Biomimetic-Type Synthesis of Benzo[*a*]naphthacenequinones Related to Pradimicinone

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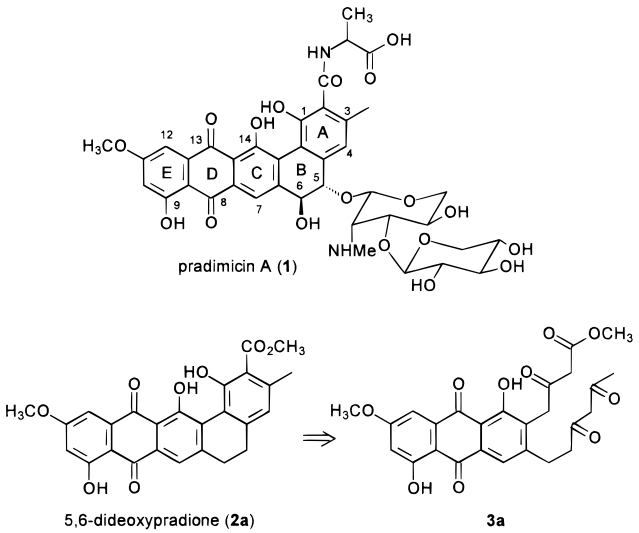
Introduction

The number of known antibiotics with the benzo[*a*]-naphthacenequinone skeleton has grown to more than 20 compounds. The most simple representatives G-2N and G-2A[1] and also derivatives of madurahydroxylactone[2] have antibacterial properties. The structurally more complex *O*-glycosidic pradimicins[3−5] [e.g., pradimicin A (**1**), Scheme 1] and benanomicins[6−8] show remarkable in vivo antifungal activity.[9−14] Mycoses (e.g., by *Pneumotis carnii*) represent severe problems in current therapy of immunodeficient patients, and there is an urgent need for new antimycotic agents.[15] Benanomicins A and B also inhibit infection of T-cells with human immunodeficiency virus (HIV) and syncytium formation by HIV.[11] At least part of the pradimicins' anticandidal effect is attributed to calcium binding of pradimicin A[16−18] and a specific binding of the sugar residues with the cell surface of fungi and viruses.[19] The biological activity depends on the presence of the short peptide chain and the glycosidic sugars at 5-OH as shown in the formula of pradimicin A.

Scheme 1



Recently, an elegant synthesis of the common pradimicin/benanomicin aglycon was described by Suzuki et al.[20] The synthesis was based on an intramolecular Heck reaction to construct the A−C biaryl bond and a samarium iodide-mediated pinacol coupling for the introduction of the two hydroxyl groups at C-5 and C-6. Previously, Diels−Alder approaches aimed at the related 5,6-dideoxy compounds failed to introduce the phenolic group at C-14.[21,22]

We now report on an alternative and efficient biomimetic-type total synthesis of the benzo[*a*]naphthacenequinone 5,6-dideoxypradinone (**2a**), in which the aryl−aryl coupling and the generation of the specific acetogenic substitution pattern of ring A takes place simultaneously by a single-step cyclization of the triketo ester **3a** (Scheme 1). We recently reported on a related biomimetic-type synthesis of G-2N and G-2A.[23] However, the presence in **2** of the phenolic hydroxyl group at C-14 instead of C-7 as in G-2N required a different synthetic strategy for the attachment of the two ketide chains on the

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anthraquinone core. In this strategy, the ketide side chains are placed in vicinal positions of the anthraquinone core to reduce the number of possible aldol condensations. Only two cyclization modes leading to linearly and angularly arranged precursors are possible. In extension to previous work, the present study also provides insight into the experimental conditions that govern these cyclization modes.

Starting Materials

Three types of substitution patterns in the anthraquinone core were investigated. These are the naturally occurring pattern **3a** and the nonnatural patterns as shown in **3b** and **3c**. The synthetic scheme anticipated first the attachment of the bottom side chain by alkylation of the β-keto ester **7** with a benzylic anthraquinone bromide such as **6d** and then the top side chain in a Stille reaction with an allyl stannane. The synthesis of the advanced precursor **8d** for the nonnatural substitution pattern was described previously.[24]

The anthraquinone **6a**, leading to the natural substitution pattern on ring E, was prepared in a Diels−Alder reaction of the chloronaphthoquinone **4** with 1-trimethylsiloxy-3-methyl-1,3-butadiene (**5**), followed by in situ PCC-oxidation of the intermediate allylic silyl ether[25] and subsequent dehalogenation by addition of triethylamine. The regiochemistry was completely directed by the chlorine atom at C-2 of the naphthoquinone.[26] Regioselective ortho-bromination using NBS in the presence of a secondary amine[27] led to the monobromide **6b**. The bromide **8e** was obtained in a similar reaction from the known phenol **8d**.[24] The subsequent benzylic bromination with NBS and the radical starter AIBN required the protection of the phenolic hydroxyl groups by acylation to prevent bromination of the aromatic nucleus. Thus, the phenol **6b** was acetylated to **6c** and brominated to **6d** in 83% overall yield. The bottom side chain was then attached by alkylation of the protected β-keto ester **7** with the benzylic bromide **6d** to afford the ester **8a**. Saponification of **8a** cleaved the methyl ester and deprotected simultaneously the phenolic hydroxyl groups. The resulting acid was then decarboxylated thermally to the required ketone **8b**.

