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First Total Synthesis of the Bioactive Anthraquinone Kwanzoquinone C and Related Natural Products by a Diels–Alder Approach

Lutz F. Tietze,*[a] Kersten M. Gericke,[a] and Carlos Güntner[b]

Dedicated to Professor Gyula Schneider on the occasion of his 75th birthday

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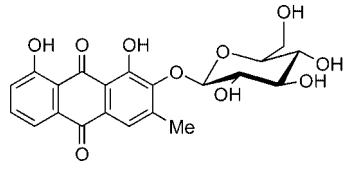
The first total synthesis of the novel anticancer agent kwanzoquinone C (**1**), an anthraquinone glycoside which has been isolated from extracts of the roots of orange daylilies (Kaempfer) (*Hemerocallis fulva*) is reported. The strategy involves the preparation of the tetrasubstituted 1,3-butadiene **6** by an electrocyclic conrotatory ring opening of the cyclobutanone *rac*-**11**, which is obtained by a [2+2] cycloaddition. Diels–Alder reaction of **6** with the juglone derivative **5** gives the bis-benzyl-protected anthraquinone **4** after aromatization. Finally, glycosidation of the phenolic hydroxy group using 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate followed by the cleavage of the benzyl ethers and the solvolysis of the acetate groups yields the natural product **1**. A related anthraquinone natural product **2** with antioxidative properties was obtained by using the 1,3-butadiene **17** and the juglone derivative **16** as substrates.

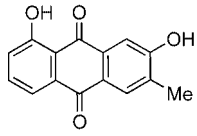
Introduction

Natural products are important lead structures for the development of novel drugs especially in the field of anticancer agents.[1] Quite a new compound from nature which might be of interest for the chemotherapy of cancer is the anthraquinone glucoside kwanzoquinone C (**1**), which has been isolated in 2002 by Nair and co-workers[2] from the extracts of Kaempfer roots (*Hemerocallis fulva*) together with a series of other hydroxylated anthraquinones (Figure 1).

Plants from the familia *Hemerocallis* are known to be applied in the traditional medicine in eastern Asia, e.g. as a remedy for schistosomiasis.[3] Kwanzoquinone C, was found to be the anthraquinone glycoside **1**, which possesses growth inhibition of four different tumor cells (GI_{50} = 3.8–7.5 μg/mL).[4] It belongs to the class of hydroxylated anthraquinones which are known to be widely represented as pigments in the plant kingdom.[5] Moreover, these compounds have a high medicinal value,[6] for instance in the treatment of a human filarial parasite, *Brugia malayi*.[7] The related anthraquinone **2**, extracted from the medicinal plant *Aster tataricus*, has been found to exert an inhibitory activity on superoxide radical generation.[8] Furthermore, macrosporin (**3**), being a metabolite of a fungal species,[9] has been proven to exhibit antibacterial properties.[10]



Kwanzoquinone C (**1**)



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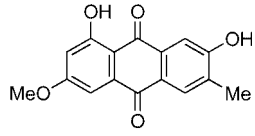


Macrosporin (**3**)

Figure 1. Structures of kwanzoquinone C (**1**), antioxidative anthraquinone **2** and macrosporin (**3**).

Most general strategies for the synthesis of hydroxylated anthraquinones employ Diels–Alder reactions using ketene silyl acetals[11] or 3-methyl-1-trimethylsiloxy-1,3-butadiene[12] and halogenated naphthoquinones as substrates. Another approach, which has recently been developed, is based on a Friedel–Crafts acylation between phthalic anhydrides and substituted benzenes.[7]

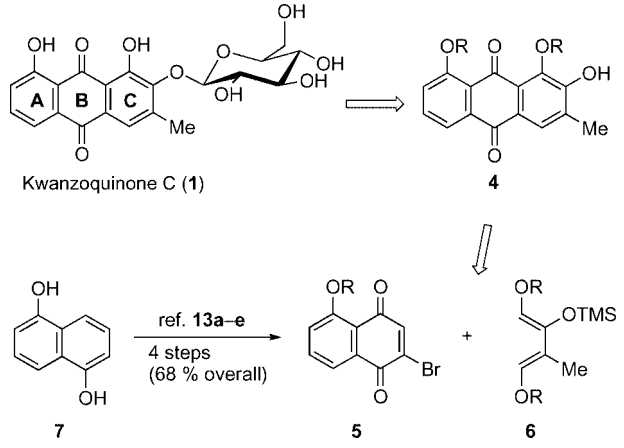
Here we describe the synthesis of **1** and **2** using a cycloaddition of a naphthoquinone and a tetrasubstituted 1,3-butadiene as key-step.

