 182.6 (s, C-9′), 187.9 (s, C-10′), 204.1 (s, C=O) ppm. IR (KBr, cm^{-1}): $\tilde{\nu} = 3435$, 2976, 2846, 1728, 1720, 1697, 1674, 1633, 1595, 1556, 1489, 1458, 1431, 1367, 1354, 1335, 1321, 1277, 1248, 1213, 1151, 1130, 1113, 1065. UV (CH_3CN): λ_{max} (lg ε) = 270 (2.89), 425 (1.47) nm. HRMS (EI, 70 eV, $C_{24}H_{24}O_8$): calcd. 440.1471, found 440.1474. $C_{24}H_{24}O_8$ (440.44): calcd. C 65.45, H 5.49; found C 65.39, H 5.25.

***tert*-Butyl (4-Acetoxy-3-acetyl-5,7-dimethoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)acetate (19b):** A solution of **19a** (0.45 mmol, 200 mg) in dry dichloromethane (15 mL) was treated at 0 °C successively with pyridine (7 mmol, 0.5 mL), acetyl chloride (7 mmol, 0.5 mL) and DMAP (5 mol %). The mixture was stirred at 20 °C for 3 h (TLC control). HCl (2 N, 20 mL) was then added and the aqueous phase was extracted with dichloromethane (2 × 40 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2) to give **19b** as orange crystals (0.44 mmol, 210 mg, 96 %, m.p. 121−123 °C). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.48$ (s, 9 H, 3 × CH_3), 2.52 (s, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 3.78 (s, 2 H, 2-H), 4.00 (s, 6 H, 2 × OCH_3), 6.82 (d, $J_{6',8'} = 2.44$ Hz, 1 H, 6′-H), 7.41 (d, $J_{6',8'} = 2.44$ Hz, 1 H, 8′-H), 8.07 (s, 1 H, 1′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (q, CH_3), 28.4 (q, 3 × CH_3), 32.0 (q, CH_3), 40.0 (t, C-2), 56.4 (q, OCH_3), 57.2 (q, OCH_3), 82.5 [s, $C(CH_3)_3$], 103.3 (d, C-8′), 105.8 (d, C-6′), 117.4 (s, C-10a′), 125.6 (s, C-4a′), 127.7 (d, C-1′), 134.3 (s, C-3′), 136.8 (s, C-2′), 138.2 (s, C-8a′), 142.6 (s, C-9a′), 147.2 (s, C-4′), 162.9 (s, C-5′), 165.0 (s, C-7′), 169.4 (s, C=O), 169.6 (s, C=O), 182.9 (s, C-9′, C-10′), 202.7 (s, C=O) ppm. UV (CH_3CN): λ_{max} (lg ε) = 269 (3.25) nm. MS (EI, 70 eV): *m*/*z* (%) = 482 (4) [M^+], 440 (14) [$M^+ - C_2H_2O$], 409 (2) [$C_{24}H_{24}O_8{}^+ - CH_3O$], 384 (18), 367 (6), 338 (15), 300 (4), 285 (5), 252 (4), 239 (7), 210 (5), 178 (30), 150 (18), 123 (10) [$C_7H_7O_2{}^+$]. HRMS (EI, 70 eV, $C_{26}H_{26}O_9$): calcd. 482.1577, found 482.1578.

