Synthesis of Angucyclines. 8. Biomimetic-Type Synthesis of Rabelomycin, Tetrangomycin, and Related Ring B Aromatic Angucyclinones

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The angucyclinones with aromatic ring B (**1a**−**c** and **2a**−**c**) are prepared in a biomimetic-type synthesis by two successive aldol cyclizations starting from the substituted naphthoquinones **12a**−**c**. In both cyclization steps the C−H acidity of the potential nucleophilic centers determines the mode of cyclization under kinetically controlled conditions. The tetrahydroanthraquinones **13a**−**c/14a**−**c** are hydroxylated at C-4 to the phenolic anthraquinones **16a**−**c** upon treatment with excess NMO.

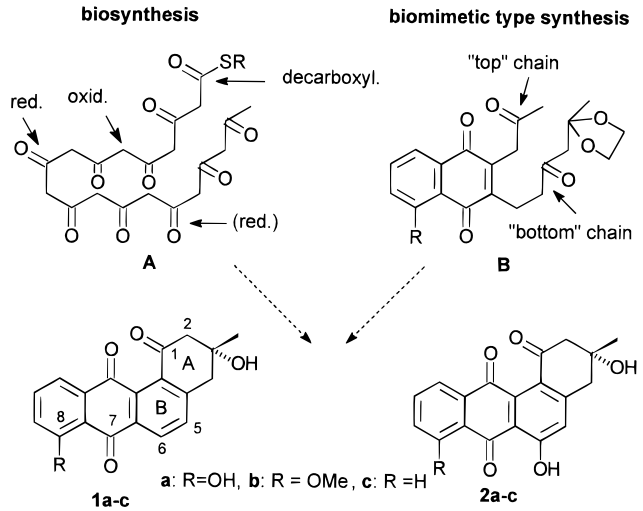
Introduction

The angucyclines are a relatively new group of antibiotics with a broad spectrum of biological activities comprising antitumor, enzyme inhibitory, antiviral, and antifungal effects.[1] In recent years, considerable effort has been made in their total synthesis, notably of the aglycon part, including several *C*-glycosides.[2] In most cases, the angularly condensed benzo[*a*]anthraquinone skeleton was constructed by a Diels−Alder reaction.[2] Yamaguchi et al.[3] used a "biomimetic type" approach in the synthesis of (−)-urdamycinone B (the antipode of the natural product) employing their previously established route of successive condensation of β-diketo or β-keto ester dianions.[4]

We now describe a different biomimetic synthesis of the ring B aromatic angucyclinones **1a**−**c** and **2a**−**c** that is based on the sequential attachment of two ketide fragments ("top" and "bottom" chains) on a [1,4]naphthoquinone core as shown in Scheme 1. This attachment on the *ortho*-positions of a six-membered nucleus restricts the many possible unwanted aldol condensations of open chain polyketides[5] to two cyclization modes designated as "linear" and "angular" according to the position of the side chaines leading finally to linearly or angularly condensed tetracycles (see below).

During or after the folding and condensation of the decaketide **A** (reviews[2,6−8]), a number of *enzymatic* modifications (mostly reductions and oxidations) are required to obtain the final natural products as indicated in Scheme 1. We introduced several simplifications in the precursor **B** as compared to **A** designed for the *chemical* biomimetic-type synthesis of angucyclinones: omission of the ester group in the top chain and of the carbonyl

Scheme 1



group on the quasi-benzylic position in the bottom chain as well as protection of one of the two carbonyl groups. These changes are closely connected with the question of linear versus angular condensation to anthracyclines or angucyclines, respectively. Previously, we observed that the presence of the quasi benzylic carbonyl group in the bottom chain led to the linearly arranged aklanonic acid, the biosynthetic precursor of the anthracyclines.[9] We assumed that modification of the nucleophilicity by omitting the benzylic carbonyl group might lead to the angular condensation products (vide infra). Thus, a major objective of the present study is to investigate the factors that control the cyclization mode of oligoketides such as **B** in the *chemical* synthesis of **1a**−**c** and **2a**−**c**.

Results and Discussion

The attachment of the two side chains outlined in Scheme 2 was previously tested with model naphthoquinones (e.g., X = H in **3c**).[10] The starting materials for this investigation were readily accessible from known compounds. Thus, 2-bromo-3-(bromomethyl)juglone (**3a**) was prepared by acidic saponification of the corresponding acetate **3d** obtained by NBS-bromination of 5-acetoxy-

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(1) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103−137.
(2) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *118*, 127−195.
(3) Yamaguchi, M.; Okuma, T.; Horiguchi, A.; Ikeura, C.; Minami, T. *J. Org. Chem.* **1992**, *57*, 1647−1649.
(4) Yamaguchi, M.; Hasebe, K.; Higashi, H.; Uchida, M.; Irie, A.; Minami, T. *J. Org. Chem.* **1990**, *55*, 1611−1623.
(5) Harris, T. M.; Harris, C. M.; Hindley, K. B. *Fortschr. Chem. Org. Naturstoff.* **1974**, *31*, 217−282.
(6) Simpson, T. J. *Nat. Prod. Rep.* **1987**, *4*, 339.
(7) O'Hagan, D. *The Polyketide Metabolites*; Ellis Horwood: Chichester, 1991.
(8) O'Hagan, D. *Nat. Prod. Rep.* **1995**, *12*, 1−32.
(9) Krohn, K.; Schäfer, G. *Liebigs Ann.* **1996**, 265−270.
(10) Krohn, K.; Böker, N. *J. Prakt. Chem.* **1997**, *339*, 114−120.

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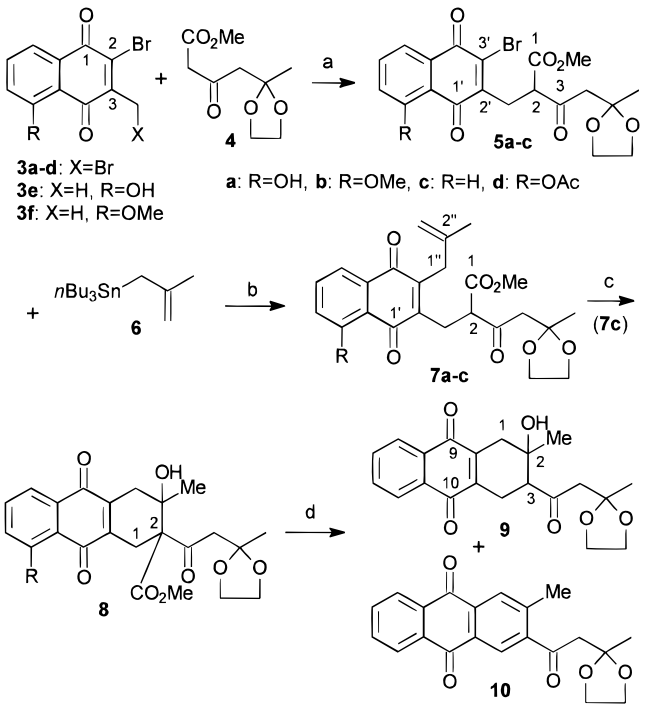
Scheme 2[a]



[a] Key: (a) base, −20 °C, 0.5 h (**5a**, 78%; **5b**, 88%; **5c**, 86%); (b) $Pd(PPh_3)_4$/CuBr, dioxane, reflux, 7−9 h (**7a**, 78%; **7b**, 78%; **7c**, 92%); (c) OsO_4, $NaIO_4$ (**8**, 52%); (d) $(n-Bu_3Sn)_2O$, reflux (**9**, 23%; **10**, 53%).

2-bromo-3-methyl[1,4]naphthoquinone,[11] obtained from 1,5-diacetoxynaphthalene by NBS bromination[12] and by radical iron-mediated methylation with DMSO.[11] The corresponding methyl ether **3b** was synthesized by saponification of **3d** to **3e** followed by methylation to **3f** and NBS bromination. Finally, the dibromide **3c** (R = H) leading to the not naturally occurring angucyclines **1c** and **2c** was obtained by NBS-bromination of the known 2-bromo-3-methyl-[1,4]naphthoquinone.[13]

The two bromine atoms in **3a**−**c** have different chemical reactivity that is exploited in the regiospecific attachment of the two different ketide side chains. The bromine in the quasi-benzylic position is easily displaced in a S_N2 reaction by the anion of the β-keto ester **4**[14] to yield the corresponding alkylation products **5a**−**c** in 78, 88, and 86% yield, respectively. The vinylic bromine at C-2 of **3a**−**c** has the important function of protecting the electrophilic site at C-2 from unwanted Michael addition of the stabilized anion of **4**. The attachment of the second "top" side chain was investigated in an earlier study.[10] The best procedure proved to be a two-step sequence making use of the vinylic bromine atom at C-2 of **3a**−**c** in a palladium-catalyzed Stille reaction[15−17] with the allylstannane **6** to afford the bisalkylated naphthoquinones **7a**−**c** (78, 76, and 92% yield).[10] The synthetic scheme envisioned a cleavage of the double bond in the top side chain to yield the corresponding ketones. Ozonolysis of **7c** showed that the quinoid double bond was also effected to some extent, and therefore, the Lemieux−Johnson[18] procedure (OsO_4/$NaIO_4$) was used to cleave the olefin.