[a] Institut für Organische und Biomolekulare Chemie, Georg-August-Universität,
Tammannstr. 2, 37077 Göttingen, Germany
Fax: +49-551-399-476
E-mail: ltietze@gwdg.de
[b] MBM ScienceBridge GmbH, Georg-August-Universität Göttingen,
Hans-Adolf-Krebs-Weg 1, 37077 Göttingen, Germany

Results and Discussion

1. Total Synthesis of Kwanzoquinone C

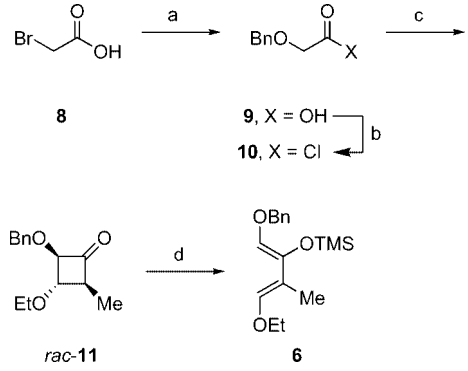
According to the retrosynthetic analysis of kwanzoquinone C (**1**) as shown in Scheme 1, the glycosidation should be performed as one of the last steps, because the sensitivity of aromatic glycosides is rather high. The approach therefore led to the protected anthraquinone **4**, which should be accessible by a Diels–Alder reaction followed by an aromatization of the bromo-naphthoquinone **5** and the tetrasubstituted 1,3-butadiene **6**.



Scheme 1. Retrosynthetic analysis of kwanzoquinone C (**1**).

The synthesis of the dienophile **5** was carried out according to a known procedure starting with 1,5-dihydroxynaphthalene (**7**) to give the desired compound within four steps and an overall yield of 68% (Scheme 1).[13] We anticipated that the bromo substituent in 2 position in **5** is necessary to assure the desired regioselectivity in the cycloaddition on the one hand and on the other hand to guarantee a facile aromatization of C-ring by elimination of hydrogen bromide. It was known that the bromine can act as a control element to allow a C–C bond formation between the electron-rich end of the diene and the unsubstituted carbon of the quinone.[14] Furthermore, we decided to protect the phenolic hydroxy group as benzyl ether because it exhibits a good stability against acidic condition, and it should be easily removable within the last steps without affecting the sensitive glycosidic bond.

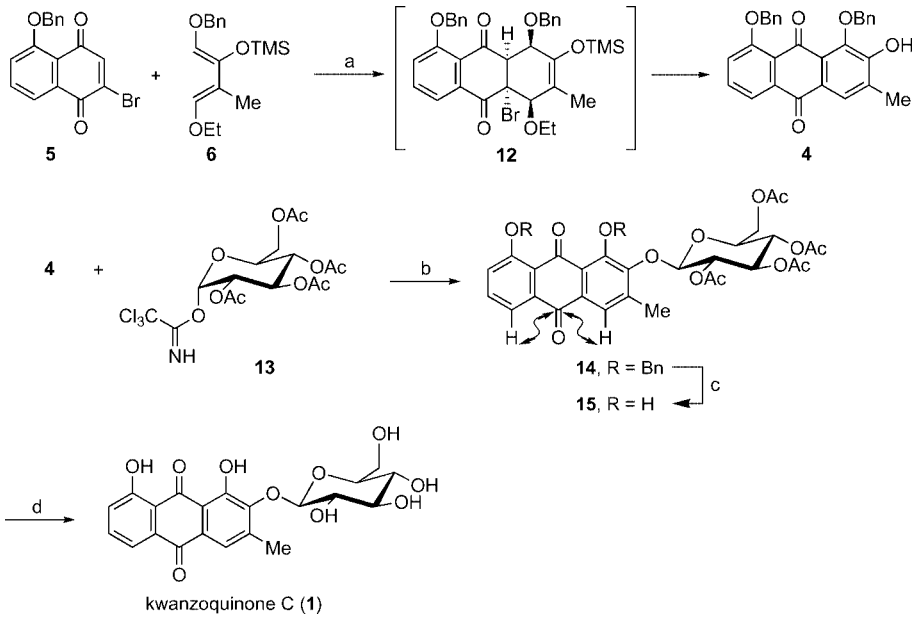
For the Diels–Alder reaction with **5** we synthesized the novel tetrasubstituted 1,3-butadiene **6** containing an ethoxy group at C-4. We assumed that the latter would act as a leaving group during the aromatization step, and thus allowing a selective construction of the C-ring moiety. For the preparation of **6** we used a method which we had already established in our approach towards a total synthesis of mensacarcin.[15] Starting from bromoacetic acid (**8**), in a two-step procedure[16] the acid chloride **10** was obtained, which was treated with triethylamine to give the transient ketene needed for the [2+2] cycloaddition with commercially available (*E*/*Z*) ethyl propenyl ether (Scheme 2). The reaction led to the cyclobutanone *rac*-**11** as an almost single diastereoisomer in 62% yield. The stereoselective formation of *rac*-**11** can be explained by the observation made by Scheeren[17] that cyclobutanones of type *rac*-**11** isomerize to the *trans* diastereomer under basic conditions. The needed butadiene **6** can then be obtained from *rac*-**11** by an electrocyclic conrotatory ring opening of the corresponding TMS enol ether.[17,18] The reaction was carried out by treatment of *rac*-**11** with TMSCl in the presence of Et_3N to yield the TMS enol ether, which without isolation was heated to 60 °C to give the butadiene **6**. It was used for the next step without purification because it is not stable neither during chromatography nor distillation, in the latter case due to its high boiling point.



