Synthesis of a Mumbaistatin Analogue through Cross-Coupling

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Abstract: Studies on the total synthesis of mumbaistatin, the strongest natural inhibitor of G6P-T1, have culminated in the synthesis of a 4″,8-dideoxy analogue. Key steps include a Diels–Alder reaction for the construction of the functionalized anthraquinone, a palladium-catalyzed Stille coupling to generate a tetra-*ortho*-substituted diarylmethane, and a titanium-mediated alkynylation of an aldehyde to complete the carbon skeleton of mumbaistatin. Radical bromination of the methylene bridge afforded a lactone, which resembles the target structure in its cyclized form.

Key words: mumbaistatin, diabetes, anthraquinone, benzophenone, natural product, Diels–Alder reaction, Stille reaction, titanium

The aromatic polyketide mumbaistatin (**1**; Figure 1) is the strongest naturally occurring inhibitor of glucose-6-phosphate translocase (G6P-T1) known today.[1] G6P-T1 is part of the glucose-6-phosphatase (G6Pase) enzyme complex,[2] which catalyzes the release of glucose from glucose-6-phosphate in both pathways of endogenous hepatic glucose production, gluconeogenesis and glucogenolysis. Inhibitors of this enzyme[3] are of high interest for the treatment of the non-insulin-dependent type 2 diabetes mellitus (NIDDM)[4] since G6Pase activity is elevated in animal models of type 2 diabetes and appears to contribute to the excessive hepatic glucose production, and hence to hyperglycemia, that characterizes this disease.[5]

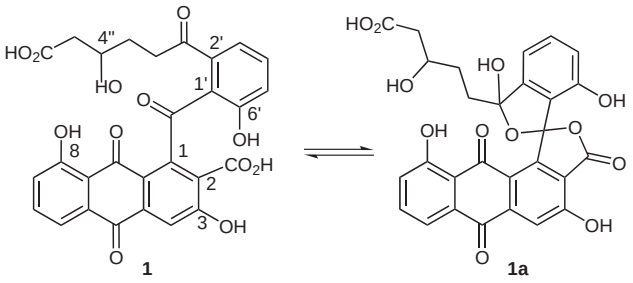
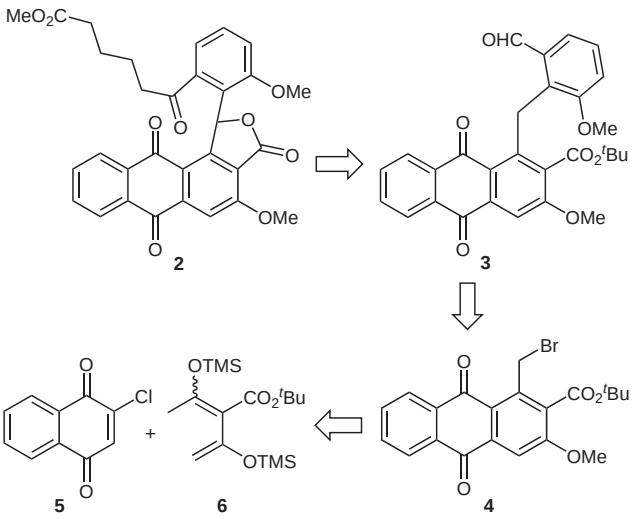


Figure 1 Structure of the open-chain (**1**) and spirocyclic hemiacetal (**1a**) forms of mumbaistatin

Because the control of hyperglycemia in NIDDM cannot satisfactorily be achieved by pharmacological interventions with common antidiabetic drugs, the development of new improved therapeutic approaches represents an important goal.[6] In this sense, the elaboration of synthetic accesses to mumbaistatin and related compounds would pave the way for further biological studies and the discovery of new compounds as potential antidiabetic drugs.