***tert*-Butyl [4-Hydroxy-5,7-dimethoxy-9,10-dioxo-3-(3-oxobutyryl)-9,10-dihydroanthracen-2-yl]acetate (20a):** A solution of the phenol ether **19b** (0.41 mmol, 200 mg) in THF (30 mL) was treated at 0 °C with LiH (4 mmol, 32 mg) and the suspension was heated to reflux for 20 h (TLC control). The mixture was carefully neutralized at 0 °C by addition of HCl (2 N, 1 mL), reduced to one fifth of its volume under reduced pressure and diluted with dichloromethane (40 mL). The organic phase was washed successively with HCl (2 N, 2 × 10 mL) and water (10 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure to afford **20a** (0.33 mmol, 158 mg, 81 %, m.p. 167 °C) as orange crystals after crystallization from dichloromethane/ethanol (1:1). ^{1}H NMR (200 MHz, $CDCl_3$) (enol): δ = 1.48 (s, 9 H, 3 × CH_3), 2.21 (s, 3 H, 4′′-H), 3.78 (s, 2 H, 2-H), 4.03 (s, 3 H, OCH_3), 4.07 (s, 3 H, OCH_3), 5.98 (s, 1 H, 2′′-H), 6.83 (d, $J_{6',8'}$ = 2.34 Hz, 1 H, 6′-H), 7.48 (d, $J_{6',8'}$ = 2.34 Hz, 1 H, 8′-H), 7.69 (s, 1 H, 1′-H), 13.71 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) (enol): δ = 25.5 (q, C-4′′), 28.4 (q, 3 × CH_3), 41.1 (t, C-2), 56.6 (q, OCH_3), 57.1 (q, OCH_3), 82.1 [s, $C(CH_3)_3$], 104.4 (d, C-2′′), 104.6 (d, C-8′), 105.3 (d, C-6′), 115.4 (s, C-10a′), 116.4 (s, C-4a′), 121.4 (d, C-1′), 132.7 (s, C-3′), 133.0 (s, C-2′), 137.8 (s, C-8a′), 141.6 (s, C-9a′), 160.7 (s, C-4′), 163.6 (s, C-5′), 166.1 (s, C-7′), 169.8 (s, C-3′′), 182.6 (s, C-1), 185.5 (s, C-1′′), 187.7 (s, C-9′), 191.8 (s, C-10′) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3427, 2979, 2932, 2845, 1734, 1628, 1595, 1559, 1487, 1455, 1368, 1324, 1251, 1212, 1150, 1113, 1063, 1040, 974. UV (CH_3CN): λ_{max} (lg ε) = 281 (4.76), 431 (1.79) nm. MS (EI, 70 eV): *m*/*z* (%) = 483 (20) [M^+ + 1], 465 (4), 427 (25), 383 (20), 365 (2), 169 (5), 85 (3), 57 (100) [$C_4H_9{}^+$]. HRMS (EI, 70 eV, $C_{26}H_{26}O_9$): calcd. 482.1577, found 482.1578. $C_{26}H_{26}O_9$ (482.48): calcd. C 64.72, H 5.43; found C 64.43, H 4.99.

***tert*-Butyl [4-Hydroxy-9,10-dioxo-3-(3-oxobutanoyl)-9,10-dihydroanthracen-2-yl]acetate (20b):**[17] The rearrangement reaction of **19b**[17] (0.23 mmol, 96 mg) was carried out as described for **20a** and afforded orange crystals of **20b** (0.20 mmol, 85 mg, 80 %, m.p. 180 °C, ref.[17] 183 °C). ^{1}H NMR (200 MHz, $CDCl_3$) (enol): δ = 1.48 (s, 9 H, 3 × CH_3), 2.21 (s, 3 H, CH_3), 3.81 (s, 2 H, 2-H), 5.99 (s, 1 H, 2′′-H), 7.77 (s, 1 H, 1′-H), 7.83−7.89 (m, 2 H, 6′-H, 7′-H), 8.27−8.37 (m, 2 H, 5′-H, 8′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) (enol): δ = 25.5 (q, CH_3), 28.4 (q, 3 × CH_3), 41.3 (t, C-2), 82.2 (s, C-1$_{tBu}$), 104.4 (d, C-2′′), 115.7 (s, C-4a′), 122.3 (d, C-1′), 127.5 (d, C-5′), 127.9 (d, C-8′), 132.3 (s, C-3′), 133.5 (s, C-8a′), 133.8 (s, C-10a′), 134.9 (d, C-7′), 135.4 (d, C-6′), 143.3 (s, C-9a′), 160.6 (s, C-2′), 169.5 (s, C-4′), 182.2 (s, C-1), 184.9 (s, C-3′′), 188.8 (s, C-9′, C-10′), 191.9 (s, C-1′′) ppm.

Methyl [4-Hydroxy-9,10-dioxo-3-(3-oxopentanoyl)-9,10-dihydroanthracen-2-yl]acetate (20c):[17] The rearrangement reaction of methyl (3-acetyl-9,10-dioxo-4-propoxy-9,10-dihydroanthracen-2-yl)acetate[17] (0.091 mmol, 36 mg) was carried out as described for **20a** and afforded orange crystals of **20c** (0.076 mmol, 30 mg, 81 %, m.p. 126 °C, ref.[17] 127 °C).

