Efficient Biomimetic-Type Synthesis of the Benzo[*a*]naphthacenequinone Antibiotics G-2A and G-2N

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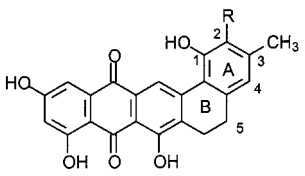
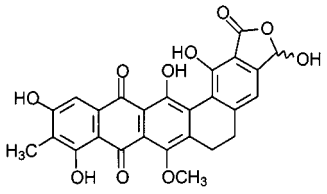
Trioxo ester **15** was prepared by attachment of two vicinal C-4 and C-6 ketide side chains on the anthraquinone core (**6b**). Mild base treatment of **15** initiated successive aldol condensations to produce the benzo[*a*]naphthacenequinone **16** regioselectively in one operation. Deprotection of **16** afforded the antibiotic G-2A (**1**) and decarboxylation of **1** lead to G-2N (**2**).

The structurally most simple natural products with the benzo[*a*]naphthacenequinone skeleton named G-2A (**1**) and G-2N (**2**) were isolated in 1984 by Gerber and Lechevalier from the actinomycete *Frankia* sp. G2.[1] The initially proposed structures were revised later by Hauser and Caringal[2] by comparison of synthetic material with the original structures. In the meantime, the number of known antibiotics of this class has grown to over twenty compounds. Whereas G-2A (**1**) and G-2N (**2**)[1] and also derivatives of madurahydroxylactone (**3**)[3] have antibacterial activity, the related *O*-glycosidic pradimicins[4][5] and benanomicins[6][7] possess remarkable in vivo antifungal properties.[8] There is an urgent need for new antifungal agents because mycoses pose a severe problem in current therapy of immunodeficient patients.[9]



G-2A (**1**): R = CO_2H
G-2N (**2**): R = H



madura hydroxylactone (**3**)

A previous synthesis of G-2N (**2**)[10] and approaches to the benanomicin family[11–13] relied on the Diels–Alder reaction in the construction of the benzo[*a*]naphthacenequinone skeleton, whereas an intramolecular Stille coupling was the key step in the synthesis of G-2A (**1**) and G-2N (**2**) by Kelly et al.[14] We now report on an efficient biomimetic-type total synthesis of the benzo[*a*]naphthacenequinone pigments **1** and **2**, in which the problems of aryl–aryl coupling and the generation of the specific acetogenic substitution pattern of the polyketide natural products are solved simultaneously in a single step.

The synthetic strategy anticipated the attachment of two short ketide chains on vicinal positions on an anthraquinone core in an extension of an earlier approach to the aromatic angucycline antibiotics.[15] This approach reduces the large number of possible unwanted aldol reactions of highly reactive polyketide intermediates. In addition, the careful choice of protecting groups is also a requirement for selective cyclizations, as has been shown by the pioneering work of Harris et al.[16]

The required anthraquinone, **6b**, that allowed the later attachment of the ketide side chains was prepared by Diels–Alder reaction of the chloronaphthoquinone (**4**)[17] and the diene **5**.[18] A 2:3 mixture of the phenol **6a** [30%, characterized as the bis(pivaloate) **6c**] and the ethyl ether **6b** (45%) was obtained after acid-catalyzed aromatization of the primary non-isolated Diels–Alder adduct (Scheme 1). Both products were, in principle, amenable to the anticipated further transformations, but the ethyl ether **6b** was taken for the subsequent steps because one of the phenolic hydroxy groups was already protected. After some experimentation with the corresponding acetates it was found that the pivaloyl esters were more stable, and the dipivaloate **7** was brominated with NBS at the benzylic position to form the monobromide **8** (93%). The sterically demanding pivaloate group effectively inhibited the formation of a dibromide which is normally the major product in the NBS bromination of unhindered benzylic positions. Alkylation of ethyl 5,5-diethylenedioxo-3-oxohexanecarboxylate (**9**)[19] with the benzylic bromide **8** afforded the ester **10** without cleavage of the pivaloate protecting groups. Both the pivaloyl and the methyl esters were saponified by mild treatment of **10** with 1 N NaOH in ethanol. The resulting crude β-oxo acid was directly decarboxylated by heating to 100°C to yield the phenolic ketone **11** in 89% total yield. NMR analysis revealed that the phenolic ketone **11** existed as a 2:1 mixture of the free ketone with the corresponding hemiacetal in $CDCl_3$ solution. This equilibrium did not prevent the subsequent selective reaction of the *non-chelated* phenolic group at C-3 to form the monotriflate **12** in 93% yield. In spite of steric hindrance, the triflate **12** reacted cleanly with the allylstannane **13**[20] to yield the (*E*)-vinyl ether **14** (82%) with dichloro palladium 1,1-bis(diphenylphosphanyl)-ferrocene [$PdCl_2$(dppf)][21] as the catalyst. The vinyl ether **14** was cleaved quantitatively to the corresponding trioxo