Since the structure of mumbaistatin was elucidated in 2001,[1b] two unrelated synthetic efforts towards this polyketide have been reported by the groups of Schmalz[7] and Krohn.[8] While this has culminated in the preparation of some interesting simplified analogues, the particular problems associated with the total synthesis of mumbaistatin (as a tetra-*ortho*-substituted benzophenone) became apparent, and neither approach allowed for completion of the carbon skeleton of the target structure. We herein disclose a solution to this problem by presenting a synthesis of lactone **2**, which resembles mumbaistatin in its cyclized form (**1a**; Figure 1).



Scheme 1 Retrosynthetic analysis

As shown in Scheme 1, our strategy (retrosynthetic analysis) is based on the consideration that lactone **2** could be derived from the diaryl intermediate **3** upon introduction of the alkyl side chain via nucleophilic addition to the aldehyde and subsequent oxidation (functionalization of the methylene bridge). In the key disconnection, the tetra-*ortho*-substituted diarylmethane **3** is traced back to the substituted anthraquinone **4** which would be equipped with a 'northern' aromatic part by means of metal-catalyzed cross-coupling. The intermediate **4**, in turn, should be accessible from the building blocks **5** and **6** using Diels–Alder methodology.[9]

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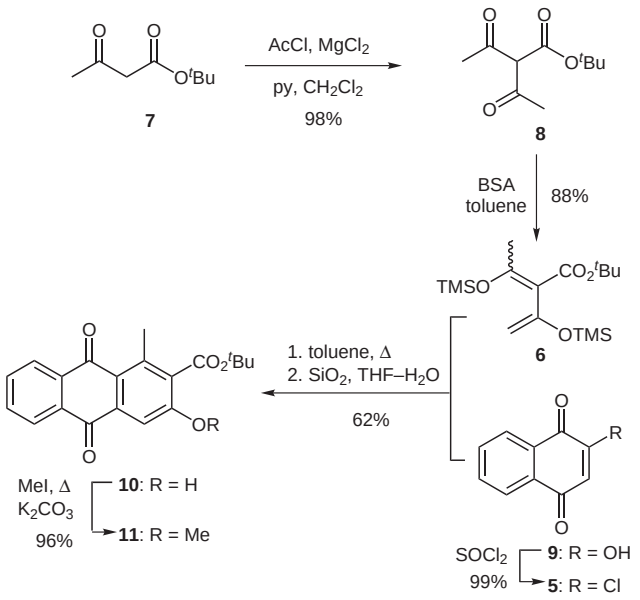
Starting from *tert*-butyl acetoacetate (**7**), reaction with AcCl in the presence of $MgCl_2$ and pyridine afforded the C-acetylated derivative **8**, which upon treatment with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in toluene at room temperature[9b] yielded the diene **6** as a mixture of *E*- and *Z*-isomers (Scheme 2). The dienophile **5** was obtained in quantitative yield from 2-hydroxynaphthoquinone (**9**) by refluxing it with thionyl chloride.



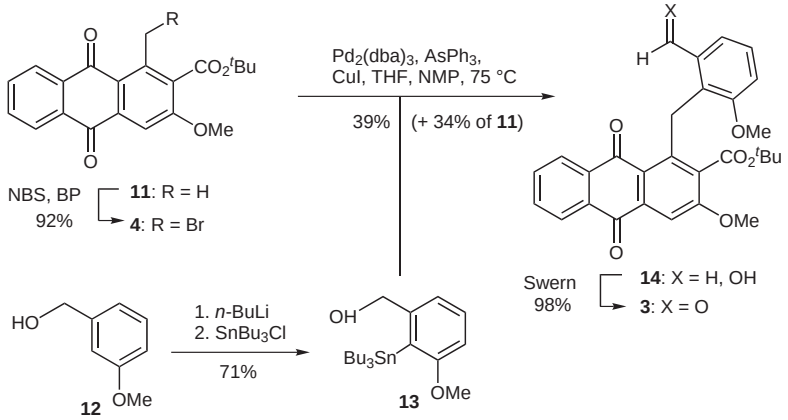
Scheme 2 Synthesis of the anthraquinone **11**

The Diels–Alder reaction between **5** and **6** was performed in refluxing toluene. On treatment of the crude product with wet silica in THF, aromatization and O-desilylation occurred to afford the anthraquinone **10** in 62% yield after purification. Various attempts to improve the yield of this transformation, for instance by addition of a Lewis acid, were not successful.