Methyl (9,11-Dimethoxy-2-methyl-4,7,12-trioxo-7,12-dihydro-4*H*-1-oxabenzo[*a*]anthracen-5-yl)acetate (21a): 20a (0.149 mmol, 72 mg) was dissolved in trifluoroacetic acid (1 mL) at 0 °C. After 20 min, the solution was warmed to 20 °C for 10 min. Dichloromethane (10 mL) was then added and the solvent was removed under reduced pressure. The procedure was repeated twice to remove traces of trifluoroacetic acid. The crude product was dissolved in dichloromethane (10 mL) and treated with a CH_2N_2 solution (0.30 mmol/mL, 0.50 mL) to esterify the carboxylic acid group. The solvent was removed under reduced pressure and the crude product was purified by crystallization from dichloromethane/diethyl ether to afford **21a** as orange crystals (0.142 mmol, 60 mg, 95 %, m.p. 295 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, 13′-H), 3.76 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 4.35 (s, 2 H, 2-H), 6.24 (s, 1 H, 3′-H), 6.87 (d, $J_{8',10'}$ = 2.44 Hz, 1 H, 10′-H), 7.40 (d, $J_{8',10'}$ = 2.44 Hz, 1 H, 8′-H), 7.98 (s, 1 H, 6′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.9 (q, C-13′), 42.2 (t, C-2), 52.5 (q, OCH_3), 56.5 (q, OCH_3), 57.1 (q, OCH_3), 103.0 (d, C-8′), 106.0 (d, C-10′), 112.7 (d, C-3′), 118.0 (s, C-11a′), 124.1 (s, C-12a′), 125.9 (d, C-6′), 126.9 (s, C-4a′), 135.6 (s, C-5′), 136.3 (s, C-7a′), 141.4 (s, C-6a′), 156.4 (s, C-12b′), 162.4 (s, C-11′), 164.8 (s, C-2′), 167.2 (s, C-9′), 171.4 (s, C-1), 179.2 (s, C-4′), 180.0 (s, C-7′), 183.3 (s, C-12′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 422 (60) [M^+], 390 (100), 362 (80); 334 (20), 305 (25), 276 (10), 233 (5), 181 (16), 167 (18), 138 (5), 44 (5), 28 (4). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3437, 3082, 2989, 2952, 2846, 1736, 1678, 1653, 1624, 1591, 1558, 1466, 1437, 1392, 1373, 1344, 1325, 1302, 1279, 1240, 1215, 1200, 1182, 1165, 1140, 1113, 1065, 1043. HRMS (EI, 70 eV, $C_{23}H_{18}O_8$): calcd. 422.1001, found 422.1018.

Methyl (2-Methyl-4,7,12-trioxo-7,12-dihydro-4*H*-1-oxabenzo[*a*]anthracen-5-yl)acetate (21b): The ring closure of **20b** (0.187 mmol, 79 mg) was carried out as described for **21a** to afford red crystals of **21b** (0.166 mmol, 60 mg, 89 %, m.p. 197−204 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 3.77 (s, 3 H, CH_3), 4.40 (s, 2 H, 2-H), 6.29 (s, 1 H, 3′-H), 7.81−7.93 (m, 2 H, 8′-H, 11′-H), 8.11 (s, 1 H, 6′-H), 8.30−8.37 (m, 2 H, 9′-H, 10′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.3 (q, CH_3), 42.0 (t, CH_2, C-2), 52.2 (q, OCH_3), 112.5 (d, C-3′), 121.9 (s, C-12b′), 126.3 (s, C-4a′), 126.5 (d, C-6′), 127.1 (d, C-11′), 127.5 (d, C-8′), 132.2 (s, C-7a′), 134.3 (s, C-6a′), 134.6 (d, C-9′), 135.1 (d, C-10′), 136.5 (s, C-11a′), 142.7 (s, C-5), 156.8 (s, C-12b′), 167.5 (s, C-2′), 171.2 (s, C-1), 179.2 (s, C-12′), 181.2 (s, C-7′), 182.4 (s, C-4′). UV (CH_3CN): λ_{max} (lg ε) = 279 (4.28), 373 (1.97) nm. MS (EI, 70 eV): *m*/*z* (%) = 362 (32) [M^+], 330 (64), 302 (48), 274 (52), 248 (30), 231 (22), 205 (24), 165 (10), 151 (16), 109 (8), 91 (24), 57 (10), 28 (28). ($C_{21}H_{14}O_6$, 362.33): calcd. C 69.61, H 3.89; found C 68.93, H 3.49.

Methyl (2-Ethyl-4,7,12-trioxo-7,12-dihydro-4*H*-1-oxabenzo[*a*]anthracen-5-yl)acetate (21c): The ring closure of **20c** (0. 071 mmol, 28 mg) was carried out as described for **21a** to afford red crystals of **21c** (0.048 mmol, 18 mg, 68 %, m.p. 268−270 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 (t, $J_{1'',2''}$ = 7.52 Hz, 3 H, 2-H′′), 2.81 (q, $J_{1'',2''}$ = 7.52 Hz, 2 H, 1-H′′), 3.72 (s, 3 H, OCH_3), 4.34 (s, 2 H, CH_2), 6.26 (s, 1 H, 3-H), 7.76−7.90 (m, 2 H, 9-H′, 10-H′), 8.06 (s, 1 H, 6-H′), 8.24−8.32 (m, 2 H, 8-H′, 11-H′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.2 (q, C-2′′), 27.8 (t, C-1′′), 42.3 (t, C-2), 52.5 (q, OCH_3), 111.2 (d, C-3′), 122.2 (s, C-12a′), 126.6 (d, C-6′), 127.4 (d, C-8′/C-11′), 127.7 (d, C-8′/C-11′), 132.4 (s, C-4a′), 134.4 (d, C-9′/C-10′), 134.9 (s, C-7a′, C-11a′), 135.3 (d, C-9′/C-10′), 136.7 (s, C-5′), 142.9 (s, C-6a′), 171.4 (s, C-12b′), 172.0 (s, C-2′), 179.5 (s, C-7′, C-12′), 181.3 (s, C-1), 182.7 (s, C-4′) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3521, 3460, 2916, 2850, 1747, 1716, 1674, 1651, 1589, 1466, 1439, 1389, 1369, 1346, 1323, 1284, 1254, 1200, 1173.