To investigate the effect of the neighboring phenolic hydroxy group on the subsequent Stille coupling with the allylstannane **9**,[23] the phenols **8b** and **8e** were methylated to the corresponding methyl ethers **8c** and **8f**, respectively. Next, the Stille reaction was studied with the two phenols **8b** and **8e** and the two methyl ethers **8c** and **8f**.[28] The procedure of Echavarren et al.[29] was employed using dichloro[1,1′bis(diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$(dppf)][30] or $Pd(PPh_3)_4$ as the catalyst and cuprous bromide as the cocatalyst. Generally, the methyl ethers **10b** and **10d** were formed in better yields than the corresponding phenols **10a** and **10c** (55 and 81% as compared to 45 and 55%, respectively). Yields were lower with the oxygen-substituted more electron-rich bromides **8b** and **8c** corresponding to the natural substitution pattern. The yields were not improved by the modification of the Stille reaction recently proposed by Corey et al.[31]

To study the anticipated biomimetic aldol cyclizations, the protecting enol ether and the ketal in **10** had to be cleaved. Preliminary studies showed that a selective cleavage of the enol ether was possible by careful treatment with dilute HCl. Thus, the reaction of **10c** led to the diketo ester **11a** (52%) and the Michael adduct (**12**) (42%). Michael addition to the unsaturated upper side chain was not possible with the methyl ether **10d** and the yield in the acid-catalyzed cleavage of diketone **11b** increased to 83%. Prolonged treatment of the ketals **10a**, **10c**, and **10d** with stronger acid or higher temperatures afforded the triketo esters **3a**, **3b**, and **3c** which predominately occurred in the enol form (ca. 80%) in $CDCl_3$ solution (NMR analysis).

The stage was now set to study the mild base-catalyzed (K_2CO_3/2-propanol) aldol reactions with the two partially deprotected ketals **11a** and **11b** and the three fully deprotected triketo esters **3a**−**c**. Interestingly, both of the ketals **11a** and **11b** gave a mixture of the "angularly" substituted naphthacenequinones **13a** and **13b** (Scheme 3, path a) and "linearly" substituted (path b) cyclization products **14a** and **14b** in a ca. 2−3:1 ratio. No significant effect of the protection of the phenolic hydroxyl group by methylation on the isomeric ratio was observed. Only angularly arranged cyclization products were found in a previous study with related compounds in which the ketide chains were attached to a naphthoquinone core.[32] The present finding is in agreement with our previous statement that the more C-H-acidic carbon at C-4 acts as the nucleophile to attack the electrophilic carbonyl at C-3″. However, in the present case, anion stabilization at C-4 is phenylogous with respect to the quinone carbonyls in contrast to a greater vinylogous stabilization for the quasi benzylic enolate in the naphthoquinone case studied earlier.[32] Thus, the alternative pathway b, leading to precursors **14a** and **14b** of linearly condensed pentacyclic polyketides, is also realized to some extent with the anthraquinone keto esters of type **12**. Fortunately, a single-crystal X-ray analysis was possible with the tetrahydro naphthacene **13b**, confirming the trans arrangement of the side chains on ring A as shown in Figure 1. The phenol **13a** had the same stereochemistry as deduced by comparison of the NMR spectra that were superimposable in the relevant parts of the spectrum **13b**.

A totally different behavior was found in the base-catalyzed cyclization of the triketo esters **3a**−**c**. In all cases, only one single orange-red colored nonpolar cyclization product could be isolated that proved to be the angularly condensed benzo[*a*]naphthacene derivatives **2a** and **2c**. As expected, the high melting compounds showed relatively strong chelation of 1-OH to the angular neighboring hydroxy or methoxy group (δ = ca. 10 ppm for 1-OH in the ^{1}H NMR spectra). The very poorly soluble cyclization product resulting from **3b** was characterized as the corresponding pivaloate **2b**. No linear condensation products derived from precursors related to **14a/b** nor intermediate aldol products could be detected. Water elimination must occur very rapidly even under the very

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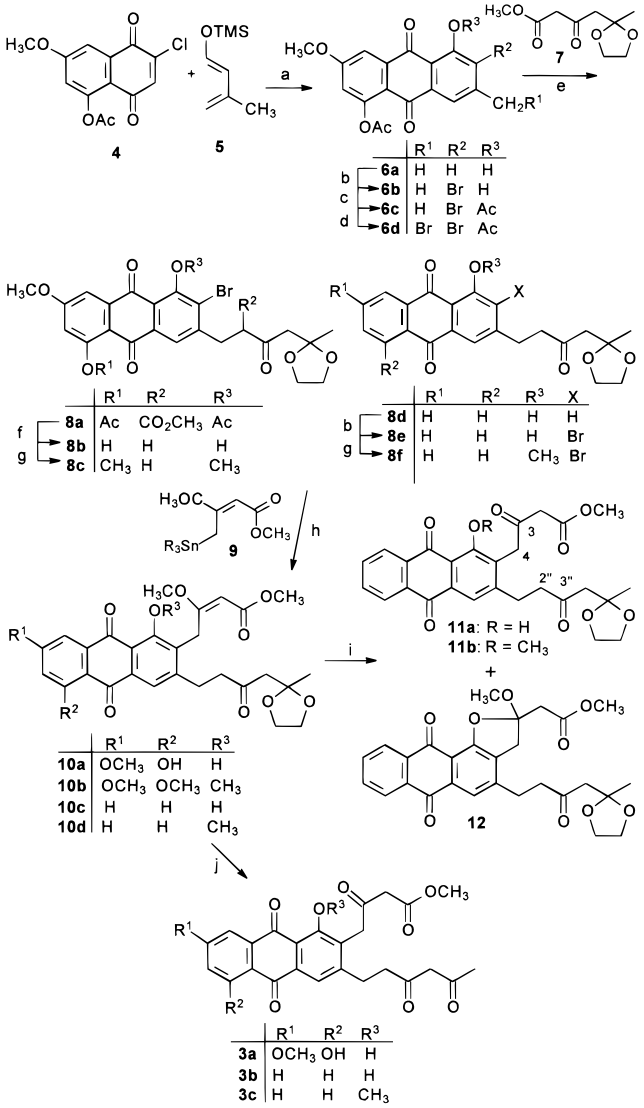
Scheme 2[a]



[a] Key: (a) (1) toluene, 20 °C, 8 h, (2) PCC, AcOH in CH_2Cl_2, rt, 30 h, (3) Et_3N in CH_2Cl_2, rt, 30 min (85%); (b) NBS, $(i\text{-Pr})_2NH$, CH_2Cl_2, rt 1 h, (96%); (c) Ac_2O, H_2SO_4, 25 °C, 2 h (92%); (d) NBS, AIBN, Ac_2O, 115 °C, 3 h (90%); (e) **7**, NaH, THF, 0 °C; TBAI, rt, 5 h (81%); (f) (1) 1 N NaOH, EtOH, 25 °C, 5 h, (2) 100 °C, 10 min (85%); (g) Ag_2O (for **8c**), K_2CO_3 (for **8f**), MeI, (90%); (h) $Pd(PPh_3)_4$, CuBr, dioxane, 95 °C, 7 h, **10a** (45%), **10b** (55%), **10c** (55%), **10d** (81%); (i) CH_2Cl_2, 3 N HCl, 3 d, 20 °C, **11a** (52%), **12** (42%); (j) CH_2Cl_2, concentrated HCl, 3.5 h, 20 °C (80%).