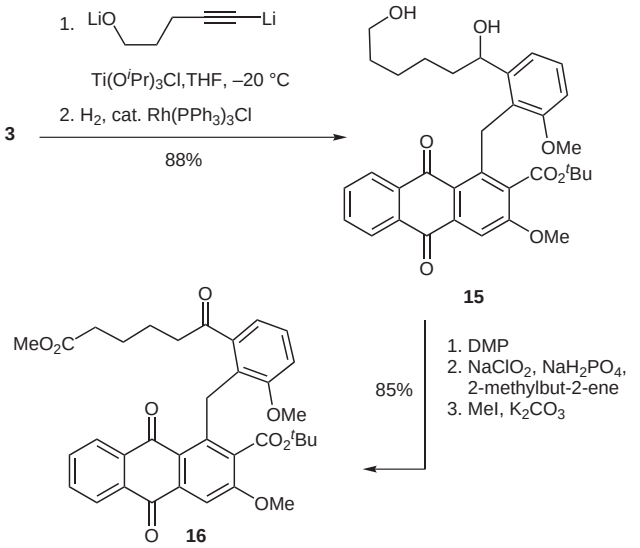
To prepare for the planned coupling step, the anthraquinone **10** was converted into the benzylic brominated derivative **4** in high yield through O-methylation (MeI and K_2CO_3) and subsequent radical bromination of the intermediate **11** using *N*-bromosuccinimide and catalytic amounts of benzoyl peroxide (BP) (Scheme 3). As a method for the connection of the two aromatic parts of the target structure by sp^3–sp^2 cross-coupling,[10] we focused on the Pd-catalyzed Stille reaction[11] since this method is known to be particularly useful for the synthesis of diarylmethanes.[12] However, there were no examples in the literature for the preparation of tetra-*ortho*-substituted diarylmethanes through benzyl–aryl Stille coupling.

As a coupling partner for the benzyl bromide **4** we used the very robust arylstannane **13**,[13] which was obtained by *ortho*-lithiation of commercially available 3-methoxy benzyl alcohol (**12**) with *n*-BuLi (2.2 equiv) in toluene and subsequent quenching of the resulting dianion with tributyltin chloride (Scheme 3). Among several protocols tested for the Stille coupling,[11a] the Farina conditions[14] gave the best results. Thus, when a mixture of **4** and **13** in a 1:1 THF–*N*-methyl-2-pyrrolidone (NMP) solvent mixture was heated to 75 °C for 20 hours under strict exclusion of oxygen in the presence of $Pd_2(dba)_3$ (1 mol%), triphenylarsine (4 mol%) and copper iodide (2 mol%), the diarylmethane **14** was formed in 39% yield besides 34% of the debrominated starting material **11**, which could be recycled. In the preparative routine, crude **14** was best used without total purification and directly oxidized under Swern conditions.[15] This way, the pure aldehyde **3** was obtained in at least 38% overall yield from **4**.

It should be mentioned that various efforts to replace the stannane **13** in the Stille reaction with **4** by related compounds already containing the higher alkyl side chain were not successful. Thus, it appeared feasible to take **3** as a substrate for the introduction of the side chain via nucleophilic addition of an appropriate metal reagent to the aldehyde functionality. However, this turned out to be much more difficult than expected, and a variety of alkyl and alkynyl reagents based on Li, Mg, Ce, Zn, Zr, Al and Sm proved to be unsuitable for this purpose (low yields due to side reactions such as addition to an anthraquinone carbonyl group). Fortunately, we finally succeeded to convert **3** into the intermediate **15** in high yield through Ti-mediated alkynyl addition[16] and subsequent hydrogenation of the triple bond using Wilkinson's catalyst[17] (Scheme 4).