Scheme 2. Synthesis of the 1,3-butadiene **6**; (a) Na, BnOH, THF, room temp., 18 h, 73%; (b) $SOCl_2$, DMF (cat.), CH_2Cl_2, reflux 4 h, 97%; (c) (*E*/*Z*) ethyl propenyl ether, Et_3N, CH_3CN, 60 °C, 105 min, 62%; (d) Et_3N, TMSCl, 60 °C, 3 h.

With the building blocks **5** and **6** in hand, the cycloaddition was carried out in dichloromethane at low temperature to avoid the formation of the unwanted regioisomer employing an excess of the diene **6** (Scheme 3). The cycloadduct, which presumably has the structure as depicted in **12**, was formed smoothly, and after complete consumption of the dienophile **5** the solvent was removed and the crude product directly subjected to the aromatization procedure. Unexpectedly, in the beginning this turned out to be very problematic. Treatment of the cycloadduct **12** in THF[19] or chloroform[20] with aqueous hydrogen chloride as well as the usage of acetic acid[21] or silica gel[22] in boiling toluene failed completely, furnishing only complex mixtures of reaction products. Furthermore, we tried the application of TBAF, again with a negative result. Finally, a very short treatment with 1% TFA in methanol and a subsequent quenching with aqueous potassium carbonate led to the desired anthraquinone **4** in 64% yield. The formation of **4** is assumed to proceed via an initial cleavage of the TMS enol ether in the primarily obtained cycloadduct **12** caused by the TFA followed by an elimination of hydrogen bromide under basic conditions and the final elimination of ethoxide to give the thermodynamically favored aromatic C-ring.

For the following glycosidation we chose the trichloroacetimidate method developed by Schmidt[23] because it is best suitable for the formation of aryl β-glucosides with high selectivity using the acetyl-protected trichloroacetimidate **13**[24,25] as donor. The glycosidation was carried out in

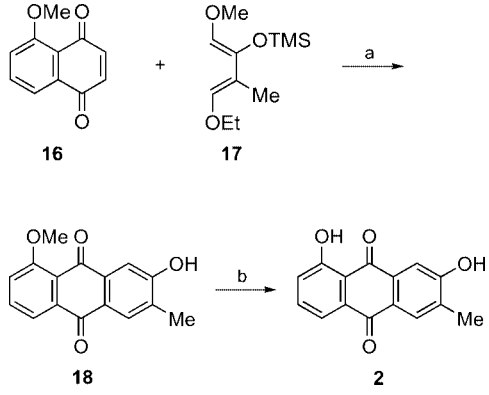


Scheme 3. Synthesis of kwanzoquinone C (**1**); (a) 1) CH_2Cl_2, –10 °C, 20 h, 2) 1% TFA, MeOH, room temp., 2 min, 3) 1 M K_2CO_3, room temp., 5 min, 64%; (b) cat. $BF_3{\cdot}Et_2O$, CH_2Cl_2, –10 °C, 30 min, 94%; (c) 1) HCO_2NH_4, cat. Pd/C, THF/MeOH/H_2O (3:1:0.25), room temp., 30 min, 2) air, 5 min, 80%; (d) 1) NaOMe, MeOH, room temp., 1 h, 2) IR-120, 100%.