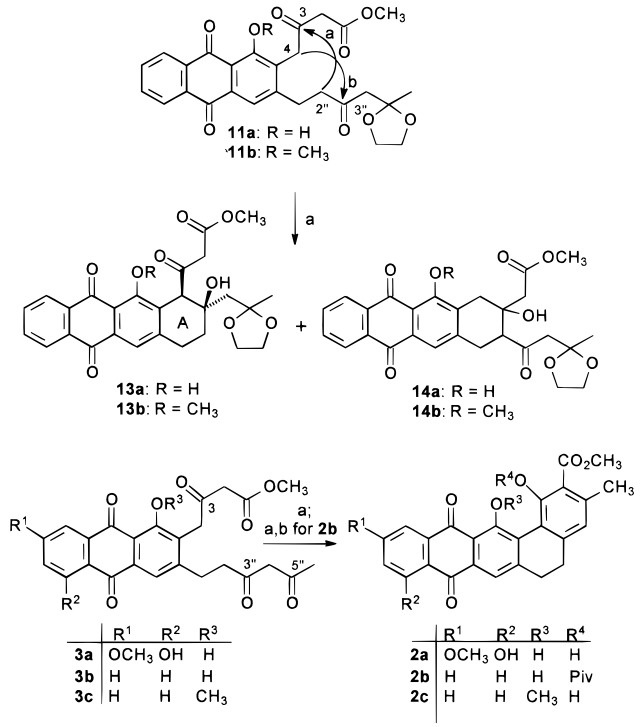
mild conditions. This is in contrast to biomimetic aldol cyclization of this type lacking the ester on C-2.[32] Evidently, the stabilized keto ester enolate facilitates the initial β-elimination of water followed by the easy second elimination to yield the phenolic ring A. Interestingly, also in nature, not a single benzo[*a*]naphthacene polyketide derived antibiotic has yet been isolated with a hydroaromatic ring A in the presence of an ester group at C-2.

In summary, triketoesters of type **3** cyclize under mild basic conditions with complete regioselectivity via two successive aldol reactions and 2-fold elimination of water to yield the pentacyclic benzo[*a*]naphthacenequinones of the pradinone derivatives **2** in a one-pot reaction.

Experimental Section

For general methods and instrumentation see ref 33. The assignments in the NMR spectra were made by two-dimensional NMR experiments.

Scheme 3[a]



[a] Key: (a) K_2CO_3, 2-propanol, CH_2Cl_2, 45 °C, **13a** (57%), **14a** (24%), **13b** (60%), **14b** 22%, **2a** (70%), **2b** (63%), **2c** (69%); (b) CH_2Cl_2·Py, DMAP, PivCl (63%).

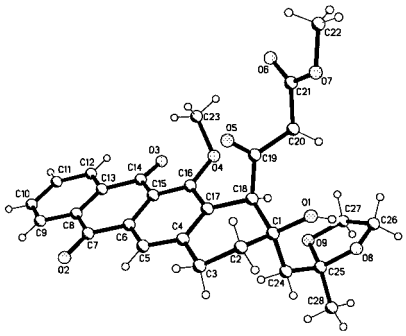


Figure 1. Crystal structure of **13b**.

5-Hydroxy-3-methoxy-7-methyl-9,10-anthraquinon-1-yl Acetate (6a). A solution of naphthoquinone **4**[34] (500 mg, 1.78 mmol) in toluene (10 mL) was treated under argon with a solution of the diene **5**[26] (1.02 g, 3.56 mmol) in toluene (5 mL). After the mixture was stirred for 8 h (TLC monitoring), the solvent was evaporated and the residue redissolved in diethyl ether. Pyridinium chlorochromate (PCC, 765 mg, 3.56 mmol) and acetic acid (2 mL) were then added, and stirring was continued for 12 h. The solution was filtered over a short column of silica gel and the solvent removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (10 mL) and the intermediate chloride dehalogenated by addition of triethylamine (359 mg, 3.56 mmol). The reaction was quenched after 1 h by addition of HCl (0.1 N, 20 mL), the aqueous phase was extracted with CH_2Cl_2 (50 mL), and the combined organic phases were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue crystallized from CH_2Cl_2/Et_2O to afford **6a** (500 mg, 85%): mp 194−196 °C as yellow needles; UV (methanol) λ_{max} (log ϵ) 387 nm (3.64), 339 (3.46), 273 (4.31),

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215.5 (4.23); IR (KBr) $\tilde{\nu}$ 3425 cm^{-1} (OH), 3083 (CH), 2916 (CH), 1766 (C=O, ester), 1666 (C=O), 1641 (C=O), 1597 (C=C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3 H, $COCH_3$), 2.50 (s, 3 H, 7′-CH_3), 4.00 (s, 3 H, OCH_3), 6.91 (d, $J_{2,4}$ = 2.5 Hz, 1 H, 2′-H or H-4′), 7.06 (d, 1 H, 6′-H or 8′-H), 7.56 (d, $J_{2,4}$ = 2.5 Hz, 1 H, 2′-H or H-4′), 7.73 (d, 1 H, 6′-H or 8′-H), 12.38 (s, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.61 (q, $COCH_3$), 22.73 (q, 7′-CH_3), 56.61 (q, OCH_3), 110.04 (d, C-2′ or C-4′), 114.02 (s, C-4a′ or C-9a′), 116.39 (d, C-2′or C-4′), 119.03 (s, C-4a′ or C-9a′), 121.17 (d, C-6′ or C-8′), 123.71 (d, C-6′ or C-8′), 134.27, 137.48 (2 × s, C-8a′ and C-10a′), 149.49 (s, C-7′), 152.98 (s, C-1′ or C-5′), 162.95 (s, C-1′ or C-5′), 164.78 (s, C-3′), 169.27 (s, $COCH_3$), 180.65, 187.36 (2 × s, C-9′and C-10′); MS (EI/185 °C) *m*/*z* 327 (2) [M^+ + 1], 284 (46), [M^+ + 1 − $COCH_3$], 267 (2) [M^+ − $OCOCH_3$], 43 (100) [$COCH_3^+$]. Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.47; H, 4.41.