Scheme 3 The key Stille cross-coupling step



Scheme 4 Introduction of the alkyl side chain

Oxidation of **15** employing the Dess–Martin periodinane (DMP) reagent[18] followed by treatment of the resulting aldehyde with sodium chlorite[19] produced a keto acid, which was further converted into the methyl ester **16** by treatment with methyl iodide in the presence of potassium carbonate (85% yield over 3 steps).

While the diarylmethane derivative **16** already contains the complete carbon skeleton of mumbaistatin, an important remaining question was whether the functionalization (oxidation) of the methylene bridge could be achieved in the presence of the various functional groups. For this purpose we tested the reaction of **16** with a variety of potentially suitable reagents (or combinations) such as $RuCl_3$/$NaIO_4$,[20] $KMnO_4$/$CuSO_4$,[21] CrO_3/$(NBu_4)IO_4$,[22] *t*-BuOOH/PCC[23] or O_2/CuCl/hydroxyphthalimide;[24] however, all these methods failed.

Nevertheless, when we attempted to functionalize the central methylene group of **16** by radical bromination, i.e. by heating it in CCl_4 with *N*-bromosuccinimide in the presence catalytic amounts of dibenzoyl peroxide (BP) under additional irradiation, the lactone **2** was formed in 83% isolated yield[25] (Scheme 5). The structure of this product, which clearly resembles mumbaistatin in its cyclized form (**1a**) was proven by X-ray crystallography (Figure 2).

The smooth formation of **2** under the conditions of the radical bromination challenged us to probe this type of transformation also with the corresponding methyl ester **17**, prepared from **16** through cleavage of the *tert*-butyl ester (with TMSOTf) and subsequent esterification using methyl iodide and a base (Scheme 5). We were then surprised to find that on submission of **17** to the same radical conditions as before neither lactonization nor bromination at the methylene bridge position occurred. Instead, the α-bromoketone **18** was isolated as the only main product.

In summary, we have elaborated a synthetic route to compound **2**, which contains the complete carbon skeleton of mumbaistatin (**1**) and represents the closest structural

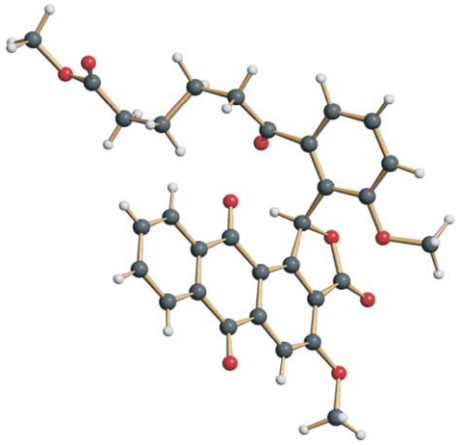
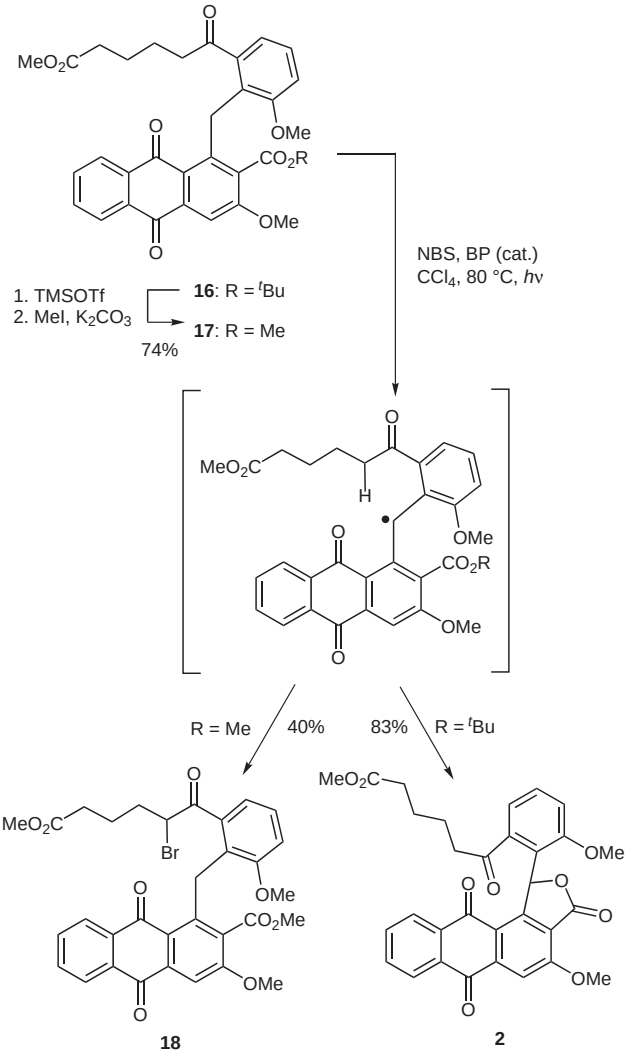