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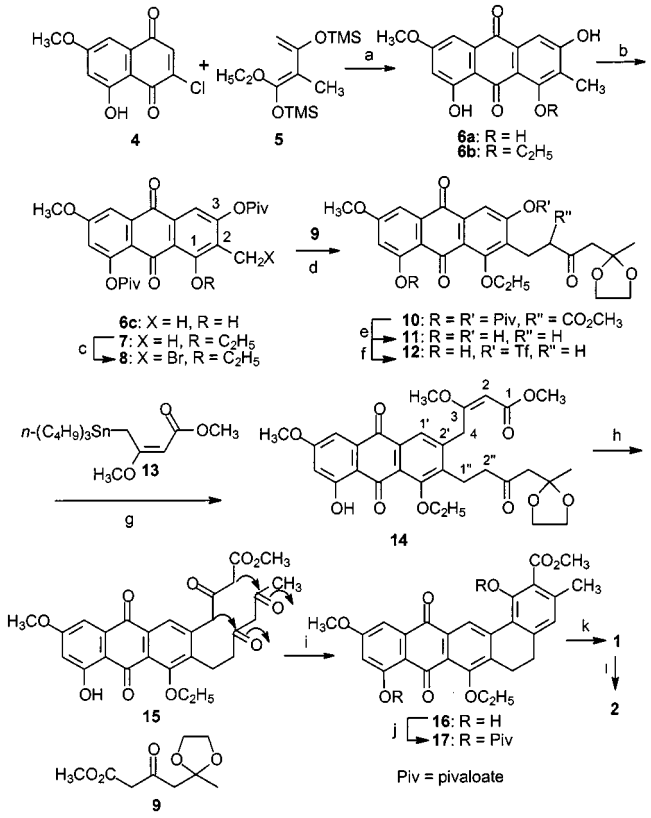
ester **15**, and the stage was set for the crucial cyclization experiments. In fact, mild basic treatment of **15** with potassium carbonate in 2-propanol initiated the aldol reactions, as indicated in Scheme 1, to afford one single benzo[*a*]naphthacenequinone **16**. The phenolic cyclization product **16** was of extremely low solubility and was therefore transformed into the more soluble dipivaloate **17** for characterization.



Scheme 1. a) 1. Toluene, 6 h, 20°C; 2. conc. HCl, THF (30% **6a**, 45% **6b**). − b) Me_3CCOCl, DMAP, pyridine (54%). − c) NBS, AIBN, CCl_4, reflux (93%). − d) Ethyl 5,5-diethylenedioxo-3-oxohexanecarboxylate (**9**), NaH (87%). − e) 1.1 N NaOH, EtOH; 2. 100°C (89%). − f) Tf_2O, 2,6-lutidine (93%). − g) Allylstannane **13**, $PdCl_2$(dppf), CuBr, dioxane, 3 h, 90°C (82%). − h) 1 N HCl, THF, reflux (95%). − i) K_2CO_3, *i*PrOH. − j) Me_3CCOCl, DMAP (74%). − k) $AlCl_3$/NaCl, 150°C, 5 min (87%). − l) Py/HCl, 160°C, 6 h (69%).[14] − AIBN = azoisobutyronitrile, NBS = *N*-bromosuccinimide, DMAP = 4-(dimethylamino)pyridine, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene

The spectral data of this dipivaloate **17** were in complete agreement with the expected benzo[*a*]naphthacenequinone skeleton. Interestingly, the presence of the ester group initiated the complete aromatization of the intermediate aldol products that could not even be detected by TLC. This is in contrast to experiments with similar precursors lacking this ester group, where the hydroaromatic primary aldol products can be isolated.[15] Interestingly, ring A is aromatic in **all** natural products of related benzo[*a*]naphthacenequinone structures isolated to date with an ester group on this ring. It is further worth noting that only one cyclization mode to the *angularly* condensed system was realized under the mild basic conditions with the trioxo ester **15**, whereas partially protected analogues always also gave some of the linearly condensed cyclization products. Finally, to complete the synthesis of the natural pigment, the diverse protecting groups of **16** were simultaneously cleaved by a short melt in $AlCl_3$/NaCl at 150°C[14][22] to yield the natural product G-2A (**1**), which was further thermally decarboxylated to afford G-2N (**2**).[14] The biomimetic-type synthesis of **1** can be extended easily to other members of the benzo[*a*]naphthacenequinone antibiotics such as the pradimicins and benanomicins.

Experimental Section

General methods and instrumentation are given elsewhere.[23]

1-Ethoxy-2-methyl-1,3-bis(trimethylsiloxy)buta-1,3-diene (5): A solution of ethyl 3-methylacetoacetate (5.00 g, 34.68 mmol) in dry *n*-hexane (40 mL) was treated under argon with triethylamine (4.21 g, 41.62 mmol). Trimethylsilyl chloride (4.14 g, 38.15 mmol) was then added dropwise and the suspension was stirred for 12 h. The mixture was filtered and the residue concentrated in vacuo to yield 6.75 g of crude ethyl 2-methyl-3-(trimethylsiloxy)but-2-enoate. This ester (2.00 g, 9.24 mmol) was then added dropwise to a solution of LDA (10.16 mmol) in dry THF (15 mL) at −78°C under argon, and after 30 min trimethylsilyl chloride (1.21 g, 11.09 mmol) was added slowly. The mixture was stirred for 1 h at 0°C and the solvent was evaporated under reduced pressure. *n*-Pentane (40 mL) was added to the suspension, the lithium chloride was removed by filtration and the filtrate was concentrated under reduced pressure to afford the diene **5**[18] (2.45 g, 92%) as a 4:1 (*E*)/(*Z*) mixture that was used without further purification.