A surprising result was obtained when this method was first applied to the keto ester **7c**. The expected ketone could not be isolated but immediately cyclized to the *linearly* condensed tricyclic β-hydroxy ester **8**. This cyclization already occurred under the very mild and essentially neutral conditions of the Johnson−Lemieux reaction. It demonstrated the high reactivity of oligoketides if centers of high nucleophilicity and electrophilicity are opposed to each other in favorable six-membered transition states. It also confirmed our initial assumption to reduce the nucleophilicity of C-2′ by omitting the neighboring quasi-benzylic keto group to prevent a linear cyclization mode. The β-hydroxy ester **8** could be demethoxycarbonylated by treatment with bis(*n*-tributyltin) oxide[19] to afford small amounts of **9** (23%) and the major aromatization product **10** (53%). This anthraquinone is the decarboxylation product of a 4,6-dideoxyaklanonic acid derivative, an interesting precursor for dideoxy anthracycline antibiotics.[20−22]

To probe the possible angular cyclization, the ester group in **7a**−**c** had to be removed. Bis(*n*-tributyltin) oxide, introduced by Mata and Mascaretti[19] for mild decarboxylations, was the ideal reagent for this purpose because the naphthoquinones **7a**−**c** were unstable under prolonged treatment with base. By use of this tin reagent the olefinic ketones **11a**−**c** were isolated in 65, 78, and 83% yield. Treatment of the olefins **11a**−**c** with the Lemieux−Johnson reagent[18] then afforded the ketones **12a**−**c** as stable materials (78, 77, and 81% yield).

The crucial first cyclization experiment was then performed using potassium carbonate in 2-propanol as the mild base. In accordance with our reasoning, the doubly activated and highly nucleophilic position at C-1″ added to the carbonyl group at C-3′ to form diastereomeric mixtures **13a**−**c**/**14a**−**c** of cyclization products (66, 86, and 68% yield). Protection of the second carbonyl group as a ketal in the bottom side chain was also required for this first aldol cyclization. Enolate formation under basic conditions in a 1,3-diketo bottom side chain would significantly reduce the electrophilicity of the C-3′ carbonyl group and thus prevent addition of C-1″ to C-3′ or give rise to mixtures of aldol condensation products. A low selectivity in the formation of the diastereomeric acyclic β-hydroxy ketones **13a**−**c** and **14a**−**c** was observed (**a**, 1.4:1; **b**, 2.4:1; **c**, 2.4:1). A separation could be achieved in the case of **13b**/**14b** and **13c**/**14c** by crystallization of one isomer. A straightforward assignment of the configuration was not possible on the basis of the NMR spectra because of the absence of a proton on C-2. Fortunately, crystals of good quality for X-ray structure determination of one isomer were obtained, showing that this crystalline isomer can be assigned the *Z*-configura-

(11) Wurm, G.; Geres, U. *Arch. Pharm. (Weinheim)* **1984**, *317*, 606−609.
(12) Grunwell, J. R.; Heinzman, S. W. *Tetrahedron Lett.* **1980**, *21*, 4305−4308.
(13) Adams, R.; Geissman, T. A.; Baker, B. R. *J. Am. Chem. Soc.* **1941**, *63*, 528.
(14) Krohn, K.; Böker, N.; Gauhier, A.; Schäfer G.; Werner, F. *J. Prakt. Chem.* **1996**, *338*, 349−354.
(15) Stille, J. K. *Angew. Chem.* **1986**, *98*, 504−519.
(16) Echavarren, A. M.; Tamayo, N.; Cárdenas, D. J. *J. Org. Chem.* **1994**, *59*, 6075−6083.
(17) Tamayo, N.; Echavarren, A. M.; Paredes, M. C. *J. Org. Chem.* **1991**, *56*, 6488−6491.
(18) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(19) Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1988**, *29*, 6893−6896.
(20) Wagner, C.; Eckardt, K.; Schumann, G.; Ihn, W.; Tresselt, D. *J. Antibiot.* **1984**, *37*, 691−692.
(21) Eckardt, K.; Tresselt, D.; Schumann, G.; Ihn, W.; Wagner, C. *J. Antibiot.* **1985**, *38*, 1034−1039.
(22) Krohn, K.; Roemer, E.; Top, M.; Wagner, C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1151−1152.

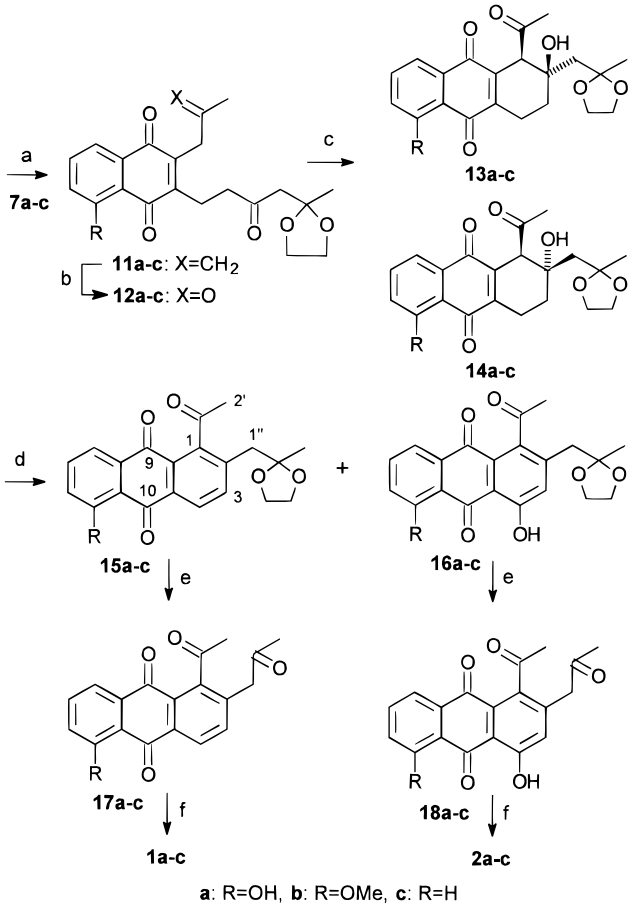
tion **13c** (Figure 1 in the Supporting Information shows the molecular structure of **13c**). Interestingly, a second independent molecule in the asymmetric unit shows a different conformation by 180° rotation about the C11−C17 bond (not shown). By comparing the integrals in the NMR spectra of the diastereomeric mixtures **13a**−**c**/**14a**−**c** it could be shown that the major products including the two crystalline isomers **13b** and **13c** have the *Z*-configuration.

The primary cyclization products **13a**−**c**/**14a**−**c** are possible precursors for the large group of biologically active angucyclines that are *not* aromatic in ring B. In the present study we focused our interest on the synthesis of the simpler aromatic representatives related to tetrangomycin (**1a**) and rabelomycin (**2a**). Thus, the next steps in the synthesis would be β-elimination of the hydroxy group followed by dehydrogenation to anthraquinone derivatives such as **15a**−**c**. However, the β-hydroxy ketones **13a**−**c**/**14a**−**c** were surprisingly stable and resisted the usual procedures for β-elimination, and no definite products could be isolated under a great variety of reaction conditions. An explanation could be that deprotonation at C-1 required for E2 elimination is disfavored because the negatively charged oxygen of the *planar* enolate would electronically and sterically interact with the angular quinone carbonyl group.