Figure 2 Structure of lactone **2** in the crystalline state



Scheme 5 'Radical bromination' of **16** or **17**

analogue of this important natural product ever prepared by total synthesis. Starting from 2-hydroxynaphthoquinone (**9**) the sequence developed needs only twelve linear steps to give **2** in ca. 15% overall yield. The key steps are:

(1) the construction of a highly hindered tetra-*ortho*-substituted diarylmethane by means of a Stille cross-coupling, (2) the use of a titanium-mediated alkynylation to alkylate an unreactive aldehyde in the presence of the anthraquinone unit, and (3) the functionalization of the diarylmethane methylene bridge under the conditions of a radical bromination.

Current efforts in this laboratory are now directed to the application of this strategy to the synthesis of mumbaistatin and biologically active analogues thereof.

Acknowledgment

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(25) **3-Hydroxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic Acid *tert*-Butyl Ester (10)**: To a solution of naphthoquinone **5** (6.20 g, 32.3 mmol, 1.0 equiv) in toluene (220 mL) was added the diene **6** (22.25 g, 64.6 mmol, 2.0 equiv) and the mixture was refluxed for 36 h. Then the solvent was removed in vacuo and the oily residue was dissolved in THF (100 mL), containing H_2O (5.0 mL). The black solution was allowed to stir for 15 h at r.t., before silica gel 60 (50 g) was added and the suspension was evaporated to dryness in vacuo. The silica-containing crude product was added to the top of a flash SiO_2 column and the product was eluted with cyclohexane–EtOAc (4:1). Evaporation of the solvent afforded a crude product, which was recrystallized from cyclohexene–EtOAc (4:1) to yield the anthraquinone **10** (6.80 g, 20.1 mmol, 62%) as a yellow solid; TLC: R_f 0.18 (cyclohexane–EtOAc, 4:1); mp 250 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.59 (s, 9 H, OMe_3), 2.62 (s, 3 H, Me), 7.59 (s, 1 H, H-4), 7.59–7.88 (m, 2 H, H-6, H-7), 8.06–8.10 (m, 2 H, H-5, H-8), 11.35 (s, 1 H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.74 (q, Me), 27.68 (q, $OCMe_3$), 82.09 (s, $OCMe_3$), 111.60 (d, C-4), 123.03 (s, C-2), 125.91, 126.63 (2 × s,C-5, C-8), 130.58, 131.32 (3 × s, C-4a, C-9a), 133.32, 134.45 (2 × s, C-6, C-7), 136.08 (s, C-8a, C-10a), 139.56 (s, C-1), 157.80 (s, C-3), 165.82 [C(O)O*t*-Bu], 182.30, 182.85 (2 × s, C-9, C-10). IR: 3366 (br m), 2976 (w), 1725 (s), 1665 (vs), 1570 (vs), 1365 (m), 1308 (s), 1249 (s), 1146 (s), 712 (vs) cm^{-1}. MS (EI-DIP; 70 eV): *m*/*z* (%) = 338 (1) [M]$^+$, 282 (54) [M–C_4H_8]$^+$, 264 (100), 236 (18), 180 (12), 152 (38), 76 (12), 57 (72). HRMS (EI, 70 eV): *m*/*z* [M]$^+$ calcd for $C_{20}H_{18}O_5$: 338.1154; found: 338.115 ± 0.002. The X-ray crystal structure data of compound **10** has been deposited at the Cambridge Crystallographic Data Centre and was allocated the deposition number 632347.
1-(2-Hydroxymethyl-6-methoxybenzyl)-3-methoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic Acid *tert*-Butyl Ester (14): A Schlenk flask was charged under argon with degassed NMP (7 mL) and THF (7 mL), bromide **4** (415 mg, 0.96 mmol, 1.0 equiv), $Pd_2(dba)_3$ (8.9 mg, 9 μmol, 1 mol%), $AsPh_3$ (11.6 mg, 38 μmol, 4 mol%) and copper(I) iodide (3.5 mg, 19 μmol, 2 mol%) was added. Then (3-methoxy-2-tributylstannanylphenyl)methanol (**13**; 530 mg, 1.24 mmol 1.3 equiv) was added and the reaction mixture was stirred at 75 °C for 20 h. Then, EtOAc (30 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a brown