1,3,8-Trihydroxy-6-methoxy-2-methyl-9,10-anthraquinone (6a) and 1-Ethoxy-3,8-dihydroxy-6-methoxy-2-methyl-9,10-anthraquinone (6b): A mixture of naphthoquinone **4**[17] (0.50 g, 2.10 mmol) and diene **5** (1.21 g, 4.20 mmol) in dry toluene (20 mL) was stirred under argon for 6 h at 20°C. The solvent was evaporated under reduced pressure and the residue re-dissolved in a mixture of THF (20 mL) and conc. HCl (4 mL). The mixture was heated under reflux for 1 h, diluted with water (30 mL) and the remaining THF removed under reduced pressure. The 3:4.5 mixture of **6a**[24] and **6b** (0.51 g, 75%) was isolated by filtration. The almost insoluble phenols **6a** and **6b** were characterized as the bis(pivaloates) **6c** and **7**. − IR (KBr) of **6b**: $\tilde{\nu}$ = 3395 cm^{-1} (OH), 2991, 2966, 2924 (CH), 1676 (C=O, quinone), 1631, 1604, 1571 (C=C, Ar); − ^{1}H NMR of **6b**: (200 MHz, [D$_6$]DMSO): δ = 1.41 (t, *J* = 6.8 Hz, 3 H, OCH_2CH_3), 2.12 (s, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 3.94 (q, *J* = 6.8 Hz, 2 H, OCH_2CH_3), 6.74 (d, $J_{7,5}$ = 2.5 Hz, 1 H, 7-H), 7.01 (d, $J_{5,7}$ = 2.5 Hz, 1 H, 5-H), 7.41 (s, 1 H, 4-H), 11.13 (s, 1 H, OH), 13.46 (s, 1 H, OH). − $C_{26}H_{28}O_8$ (468.50): calcd. C 66.66, H 6.02; found C 66.70, H 5.98.

3,8-Bis(2,2-dimethylpropionyloxy)-1-hydroxy-6-methoxy-2-methyl-9,10-anthraquinone (6c) and 3,8-Bis(2,2-dimethylpropionyloxy)-1-ethoxy-6-methoxy-2-methyl-9,10-anthraquinone (7): A suspension of the anthraquinones **6a** and **6b** (2.52 g, 8.42 mmol) and DMAP (0.10 g, 0.84 mmol) in a mixture of dry CH_2Cl_2 (80 mL) and dry pyridine (10 mL) was treated with pivaloyl chloride (6.09 g, 50.5 mmol). The mixture was stirred for 12 h at 20°C, then poured into ice-cold 1 N HCl (100 mL) and extracted three times with CH_2Cl_2 (60 mL). The combined organic phases were washed successively with 1 N HCl (60 mL) and water (60 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was separated by chromatography on silica gel (CH_2Cl_2) to yield yellow

6c (1.46 g, 37%; m.p. 209°C) and **7** (2.26 g, 54%; m.p. 177°C) as faint yellow crystals.

Data for 6c: IR (KBr): $\tilde{\nu}$ = 3440 cm^{-1} (OH), 2976, 2935 (CH), 1755 (C=O, ester), 1676 (C=O, quinone), 1630, 1601 (C=C, Ar). − UV (CH_2Cl_2): λ_{max} (lg ε) = 228 nm (4.29), 271 (4.58), 414 (3.91). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 1.49 [s, 9 H, $C(CH_3)_3$], 2.18 (s, 3 H, CH_3), 4.00 (s, 3 H, OCH_3), 6.83 (d, $J_{7,5}$ = 2.6 Hz, 1 H, 7-H), 7.44 (s, 1 H, 4-H), 7.72 (d, $J_{5,7}$ = 2.6 Hz, 1 H, 5-H), 13.38 (s, 1 H, OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.64 (q, CH_3), 27.58 and 27.67 [q, $C(CH_3)_3$], 39.63 and 39.79 [s, $C(CH_3)_3$], 56.68 (q, OCH_3), 110.54 (d), 113.78 (d), 114.11 (s), 116.47 (d), 118.97 (s), 127.78 (s), 131.31 (s), 137.17 (s), 153.78 (s), 155.26 (s), 162.98 (s), 165.12 (s), 176.24 and 177.00 (s, CO_2Piv), 181.58 (s, C-10), 186.87 (s, C-9). − MS (EI/130°C): *m*/*z* (%) = 468 (59) [M^+], 384 (33) [$M^+ - C_5H_8O$], 300 (82) [$M^+ - 2 \times C_5H_8O$], 85 (38) [$C_5H_9O^+$], 57 (100) [$C_3H_5O^+$]. − HRMS: $C_{26}H_{28}O_8$: calcd. 468.178; found 468.178 ± 3 ppm.