dichloromethane at –10 °C with $BF_3{\cdot}OEt_2$ as catalyst and 4-Å molecular sieves to afford the β-glycoside **14** within 30 min in 94% yield with only traces of the α-anomer, which could be removed by chromatography. At this stage the regioselectivity of the Diels–Alder reaction could be unambiguously deduced from HMBC-^{1}H NMR experiments showing a clear correlation of one carbonyl group of the anthraquinone system with two *ortho*-hydrogen atoms at the aromatic rings as depicted in **14**. The removal of the benzyl protecting groups to give **15** was achieved under mild conditions using transfer-hydrogenolysis with ammonium formate as hydrogen source in 80% yield. In contrast, the application of gaseous hydrogen led to an additional reduction of the aromatic system with formation of an anthracenediol. The latter side-reaction was also observed to a small extent during the transfer-hydrogenolysis, if the reaction was carried out for too long. However, the anthracenediol can be reoxidized by bubbling air through the reaction solution. Finally, the acetate protecting groups at the glucose moiety in **15** were removed by solvolysis according to Zemplén[26] using NaOMe in methanol. Kwanzoquinone C (**1**) could be obtained by acidic work up with ion exchange resin IR-120 in quantitative yield and high purity. The ^{1}H NMR and ^{13}C spectra of the compound isolated by Nair[2] and synthetic compound **1** are in a good agreement in all respects, including chemical shifts as well as coupling constant values.

2. Synthesis of the Anthraquinone 2

In addition to the synthesis of kwanzoquinone C (**1**) we also prepared the natural anthraquinone **2** employing a similar procedure. Cycloaddition of *O*-methyl juglone (**16**) and the tetrasubstituted diene **17**, which we have already used during our approach towards the total synthesis of mensacarcin, led to **18** after a twofold elimination (Scheme 4).[15] This was achieved by treatment of the crude cycloaddition product with 2 N HCl in refluxing THF. Because there is no halogen atom present which could eliminate, both the methoxy and ethoxy group are lost during this step to afford the anthraquinone **18** in a very high yield of 92%. The sequence was completed by deprotection of the methyl ether in **18** with hydrogen bromide in refluxing acetic acid to furnish the target compound **2** in a nearly quantitative yield of 96%.



Scheme 4. Synthesis of natural product (**2**); (a) 1) CH_2Cl_2, 0 °C, 3.5 h, 2) 2 N HCl, THF, reflux, 20 h, 92%; (b) HBr, HOAc, 100–110 °C, 2 h, 96%.

In conclusion we have completed the first total synthesis of the novel anticancer agent kwanzoquinone C (**1**) as well as of the related natural anthraquinone **2**, which shows antioxidative properties. The newly developed tetrasubstituted dienes **6** and **17** are versatile substrates for the Diels–Alder

cycloaddition with naphthoquinones to give highly substituted cycloadducts. Moreover, different aromatization procedures allowed us to control the substitution pattern at the C-ring of the resulting anthraquinones.

Experimental Section

General: All reactions were performed in flame-dried glassware under argon. Solvents were dried and purified according to the method defined by Perrin and Armarego.[27] Commercial reagents were used without further purification. Thin-layer chromatography (TLC) was carried out on precoated Alugram SIL G/UV$_{254}$ (0.25 mm) plates from Macherey–Nagel & Co. Column chromatography was carried out on Kieselgel 60 from Merck with particle size 0.063–0.200 mm for normal pressure and 0.020–0.063 mm for flash chromatography. Melting points were recorded with a Mettler FP61 and are uncorrected. IR spectra were determined with a Bruker Vektor 22, UV/Vis spectra with a Perkin–Elmer Lambda 2, and mass spectra with a Varian MAT 311A, Varian MAT 731 for EI-HRMS, and a Bioapex fourier transformation ion cyclotron resonance mass spectrometer for ESI-HRMS. ^{1}H NMR spectra were recorded with a Varian UNITY-300 MHz and ^{13}C NMR spectra at 75 MHz. Spectra were taken at room temperature in deuteriated solvents as indicated using the solvent peak as internal standard. Elemental analysis was performed at the Mikroanalytisches Labor des Institutes für Organische und Biomolekulare Chemie der Universität Göttingen.