residue, which was purified by column chromatography (silica gel, cyclohexane–EtOAc, 7:3). After evaporation of the solvent the desired product **14** (183 mg, 376 μmol, 39%; still contaminated with impurities) was obtained as a yellow solid in a total weight of 250 mg along with the debrominated compound **11** (141 mg, 327 μmol, 34%). Usually, the product **14** was used for the next step (Swern oxidation) without further purification. For analytical purposes a small sample of pure **14** was prepared by column chromatography (silica gel, CH_2Cl_2–EtOAc, 30:1–10:1); TLC: R_f 0.24 (cyclohexane–EtOAc, 2:1); mp 195 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, $OCMe_3$), 2.99 (t, $^3J_{H,H}$ = 5.0 Hz, 1 H, CH_2OH), 3.42 (s, 3 H, OMe at C-2′), 4.01 (s, 3 H, OMe at C-3), 4.64 (d, $^3J_{H,H}$ = 4.5 Hz, 2 H, CH_2OH), 4.68 (s, 2 H, CH_2-at C-1), 6.66 (dd, $^4J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 8.0 Hz, 1 H, H-3′), 7.01 (dd, $^4J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 7.5 Hz, 1 H, H-5′), 7.12 (app t, $^3J_{H,H}$ = 8.0 Hz, 1 H, H-4′), 7.63–7.69 (m, 2 H, H-6, H-7), 7.73 (s, 1 H, H-4), 7.95–8.02, 8.13–8.20 (2 × m, 1 H, H-5, H-8), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.88 (q, $COMe_3$), 30.22 (t, CH_2 at C-1), 55.53 (q, OMe at C-2′), 56.27 (q, OMe at C-3), 63.30 (t, CH_2OH), 83.01 (s, $OCMe_3$), 107.20 (d, C-4), 110.98 (d, C-3′), 121.91 (d, C-5′), 125.70, 126.08 (2 × s, C-4a, C-9a), 126.08, 126.37, 126.98 (3 × d, C-4′, C-5, C-8), 132.15 (s, C-2), 133.05, 134.17 (2 × d, C-6, C-7), 135.00 (s, C-8a, C-10a), 136.79 (s, C-1), 140. 55 (s, C-6′), 144.67 (s, C-1′), 157.88 (s, C-2′), 159.44 (s, C-3), 166.40 [s, C(O)O*t*-Bu], 183.11, 183.41 (2 × s, C-9, C-10). IR: 3533 (br m), 3071 (w), 2976 (m), 1716 (s), 1667 (s), 1574 (vs), 1461 (s), 1280 (vs), 1141 (vs), 1097 (s), 1097 (s), 1020 (m), 713 (vs) cm^{-1}. MS (EI–DIP; 70 eV): *m*/*z* (%) = 488 ([M]$^+$; 414, >1), 414 (35), 369 (100), 355 (11), 339 (9), 226 (8), 57 (33). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{28}O_7$: 511.1733; found: 511.173 ± 0.002.