Data for 7: IR (KBr): $\tilde{\nu}$ = 2976 cm^{-1}, 2935 (CH), 1749 (C=O, ester), 1673 (C=O, quinone), 1604 (C=C, Ar). − UV (CH_2Cl_2): λ_{max} (lg ε) = 228 nm (4.25), 269 (4.65), 358 (3.82). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 1.47 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.51 [s, 9 H, $C(CH_3)_3$], 2.22 (s, 3 H, CH_3), 3.97 (s, 3 H, OCH_3), 4.00 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 6.85 (d, $J_{7,5}$ = 2.7 Hz, 1 H, 7-H), 7.64 (d, $J_{5,7}$ = 2.7 Hz, 1 H, 5-H), 7.71 (s, 1 H, 4-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.63 (q, CH_3), 16.12 (q, OCH_2CH_3), 27.60 [q, 2 × $C(CH_3)_3$], 39.60 and 39.79 [s, $C(CH_3)_3$], 56.57 (q, OCH_3), 70.94 (t, OCH_2CH_3), 109.23 (d, C-5), 116.53 and 117.03 (d, C-4 and C-7), 121.14 (s), 125.06 (s), 133.37 (s), 134.37 (s), 136.19 (s), 152.62 (s), 154.18 (s), 159.65 (s), 163.90 (s), 176.32 and 176.93 (s, CO_2Piv), 180.79 and 182.45 (s, C-9 and C-10). − MS (EI/200°C): *m*/*z* (%) = 496 (9) [M^+], 411 (55) [$M^+ - C_5H_9O$], 87 (100) [$C_4H_7O_2^+$]. − HRMS: $C_{28}H_{32}O_8$: calcd. 496.209; found 496.209 ± 3 ppm. − $C_{28}H_{32}O_8$ (496.56): calcd. C 67.73, H 6.50; found C 67.68, H 6.56.

2-(Bromomethyl)-3,8-bis(2,2-dimethylpropionyloxy)-1-ethoxy-6-methoxy-9,10-anthraquinone (8): A suspension of **7** (1.10 g, 2.22 mmol), NBS (0.79 g, 4.44 mmol) and AIBN (50 mg) in CCl_4 (50 mL) was heated at reflux for 3 h. The mixture was filtered, the filtrate concentrated under reduced pressure, and a solution of the residue in CH_2Cl_2 (10 mL) was filtered through a short column of silica gel (CH_2Cl_2) to yield **8** (1.19 g, 93%) as a yellow solid; m.p. 169°C. − IR (KBr): $\tilde{\nu}$ = 2977 cm^{-1} (CH), 1758 (C=O, ester), 1674 (C=O, quinone), 1603 (C=C, Ar). − UV (CH_2Cl_2): λ_{max} (lg ε) = 229 nm (4.42), 277 (4.57), 354 (3.72). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 1.50 [s, 9 H, $C(CH_3)_3$], 1.56 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 3.96 (s, 3 H, OCH_3), 4.15 (q, *J* = 6.9 Hz, 2 H, OCH_2CH_3), 4.56 (s, 2 H, CH_2Br), 6.84 (d, $J_{7,5}$ = 2.7 Hz, 1 H, 7-H), 7.62 (d, $J_{5,7}$ = 2.7 Hz, 1 H, 5-H), 7.80 (s, 1 H, 4-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.14 (q, OCH_2CH_3), 20.62 (t, CH_2Br), 27.53 and 27.67 [q, $C(CH_3)_3$], 39.58 and 40.01 [s, $C(CH_3)_3$], 56.55 (q, OCH_3), 72.07 (t, OCH_2CH_3), 109.39 (d, C-5), 116.71 and 117.49 (d, C-4 and C-7), 120.97 (s), 124.94 (s), 132.60 (s), 135.34 (s), 135.97 (s), 152.67 (s), 154.01 (s), 159.76 (s), 164.08 (s), 175.82 and 176.79 (s, CO_2Piv), 180.32 and 182.05 (s, C-9 and C-10). − MS (EI/170°C): *m*/*z* (%) = 576 (11) [$M^{+81}Br$], 574 (10) [$M^{+79}Br$], 491 (29) [$M^{+81}Br - C_5H_9O$], 489 (28) [$M^{+79}Br - C_5H_9O$], 325 (25) [$M^+ - Br - 2 \times C_5H_9O$], 299 (20), 57 (100). − HRMS: C28H31O8^{79}Br: calcd. 574.120; found 574.121 ± 3 ppm. − $C_{28}H_{31}BrO_8$ (575.45): calcd. C 58.44, H 5.43; found C 58.31, H 5.50.