Therefore, we checked if the initial *dehydrogenation* with *N*-methylmorpholine *N*-oxide (NMO), a reagent introduced by Sulikowski et al.[23] into angucycline chemistry, would enhance water elimination and aromatization. This was in fact the case, and the desired aromatization products **15a**−**c** could be isolated in good yields (91, 84, and 76%) using a moderate excess of NMO. However, to our surprise and delight addition of a *larger* excess of NMO introduced a phenolic hydroxy group and **16a**−**c** were the major reaction products (54, 72, and 73% yield). Kim and Sulikowski[23] postulated a tautomeric quinone methide as a Michael acceptor of the nucleophilic NMO-oxygen as the initial step in the reaction sequence. However, reductive elimination with concomitant aromatization was observed in their examples, whereas the oxygenation at C-4 in our case required a *second* oxidation step (perhaps at C-1) to introduce a new phenolic hydroxy group at C-4. This step necessarily must occur at the stage of some intermediates prior to aromatization to **15a**−**c** because the anthraquinones **15a**−**c** are perfectly inert to NMO-treatment. For synthetic purposes, the unexpected hydroxylation step was very welcome. The tetrangomycin series **15a**−**c** as well as the rabelomycins **16a**−**c** could be prepared selectively by appropriate choice of the reaction conditions.

The final steps of the reaction sequence leading to **1a**−**c** and **2a**−**c** required the deprotection of the ketal. When the heterogeneous system silica gel/sulfuric acid/dichloromethane[24] was used, the diketones **17a**−**c** and **18a**−**c** were obtained in 78−96% yield. Again, two modes of cyclization are theoretically possible by base treatment of the diketones **17a**−**c** and **18a**−**c**. We expected that anion formation at the acetyl side chain at C-1, acidified by conjugation to the anthraquinoid system, would be the initial step under the mild basic kinetically controlled conditions (0.2 N KOH in methanol at −20 °C) in agreement with the related experiment of Yamaguchi et al.[3] Our expectation was fulfilled, and all of the four racemic natural products tetrangomycin (**1a**),[25,26] 8-*O*-methyltetrangomycin (**1b**)[27] (MM 47755),[28] rabelomycin (**2a**),[29] and 8-*O*-methylrabelomycin (**2b**)[27] as well as the not naturally occuring 8-deoxyproducts **1c** and **2c** were isolated in good to excellent yields (67−92%). Traces of the fully aromatized benzo[*a*]anthracene quinones related to tetrangulol[30] were also detected by TLC.

Scheme 3[a]



[a] Key: (a) $(n\mathrm{Bu_3Sn})_2O$, toluene, 80 °C, 24 h (**11a**, 65%; **11b**, 78%; **11c**, 83%); (b) $OsO_4/NaIO_4$, dioxane, 20 °C (**12a**, 78%; **12b**, 77%; **12c**, 81%); (c) K_2CO_3/2-PrOH, 20 °C, 4 h (**13a**/**14a**, 66%; **13b**/**14b**, 86%; **13c**/**14c**, 68%); (d) 1,2 equiv of NMO, CH_2Cl_2, 40 °C (**15a**, 91%; **15b**, 84%; **15c**, 76%); (d) 14 equiv of NMO, CH_2Cl_2, 40 °C (**16a**, 54%; **16b**, 72%; **16c**, 73%); (e) SiO_2, H_2SO_4/CH_2Cl_2 (**17a**, 96%; **17b**, 94%; **17c**, 92%; **18a**, 78%; **18b**, 93%; **18c**, 91%); (f) 0.2 N KOH, MeOH (**1a**, 90%; **1b**, 83%; **1c**, 70%; **2a**, 92%; **2b**, 88%; **2c**, 67%).

Experimental Section

For instrumentation and general procedures see ref 31.

5-Acetoxy-2-bromo-3-(bromomethyl)-[1,4]naphthoquinone (3d). A solution of 5-acetoxy-2-bromo-3-methyl-[1,4]-

(23) Kim, K.; Sulikowski; G. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2396−2398.
(24) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63−65.
(25) Kunstmann, M. P.; Mitscher, L. A. *J. Org. Chem.* **1966**, *31*, 2920−2925.
(26) Dann, M.; Lefemine, D. V.; Barbatschi, F.; Shu, P.; Kuntsmann, M. P.; Mitscher, L. A.; Bohonos, N. *Antimicrob. Agents Chemother.* **1965**, 832−835.
(27) Shigihara, Y.; Koizumi, Y.; Tamamura, T.; Homma, Y.; Isshiki, K.; Dobashi, K.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1988**, *41*, 1260−1264.
(28) Gilpin, M. L.; Balchin, J.; Box, S. J.; Tyler, J. W. *J. Antibiot.* **1989**, *42*, 627−628.
(29) Liu, W.-C.; Parker, W. L.; Slusarchyk, D. S.; Greenwood, G. L.; Graham, S. F.; Meyers, E. *J. Antibiot.* **1979**, *23*, 437−441.
(30) Brown, P. M.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 997−1000.

naphthoquinone (prepared from 1,5-diacetoxynaphthalene by NBS bromination[12] followed by radical methylation[11]) (3.0 g, 9.71 mmol), NBS (2.08 g, 11.65 mmol), and AIBN (100 mg, 0.61 mmol) in acetic acid anhydride (40 mL) was heated for 1.5 h to 90 °C (TLC control). The reaction mixture was then poured onto ice (ca. 250 g), and the precipitate was filtered off, washed with water, and dissolved in dichloromethane. The solution was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure until crystallization began, which was completed by addition of diethyl ether to afford **3d** (3.2 g, 85%) as yellow needles: mp 182 °C; IR (KBr) 1768 (C═O, ester), 1676 (C═O, quinone), 1662 (C═O, quinone), 1604, 1588 (arom C═C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 206 nm (4.18), 246 (3.70), 278 (3.85), 344 (3.20); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.47 (s, 3 H, CH_3CO_2), 4.56 (s, 2 H, CH_2Br), 7.43 (d, ^3J = 7.9 Hz, 1 H, 6-H), 7.78 (dd, ^3J = 7.9 Hz, 1 H, 7-H), 8.14 (d, ^3J = 7.9 Hz, 1 H, 8-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.08 (q, CH_3CO_2), 25.47 (t, CH_2Br), 122.81 (s, C-4a), 126.28 (d, C-6), 130.56 (d, C-8), 132.73 (s, C-8a), 135.16 (d, C-7), 139.61 (s, C-2), 147.13 (s, C-3), 150.24 (s, C-5), 169.20 (s, CH_3CO_2), 176.90 (s, C-4), 177.97 (s, C-1); MS (EI/75 °C) *m*/*z* 390 (1.3)/388 (2.5)/386 (1.2) [M^+], 348 (50)/346 (100)/344 (54) [$M^+ + 1 - CH_3CO$], 268 (20)/267 (20)/266 (20)/265 (20) [$M^+ + 1 - CH_3CO - Br$], 43 (46) [CH_3CO^+]. Anal. Calcd for $C_{13}H_8O_4Br_2$: C, 40.24; H, 2.08. Found: C, 40.14; H, 2.11.

2-Bromo-3-(bromomethyl)-5-hydroxy-[1,4]naphthoquinone (3a). A solution of acetic ester **3d** (7.0 g, 18.0 mmol) and 4-toluenesulfonic acid (3.5 g, 18.4 mmol) in methanol (145 mL) was heated for 2.5 h under reflux (TLC control). The reaction mixture was cooled to 20 °C, and the precipitate was filtered off to afford after recrystallization from CH_2Cl_2/Et_2O **3a** (4.12 g, 66%) as orange red needles. The mother liquors were evaporated to dryness at reduced pressure, dissolved in CH_2Cl_2, washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and water (50 mL), and dried (Na_2SO_4). The solution was then chromatographed on silica gel (CH_2Cl_2) to yield from the less polar fraction additional **3a** (1.12 g, total yield 5.24 g, 84%), mp 125 °C. From the polar fraction 0.59 g (11%) of 2-bromo-5-hydroxy-3-(methoxymethyl)-[1,4]naphthoquinone were obtained in the form of light orange needles: mp 108 °C; IR (KBr) 3051 (ArH), 2987 (CH), 2929 (CH), 1674 (C═O, quinone), 1637 (C═O, quinone), 1589 (C═C), 1570 (C═C), 1449 (CH) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 218 nm (4.50), 289 (4.09), 432 (3.64); ^1H NMR (200 MHz, $CDCl_3$) δ 4.61 (s, 2 H, CH_2Br), 7.33 (dd, ^4J = 1.4 Hz, ^3J = 8.2 Hz, 1 H, 6-H), 7.66 (dd, ^3J = 7.5, 8.2 Hz, 1 H, 7-H), 7.75 (dd, ^4J = 1.4 Hz, ^3J = 7.5 Hz, 1 H, 8-H), 11.80 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.30 (t, CH_2Br), 114.62 (s, C-4a), 121.47 (d, C-6), 125.75 (d, C-8), 131.35 (s, C-8a), 137.24 (d, C-7), 142.21 (s, C-2), 146.64 (s, C-3), 162.48 (s, C-5), 177.12 (s, C-1, C-4), 185.02 (s, C-1, C-4); MS (EI/55 °C) *m*/*z* 348 (50), 346 (100), 344 (50) [M^+], 267 (24), 239 (54), 237 (54), 186 (52) [$M^+ - 2 \times Br$], 158 (32), 130 (24), 102 (28). Anal. Calcd for $C_{11}H_6O_3Br_2$: C, 38.19; H, 1.75. Found: C, 38.33; H, 1.65.