6-Bromo-5-hydroxy-3-methoxy-7-methyl-9,10-anthraquinon-1-yl Acetate (6b). A solution of **6a** (480 mg, 1.47 mmol) and diisopropylamine (2 drops) in dry CH_2Cl_2 (5 mL) was treated dropwise with a solution of NBS (393 mg, 2.20 mmol) in dry CH_2Cl_2 (5 mL). The mixture was stirred for 1 h at 20 °C (TLC monitoring), diluted with CH_2Cl_2 (30 mL), and washed with 0.1 N HCl (10 mL) and water (30 mL). The organic phase was dried (Na_2SO_4) and filtered over a short column of silica gel (CH_2Cl_2), and the solvent was removed under reduced pressure to afford **6b**, 572 mg (96%), as yellow needles: mp 223 °C; UV (methanol) λ_{max} (log ϵ) 495 nm (3.26), 405 (3.61), 340 (3.41), 335 (3.41), 273 (4.37), 216 (4.22); IR (KBr) $\tilde{\nu}$ 3433 cm^{-1} (OH), 3093 (CH), 2940 (CH), 1770 (C=O, ester), 1664 (C=O), 1687 (C=O), 1600 (C=C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.50 (s, 3 H, $COCH_3$), 2.58 (s, 3 H, 7′-CH_3), 4.02 (s, 3 H, OCH_3), 6.93−6.95 (d, $J_{2,4}$ = 2.7 Hz, 1 H, 2′-H or 4′-H), 7.65 (d, $J_{2,4}$ = 2.7 Hz, 1 H, 2′-H or 4′-H), 7.76−7.77 (s, 1 H, 8′-H), 13.18 (s, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.58 (q, $COCH_3$), 24.75 (q, CH_3), 56.68 (q, OCH_3), 110.34 (d, C-2′ or C-4′), 114.31 (s, C-6′), 116.83 (d, C-2′or C-4′), 118.89 (s, C-8a′ or C-10a′), 120.66 (C-4a′ or C-9a′), 121.58 (d, C-8′), 132.33 (s, C-4a′ or C-9a′), 136.61 (s, C-8a′ or C-10a′), 149.21 (s, C-7′), 153.07 (s, C-1′ or C-5′), 159.36 (s, C-1′ or C-5′), 164.97 (s, C-3′), 169.72 (s, $COCH_3$), 180.05, 187.48 (2 × s, C-9′ and C-10′); MS (EI/191 °C) *m*/*z* (%) 404/406 (11) [M^+], 362 (100) [M^+ − $COCH_3$], 334 (5), 305 (5), 362 (50), 281 (2) [M^+ − Br − $COCH_3$], 43 (47) [$COCH_3^+$]. Anal. Calcd for $C_{18}H_{13}BrO_6$: C, 53.36; H, 3.23. Found: C, 53.02; H, 2.98.

5-Acetoxy-2-bromo-7-methoxy-3-methyl-9,10-anthraquinon-1-yl Acetate (6c). A solution of the phenol **6b** (590 mg, 1.45 mmol) in acetic anhydride (12 mL) was treated with concentrated H_2SO_4 (0.3 mL), and the mixture was stirred for 2 h at 20 °C. The reaction was then quenched by addition of ice−water (10 mL), and the precipitate was filtered off and crystallized from CH_2Cl_2/Et_2O to yield the diacetate **6c** (600 mg, 92%) as yellow crystals: mp 222 °C; UV (methanol) λ_{max} (log ϵ) 339 nm (3.71), 273 (4.47), 215.5 (4.34); IR (KBr) $\tilde{\nu}$ 3093 cm^{-1} (CH), 2940 (CH), 1773 (C=O, ester), 1673 (C=O), 1605, 1585 (C=C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.50 (s, 3 H, $COCH_3$), 2.56 (s, 3 H, $COCH_3$), 2.61 (s, 3 H, 7′-CH_3), 3.99 (s, 3 H, OCH_3), 6.90−6.91 (d, $J_{6,8}$ = 2.7 Hz, 1 H, 6′-H or 8′-H), 7.66−7.67 (d, $J_{6,8}$ = 2.7 Hz, 1 H, 6′-H or 8′-H), 8.08 (s, 1 H, 4′-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.37 (q, $COCH_3$), 21.53 (q, $COCH_3$), 24.57 (q, CH_3), 56.57 (q, OCH_3), 110.16 (d, C-6′ or C-8′), 116.28 (d, C-6′or C-8′), 118.20 (s, C-2′), 123.29 (s, C-4a′ or C-9a′), 127.18 (d, C-4′), 128.22 (C-4a′ or C-9a′), 134.33 (2 × s, C-8a′ and C-10a′), 137.70 (s, C-3′), 147.22 (s, C-1′ or C-5′), 152.55 (s, C-1′ or C-5′), 164.99 (s, C-7′), 168.65 (s, $COCH_3$), 169.66 (s, $COCH_3$), 179.87 (s, C-9′ or C-10′), 180.43 (s, C-9′ or C-10′); MS (EI/161 °C) *m*/*z* 446/448 (5) [M^+], 406 (18) [M^+ + 3 − $COCH_3$], 366 (75) [M^+ − Br], 305 (5), 43 (100) [$COCH_3^+$]. Anal. Calcd for $C_{20}H_{15}79BrO_7$: C, 53.71; H, 3.38. Found: C, 53.49; H, 3.28.