Methyl 2-[3,8-Bis(2,2-dimethylpropionyloxy)-1-ethoxy-6-methoxy-9,10-dioxo-9,10-dihydroanthracene-2-ylmethyl]-4-(2-methyl[1,3]dioxolan-2-yl)-3-oxobutanoate (10): The sodium salt of methyl 5,5-diethylenedioxo-3-oxohexanoate (**9**)[25] was prepared by stirring a solution of the ester **9** (1.02 g, 5.04 mmol) in dry THF (15 mL) with NaH (0.12 g, 5.04 mmol, 80%) under argon for 30 min at 20°C. This solution was added dropwise under argon at 20°C to a solution of the bromide **8** (1.45 g, 2.52 mmol) and tetrabutylammonium iodide (0.19 g, 0.50 mmol) in dry THF (25 mL). After 5 h of stirring, the mixture was poured into ice-cold 1 N HCl (100 mL) and extracted three times with CH_2Cl_2 (50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (Et_2O/*n*-hexane, 6:4) to yield **10** (1.53 g, 87%) as a yellow oil. − IR (KBr): $\tilde{\nu}$ = 2979 cm^{-1} (CH), 1756 (C=O, ester), 1675 (C=O, quinone. − UV (CH_2Cl_2): λ_{max} (lg ε) = 227 nm (4.36), 273 (4.60), 356 (3.74). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, CH_3), 1.43 [s, 9 H, $C(CH_3)_3$], 1.50 [s, 9 H, $C(CH_3)_3$], 1.52 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 2.78 (d, $J_{gem.}$ = 14.3 Hz, 1 H, 4-H), 2.93 (d, $J_{gem.}$ = 14.3 Hz, 1 H, 4-H), 3.14−3.21 (m, 2 H, 1′′-H), 3.66 (s, 3 H, CO_2CH_3), 3.90 (s, 3 H, OCH_3), 3.98−4.03 (m, 6 H, OCH_2CH_3, OCH_2CH_2O), 4.14 (pt, $J_{2,1''}$ = 7.9 Hz, $J_{2,1''}$ = 6.3 Hz, 1 H, 2-H), 6.86 (d, $J_{7',5'}$ = 2.5 Hz, 1 H, 7′-H), 7.66 (d, $J_{5',7'}$ = 2.5 Hz, 1 H, 5′-H), 7.71 (s, 1 H, 4′-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.17 (q, OCH_2CH_3), 23.75 (t, C-1′′), 24.69 (q, CH_3), 27.46 and 27.65 [q, $C(CH_3)_3$], 39.59 and 39.82 [s, $C(CH_3)_3$], 51.21 (t, C-4), 52.96 (q, CO_2CH_3), 56.58 (q, OCH_3), 58.59 (d, C-2), 64.88 and 65.02 (t, OCH_2CH_2O), 71.44 (t, OCH_2CH_3), 108.14 (s), 109.25 (d, C-5′), 116.67 and 117.43 (d C-4′ and C-7′), 121.16 (s), 124.54 (s), 134.19 (s), 134.33 (s), 136.13 (s), 152.61 (s), 154.00 (s), 160.36 (s), 164.00 (s), 170.14 (s, CO_2CH_3), 176.48 and 176.77 (s, CO_2Piv), 180.63 and 182.33 (s, C-9′ and C-10′), 201.20 (s, C-3). − MS (EI/170°C): *m*/*z* (%) = 696 (5) [M^+], 611 (16) [$M^+ - C_5H_9O$], 87 (100) [$C_4H_7O_2^+$], 57 (43). − HRMS: $C_{37}H_{44}O_{13}$: calcd. 696.278; found 696.279 ± 3 ppm. − $C_{37}H_{44}O_{13}$ (696.75): calcd. C 63.78, H 6.37; found C 62.87, H 6.45.

1-Ethoxy-3,8-dihydroxy-6-methoxy-2-[4-(2-methyl[1,3]dioxolan-2-yl)-3-oxobutyl]-9,10-anthraquinone (11): A solution of the triester **10** (1.40 g, 2.01 mmol) in EtOH (60 mL) was stirred under argon with 1 N NaOH (60 mL) for 12 h. The mixture was acidified by addition of 1 N HCl (80 mL) and extracted three times with EtOAc (60 mL). The combined organic phases were washed with water (60 mL) and brine (60 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The oily residue was heated for 10 min to 100°C and the crude ketone was purified by flash chromatography on silica gel (Et_2O/*n*-hexane, 80:20) to yield **11** (0.84 g, 89%) as an orange solid; m.p. 158°C. − The NMR spectra revealed an equilibrium of the ketone with the corresponding hemiacetal in $CDCl_3$ solution. −IR (KBr): $\tilde{\nu}$ = 3399 cm^{-1} (OH), 2927 (CH), 1707, 1629, 1585 (C=C, Ar). − UV (CH_2Cl_2): λ_{max} (lg ε) = 228 nm (4.34), 288 (4.57), 357 (3.65), 433 (3.89). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.55 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 2.84 (s, 2 H, 4′-H), 2.94−3.02 (m, 2 H, 1′-H), 3.10−3.15 (m, 2 H, 2′-H), 3.87−3.96 (m, 7 H, OCH_3, OCH_2CH_2O), 4.10 (q, *J* = 6.9 Hz, 2 H, OCH_2CH_3), 6.68 (d, $J_{7,5}$ = 2.5 Hz, 1 H, 7-H), 7.28 (d, $J_{5,7}$ = 2.5 Hz, 1 H, 5-H), 7.59 (s, 1 H, 4-H), 9.10 (s, 1 H, OH), 13.40 (s, 1 H, OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.20 (q, OCH_2CH_3), 16.82 (t, C-1′), 25.05 (q, CH_3), 45.08 (t, C-2′), 51.75 (t, C-4′), 56.32 (q, OCH_3), 65.09 and 65.28 (t, OCH_2CH_2O), 70.36 (t, OCH_2CH_3), 106.80 (d, C-5), 107.61 (d, C-7), 108.17 (s), 110.39 (s), 111.39 (s), 113.55 (d, C-4), 125.37 (s), 134.70 (s), 134.79 (s), 158.85 (s), 160.13 (s), 165.59 (s, C-3 and C-8), 182.79 (s, C-10), and 186.94 (s, C-9), 212.42 (s, C-3′). − MS (EI/235°C): *m*/*z* (%) = 470 (5) [M^+], 339 (9), 299 (10), 87 (100) [$C_4H_7O_2^+$], 43 (19) [$C_2H_3O^+$]. − HRMS: $C_{25}H_{26}O_9$: calcd.