1-[2-(1,6-Dihydroxyhexyl)-6-methoxybenzyl]-3-methoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic Acid *tert*-Butyl Ester (15): A solution of pent-4-yn-1-ol (210 mg, 2.39 mmol, 4.0 equiv) in THF (4 mL) was cooled to 0 °C. Then a 1.6 M solution of *n*-BuLi in hexane (3.0 mL, 4.77 mmol, 8.0 equiv) was added slowly. After 15 min, the stirred reaction mixture was cooled to –60 °C, and $TiCl(O\textit{i}\text{-}Pr)_3$ (1.32 g, 4.95 mmol, 8.3 equiv) dissolved in THF (2 mL) was added. The solution was stirred at –60 °C for further 1.5 h and aldehyde **3** (290 mg, 0.60 mmol, 1.0 equiv) in THF (6 mL) was added via cannula. The reaction mixture was stirred at –60 °C for 30 min, warmed from –60 °C to –20 °C, stirred for 15 h, quenched with sat. NH_4Cl, warmed to r.t., and diluted with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2 ×), the combined organic extracts were dried over $MgSO_4$, concentrated and purified by column chromatography (silica gel, cyclohexane–EtOAc, 4:6) to give the corresponding addition product(alkyne) as a yellow oil (305 mg, 0.54 mmol). To a solution of the alkyne (305 mg, 0.54 mmol, 1.0 equiv) in toluene (15 mL), $Rh(PPh_3)_3Cl$ (52 mg, 0.06 mmol, 9 mol%) was added under argon. The resulting suspension was then stirred under an atmosphere of hydrogen (3 atm) at r.t. for 15 h. Then the solvent was evaporated and the residue was purified by column chromatography (silica gel, cyclohexane–ethyl acetate, 4:6) to give compound **15** (298 mg, 0.52 mmol, 87% overall yield) as a yellow solid; TLC: R_f 0.31 (cyclohexane–EtOAc, 4:6); mp 66.0 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.27–1.54 [m, 4 H, $HO(CH_2)_2(CH_2)_2$], 1.40 (s, 9 H, $COMe_3$), 1.55–1.90 (m, 4 H, $HOCH_2CH_2$, $HOCHCH_2$), 3.38 (s, 3 H, OMe), 3.56 (t, $J_{H,H}$ = 6.5 Hz, 2 H, $HOCH_2$), 4.00 (s, 3 H, OMe), 4.43 (d, $J_{H,H}$ = 16.0 Hz, 1 H, CH_2Ar_2), 4.83 (d, $J_{H,H}$ = 16.0 Hz, 1 H, CH_2Ar_2), 5.12–5.19 (m, 1 H, HCOH), 6.55–6.60 (m, 1 H, H-5′), 7.11–7.14 (m, 2 H, H-3′, H-4′), 7.63–7.68 (m, 2 H, H-6, H-7), 7.74 (s, 1 H, H-4), 7.90–7.95, 8.13–8.17 (2 × m, 2 H, H-5, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.60 (t, CH_2), 25.90 (t, CH_2), 28.01 (q, $OCMe_3$), 29.80 (t, CH_2Ar_2), 32.67 (t, CH_2), 37.48 (t, CH_2), 55.23 (q, OMe at C-6′), 56.29 (q, OMe at C-3), 62.79 (t, $HOCH_2$), 69.94 (d, CHOH), 82.98 (s, $OCMe_3$), 107.18 (d, C-4), 109.93 (d, C-5′), 118.55 (d, C-3′), 120.39 (s, C-2), 125.10, 125.66 (2 × s, C-4a, C-9a), 126.45, 127.02, 127.21 (3 × d, C-4′, C-5, C-8), 132.19 (s, C-1′), 133.11, 134.25 (2 × d, C-6, C-7), 135.11, 136.90 (2 × s, C-8a, C-10a), 145.40, 145.51 (2 × s, C-2′, C-1), 157.42 (s, C-6′), 159.59 (s, C-3), 166.47 (s, $CO_2\textit{t}$-Bu), 183.14, 183.59 (2 × s, C-9, C-10). IR: 3406 (m, br), 2936 (m), 1719 (s), 1668 (s), 1574 (vs), 1462 (s), 1330 (s), 1281 (vs), 1142 (vs), 1090 (s), 1088 (s), 714 (vs) cm^{-1}. MS (EI-DIP; 70 eV): *m*/*z* (%) = 220, 205, 181, 177, 145, 91, 57. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{38}O_8$: 597.2465; found: 597.246 ± 0.002.