5-Acetoxy-2-bromo-3-bromomethyl-7-methoxy-9,10-anthraquinon-1-yl Acetate (6d). A solution of **6c** (450 mg, 1.01 mmol), NBS (213 mg, 1.2 mmol), and AIBN (50 mg, 0.3 mmol) in acetic anhydride (12 mL) was refluxed for 3 h. The mixture was poured into water, stirred until the hydrolysis of the anhydride was completed, and then filtered off. The crystals were dissolved in CH_2Cl_2, the solution was filtered through a short column of silica gel, and the eluate was evaporated at reduced pressure to afford **3d** as yellow crystals: 477 mg (90%); mp 195.3 °C; UV (methanol) λ_{max} (log ϵ) 322 nm (4.05), 275.5 (4.62), 217.5 (4.58); IR (KBr) $\tilde{\nu}$ 3436 cm^{-1} (OH), 2939 (CH), 2841 (CH), 1776 (C=O, ester), 1675 (C=O), 1687 (C=O), 1602, 1585 (C=C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.51 (s, 3 H, $COCH_3$), 2.58 (s, 3 H, $COCH_3$), 4.00 (s, 3 H, OCH_3), 4.70 (s, 2 H, CH_2Br), 6.94 (d, $J_{8,6}$ = 2.5 Hz, 1 H, 6′-H or 8′-H), 7.65 (d, $J_{8,6}$ = 2.5 Hz, 1 H, 6′-H or 8′-H), 8.30 (s, 1 H, 4′-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.39 (q, $COCH_3$), 21.57 (q, $COCH_3$), 32.15 (t, CH_2Br), 56.67 (q, OCH_3), 110.38 (d, C-6′ or C-8′), 116.55 (d, C-6′or C-8′), 118.19 (s, C-2′), 125.06 (s, C-8a′ or C-10a′), 127.67 (d, C-4′), 127.73 (s, C-4a′ or C-9a′), 134.87 (s, C-4a′ or C-9a′), 137.65 (s, C-8a′ or C-10a′), 145.11 (s, C-3′), 148.49 (s, C-1′ or C-5′), 152.78 (s, C-1′ or C-5′), 165.25 (s, C-7′), 168.53 (s, $COCH_3$), 169.72 (s, $COCH_3$), 179.21 (s, C-9′ or C-10′), 180.34 (s, C-9′ or C-10′); MS (EI/164 °C) *m*/*z* 526 (2) [M^+], 520 (10), 484 (20) [M^+ + 1 − $COCH_3$], 442 (55) [M^+ + 2 − 2 × $COCH_3$], 404 (8) [M^+ + 1 − Br − $COCH_3$], 362 (50) [M^+ + 2 − 2 × $COCH_3$ − Br], 43 (100) [$COCH_3^+$]. Anal. Calcd for $C_{20}H_{14}Br_2O_7$: C, 45.66; H, 2.68. Found: C, 46.24, H, 2.70.

Methyl 2-(4,8-Diacetoxy-3-bromo-6-methoxy-9,10-dioxo-9,10-dihydroanthracen-2-ylmethyl)-4-(2-methyl[1,3]-dioxolan-2-yl)-3-oxobutanoate (8a). A solution of the sodium salt of methyl 4-(2-methyl-[1,3]dioxolan-2-yl)-3-oxobutanoate (**7**)[32] (208 mg, 0.95 mmol, and NaH, 25 mg, 1.02 mmol) in 5 mL of dry THF was added at 0 °C to the solution of the dibromide **6d** (250 mg, 0.475 mmol) and TBAI (20 mg, 54 μmol) in dry THF (10 mL). The mixture was stirred for 5 h at 20 °C (TLC monitoring), diluted by addition of Et_2O (50 mL), and quenched by addition of saturated NH_4Cl solution (40 mL) and of 1 N HCl (2 mL). The aqueous phase was extracted with Et_2O (30 mL), and the combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 99/1) to yield **8a**, 250 mg (81%), as a yellow solid: mp 125 °C; UV (methanol) λ_{max} (log ϵ) 275 nm (4.47), 215 (4.44); IR (KBr) $\tilde{\nu}$ 2985 cm^{-1} (CH), 2945 (CH), 1773 (C=O, ester), 1748 (C=O, ester), 1717 (C=O), 1674 (C=O), 1603, 1585 (C=C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, 3 H, dioxolane-CH_3), 2.50 (s, 3 H, $COCH_3$), 2.56 (s, 3 H, $COCH_3$), AB-system: [δ_A = 2.92, δ_B = 3.02 (d), J_{AB} = 13.8 Hz, 2 H, 4-H], 3.44−3.47 (m, 2 H, CH_2), 3.75 (s, 3 H, ester-OCH_3), 3.97−3.99 (m, 4 H, OCH_2CH_2O), 4.00 (s, 3 H, OCH_3), 4.23−4.35 (m, 1 H, 2-H), 6.91−6.92 (s, $J_{5,7}$ = 2.6 Hz, 1 H, 5′-H or 7′-H), 7.65−7.66 (d, $J_{5,7}$ = 2.7 Hz, 1 H, 5′-H or 7′-H), 8.11 (d, 1 H, 1′-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.38 (q, $COCH_3$), 21.60 (q, $COCH_3$), 24.81 (q, dioxolane-CH_3), 35.24 (t, CH_2), 51.41 (t, C-4), 53.22 (q, ester-OCH_3), 56.63 (q, OCH_3), 58.59 (d, C-2), 64.33 (t, OCH_2CH_2O), 64.58 (t, OCH_2CH_2O), 108.24 (s, dioxolane-OCO), 110.21, 116.49 (2 × d, C-5′ and C-7′), 118.27 (s, C-8a′ or C-10a′), 123.75 (s, C-3′), 128.08 (d, C-1′), 134.23 (s, C-8a′ or C-10a′), 137.66 (2 × s, C-4a′ and C-9a′), 146.88 (s, C-2′), 148.08 (s, C-4′), 152.65 (s, C-6′ or C-8′), 165.07 (2 × s, C-6′ and C-8′), 168.63 (s, $COCH_3$), 169.09 (s, $COCH_3$), 169.80 (s, C-1), 179.70, 180.56 (s, C-9′ and C-10′), 200.49 (s, C-3); MS (EI/212 °C) *m*/*z* 646 (1) [M^+], 603 (0.5) [M^+ − $COCH_3$]. Anal. Calcd for $C_{29}H_{27}BrO_{12}$: C, 53.80; H, 4.20. Found: C, 54.18; H, 4.11.