470.157; found 470.158 ± 3 ppm. − $C_{25}H_{26}O_9$ (470.48): calcd. C 63.82, H 5.57; found C 62.70, H 5.87.

1-Ethoxy-8-hydroxy-6-methoxy-2-[4-(2-methyl[1,3]dioxolan-2-yl)-3-oxobutyl]-3-(trifluoromethanesulfonyloxy)-9,10-anthraquinone (12): A solution of **11** (0.84 g, 1.79 mmol) in a mixture of dry CH_2Cl_2 (60 mL) and 2,6-lutidine (0.38 g, 3.58 mmol) was treated for 1 h under argon with trifluoromethanesulfonic anhydride (0.61 g, 2.15 mmol). The solution was poured into ice-cold 1 N HCl (50 mL), the aqueous phase was extracted twice with CH_2Cl_2 (30 mL) and the combined organic phases were washed with water (60 mL) and brine (60 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield **12** (0.96 g, 93%) as a yellow solid; m.p. 121°C. − IR (KBr): $\tilde{\nu}$ = 3431 cm^{-1} (OH), 2976, 2893 (CH), 1712, 1676 (C=O, quinone), 1628, 1587 (C=C, Ar). − UV (CH_2Cl_2): λ_{max} (lg ε) = 246 nm (4.49), 270 (4.37), 288 (4.39), 349 (3.77), 418 (3.93). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.57 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 2.81 (s, 2 H, 4′-H), 2.87−3.14 (m, 4 H, 1′-H, 2′-H), 3.97 (s, 4 H, OCH_2CH_2O), 3.98 (s, 3 H, OCH_3), 4.13 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 6.76 (d, $J_{7,5}$ = 2.5 Hz, 1 H, 7-H), 7.35 (d, $J_{5,7}$ = 2.5 Hz, 1 H, 5-H), 8.03 (s, 1 H, 4-H), 13.06 (s, 1 H, OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.12 (q, OCH_2CH_3), 19.86 (t, C-1′), 24.90 (q, CH_3), 43.21 (t, C-2′), 52.03 (t, C-4′), 56.52 (q, OCH_3), 65.05 (t, OCH_2CH_2O), 72.42 (t, OCH_2CH_3), 107.87 and 107.96 (d, C-5 and C-7), 108.22 (s), 111.66 (s), 116.82 (d, C-4), 119.55 (s), 125.67 (s), 134.13 (s), 135.36 (s), 138.16 (s), 151.98 (s), 161.20 (s), 166.10 (s), 166.45 (s), 181.04 (s, C-9), 186.09 (s, C-10), 205.76 (s, C-3′). − MS (EI/200°C): *m*/*z* (%) = 602 (2) [M^+], 516 (5) [$M^+ - C_4H_6O_2$], 473 (4), 339 (6), 87 (100) [$C_4H_7O_2^+$], 43 (13) [$C_2H_3O^+$]. − HRMS: $C_{26}H_{25}F_3O_{11}S$: calcd. 602.106; found 602.107 ± 3 ppm.