Synthesis of Kwanzoquinone C (1)

Benzyloxyacetic Acid (9): Benzyl alcohol (250 mL) was treated with small portions of sodium (57.5 g, 2.50 mol) with mechanical stirring at 20 °C . After the gas evolution had ceased the mixture was heated to 100–120 °C until the conversion of the sodium metal was completed. The solution was cooled to 20 °C, diluted with THF (800 mL) and then bromoacetic acid (**8**, 70 g, 0.50 mol) in THF (200 mL) was added dropwise within 30 min. After being stirred for 12 h the thick, white suspension was dissolved by addition of H_2O (1.2 L). After phase separation, the aqueous layer was washed with Et_2O (5×400 mL), and acidified at 0 °C with a 5 N HCl solution to pH 1–2. The aqueous layer was extracted with Et_2O (3×400 mL) and the combined organic layers were washed successively with H_2O (500 mL) and brine (500 mL). After drying ($MgSO_4$), filtration and concentration under reduced pressure, the crude product was distilled in vacuo over a 10-cm Vigreux column to afford benzyloxyacetic acid (**9**, 64.2 g, 77%) as a colorless, vicious liquid. B.p. 141 °C (0.2 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.15 (s, 2 H, 2-CH_2), 4.65 (s, 2 H, CH_2Ph), 7.27–7.43 (m, 5 H, Ph-H), 9.89 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 66.48, 73.41, 128.1, 128.2, 128.6, 136.5, 175.6 ppm. IR (film): $\tilde{\nu}$ = 3033, 2918, 1731, 1497, 1455, 1429, 1208 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 206.0 (3.906), 251.5 (2.091), 257.0 (2.215), 263.0 nm (2.095). MS (EI, 70 eV): *m*/*z* (%) = 166.1 (5) [M]$^+$, 91.1 (100) [C_7H_7]$^+$. $C_9H_{10}O_3$ (166.17): calcd. C 65.05, H 6.07; found C 65.28, H 5.85.

Benzyloxyacetyl Chloride (10): Thionyl chloride (274 mL, 3.76 mol) was added dropwise to a solution of benzyloxyacetic acid (**9**, 104 g, 0.626 mol) and a cat. amount of DMF (0.1 mL) in CH_2Cl_2 (500 mL) at 0 °C over 30 min. After being heated under reflux for 4 h the solvent and the excess of thionyl chloride was removed under reduced pressure. The residue was distilled in vacuo in a 10-cm Vigreux column to give **10** (104 g, 90%) as a pale yellow liquid. B.p. 85–87 °C (0.5 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.42 (s, 2 H, 2-CH_2), 4.66 (s, 2 H, CH_2Ph), 7.30–7.41 ppm (m, 5 H, Ph-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 73.56, 74.79, 128.1, 128.4, 128.7, 136.1, 171.8 ppm. IR (film): $\tilde{\nu}$ = 3066, 3033, 2877, 1802, 1651, 1455, 1413, 1263, 1212 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 257.0 (2.381), 251.5 (2.323), 263.0 nm (2.273). MS (EI, 70 eV): *m*/*z* (%) = 184.1 (1) [M]$^+$, 107.1 [M – C_6H_5]$^+$, 91.1 (100) [C_7H_7]$^+$. HRMS (EI): calcd. for $C_9H_9ClO_2$: 184.0291; confirmed. $C_9H_9ClO_2$ (184.62): calcd. C 58.55, H 4.91; found C 58.27, H 4.76.