UV (CH_3CN): λ_{max} (lg ε) = 275 (4.32), 335 (1.74), 372 (1.57) nm. HRMS (EI, 70 eV, $C_{22}H_{16}O_6$): calcd. 376.0947, found 376.0849. $C_{22}H_{16}O_6$ (376.36): calcd. C 70.21, H 4.29; found C 69.91, H 4.44.

Methyl (11-Hydroxy-9-methoxy-2-methyl-4,7,12-trioxo-7,12-dihydro-4*H*-1-oxabenzo[*a*]anthracen-5-yl)acetate (22d): To a solution of **21a** (2.2 mg, 0.0053 mmol) in dry CH_2Cl_2 (10 mL) was added a solution of BBr_3 in CH_2Cl_2 (1 mmol/mL, 4 mL) and the solution stirred for 3 h. Dichloromethane (30 mL) was added and the solution washed successively with a concd. $NaHCO_3$ solution (10 mL) and water (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford **22d** as red crystals (1.6 mg, 0.0040 mmol, 75 %, m.p. 252−254 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 6.29 (s, 1 H, 3′-H), 6.81 (d, $J_{8',10'}$ = 2.57 Hz, 1 H, 10′-H), 7.40 (d, $J_{8',10'}$ = 2.57 Hz, 1 H, 8′-H), 8.08 (s, 1 H, 6′-H), 13.07 (s, 1 H, OH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.5 (q, CH_3), 41.7 (t, CH_2), 51.9 (q, OCH_3), 55.9 (q, OCH_3), 107.2 (d, C-8′), 107.5 (d, C-10′), 111.2 (d, C-3′), 112.3 (s, C-11a′), 121.2 (s, C-4a′, C-12a′), 126.3 (d, C-6′), 133.4 (s, C-7a′), 136.1 (s, C-6a′), 142.7 (s, C-5′), 156.3 (C-12b′), 165.3 (s, C-11′), 165.7 (s, C-9′), 166.4 (s, C-2′), 170.5 (s, C-1), 178.3 (s, C-12′), 181.4 (s, C-7′), 185.2 (s, C-4′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 408 (20) [M$^+$], 376 (48), 348 (92), 320 (34), 306 (12), 277 (6), 249 (6), 221 (5). HRMS (EI, 70 eV, $C_{22}H_{16}O_8$): calcd. 408.0845, found 408.0847.

Premithramycinone H (2):[6] A solution of BBr_3 in CH_2Cl_2 (1 mmol/mL, 4 mL) was added to a solution of **21a** (122 mg, 0.29 mmol) in dry CH_2Cl_2 (30 mL). After stirring for 6 h, dichloromethane (30 mL) was added and the solution washed successively with concd. $NaHCO_3$ solution (20 mL) and water (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield **2** as red crystals (84 mg, 0.21 mmol, 74 %), m.p. 254−260 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 3.73 (s, 3 H, OCH_3), 4.38 (s, 2 H, CH_2), 6.28 (s, 1 H, 3′-H), 7.47 (s, 2 H, 8′-H, 10′-H), 8.09 (s, 1 H, 6′-H), 13.69 (s, 1 H, OH) ppm. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 2.44 (d, $J_{3',13'}$ = 0.7 Hz, 3 H, CH_3), 3.56 (s, 3 H, OCH_3), 4.12 (s, 2 H, CH_2), 6.38 (d, $J_{3',13'}$ = 0.7 Hz, 1 H, 3′-H), 6.93 (d, $J_{8',10'}$ = 2.8 Hz, 1 H, 10′-H), 7.19 (d, $J_{8',10'}$ = 2.8 Hz, 1 H, 8′-H), 7.94 (s, 1 H, 6′-H), 10.32 (s, 1 H, OH), 13.02 (s, 1 H, OH) ppm. MS (EI, 70 eV): *m*/*z* (%) = 394 (10) [M$^+$], 368 (5), 348 (6), 279 (10), 177 (10), 167 (12), 149 (30), 96 (45), 69 (56), 57 (100), 43 (82).

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