Data for 2-bromo-5-hydroxy-3-(methoxymethyl)-[1,4]-naphthoquinone: IR (KBr) 2938 (CH), 1680 (C═O, quinone), 1640 (C═O, quinone), 1598 (C═C), 1592 (C═C), 1572 (C═C), 1473, 1454 (CH), 1439, 1393, 1369, 1348, 1267 (CO), 1232 (CO) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 215 nm (4.57), 286 (4.18), 325 (2.99), 430 (3.76); ^1H NMR (200 MHz, $CDCl_3$) δ 3.50 (s, 3 H, OMe), 4.66 (s, 2 H, CH_2OMe), 7.31 (dd, ^4J = 1.4 Hz, ^3J = 8.2 Hz, 1 H, 6-H), 7.64 (dd, ^3J = 7.5, 8.1 Hz, 1 H, 7-H), 7.73 (dd, ^4J = 1.3 Hz, ^3J = 7.5 Hz, 1 H, 8-H), 11.91 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 59.90 (q, OMe), 68.35 (t, CH_2O), 115.10 (s, C-4a), 121.20 (d, C-6), 125.60 (d, C-8), 131.35 (s, C-8a), 136.91 (d, C-7), 143.70 (s, C-2), 145.70 (s, C-3), 162.32 (s, C-5), 177.50 (s, C-1), 186.57 (s, C-4); MS (EI/60 °C) *m*/*z* 298/296 (100) [M^+], 283/281 (93) [$M^+ - CH_3$], 255 (18), 253 (22), 237 (8), 217 (8), 202 (8), 187 (8), 174 (16), 173 (45), 157 (7), 145 (14), 130 (6), 102 (9), 89 (8), 63 (10), 45 (3). Anal. Calcd for $C_{12}H_9O_4Br$: C, 48.51; H, 1.36. Found: C, 48.38; H, 1.49.

2-Bromo-5-hydroxy-3-methyl-[1,4]naphthoquinone (3e). A solution of 5-acetoxy-2-bromo-3-methyl-[1,4]naphthoquinone[11] (2.0 g, 6.5 mmol) and 4-toluenesulfonic acid (325 mg, 2.0 mmol) in methanol (130 mL) was refluxed for 3 h under argon. The solvent was removed under reduced pressure and the residue redissolved in CH_2Cl_2 (50 mL), washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4), and evaporated at reduced pressure. The residue was purified by filtration over a batch of silica gel (CH_2Cl_2) and crystallized from petroleum ether to yield **3e** (1.65 g, 96%), mp 139 °C; IR (KBr) 1671 (quinone C═O) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 214 nm (4.33), 243 (3.77), 285 (4.01), 427 (3.57); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3 H, CH_3), 7.28 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1 H, 6-H), 7.61 (dd, ^3J = 7.8 Hz, 1 H, 7-H), 7.71 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1 H, 8-H), 11.93 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.23 (q, CH_3), 114.41 (s, C-4a), 120.56 (d, C-6), 124.73 (d, C-8), 131.17 (s, C-8a), 136.33 (d, C-7), 139.84 (s, C-2), 148.31 (s, C-3), 161.82 (s, C-5), 176.33 (s, C-1), 187.03 (s, C-4); MS (EI) *m*/*z* 266 (86)/268 (86) [M^+], 187 (100) [$M^+ - Br$]. Anal. Calcd for $C_{11}H_7O_3Br$: C, 49.47; H, 2.64. Found: C, 49.36; H, 2.72.

2-Bromo-3-methyl-5-methoxy-[1,4]naphthoquinone (3f). A solution of **3e** (200 mg, 750 μmol) and methyl iodide (215 mg, 1.5 mmol) in dry acetone (12 mL) was treated with Ag_2O (465 mg, 2 mmol), and the suspension was stirred for 24 h at 20 °C. The solvent was removed under reduced pressure, the residue suspended in CH_2Cl_2 (5 mL) filtered, and the filtrate purified by flash chromatography on silica gel to afford **3f** (197 mg, 93%) as yellow needles: mp 139.5 °C (petroleum ether); IR (KBr) 2925 (CH), 1674 (quinone CO), 1655 (quinone CO), 1650, 1586 (arom C═C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 211 nm (4.35), 245 (3.92), 279 (4.00), 399 (3.49); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3 H, CH_3), 4.02 (s, 3 H, OCH_3), 7.31 (d, ^3J = 8.1 Hz, 1 H, 6-H), 7.67 (dd, ^3J = 8.1 Hz, 1 H, 7-H), 7.82 (d, ^3J = 8.1 Hz, 1 H, 8-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.16 (q, CH_3), 56.45 (q, OCH_3), 118.03 (d, C-6), 119.28 (s, C-4a), 120.27 (d, C-8), 133.32 (s, C-8a), 134.89 (d, C-7), 136.11 (s, C-2), 150.22 (s, C-3), 159.91 (s, C-5), 176.49 (s, C-4), 177.88 (s, C-1); MS (EI/80 °C) *m*/*z* 280 (92)/282 (92) [M^+], 201 (100) [$M^+ - Br$]. Anal. Calcd for $C_{12}H_9O_3Br$: C, 51.27; H, 3.23. Found: C, 51.38; H, 3.39.

2-Bromo-3-(bromomethyl)-5-methoxy-[1,4]naphthoquinone (3b). A solution of **3f** (500 mg, 1.78 mmol) was brominated as described for **3d** with NBS (380 mg, 2.14 mmol) and AIBN (18 mg, 0.1 mmol) in acetic acid anhydride (7 mL) (3 h under argon) to yield **3b** (560 mg, 88%): mp 193 °C; IR (KBr) 1675 (quinone CO), 1655 (quinone CO), 1604, 1584 (arom C═C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 215 nm (4.34), 243 (3.90), 281 (3.94), 405 (3.44); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.04 (s, 3 H, OCH_3), 4.61 (s, 2 H, CH_2Br), 7.36 (d, ^3J = 8.0 Hz, 1 H, 6-H), 7.71 (dd, ^3J = 8.0 Hz, 1 H, 7-H), 7.83 (d, ^3J = 8.0 Hz, 1 H, 8-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.97 (t, CH_2Br), 56.62 (q, OCH_3), 118.53 (d, C-6), 118.78 (s, C-4a), 120.53 (d, C-8), 133.17 (s, C-8a), 135.42 (d, C-7), 138.13 (s, C-2), 147.58 (s, C-3), 160.33 (s, C-5), 177.82 (s, C-4), 178.26 (s, C-1); MS (EI/80 °C) *m*/*z* 362 (10)/360 (20)/358 (10) [M^+], 280 (100)/278 (88) [$M^+ - Br$], 253 (18), 251 (18), 200 (22) [$M^+ - 2$ Br]. Anal. Calcd for $C_{12}H_8O_3Br_2$: C, 40.04; H, 2.24. Found: C, 39.91; H, 2.40.