2-Benzyloxy-3-ethoxy-4-methylcyclobutanone (*rac*-11): Compound **10** (42.9 g, 0.232 mol) was added dropwise with vigorously stirring to a solution of ethyl 1-(*E*/*Z*) propenyl ether (25.0 g, 0.290 mol) and triethylamine (35.2 mL, 0.251 mol) in acetonitrile (85 mL) at 0 °C within 15 min. Then the reaction mixture was placed in a prewarmed oil bath at 65–75 °C and stirred for 105 min. The solvent was removed under reduced pressure and the slurry suspended in Et_2O (150 mL), filtered through a sintered-glass-fritted funnel (porosity 3). After removing the solvent in vacuo the crude product was subjected to silica gel flash chromatography (pentane/EtOAc, 20:1). Concentration of the appropriate fractions afforded cyclobutanone *rac*-**11** (33.2 g, 61%) as a colorless oil. R_f = 0.38 (pentane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.27 (m, 6 H, OCH_2CH_3, 4-CH_3), 2.96 (dq, *J* = 7.2, 4.2 Hz, 1 H, 4-H), 3.60 (dq, *J* = 7.0, 1.2 Hz, 2 H, O$CH_bH_aCH_3$), 3.73 (dd, *J* = 6.6, 5.4 Hz, 1 H, 3-H), 4.66 (d, *J* = 11.9 Hz, 1 H, OCH_bPh), 4.67 (dd, *J* = 5.4, 4.2 Hz, 1 H, 2-H), 4.81 (d, *J* = 11.5 Hz, 1 H, OCH_aHPh), 7.27–7.40 ppm (m, 5 H, Ph-H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 11.60, 15.21, 51.79, 65.74, 72.49, 77.78, 90.69, 128.0, 128.1, 128.4, 137.0, 206.9 ppm. UV (CH_3CN): λ_{max} (lgε) = 192.5 (4.405), 242.0 (1.955), 279.5 (1.999), 312.5 nm (1.694). IR (film): $\tilde{\nu}$ (cm^{-1}) = 3065, 3033, 2975, 2874, 1781, 1703, 1497, 1455, 1376, 1356, 1311, 1210 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 234.2 (1) [M]$^+$, 107.1 (8) [M – C_6H_5], 91.1 (100) [C_7H_7]$^+$. HRMS (EI): calcd. for $C_{14}H_{18}O_3$: 234.1256; confirmed.

[(1*Z*,3*E*)-1-Benzyloxy-4-ethoxy-3-methylbuta-1,3-dien-2-yloxy]trimethylsilane (6): TMSCl (2.80 mL, 21.9 mmol) was added dropwise to a solution of cyclobutanone **10** (3.41 g, 14.6 mmol) and triethylamine (6.15 mL 43.8 mmol) in acetonitrile (11 mL) at 20 °C. Then the mixture was placed in a prewarmed oil bath at 65–75 °C and stirred for 4 h (TLC control). After removing the solvent under reduced pressure, the slurry was suspended in Et_2O (100 mL), and filtered through a sintered-glass-fritted funnel (porosity 3). Removal of the solvent in vacuo afforded the crude product **6** as slightly reddish oil, which was used directly for the next step (4.31 g).

1,8-Bis(benzyloxy)-2-hydroxy-3-methylanthraquinone (4): Diene **6** (4.31 g, ca. 14.1 mmol) was added dropwise to a solution of naphthoquinone **5** (1.10 g, 3.21 mmol) in CH_2Cl_2 (50 mL) at –10 °C with stirring over 10 min. Stirring was continued for 20 h at –10 °C, and the reaction mixture was concentrated under reduced pressure. The residue was treated at 20 °C with 1% TFA in methanol (60 mL) and stirred for 2 min, then 1 M aqueous K_2CO_3 solution (15 mL) was added (color change from yellow to deep red, one must strictly keep to the reaction time). After stirring for 5 min the mixture was poured into ice-cold 1 N HCl solution (200 mL). The yellow precipitate was filtered, washed with pentane (100 mL), and then subjected to silica gel chromatography (CH_2Cl_2 + 1% acidic acid). Concentration of the appropriate fractions afforded the anthraquinone **4** (920 mg, 64%) as a pale yellow solid. R_f = 0.31 (pentane/EtOAc, 4:1). M.p. 194 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (d, *J* = 0.6 Hz, 3 H, Ar-CH_3), 5.14 (s, 2 H, OCH_2Ph), 5.29 (s, 2 H, OCH_2Ph), 6.58 (s, 1 H, OH), 7.26–7.43 (m, 7 H, 2×*p*-Ph-H, 4×*m*-Ph-H, 7-H), 7.49–7.65 (m, 5 H, 4×*o*-Ph-H, 6-H), 7.86–

7.91 (m, 2 H, 4-H, 5-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 15.97, 71.38, 77.23, 119.7, 119.9, 124.3, 125.7, 125.8, 126.8, 127.7, 128.5, 128.7, 128.8, 128.8, 130.1, 134.0, 135.4, 136.5, 136.7, 144.3, 153.9, 158.6, 182.5, 182.5. IR (KBr): $\tilde{\nu}$ = 3434, 2898, 1677, 1591, 1496, 1470, 1454, 1377, 1312, 1258 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 268.5 (4.433), 367.0 (3.915), 538.5 nm (2.763). MS (EI, 70 eV): *m*/*z* (%) = 922.9 (100) [2×M + Na]$^+$, 473.1 (54) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{29}H_{22}O_5$ + H$^+$: 451.15400; found 451.15421; calcd. for $C_{29}H_{22}O_5$ + Na$^+$: 473.13594; found 473.13616. $C_{29}H_{22}O_5$ (450.48): calcd. C 77.32, H 4.92; found C 77.05, H 5.11.