6-{3-Methoxy-2-(4-methoxy-3,6,11-trioxo-1,3,6,11-tetrahydroanthra[1,2-*c*]furan-1-yl)-phenyl}-6-oxohexanoic Acid Methyl Ester (2): Compound **16** (165 mg, 0.28 mmol, 1.0 equiv), *N*-bromosuccinimide (98 mg, 0.55 mmol, 2.0 equiv) and benzoyl peroxide (3.3 mg, 0.01 mmol, 5 mol%) were dissolved in CCl_4 (15 mL) and refluxed under irradiation with a 150-W lamp for 3 h. After this time, the reaction mixture was quenched with a sat. solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, concentrated and purified by column chromatography (silica gel, cyclohexane–EtOAc 3:7) to yield lactone **2** (124 mg, 0.23 mmol, 83%) as a yellow solid; TLC: R_f 0.39 (cyclohexane–EtOAc, 3:7); mp 142.5 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.70–2.00 [m, 4 H, $MeO_2CCH_2(CH_2)_2$], 2.35–2.45 (m, 2 H, $MeO_2CCH_2CH_2$), 3.25–3.45 (m, 2 H, $ArCOCH_2CH_2$), 3.35 (s, 3 H, OMe), 3.62 (s, 3 H, CO_2Me), 4.19 (s, 3 H, OMe), 6.77–6.80 (m, 1 H, H-5′), 7.23–7.32 (m, 2 H, H-3′, H-4′), 7.49 (s, 1 H, $CHOHAr_2$), 7.68–7.74 (m, 2 H, H-6, H-7), 7.83 (s, 1 H, H-4), 7.95–8.00, 8.18–8.23 (2 × m, 2 H, H-5, H-8). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.53 (t, CH_2), 24.61 (t, CH_2), 33.99 (t, CH_2), 41.71 (t, CH_2), 51.45 (q, CO_2Me), 55.68 (q, OMe at C-6′), 56.88, 57.14 (d, q, $CHOAr_2$, OMe at C-3), 109.30 (d, C-4), 114.19 (d, C-5′), 119.61 (d, C-3′), 120.56, 120.84 (2 × s, C-2, C-1′), 127.08, 127.40, 129.73 (3 × d, C-4′, C-5, C-8), 132.75, 133.15 (2 × s, C-4a, C-9a), 133.91, 134.49 (2 ×d, C-6, C-7), 139.43, 142.98 (2 × s, C-8a, C-10a), 155.98, 158.63 (2 × s, C-2′, C-1), 161.36 (s, C-6′), 167.25 (s, C-3), 173.95 (s, CO_2Me), 180.43 (s, $ArCO_2$), 182.35, 182.46 (2 × s, C-9, C-10), 204.76 (s, $COCH_2$). IR: 3093 (w), 2944 (m), 1763 (vs), 1733 (s), 1674 (vs), 1597 (vs), 1583 (vs), 1456 (s), 1333 (vs), 1292 (vs), 1275 (vs), 1060 (vs), 1009 (vs), 712 (s) cm^{-1}. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{26}O_9$: 565.1475; found: 565.147 ± 0.002. The X-ray crystal structure of compound **2** has been deposited at the Cambridge Crystallographic Data Centre and was allocated the deposition number 632345.