Methyl 4-{4-Ethoxy-5-hydroxy-7-methoxy-3-[4-(2-methyl[1,3]dioxolan-2-yl)-3-oxobutyl]-9,10-dioxo-9,10-dihydroanthracene-2-yl}-3-methoxybut-2-enoate (14): A solution of **12** (0.86 g, 1.43 mmol), stannane **13**[20] (1.21 g, 2.86 mmol) and the catalyst $PdCl_2$(dppf)[21] (0.11 g, 10 mol-%) in dry dioxane (60 mL) was stirred under argon for 3 h at 90°C. The mixture was then filtered through a short silica gel column (CH_2Cl_2) to remove the catalyst. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) to yield **14** (0.69 g, 82%) as yellow needles; m.p. 150°C. − IR (KBr): $\tilde{\nu}$ = 3430 cm^{-1} (OH), 2978, 2944, 2896 (CH), 1712 (C=O, ester), 1672 (C=O, quinone), 1626, 1586 (C=C, Ar). − UV (CH_2Cl_2): λ_{max} (lg ε) = 232 nm (4.60), 270 (4.46), 412 (3.97). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 3 H, CH_3), 1.54 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 2.80 (s, 2 H, 4′′-H), 2.82−3.06 (m, 4 H, 1′′-H, 2′′-H), 3.68 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.97 (s, 4 H, OCH_2CH_2O), 4.05 (q, *J* = 6.9 Hz, 2 H, OCH_2CH_3), 4.34 (s, 2 H, 4-H), 5.27 (s, 1 H, 2-H), 6.70 (d, $J_{6',8'}$ = 2.4 Hz, 1 H, 6′-H), 7.29 (d, $J_{8',6'}$ = 2.4 Hz, 1 H, 8′-H), 7.86 (s, 1 H, 1′-H), 13.30 (s, 1 H, OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.17 (q, OCH_2CH_3), 21.60 (t, C-1′′), 24.86 (q, CH_3), 35.73 (t, C-4), 43.88 (t, C-2′′), 51.53 (q, CO_2CH_3), 52.03 (t, C-4′′), 56.31 (q, OCH_3), 56.33 (q, OCH_3), 65.02 (t, OCH_2CH_2O), 71.28 (t, OCH_2CH_3), 93.06 (d, C-2), 107.01 and 107.40 (d, C-6′ and C-8′), 108.24 (s), 111.93 (s), 124.02 (s), 125.09 (d, C-1′), 133.48 (s), 134.77 (s), 144.00 (s), 144.86 (s), 159.03 (s), 165.75 (s), 165.99 (s), 168.09 (s, C-1), 172.06 (s, C-3), 182.80 (s, C-9′), 187.55 (s, C-10′), 206.79 (s, C-3′′). − MS (EI/180°C): *m*/*z* (%) = 582 (14) [M^+], 87 (100) [$C_4H_7O_2^+$]. − HRMS: $C_{31}H_{34}O_{11}$: calcd. 582.210; found 582.210 ± 3 ppm. − $C_{31}H_{34}O_{11}$ (582.60): calcd. C 63.91, H 6.37; found C 63.34, H 5.88.

Methyl 4-[3-(3,5-Dioxohexyl)-4-ethoxy-5-hydroxy-7-methoxy-9,10-dioxo-9,10-dihydroanthracene-2-yl]-3-oxobutanoate (15): A solution of **14** (0.20 g, 0.34 mmol) in a mixture of THF (10 mL) and 1 N HCl (5 mL) was heated under reflux for 3 h. The solution was diluted with water (15 mL) and extracted three times with CH_2Cl_2 (15 mL). The combined organic phases were washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (CH_2Cl_2/MeOH, 99:1) to afford **15** (0.17 g, 95%) as a yellow solid; m.p. 179°C. − The NMR spectra showed that the 1,3-dione **15** was almost completely enolized in $CDCl_3$ solution. − IR (KBr): $\tilde{\nu}$ = 3429 cm^{-1} (OH), 2981 (CH), 1746, 1714 (C=O, ester), 1627 (C=O, quinone), 1578 (C=C, Ar). − UV (CH_2Cl_2): λ_{max} (lg ε) = 229 nm (4.50), 272 (4.66), 415 (4.06). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.58 (t, *J* = 6.8 Hz, 3 H, OCH_2CH_3), 2.05 (s, 3 H, CH_3), 2.59−2.66 (m, 2 H, 1′′-H), 2.89−2.99 (m, 2 H, 2′′-H), 3.66 (s, 2 H, 2-H), 3.81 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.11 (q, *J* = 6.8 Hz, 2 H, OCH_2CH_3), 4.20 (s, 2 H, 4-H), 5.49 (s, 1 H, 4′′-H), 6.73 (d, $J_{6',8'}$ = 1.9 Hz, 1 H, 6′-H), 7.32 (d, $J_{8',6'}$ = 1.9 Hz, 1 H, 8′-H), 7.87 (s, 1 H, 1′-H), 13.25 (s, 1 H, OH), 15.34 (s, 1 H, OH). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.27 (q, OCH_2CH_3), 23.98 (t, C-1′′), 24.80 (q, CH_3), 38.31 (t, C-2′′), 48.53 and 49.20 (t, C-2 and C-4), 53.05 (q, CO_2CH_3), 56.40 (q, OCH_3), 71.43 (t, OCH_2CH_3), 100.45 (d, C-4′′), 107.18 and 107.60 (d, C-6′ and C-8′), 111.93 (s), 124.77 (s), 126.71 (d, C-1′), 133.78 (s), 134.64 (s), 140.84 (s), 144.02 (s), 159.45 (s), 165.82 and 166.15 (s, C-5′ and C-7′), 167.59 (s, C-1), 182.54 (s, C-9′), 187.36 (s, C-10′), 190.11 and 194.32 (s, C-3′′ and C-5′′), 199.14 (s, C-3). − MS (EI/170°C): *m*/*z* (%) = 524 (34) [M^+], 466 (100) [$M^+ - C_3H_6O^+$], 378 (77), 337 (56), 309 (45), 297 (33), 85 (32), 43 (90) [$C_2H_3O^+$], 31 (57) [CH_3O^+]. − HRMS: $C_{28}H_{28}O_{10}$: calcd. 524.168; found 524.167 ± 3 ppm. − $C_{28}H_{28}O_{10}$ (524.52): calcd. C 64.12, H 5.38; found C 64.16, H 5.35.