1,8-Bis(benzyloxy)-3-methyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)anthraquinone (14): A solution of the anthraquinone **4** (450 mg, 1.00 mmol) and freshly activated 4-Å molecular sieves (3 g) in CH_2Cl_2 (60 mL) was treated at –10 °C with a solution of the trichloroacetimidate **13** (985 mg, 2.00 mmol) in CH_2Cl_2 (12 mL). After being stirred for 30 min $BF_3{\cdot}OEt_2$ (25.0 μL, 0.200 mmol) in CH_2Cl_2 (3 mL) was added dropwise at –10 °C. The mixture was stirred for another 30 min at the same temperature after which the reaction was quenched by slow addition of MeOH (50 mL). The solution was filtered and the residue washed carefully with CH_2Cl_2 and MeOH. The combined organic phases were washed with half-concentrated $NaHCO_3$ solution (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was subjected to silica gel flash chromatography (CH_2Cl_2/EtOAc, 20:1 → 10:1), and after concentration of the appropriate fractions the glycoside **14** (733 mg, 94%) was obtained as a pale yellow solid. R_f = 0.42 (pentane/EtOAc, 3:2). M.p. 203 °C. $[\alpha]_D^{20}$ = +26.7 (*c* = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90, 1.93, 1.98, 2.00 [s, 12 H, 4×C(O)CH_3], 2.35 (s, 3 H, Ar-CH_3), 3.55 (m_c, 1 H, H-5′), 3.83 (dd, *J* = 12.3, 2.2 Hz, 1 H, 6′-H_b), 4.14 (dd, *J* = 12.1, 4.5 Hz, 1 H, 6′-H_a), 5.01–5.21 (m, 4 H, 4′-H, 5′-H, OCH_2Ph), 5.23 (s, 2 H, OCH_2Ph), 5.31 (br. t, *J* = 8.8 Hz, 1 H, 2′-H), 5.67 (d, *J* = 7.9 Hz, 1 H, 1′-H), 7.26–7.39 (m, 7 H, 2×*p*-Ph-H, 4×*m*-Ph-H, 7-H), 7.53–7.64 (m, 5 H, 4×*o*-Ph-H, 6-H), 7.81 (d, *J* = 6.9 Hz, 1 H, 5-H), 7.85 (s, 1 H, 4-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.40, 20.46, 20.94, 20.56, 61.11, 68.04, 70.89, 71.86, 71.90, 72.88, 76.05, 99.46, 119.4, 119.4, 124.3, 125.1, 126.7, 127.7, 128.2, 128.2, 128.4, 128.5, 128.7, 129.9, 134.0, 134.9, 136.2, 136.3, 140.0, 150.0, 152.7, 158.2, 169.4, 169.4, 170.1, 170.3, 182.2, 182.9 ppm. IR (KBr): $\tilde{\nu}$ = 2946, 1754, 1673, 1586, 1499, 1456, 1372, 1332, 1283, 1242 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 260.5 (4.447), 367.5 nm (3.723). MS (ESI): *m*/*z* (%) = 1582.6 (83) [2×M + Na]$^+$, 803.2 (100) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{43}H_{40}O_{14}$ + H$^+$: 781.24908; found: 781.24913; calcd. for $C_{43}H_{40}O_{14}$ + Na$^+$: 803.23103; found: 803.23095.