2-[(3-Bromo-8-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoic Acid Methyl Ester (5a). A solution of dibromide **3a** (2.00 g, 5.78 mmol) in dry THF (50 mL) was cooled under nitrogen to −20 °C (solution A). In a second vessel the sodium salt of β-keto ester **4** (2.34 g, 11.58 mmol) was prepared under nitrogen in dry THF (30 mL) by addition of NaH (278 mg, 11.58 mmol) (solution B). Solution B was then added dropwise at −20 °C via a Teflon tube to solution A, and the resulting mixture was stirred for ca. 30 min at −20 °C (TLC control). The reaction was then quenched by addition of a mixture of 1 N HCl (15 mL) and saturated aqueous NH_4Cl, and the mixture was extracted with Et_2O (3 × each 50 mL). The combined organic phases were washed successively with NH_4Cl solution (100 mL) and brine (50 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The residue slowly crystallized (2 d) from a mixture of CH_2Cl_2 (ca. 2−3 mL) and Et_2O (ca. 2 mL) to yield **5a** (2.11 g, 78%) as an orange solid: mp 100 °C; IR (KBr) 3187 (OH), 2985 (CH), 2897 (CH), 1744 (C═O, ester), 1718 (C═O, ketone), 1671 (C═O, quinone),

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1639 (C═O, quinone), 1589 (C═C), 1572 (C═C), 1455 (CH) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 215 nm (4.60), 287 (4.19), 428 (3.78); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 3 H, dioxolane-CH_3), AB-system (δ_A = 2.82, δ_B = 3.05, ^2J = 13.6 Hz, 2 H, 4-H), 3.43 (m, 2 H, quinone-CH_2), 3.70 (s, 3 H, OMe), 3.92 (s, 4 H, OCH_2CH_2O), 4.18 (t, 1 H, 2-H), 7.29 (d, 1 H, 7′-H), 7.59−7.74 (m, 2 H, 6′-H and 5′-H), 11.90 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.75 (q, dioxolane-CH_3), 29.71 (t, quinone-CH_2), 51.35 (t, C-4), 53.24 (q, OMe), 57.18 (d, C-2), 64.89, 65.14 (2 × t, OCH_2CH_2O), 108.30 (s, dioxolane-OCO), 114.71 (s, C-8a′), 121.17 (d, C-7′), 125.31 (d, C-5′), 131.39 (s, C-4a′), 136.91 (d, C-6′), 141.45 (s, C-3′), 149.04 (s, C-2′), 162.26 (s, C-8′), 169.45 (s, C-1), 177.11 (s, C-1′, C-4′), 187.06 (s, C-1′, C-4′), 200.42 (s, C-3); MS (EI/120 °C) *m*/*z* 453/451 (1) [$M^+ - CH_3$], 335/333 (3), 279 (2), 241 (1), 239 (2), 237 (2), 227 (2), 200 (1), 199 (6), 186 (1), 171 (3), 170 (1), 129 (2), 113 (6), 89 (2), 87 (100) [$CH_3C(OCH_2CH_2O)^+$], 59 (2). Anal. Calcd for $C_{20}H_{19}O_8Br$: C, 51.41; H, 4.10. Found: C, 51.27; H, 4.24.

2-[8-Hydroxy-3-(2-methylallyl)-1,4-dioxo-1,4-dihydronaphthalen-2-ylmethyl]-4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoic Acid Methyl Ester (7a). A solution of keto ester **5a** (1.0 g, 2.14 mmol) in dry 1,4-dioxane (20 mL) was treated under argon with $Pd(PPh_3)_4$ (140 mg, 0.12 mmol), CuBr (110 mg, 0.77 mmol), and tributyl(2-methylallyl)stannane[32] (**6**) (830 mg, 2.40 mmol) (compare with ref 10). The mixture was refluxed for ca. 7 h (TLC control), and the solvent was removed under reduced pressure at 40 °C. The residue was redissolved in CH_2Cl_2 (ca. 1−2 mL) and purified by column chromatography on silica gel (elution with petroleum ether and then with a 2:1 mixture of petroleum ether/AcOEt) to yield **7a** (740 mg, 78%) as an orange oil: IR (KBr) 2954 (CH), 2926 (CH), 2855 (CH), 1743 (C═O, ester), 1719 (C═O, ketone), 1655 (C═O, quinone), 1637 (C═O, quinone) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 214 nm (4.49), 273 (4.11), 349 (3.74); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (s, 3H, dioxolane-CH_3), 1.83 (s, 3 H, 2″-CH_3), AB-system (δ_A = 2.82, δ_B = 3.03, ^2J = 13.4 Hz, 2 H, 4-H), 3.13 (d, 2 H, quinone-CH_2), 3.48 (s, 2 H, 1″-H), 3.71 (s, 3 H, OMe), 3.83−3.99 (m, 4 H, OCH_2CH_2O), 4.24 (t, 1 H, 2-H), 4.51, 4.77 (2 × s, 2 H, 3″-H), 7.19−7.27 (m, 1 H, 7′-H), 7.55−7.63 (m, 2 H, 5′-H and 6′-H), 12.05 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.01, 24.62 (2 × q, dioxolane-CH_3 and C-2″-CH_3), 25.82 (t, quinone-CH_2), 34.13 (t, C-1″), 51.73 (t, C-4), 53.11 (d, C-2), 58.29 (q, OMe), 64.84, 65.02 (2 × t, OCH_2CH_2O), 108.29 (s, dioxolane-OCO), 111.78 (t, C-2″-CH_2), 115.77 (s, C-8a′), 119.72 (d, C-7′), 124.29 (d, C-5′), 132.43 (s, C-4a′), 136.65 (d, C-6′), 142.66 (s, C-3′), 145.08 (s, C-2″), 148.44 (s, C-2′), 161.62 (s, C-8′), 169.59 (s, C-1), 183.38 (s, C-1′, C-4′), 190.37 (s, C-1′, C-4′), 201.49 (s, C-3); MS (EI/95 °C) *m*/*z* 442 (4) [M^+], 356 (6) [$M^+ - CH_3C(OCH_2CH_2O) + 1$], 279 (12), 241 (15) [$M^+ - CH_3C(OCH_2CH_2O)CH_2COCHCO_2CH_3$], 240 (38), 225 (8), 167 (15), 149 (46), 113 (4), 97 (4), 87 (100) [$CH_3C(OCH_2CH_2O)^+$], 71 (11), 57 (15). Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.01; H, 6.07.

3-Hydroxy-3-methyl-2-[(2-methyl-1,3-dioxolan-2-yl)-acetyl]-9,10-dioxo-1,2,3,4,9,10-hexahydroanthracene-2-carboxylic Acid Methyl Ester (8). The Lemieux−Johnson[18] reaction was carried out with **7c** (400 mg, 0.94 mmol) as described for **11a** (see below) using OsO_4 solution (2.3 mL, 2 × 10^{-2} M in 2-methyl-2-propanol) and $NaIO_4$ (2 × each 220 mg, 1 mmol) in dioxane (28 mL) and water (28 mL) (24 h) to yield after thin layer chromatography on silica gel (petroleum ether/AcOEt: 2/1) **8** (210 mg, 52%) as a yellow solid: mp 148 °C; IR (KBr) 3470 (OH), 2990 (CH), 2886 (CH), 1750 (ester CO), 1713 (aliph CO), 1661 (quinone CO), 1653 (quinone CO), 1636, 1591 (arom C═C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 204 nm (4.17), 245 (4.26), 269 (4.13); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3 H, dioxolane-CH_3), 1.45 (s, 3 H, C-3 CH_3), 2.87−3.12 (m, 2 H, 1-H, 4-H), AB-system [δ_A = 2.94 (d), δ_B = 3.06 (d), (^2J = 16.1 Hz, 2 H, 2′-H)], 3.22−3.46 (m, 2 H, 1-H, 4-H), 3.77 (s, 3 H, OCH_3), 3.85 (s, 1 H, OH), 3.90 (s, 4 H, OCH_2-CH_2O), 7.67−7.75 (m, 2 H, 6-H, 7-H), 8.03−8.11 (m, 2 H, 5-H, 8-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.97 (q, dioxolane-CH_3), 25.31 (q, C-3 CH_3), 28.92 (t, C-1, C-4), 37.77 (t, C-1, C-4), 50.00 (t, C-2′), 53.49 (q, ester-OCH_3), 65.05 (t, OCH_2CH_2O), 65.14 (t, OCH_2CH_2O), 65.86 (s, C-2), 72.29 (s, C-3), 108.50 (s, dioxolane-OCO), 126.70 (d, C-5, C-8), 126.75 (d, C-5, C-8), 132.38 (s, C-8a, C-10a), 132.51 (s, C-8a, C-10a), 134.03 (d, C-6, C-7), 134.06 (d, C-6, C-7), 141.23 (s, C-9a, C-4a), 142.28 (s, C-9a, C-4a), 172.81 (s, ester CO), 184.17 (s, C-9, C-10), 184.22 (s, C-9, C-10), 201.76 (s, C-1′); MS (EI/100 °C) *m*/*z* 428 (0.3) [M^+], 413 (0.9) [$M^+ - CH_3$], 381 (0.2) [$M^+ - 1 - (CH_3, OCH_3)$], 368 (0.2) [$M^+ - 1 - CO_2CH_3$], 87 (100) [$CH_3C(OCH_2CH_2O)^+$]. Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.34; H, 5.51.