2-Bromo-1,5-dihydroxy-7-methoxy-3-[4-(2-methyl[1,3]-dioxolan-2-yl)-3-oxbutyl]-9,10-anthraquinone (8b). A solution of ester **8a** (300 mg, 0.46 mmol) in ethanol (15 mL) was stirred for 5 h under nitrogen with 1 N NaOH (15 mL). The mixture was acidified by addition of HCl (1 n, 18 mL) and extracted with AcOEt (30 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated at reduced pressure. The residue was heated for 10 min to 100 °C to effect decarboxylation. Flash chromatography on a short column of silica gel (CH_2Cl_2/MeOH: 98/2) afforded **8b**, 199 mg (85%), as an orange solid: mp 170 °C; UV (methanol) λ_{max} (log ϵ) 355 nm (3.23), 271 (3.95), 260 (3.96), 241 (3.98), 225 (3.94), 204 (3.98); IR (KBr) $\tilde{\nu}$ 3447 cm^{-1} (OH), 2980 (CH), 2937 (CH), 1714, 1607 (C=O), 1637, 1570 (C=C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 3 H, dioxolane-CH_3), 2.87 (s, 2 H, 4′-H), 2.92−3.00 (t, 2 H, 1′-H or 2′-H), 3.15−3.22 (t, 2 H, 1′-H or 2′-H), 3.97 (s, 4 H, OCH_2-CH_2O), 4.00 (s, 3 H, OCH_3), 6.71−6.73 (d, $J_{6,8}$ = 2.5 Hz, 1 H, 6-H or 8-H), 7.37−7.38 (d, $J_{6,8}$ = 2.5 Hz, 1 H, 6-H or 8-H), 7.72 (s, 1 H, 4-H), 12.83 (s, OH), 13.36 (s, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.91 (q, dioxolane-CH_3), 31.56 (t, C-1′ or C-2′), 43.20, (t, C-1′ or C-2′), 52.19 (t, C-4′), 56.57 (q, OCH_3), 65.08 (t, OCH_2-CH_2O), 65.08 (t, OCH_2CH_2O), 107.50 (d, C-6 or C-8), 108.24 (s, dioxolane-OCO), 108.56 (d, C-6 or C-8), 114.87 (s, C-2), 118.27

(s, C-8a or C-10a), 120.63 (t, C-4′), 121.18, 132.00 (2 × s, C-4a and C-9a), 134.62 (s, C-8a or C-10a), 151.44 (s, C-3), 159.95 (s, C-1 or C-5), 166.09 (s, C-1 or C-5), 166.86 (s, C-7), 186.70 (s, C-9 or C-10), 187.56 (s, C-9 or C-10), 206.49 (s, C-3′); MS (EI/186 °C) *m*/*z* 504 (<1) [M^+], 87 (100) [$C_4H_7O_2^+$], 43 (70) [$C_2H_3O^+$]. Anal. Calcd for $C_{23}H_{21}BrO_8$: C, 54.67; H, 4.19. Found: C, 55.68; H, 4.52.

2-Bromo-1,5,7-trimethoxy-3-[4-(2-methyl-[1,3]dioxolan-2-yl)-3-oxobutyl]-9,10-anthraquinone (8c). A suspension of dry, freshly prepared Ag_2O (52 mg, 228 μmol), **8b** (30 mg, 57 μmol), and MeI (64 mg, 456 μmol) in dry CH_2Cl_2 (2 mL) was stirred at 20 °C under nitrogen for 6 h (TLC monitoring). The silver residues were filtered off, the filtrate concentrated at reduced pressure, and the residue was purified by column chromatography on silica gel to yield **8c**, 28 mg (90%), as a yellow solid: mp 90−92 °C; UV (methanol) λ_{max} (log ϵ) 359 nm (3.60), 276 (4.20), 230 (4.19), 225 (4.06), 201 (4.36); IR (KBr) $\tilde{\nu}$ =3426 cm^{-1} (OH), 2982 (CH), 2939 (CH), 1713, 1677 1600 (C=O), 1579 (C=C); ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 3 H, dioxolane-CH_3), 2.84 (s, 2 H, 4′-H), 2.92−3.00 (t, 2 H, 1′-H or 2′-H), 3.15−3.24 (t, 2 H, 1′-H or 2′-H), 4.00 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.03 (s, 4 H, OCH_2CH_2O), 4.04 (s, 3 H, OCH_3), 6.78−6.80 (d, $J_{6,8}$ = 2.38 Hz, 1 H, 6-H or 8-H), 7.43−7.44 (d, $J_{6,8}$ = 2.38 Hz, 1 H, 6-H or 8-H), 7.99 (s, 1 H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.94 (q, dioxolane-CH_3), 31.60 (t, C-1′ or C-2′), 43.45, (t, C-1′ or C-2′), 52.19 (t, C-4′), 56.41 (q, OCH_3), 56.98 (q, OCH_3), 62.01 (q, OCH_3), 65.09 (2 × t, OCH_2CH_2O), 103.72, 104.74 (2 × d, C-6 and C-8), 108.24 (s, dioxolane-OCO), 124.93 (d, C-4), 128.77 (s, C-2), 135.90 (2 × s, C-8a′ and C-10a′), 138.95 (2 × s, C-4a and C-9a), 149.39 (s, C-3), 157.40 (s, C-1 or C-5), 162.63 (s, C-1 or C-5), 165.51 (s, C-7), 180.45 (s, C-9 or C-10), 182.03 (s, C-9 or C-10), 206.02 (s, C-3′); MS (EI/186 °C) *m*/*z* 533 (6) [M^+], 453 (5.6) [M^+ − Br], 437 (6), 87 (100) [$C_4H_7O_2^+$], 43 (44) [$C_2H_3O^+$]; HRMS (EI) calcd for $C_{25}H_{25}BrO_8$ 532.0736, found 532.0736 ± 3 ppm.