Methyl 1,9-Bis(2,2-dimethylpropionyloxy)-7-ethoxy-11-methoxy-3-methyl-8,13-dioxo-5,6,8,13-tetrahydrobenz[*a*]naphthacene-2-carboxylate (17): A solution of **15** (62 mg, 0.12 mmol) in a mixture of 2-propanol (4 mL) and CH_2Cl_2 (4 mL) was treated with powdered K_2CO_3 (163 mg, 1.20 mmol) and the suspension was stirred for 5 h at 45°C (TLC monitoring). The mixture was acidified by addition of 1 N HCl, extracted three times with CH_2Cl_2 (20 mL) and concentrated under reduced pressure to yield crude methyl 7-ethoxy-1,9-dihydroxy-11-methoxy-3-methyl-8,13-dioxo-5,6,8,13-tetrahydrobenz[*a*]naphthacene-2-carboxylate (**16**) (60 mg, quantitative). Part of this solid (15 mg, 0.03 mmol) was converted into the dipivaloate for characterization as described above for **7** to yield **17** (15 mg, 74%) as a yellow solid; m.p. 68−70°C. − IR (KBr): $\tilde{\nu}$ = 2973 cm^{-1}, 2931 (CH), 1758, 1734 (C=O, ester), 1673 (C=O, quinone), 1603, 1581 (C=C, Ar). − UV (CH_2Cl_2): λ_{max} (lg ε) = 230 nm (4.59), 297 (4.76), 374 (3.88). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 [s, 9 H, $C(CH_3)_3$], 1.53 (t, *J* = 6.8 Hz, 3 H, OCH_2CH_3), 1.53 [s, 9 H, $C(CH_3)_3$], 2.41 (s, 3 H, CH_3), 2.75−2.82 (m, 2 H, -H), 3.02 (br. s, 2 H, -H), 3.95 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.03 (q, *J* = 6.8 Hz, 2 H, OCH_2CH_3), 6.86 (d, $J_{10,11}$ = 2.7 Hz, 1 H, 10-H), 7.10 (s, 1 H, 4-H), 7.68 (d, $J_{11,12}$ = 2.7 Hz, 1 H, 12-H), 8.58 (s, 1 H, 14-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.02 (q, OCH_2CH_3), 20.22 (q, CH_3), 22.18 (t), 27.54 and 27.71 [q, $C(CH_3)_3$], 29.31 (t), 39.63 [s, 2 × $C(CH_3)_3$], 52.80 (q, CO_2CH_3), 56.57 (q, OCH_3), 70.91 (t, OCH_2CH_3), 109.08 (d, C-12), 116.57 (d, C-10), 121.24 (s), 122.29 (d, C-14), 125.64 (s), 126.33 (s), 127.48 (s), 128.01 (d, C-4), 132.67 (s), 136.47 (s), 137.86 (s), 138.06 (s), 141.46 (s), 142.56 (s), 146.12 (s), 152.56 (s), 156.52 (s), 163.90 (s), 167.60 (s, CO_2CH_3), 176.72 and 177.15 (s, CO_2Piv), 181.07 and 182.94 (s, C-8 and C-13). − MS (EI/200°C): *m*/*z* (%) = 656 (15) [M^+], 571 (43) [$M^+ - C_5H_9O$], 487 (68), 454 (35), 427 (14), 57 (100) [$C_3H_5O^+$]. − HRMS: $C_{38}H_{40}O_{10}$: calcd. 656.262; found 656.262 ± 3 ppm.

G-2A (1) and G-2N (2): A mixture of $AlCl_3$ (2.50 g, 18.75 mmol) and NaCl (0.50 g, 8.56 mmol) was heated under argon to 150°C. Compound **16** (40 mg, 0.08 mmol, obtained from the cyclization of **15**, see above) was then added in one portion. The melt was hydrolyzed after 5 min at 150°C by addition of a mixture of ice (100 g) and conc. HCl (10 mL). The suspension was stirred for 30 min at 20°C, and then for 5 min at 50°C. The suspension was filtered to yield **1**[1] as an almost insoluble violet powder (31 mg, 87%). − MS (DCI/NH_3): *m*/*z* (%) = 432 (0.5) [M^+], 388 (73) [$M^+ - CO_2$], 148 (100). − HRMS: $C_{23}H_{16}O_6$: calcd. 388.094; found 388.094 ± 3 ppm. − Decarboxylation of the acid **1** (10 mg) was performed as described in the literature[14] to yield G-2N (**2**) (6 mg, 69%).

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