Reaction of 8 with Bis(tributyltin) Oxide. A solution of **8** (80 mg, 0.19 mmol) was treated with bis(tributyltin) oxide (225 mg, 377 mmol) in toluene (2 mL) as described for **11a** (see below) for 10 h. The products were separated by thin layer chromatography on silica gel (petroleum ether/AcOEt: 2/1) to afford the anthraquinone **10** (35 mg, 53%), mp 143 °C, from the less polar fraction and compound **9** (16 mg, 23%), mp 139 °C, from the polar fraction.

Data for 2-methyl-3-[(2-methyl-1,3-dioxolan-2-yl)acetyl]anthraquinone (10): IR (KBr) 2925 (CH), 1718 (aliph CO), 1702, 1676 (aliph CO) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 208 nm (4.72), 252 (4.79), 262 (4.81); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 3 H, dioxolane-CH_3), 2.64 (s, 3 H, C-2 CH_3), 3.38 (s, 2 H, 2′-H), 3.89−3.97 (m, 4 H, OCH_2CH_2O), 7.78−7.87 (m, 2 H, 6-H, 7-H), 8.16 (s, 1 H, 1-H, 4-H), 8.28−8.35 (m, 2 H, 5-H, 8-H), 8.52 (s, 1 H, 1-H, 4-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.68 (q, C-2 CH_3), 25.31 (q, dioxolane-CH_3), 51.08 (t, C-2′), 65.11 (t, OCH_2CH_2O), 108.68 (s, dioxolane-OCO), 127.72 (d, C-5, C-8), 127.80 (2 × d, C-1, C-4, C-5, C-8), 130.68 (d, C-1, C-4), 131.50 (s, C-4a, C-8a, C-9a, C-10a), 133.94 (2 × s, C-4a, C-8a, C-9a, C-10a), 134.45 (s, C-4a, C-8a, C-9a, C-10a), 134.71 (d, C-6, C-7), 134.78 (d, C-6, C-7), 144.15 (s, C-2, C-3), 145.06 (s, C-2, C-3), 182.85 (s, C-9, C-10), 183.15 (s, C-9, C-10), 200.78 (s, C-1′).

Data for 2-hydroxy-2-methyl-3-[(2-methyl-1,3-dioxolan-2-yl)acetyl]-1,2,3,4-tetrahydroanthraquinone (9): IR (KBr) 3441 (OH), 2961 (CH), 2930 (CH), 1674 (quinone CO), 1591 (arom C═C), 1335 cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 215 nm (3.98), 260 (4.17), 332 (3.26); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (s, 3 H, dioxolane-CH_3), 1.44 (s, 3 H, C-2 CH_3), 2.59−3.20 (m, 5 H, 1-H, 2′-H, 3-H, 4-H), 3.59−3.65 (m, 1 H, 1-H, 2′-H, 3-H), 3.75−3.80 (m, 1 H, 1-H, 2′-H, 3-H), 3.99 (s, 4 H, OCH_2CH_2O), 7.67−7.75 (m, 2 H, 6-H, 7-H), 8.03−8.12 (m, 2 H, 5-H, 8-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.26 (q, dioxolane-CH_3), 25.02 (q, C-2 CH_3), 25.68 (t, C-1, C-4), 38.96 (t, C-1, C-4), 53.09 (t, C-2′), 54.99 (d, C-3), 65.05 (t, OCH_2CH_2O), 65.08 (t, OCH_2-CH_2O), 70.99 (s, C-2), 108.76 (s, dioxolane-OCO), 126.70 (d, C-5, C-8), 126.74 (d, C-5, C-8), 132.41 (s, C-8a, C-10a), 132.56 (s, C-8a, C-10a), 134.04 (d, C-6 and C-7), 142.11 (s, C-4a, C-9a), 142.90 (s, C-4a, C-9a), 184.58 (s, C-9 and C-10), 209.38 (s, C-1′); MS (EI/70 °C) *m*/*z* 336 (0.5) [$M^+ - (H_2O, CH_4)$], 335 (2.5) [$M^+ - 1 - (H_2O, CH_4)$], 250 (6) {$M^+ - 1 - [H_2O, CH_3C(OCH_2$-$CH_2O)CH_2]$}, 249 (23), 221 (6), 193 (11), 139 (3), 115 (2), 87 (100) [$CH_3C(OCH_2CH_2O)^+$], 43 (22).

5-Hydroxy-2-(2-methylallyl)-3-[4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutyl]-[1,4]naphthoquinone (11a). A solution of keto ester **7a** (450 mg, 1.02 mmol) and bis(tributyltin) oxide (1.83 g, 3.06 mmol) in dry toluene (6 mL) was stirred under argon for 30 h at 80 °C (TLC control). The mixture was diluted with Et_2O (30 mL) and stirred for 1 min after addition of 0.1 N HCl (50 mL). The phases were separated, the aqueous phase was extracted with Et_2O (3 × each 25 mL), dried (Na_2SO_4), and filtered, and the solvent was removed at reduced pressure. The residue was dissolved in CH_2Cl_2 (ca. 1 mL) and purified by column chromatography on silica gel (elution first with petroleum ether and then with petroleum ether/AcOEt 2/1) to afford **11a** (254 mg, 65%) as an orange oil: IR (KBr) 3438 (OH), 2925 (CH), 1718 (C═O, ketone), 1655 (C═O, quinone), 1635 (C═O, quinone) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 214 nm (4.44), 275 (3.99), 349 (3.62), 383 (3.49); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 3 H, dioxolane-CH_3), 1.81 (s, 3 H, C-2′-CH_3), 2.69−2.90 (m, 6 H, 1″-H, 2″-H, and 4″-H), 3.39 (s, 2 H, 1′-H), 3.95 (s, 4 H, OCH_2CH_2O), 4.54, 4.78 (2 × s, 2 H, 3′-H), 7.18−7.27 (m, 1 H, 6-H), 7.54−7.64 (m, 2 H, 7-H and 8-H), 12.14 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.64 (t, C-1″), 23.84, 24.90 (2 × q, dioxolane-CH_3 and C-2′-CH_3), 34.35

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(t, C-1′), 43.21 (t, C-2″), 52.14 (t, C-4″), 65.04 (t, OCH_2CH_2O), 108.00 (s, dioxolane-OCO), 111.88 (t, C-3′), 115.49 (s, C-4a), 119.62 (d, C-6), 124.26 (d, C-8), 132.75 (s, C-8a), 136.56 (d, C-7), 142.75 (s, C-2), 146.91 (s, C-2′), 147.76 (C-3), 161.67 (s, C-5), 184.09 (s, C-1, C-4), 190.58 (s, C-1, C-4), 206.19 (s, C-3″); MS (EI/80 °C) *m/z* 384 (3) [M^+], 366 (1), 356 (1), 298 (15) [$M^+ - H_3CC(OCH_2CH_2O) + 1$], 282 (14) [$M^+ - H_3CC(OCH_2CH_2O) - CH_3$], 255 (3), 241 (11) [$M^+ - H_3CC(OCH_2CH_2O)CH_2COCH_2$], 240 (24), 239 (5), 225 (8), 149 (10), 97 (6), 87 (100) [$H_3CC(OCH_2CH_2O)^+$], 71 (7), 57 (8), 43 (13).