Methyl 4-[1,5-Dihydroxy-7-methoxy-3-[4-(2-methyl[1,3]-dioxolan-2-yl)-3-oxobutyl]-9,10-dioxo-9,10-dihydroanthracen-2-yl]-3-methoxy-2-butenoate (10a). A mixture of **8b** (150 mg, 0.30 mmol), the allylstannane **9**[23] (248 mg, 0.59 mmol), Pd-(PPh_3)$_4$ (31 mg, 27 μmol), and CuBr (85 mg, 0.59 mmol) in dry dioxane (15 mL) was heated for 7 h under nitrogen to 95 °C (TLC monitoring). The solution was then filtered through a short column of silica gel, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford **10a**, 73 mg (45%), as a yellow solid: mp 166 °C. IR (KBr) $\tilde{\nu}$ 3425 cm^{-1} (OH), 2991 (CH), 2944 (CH), 1719, 1610 (C=O), 1500 (C=C); UV (methanol) λ_{max} (log ϵ) 258 nm (4.42), 230 (4.47), 209 (4.36), 202 (4.58); ^1H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 3 H, dioxolane-CH_3), 2.82 (s, 2 H, 4″-H), 2.87−2.90 (t, 2 H, 1′-H or 2′-H), 2.97−3.06 (t, 2 H, 1′-H or 2′-H), 3.58 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 3.99 (s, 4 H, OCH_2CH_2O), 4.53 (s, 2 H, 4-H), 5.19 (s, 1 H, 2-H), 6.72−6.73 (d, $J_{6,8}$ = 2.5 Hz, 1 H, 6′-H or 8′-H), 7.39−7.41 (d, $J_{6,8}$ = 2.5 Hz, 1 H, 6′-H or 8′-H), 7.66 (s, 1 H, 4′-H), 12.98 (s, OH), 13.07 (s, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.83 (q, dioxolane-CH_3), 27.90 (t, C-4), 28.24 (t, C-1″ or C-2″), 44.47 (t, C-1″ or C-2″), 51.42 (q, OCH_3), 52.23 (t, C-4″), 56.33 (q, OCH_3), 56.47 (q, OCH_3), 65.04 (2 × t, OCH_2CH_2O), 91.53 (d, C-2), 107.12 (d, C-6′ or C-8′), 108.06 (d, C-6′ or C-8′), 108.26 (s, dioxolane-OCO), 111.07 (s, C-8a′ or C-10a′), 114.87 (s, C-8a′ or C-10a′), 120.16 (d, C-4′), 131.81 (s, C-4a′ or C-9a′), 131.98 (s, C-4a′ or C-9a′), 135.32 (s, C-2′ or C-3′), 151.20 (s, C-2′ or C-3′), 162.47 (s, C-1′ or C-5′), 165.93 (s, C-1′ or C-5′), 168.40 (s, C-7′), 168.67 (s, C-1), 172.57 (s, C-3), 186.54 (s, C-9′ or C-10′), 187.79 (s, C-9′ or C-10′), 206.07 (s, C-3″); MS (EI/200 °C) *m*/*z* 554 (5) [M^+], 87 (100) [$C_4H_7O_2^+$], 43 (10) [$C_2H_3O^+$]; HRMS (EI) calcd for $C_{29}H_{30}O_{11}$ 554.1788, found 554.1793 ± 3 ppm.

Methyl 4-[1,5,7-Trimethoxy-3-[4-(2-methyl[1,3]dioxolan-2-yl)-3-oxobutyl]-9,10-dioxo-9,10-dihydroanthracen-2-yl]-3-methoxy-2-butenoate (10b). The methyl ether **8c** (40 mg, 75 μmol) was alkylated with **9** (62 mg, 150 μmol) as described for **10a** to yield **10b**, 23 mg (55%), as a yellow oil: UV (methanol) λ_{max} (log ϵ) 276 nm (4.18), 230 (4.31), 222 (4.15), 210 (4.13); IR (KBr) $\tilde{\nu}$ 2980 cm^{-1} (CH), 1721 (C=O, ester), 1605 (C=O), 1500 (C=C), 1405; ^1H NMR (200 MHz, $CDCl_3$) δ 1.49 (s, 3 H, dioxolane-CH_3), 2.81 (s, 2 H, 4″-H), 2.84−2.99 (m, 4 H, 1″-H and 2″-H), 3.56 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.00 (s, 4 H, OCH_2CH_2O), 4.02 (s, 3 H, OCH_3), 4.54 (s, 2 H, 4-H), 5.18 (s, 1 H, 2-H), 6.76−6.78 (d, $J_{6,8}$ = 2.3 Hz, 1 H, 6′-H or 8′-H), 7.44−7.45 (d, $J_{6,8}$ = 2.3 Hz, 1 H, 6′-H or 8′-H), 7.90 (s, 1 H, 4′-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.85 (q, dioxolane-CH_3), 27.79 (t, C-4), 28.85 (t, C-1″ or C-2″), 44.51 (t, C-1″ or C-2″), 51.41 (q, OCH_3), 52.26 (t, C-4″), 56.23 (q, OCH_3), 56.34 (q, OCH_3), 56.94 (q, OCH_3), 62.39 (q, OCH_3), 65.04 (2 × t, OCH_2CH_2O), 91.39 (d, C-2), 103.62 (d, C-6′ or C-8′), 104.49 (d, C-6′ or C-8′), 108.26 (s, dioxolan-OCO), 115.99 (s, C-8a′ or C-10a′), 123.67 (s, C-8a′ or C-10a′), 123.86 (d, C-4′), 136.05, 136.77 (2 × s, C-4a′ and C-9a′), 139.54 (s, C-2′ or C-3′), 149.61 (s, C-2′ or C-3′), 159.75 (s, C-1′ or C-5′), 162.49 (s, C-1′ or C-5′), 165 (s, C-7′), 168.49 (s, C-1), 172.57 (s, C-3), 181.17 (s, C-9′ or C-10′), 182.68 (s, C-9′ or C-10′), 206.21 (s, C-3″); MS (EI/252 °C) *m*/*z* 582 (4) [M^+], 87 (100) [$C_4H_7O_2^+$], 43 (20) [$C_2H_3O^+$]; HRMS (EI) calcd for $C_{31}H_{34}O_{11}$ 582.2101, found 582.2095 ± 3 ppm.

Methyl 4-[3-(3,5-Dioxohexyl)-1,5-dihydroxy-7-methoxy-9,10-dioxo-9,10-dihydroanthracen-2-yl]-3-oxobutanoate (3a). A solution of **10a** (20 mg, 34 μmol) in CH_2Cl_2 (6 mL) was treated at 20 °C with concentrated HCl (3 drops), and the mixture was stirred for 3.5 h (TLC monitoring). The solution was dried (Na_2SO_4), and the solvent was removed under reduced pressure and the residue crystallized from CH_2Cl_2/Et_2O to yield **3a**, 13.5 mg (80%), as a yellow solid: mp 192−194 °C, IR (KBr) $\tilde{\nu}$ 3420 cm^{-1} (OH), 3084 (CH), 2924 (CH), 1739 (C=O, ester), 1714, 1641 (C=O), 1625 (C=O), 1600 (C=C); UV (CH_2Cl_2) λ_{max} (log ϵ) 276 nm (4.18), 230 (4.31), 222 (4.15), 210 (4.13); ^1H NMR (200 MHz, $CDCl_3$ enol) δ 2.08 (s, 3 H, 6″-H), 2.63−2.70 (t, 2 H, 1″-H or 2″-H), 2.93−3.04 (t, 2 H, 1″-H or 2″-H), 3.71 (s, 2 H, 2-H), 3.81 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.14 (s, 2 H, 4-H), 5.54 (s, 1 H, 4″-H), 6.74−6.75 (d, $J_{6,8}$ = 2.5 Hz, 1 H, 6′-H or 8′-H), 7.40−7.41 (d, $J_{6,8}$ = 2.5 Hz, 1 H, 6′-H or 8′-H), 7.74 (s, 1 H, 4′-H), 12.94 (s, OH), 13.06 (s, OH), 15.23 (br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.20 (q, C-6″), 28.80 (t, C-1″ or C-2″), 38.34 (t, C-4 or C-2), 39.86 (t, C-4 or C-2), 48.77 (t, C-1″ or C-2″), 52.26 (q, CO_2CH_3), 56.87 (q, OCH_3), 99.87 (d, C-4″), 106.67 (d, C-6′ or C-8′), 107.72 (d, C-6′ or C-8′), 119.50 (d, C-4′), 128.46 (2 × s, C-8a′ and C-10a′), 131.90 (2 × s, C-4a′ and C-9a′), 134.50 (s, C-2′ or C-3′), 149.96 (s, C-2′ or C-3′), 160.91 (s, C-1′ or C-5′), 165.49 (s, C-1′ or C-5′), 166.17 (s, C-7′), 167.26 (s, C-1), 185.66 (s, C-9′ or C-10′), 187.26 (s, C-9′ or C-10′), 198.93, 192.57 (2 × s, C-3″ and C-5″), 206.21 (s, C-3); MS (EI/244 °C) *m*/*z* 496 (3) [M^+], 478 (8) [M^+ − H_2O], 438 (38) [$M^+ - 1 - CO_2CH_3$], 85 (41) [$C_4H_7O_2^+$], 44 (100) [$C_2H_3O^+ - 1$]; HRMS (EI) calcd for $C_{26}H_{24}O_{10}$ 496.1369, found 496.1356 ± 3 ppm.

Methyl (1,9,14-Trihydroxy-11-methoxy-3-methyl-8,13-dioxo-5,6,8,13-tetrahydrobenzo[*a*]naphthacen-2-yl)carboxylate (2a). A solution of **3a** (8 mg, 16 μmol) in dry 2-propanol (3 mL) and dry CH_2Cl_2 (3 mL) was treated with finely ground K_2CO_3 (50 mg, 36 mmol) and refluxed under argon for 3 h (TLC monitoring). The mixture was neutralized by addition of 1 N HCl (5 mL), the aqueous phase was extracted with CH_2Cl_2 (20 mL), the combined organic phases were washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford **2a**, 5.2 mg (70%), as an orange solid: mp 290−292 °C; UV (CH_2Cl_2) λ_{max} (log ϵ) 462 nm (3.96), 289 (4.30), 236 (4.40); ^1H NMR (200 MHz, $CDCl_3$) δ 2.51 (s, 3 H, CH_3), 2.71−2.75 (t, 2 H, 5′-H or 6′-H), 2.86−2.90 (t, 2 H, 5′-H or 6′-H), 3.99 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 6.76−6.78 (d, $J_{10,12}$ = 2.6 Hz, 2 H, 4′-H and 10′-H), 7.24−7.25 (d, $J_{10,12}$ = 2.6 Hz, 1 H, 12′-H) 7.82 (s, 1 H, 7′-H), 10.55 (C-1-OH), 12.94 (s, OH), 14.25 (s, OH); MS (EI/244 °C) *m*/*z* 460 (28) [M^+], 428 (80) [$M^+ - 1 - CH_3O$], 400 (10) [$M^+ - 1 - CO_2CH_3$]; HRMS (EI) calcd for $C_{26}H_{20}O_8$ 460.1158, found 460.1159 ± 3 ppm.

Supporting Information Available: Detailed experimental procedures and spectral data for compounds of non-natural substitution pattern **8e/f**, **10c**−**14b**, and **2b/c**, **3a/b** including information on the X-ray structure determination of **13b** as well as copies of ^1H NMR spectra of compounds **2a**, **3a**,**c**, **8c**, **10a**,**b**,**d**, **11a**,**b**, and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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