5-Hydroxy-3-[4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutyl]-2-(2-oxopropyl)-[1,4]naphthoquinone (12a). A solution of olefin **11a** (200 mg, 0.52 mmol) and $NaIO_4$ (123 mg, 0.58 mmol) in 1,4-dioxane (60 mL) and water (50 mL) was treated with a solution of OsO_4 (0.1 mL of a 0.13 M solution in water) until the starting material was completely converted (ca. 5 h, TLC control). Additional $NaIO_4$ (139 mg, 0.65 mmol) was added, and the mixture was stirred again (5 h, TLC control). The mixture was poured into water and extracted with Et_2O (5 × each 50 mL), the combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure at 40 °C. The residue was purified by column chromatography on silica gel (petroleum ether/AcOEt 1/1) to afford **12a** (157 mg, 78%) as yellow crystals: mp 72 °C; IR (KBr) 2978 (CH), 2884 (CH), 1709 (C=O, ketone), 1655 (C=O, quinone), 1638 (C=O, quinone), 1616 (C=C), 1578 (C=C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 214 nm (4.43), 250 (4.00), 272 (3.98), 420 (3.61); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 3 H, dioxolane-CH_3), 2.35 (s, 3 H, 3″-H), 2.75 (s, 2 H, 4′-H), 2.80 (s, 4 H, 1′-H and 2′-H), 3.92 (s, 2 H, 1″-H), 4.01 (s, 4 H, OCH_2CH_2O), 7.21−7.28 (m, 1 H, 6-H), 7.57−7.59 (m, 2 H, 7-H and 8-H), 12.08 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.83 (t, C-1′), 24.88 (q, dioxolane-CH_3), 30.87 (q, C-3″), 42.09, 43.24 (2 × t, C-2′ and C-1″), 52.06 (t, C-4′), 65.02 (t, OCH_2CH_2O), 108.20 (s, dioxolane-OCO), 115.47 (s, C-4a), 119.60 (d, C-6), 124.52 (d, C-8), 132.15 (s, C-8a), 136.66 (d, C-7), 143.06, 148.54 (2 × s, C-2 and C-3), 161.77 (s, C-5), 183.92 (s, C-1, C-4), 190.25 (s, C-1, C-4), 204.26 (s, C-2″), 206.56 (s, C-3′); MS (EI/90 °C) *m/z* 386 (<1) [M^+], 371 (2) [$M^+ - CH_3$], 300 (1), 285 (2) [$M^+ - CH_3C(OCH_2CH_2O)CH_2COCH_2$], 243 (10), 215 (6), 214 (12), 213 (2), 181 (3), 129 (1), 88 (5), 87 (100) [$CH_3C(OCH_2CH_2O)^+$], 69 (3), 43 (17). Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.38; H, 5.91.

***(Z)*- and *(E)*-1-Acetyl-2,5-dihydroxy-2-(2-methyl-1,3-dioxolan-2-ylmethyl)-1,2,3,4-tetrahydroanthraquinone (13a/14a).** A solution of diketone **12a** (100 mg, 0.26 mmol) in dry 2-propanol (12 mL) was treated with freshly dried K_2CO_3 (334 mg, 2.42 mmol), and the mixture was stirred for 3 h at 20 °C (TLC control). The suspension was filtered, and the filtrate was poured onto a mixture of water (50 mL) and CH_2Cl_2 (50 mL). The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × each 50 mL), and the combined organic phases were successively washed with aqueous NH_4Cl solution (150 mL) and water (100 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure at 30 °C, and the residue was purified by column chromatography on silica gel (petroleum ether/AcOEt 1/1) to yield **13a/14a** (66 mg, 66%) as an unseparable 1.4:1 mixture of diastereoisomers as yellow crystals: mp 130 °C; IR (KBr) 3475 (OH), 2976 (CH), 2941 (CH), 2887 (CH), 1709 (C=O, ketone), 1659 (C=O, quinone), 1637 (C=O, quinone), 1614 (C=C), 1577 (C=C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 213 nm (4.53), 248 (4.06), 273 (4.06), 332 (3.05), 420 (3.72); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29, 1.36 (s, 3 H, dioxolane-CH_3), AB-system (δ_A = 1.79−1.91, δ_B = 2.08−2.21, m, 2 H, 3-H), 1.99−2.05 (m, 2 H, 1″-H), 2.50, 2.54 (s, 3 H, 3′-H), AB-system (δ_A = 2.60−2.80, δ_B = 2.85−3.10, m, 2 H, 4-H), 3.97−4.20 (m, 4 H, OCH_2CH_2O), 4.44 (s, 1 H, 1-H), 4.58, 4.62, (s, 1 H, C-2-OH), 7.17−7.25 (m, 1 H, 6-H), 7.51−7.57 (m, 2 H, 7-H and 8-H), 12.07, 12.08 (s, 1 H, chel OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.63, 22.90 (t, C-4), 25.81, 26.01 (q, dioxolane-CH_3), 29.28, 29.92 (t, C-3), 33.49, 34.18 (q, C-2′), 44.26 (t, C-1″), 55.36, 57.18 (d, C-1″), 64.00, 64.10, 64.16, 64.23 (4 × t, OCH_2CH_2O), 71.53, 73.05 (s, C-2), 111.28, 111.41 (s, C-2″), 115.30 (s, C-10a), 119.32, 119.42 (d, C-6), 124.50, 124.64 (d, C-7), 132.28, 132.37 (s, C-8a), 136.43, 136.54 (d, C-8), 143.04, 143.54 (s, C-9a), 145.70, 146.59 (s, C-4a), 161.71, 161.80 (s, C-5), 183.93, 184.51 (s, C-9, C-10), 190.23 (s, C-9, C-10), 207.77, 208.73 (s, C-1′); MS (EI/100 °C) *m/z* 386 (1) [M^+], 371 (1) [$M^+ - CH_3$], 353 (1), 344 (2), 326 (2) [$M^+ - COCH_3 - OH$], 311 (2) [$M^+ - COCH_3 - OH - CH_3$], 300 (1), 282 (1), 243 (10), 242 (26) [$M^+ - COCH_3 - CH_3C(OCH_2CH_2O)CH_2$], 241 (6), 214 (8), 213 (4), 139 (2), 121 (5), 88 (5), 87 (100) [$CH_3C(OCH_2CH_2O)^+$], 59 (2), 43 (22) [$COCH_3^+$]. Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 64.96; H, 5.57.

1-Acetyl-5-hydroxy-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]anthraquinone (15a). 13a/14a (120 mg, 0.31 mmol) was treated with a solution of NMO monohydrate in CH_2Cl_2 (4.5 mL, 10.3 mg/ml, 1.1 equiv). After 20 min at 40 °C, 0.3 equiv of NMO monohydrate was added, and the volume of the solution was reduced to ca. 0.5 mL. The mixture was stirred until the starting material was converted (TLC control, ca. 40 min). The solution was diluted with CH_2Cl_2 (30 mL) and then successively washed with cold 0.2 N HCl (2 × each 20 mL) and water (25 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (CH_2Cl_2) to yield **15a** (104 mg, 91%) as yellow crystals: mp 140 °C; IR (KBr) 3449 (OH), 2986 (CH), 2937 (CH), 2885 (CH), 1688 (C=O, aryl), 1669 (C=O, quinone), 1636 (C=O, quinone), 1619 (C=C), 1573 (C=C), 1561 (C=C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 218 nm (4.29), 260 (4.38), 343 (3.34), 407 (3.67); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 3 H, dioxolane-CH_3), 2.62 (s, 3 H, 2′-H), AB-system (δ_A = 2.97 (d), δ_B = 3.18 (d), ^2J = 13.7 Hz, 2 H, 1″-H), 3.59−3.68 (m, 2 H, OCH_2CH_2O), 3.88−3.97 (m, 2 H, OCH_2CH_2O), 7.32 (dd, ^4J = 1.4 Hz, ^3J = 8.2 Hz, 1 H, 6-H), 7.67 (dd, ^3J = 7.6, 8.1 Hz, 1 H, 7-H), 7.77 (dd, ^4J = 1.4 Hz, ^3J = 7.5 Hz, 1 H, 8-H), 7.97 (d, ^3J = 8.1 Hz, 1 H, 3-H), 8.27 (d, ^3J = 8.1 Hz, 1 H, 4-H), 12.49 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.11 (q, dioxolane-CH_3), 32.47 (q, C-2′), 41.44 (t, C-1″), 65.23 (t, OCH_2CH_2O), 109.64 (s, dioxolane-OCO), 116.07 (s, C-10a), 120.32 (d, C-6), 125.00 (d, C-7), 126.91 (d, C-3), 130.70 (s, C-8a), 132.41, 133.46 (2 × s, C-4a and C-9a), 137.35 (s, C-8), 138.54 (d, C-4), 140.76 (s, C-2), 145.04 (s, C-1), 162.81 (s, C-5), 183.16 (s, C-9, C-10), 188.40 (s, C-9, C-10), 206.19 (s, C-1′); MS (EI/90 °C) *m/z* 366 (<1) [M^+], 351 (1) [$M^+ - CH_3$], 306 (2), 279 (1), 264 (1), 152 (3), 151 (2), 139 (1), 111 (1), 88 (6), 87 (100) [$CH_3C(OCH_2CH_2O)^+$], 84 (1), 57 (2), 49 (2), 43 (20) [CH_3CO^+]. Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 68.62; H, 4.80.

1-Acetyl-4,5-dihydroxy-2-[(2-methyl-1,3-dioxolane-2-yl)methyl]anthraquinone (16a). A solution of **13a/14a** (43 mg, 0.11 mmol) in CH_2Cl_2 (2.5 mL) was treated with NMO monohydrate (17 mg, 126 mmol). The reaction mixture was stirred for 39 h at 20 °C. During this time an additional 2 equiv of NMO monohydrate was added. Workup as described above gave **16a** (23 mg, 54%) as a yellow, unseparable solid of **15a**/**16a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 3 H, dioxolane-CH_3), 2.56 (s, 3 H, 2′-H), 2.88−3.14 (m, 2 H, 1″-H), 3.60−3.92 (m, 4 H, OCH_2CH_2O), 7.30 (dd, ^4J = 1.3 Hz, ^3J = 8.1 Hz, 1 H, 6-H), 7.49 (s, 1 H, 3-H), 7.63−7.79 (m, 2 H, 7-H and 8-H), 11.97 (s, 1 H, OH), 12.16 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.53 (q, dioxolane-CH_3), 32.42 (q, C-2′), 41.37 (t, C-1″), 65.26 (t, OCH_2CH_2O), 109.58 (s, dioxolane-OCO), 114.50, 115.85 (2 × s, C-4a and C-10a), 120.77 (d, C-6), 125.29 (d, C-7), 128.26 (d, C-3), 130.33 (s, C-8a), 133.46 (s, C-9a), 137.85 (d, C-8), 140.77 (s, C-2), 144.27 (s, C-1), 162.11, 162.77 (2 × s, C-5 and C-4), 182.61 (s, C-9, C-10), 193.01 (s, C-9, C-10), 205.72 (s, C-1′).

1-Acetyl-5-hydroxy-2-(2-oxopropyl)anthraquinone (17a). A suspension of silica gel (1 g) in CH_2Cl_2 (4 mL) was treated with H_2SO_4 (15% in H_2O, 100 mg, 0.17 mmol) and stirred for ca. 15 min. The anthraquinone ketal **15a** (30 mg, 0.08 mmol) was added, and the mixture was stirred until the starting material was converted (overnight, TLC control). The suspension was filtered, the silica gel washed with CH_2Cl_2, and the organic solution evaporated under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2) and crystallized from CH_2Cl_2/Et_2O to afford **17a** (25.3 mg, 96%) as yellow crystals: mp 198 °C; IR (KBr) 3416 (OH), 3081 (CH), 1716 (C=O, aliph ketone), 1691 (C=O, arom ketone), 1671 (C=O, quinone), 1638 (C=O, quinone), 1578 (C=C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 215 nm (4.48), 259 (4.53), 344 (3.49), 407 (3.84); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 3 H, 3″-H),

2.49 (s, 3 H, 2′-H), 3.86 (s, 2 H, 1″-H), 7.33 (dd, ^4J = 1.3 Hz, ^3J = 8.1 Hz, 1 H, 6-H), 7.64 (d, ^3J = 8.0 Hz, 1 H, 3-H), 7.68 (dd, ^3J = 7.6, 8.0 Hz, 1 H, 7-H), 7.70 (dd, ^4J = 1.2 Hz, ^3J = 7.5 Hz, 1 H, 8-H), 8.34 (d, ^3J = 8.0 Hz, 1 H, 4−H), 12.46 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.56 (q, C-3″), 31.98 (q, C-2′), 47.50 (t, C-1″), 116.03 (s, C-10a), 120.41 (d, C-6), 125.28 (d, C-7), 127.97 (d, C-3), 131.08 (s, C-8a), 132.92, 133.27 (2 × s, C-4a and C-9a), 137.46 (d, C-8), 137.65 (d, C-4), 137.94 (s, C-2), 143.98 (s, C-1), 162.95 (s, C-5), 183.03 (s, C-9, C-10), 188.02 (s, C-9, C-10), 204.30 (s, C-2″), 205.53 (s, C-1′); MS (EI/130 °C) *m*/*z* 322 (11) [M^+], 307 (14) [$M^+ - CH_3$], 281 (18), 280 (100) [$M^+ - CH_3CO + 1$], 265 (44), 224 (4), 152 (8), 116 (2), 43 (17) [CH_3CO^+]. Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 70.67; H, 4.21.

1-Acetyl-4,5-dihydroxy-2-(2-oxopropyl)anthraquinone (18a). A mixture of the ketals **15a/16a** (15 mg, containing 11.5 mg of **16a** (NMR), 0.03 mmol) was cleaved as described for **17a** to yield after thin layer chromatography on silica gel **18a** (8 mg, 78%) as yellow crystals: mp 212 °C; IR (KBr) 3416 (OH), 2925 (CH), 2854 (CH), 1716 (C═O, aliph ketone), 1694 (C═O, arom ketone), 1669 (C═O, quinone), 1655 (C═O, quinone), 1600 (C═C), 1561 (C═C) cm^{-1}; UV (methanol) λ_{max} (lg ϵ) 207 nm (4.27), 228 (4.43), 259 (4.28), 433 (3.87); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 3 H, 3″-H), 2.43 (s, 3 H, 2′-H), 3.80 (br s, 2 H, 1″-H), 7.14 (s, 1 H, 2-H), 7.33 (dd, 1 H, 6-H), 7.63−7.80 (m, 2 H, 7-H and 8-H), 11.95 (s, 1 H, OH), 12.22 (s, 1 H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.60 (q, C-3″), 31.93 (q, C-2′), 47.74 (t, C-1″), 114.88, 115.80 (2 × s, C-4a and C-10a), 120.89 (d, C-6), 125.59 (d, C-7), 127.61 (d, C-3), 131.00 (s, C-8a), 133.30 (s, C-9a), 137.26 (s, C-2), 138.00 (d, C-8), 141.38 (s, C-1), 162.81, 162.92 (2 × s, C-5 and C-4), 182.57 (s, C-9, C-10), 192.92 (s, C-9, C-10), 204.09 (s, C-2″), 205.29 (s, C-1′); MS (EI/125 °C) *m*/*z* 338 (28) [M^+], 323 (66) [$M^+ - CH_3$], 297 (20), 296 (100) [$M^+ - CH_3CO^+ + 1$], 281 (76) [$M^+ - CH_3$-$COCH_2^+$], 280 (54), 268 (33), 265 (18), 252 (11), 152 (6), 139 (9), 115 (2), 87 (6), 63 (2), 49 (2), 43 (32) [CH_3CO^+]. Anal. Calcd for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17. Found: C, 67.18; H, 3.98.

3,8-Dihydroxy-3-methyl-3,4-dihydro-2*H*-benzo[*a*]anthracene-1,7,12-trione (Tetrangomycin) (1a). A solution of dione **17a** (10 mg, 0.031 mmol) in KOH (0.2 N in methanol, 14 mL) was stirred at −20 °C under argon for ca. 6.5 h (TLC control). The mixture was neutralized by addition of HCl (0.1 N, 30 mL) and extracted with CH_2Cl_2 (3 × each 20 mL). The organic phase was dried (Na_2SO_4), filtered, and purified by thin layer chromatography on silica gel to afford racemic tetrangomycin (**1a**) (9 mg, 90%) as yellow crystals, mp 182 °C (mp 182−184 °C for natural tetrangomycin, ref 25) and 184−186 °C for racemic tetrangomycin, ref 33). All relevant data of the synthetic material were identical with those published for the natural product.[25] In addition to tetrangomycin, 1 mg (10%) of tetrangulol[25] was isolated.

Rabelomycin (2a). The diketone **18a** (18.5 mg, 55 mmol) was cyclized as described for **1a** to yield racemic rabelomycin **2a** (16 mg, 92%), mp 185 °C (mp 188−189 °C for natural rabelomycin[29]). All relevant data of the synthetic material were identical with those published for the natural product.[29]

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Supporting Information Available: Detailed experimental procedures and spectral data for compounds **1b**−**18b** and **1c**−**18c** including information on the X-ray structure determination of **13c** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(33) Krohn, K.; Khanbabaee, K. *Liebigs Ann. Chem.* **1994**, 1109−1112.