1,8-Dihydroxy-3-methyl-2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)anthraquinone (15): A solution of the glucoside **14** (300 mg, 0.384 mmol) and Pd/C (10 mol-%, 41 mg, 38.4 μmol) in THF/MeOH (3:1, 20 mL) was treated at 20 °C dropwise with a 25%ic aqueous solution of HCO_2NH_4 (3.88 mL, 15.4 mmol). After being stirred for 30 min the dark red mixture was filtered through a plug of Celite® and saturated aqueous NH_4Cl solution (10 mL) was added to the filtrate. Then air was bubbled through the solution until the color had changed to yellow; H_2O (50 mL) was added and the mixture extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting crude product was subjected to silica gel flash chromatography (CH_2Cl_2/EtOAc, 20:1, + 2% HOAc) and after concentration of the appropriate fractions the glycoside **15** (185 mg, 80%) was obtained as a red-brown, glass-like solid. R_f = 0.47 (pentane/EtOAc, 3:2). $[\alpha]_D^{20}$ = –58.3 (*c* = 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 [s, 3 H, OC(O)CH_3], 2.05 [s, 3 H, OC(O)CH_3], 2.07 [s, 3 H, OC(O)CH_3], 2.18 [s, 3 H, OC(O)CH_3], 2.39 (s, 3 H, Ar-CH_3), 3.76 (m_c, 1 H, 5′-H), 4.16 (dd, *J* = 12.3, 2.2 Hz, 1 H, 6′-H_b), 4.23 (dd, *J* = 12.1, 4.5 Hz, 1 H, 6′-H_a), 5.20 (m_c, 1 H, 4′-H), 5.32–5.44 (m, 3 H, 1′-H, 2′-H, 3′-H), 7.25 (dd, *J* = 8.4, 1.1 Hz, 1 H, 7-H), 7.56 (s, 1 H, 4-H), 7.66 (t, *J* = 7.8 Hz, 1 H, 6-H), 7.74 (dd, *J* = 7.5, 1.5 Hz, 1 H, 5-H), 11.85, 12.24 (s, 2 H, 2×OH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.72, 20.54, 20.58, 20.77, 61.46, 68.29, 71.38, 71.84, 72.49, 100.4, 115.0, 115.6, 120.0, 122.4, 124.4, 128.6, 133.3, 137.3, 143.1, 147.1, 154.6, 162.3, 169.4, 169.7, 170.2, 170.4, 180.8, 192.5 ppm. IR (KBr): $\tilde{\nu}$ = 2961, 1755, 1674, 1626, 1474, 1452, 1371, 1294, 1234, 1160 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 200.0 (4.373), 226.0 (4.482), 259.5 (4.432), 290.0 (3.994), 427.0 (4.028), 558.0 nm (2.742). MS (ESI): *m*/*z* (%) = 1222.8 (100) [2×M + Na]$^+$, 623.1 (21) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{29}H_{28}O_{14}$ + H$^+$: 618.18173; found: 618.18157; calcd. for $C_{29}H_{28}O_{14}$ + Na$^+$: 623.13713; found: 623.13693.

2-(β-D-Glucopyranosyloxy)-1,8-dihydroxy-3-methylanthraquinone (Kwanzoquinone C, 1): A solution of glycoside **15** (175 mg, 0.241 mmol) in MeOH (75 mL) was treated at 20 °C with NaOMe (182 μL, 0.966 mmol, 5.3 M solution in MeOH). After being stirred for 1 h Amberlite® IR-120 was added to the red solution until the color changed to yellow. Then the solution was filtered and the residue was washed carefully with CH_2Cl_2 and MeOH. Concentration of the combined organic phases furnished pure kwanzoquinone C (**1**, 104 mg, 100%) as yellow solid. R_f = 0.28 (CH_2Cl_2/MeOH, 10:1 + 1% HOAc). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.40 (s, 3 H, Ar-CH_3), 3.10–3.38 (m, 4 H, 5′-H, 4′-H, 3′-H, 2′-H), 3.45 (br. d, *J* = 11.0 Hz, 1 H, 6′-H_b), 3.64 (br. d, *J* = 11.3 Hz, 1 H, 6′-H_a), 4.35 (br. s, 1 H, OH), 4.94 (br. s, 1 H, OH), 5.08 (d, *J* = 7.4 Hz, 1 H, 1′-H and br. s, 1 H, OH), 5.45 (br. s, 1 H, OH), 7.28 (br. d, *J* = 8.4 Hz, 1 H, 7-H), 7.50 (s, 1 H, 4-H), 7.59 (br. d, *J* = 7.2 Hz, 1 H, 5-H), 7.72 (br. t, *J* = 8.1 Hz, 1 H, 6-H), 11.90, 11.97 (br. s, 2 H, 1-OH, 8-OH) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 17.57, 60.81, 69.76, 74.20, 76.35, 77.30, 103.0, 115.2, 115.8, 119.0, 121.5, 124.0, 127.8, 133.0, 137.2, 141.5, 148.0, 153.9, 161.2, 180.5, 191.4 ppm. IR (KBr): $\tilde{\nu}$ = 3529, 3442, 2923, 1672, 1624, 1570, 1473, 1420, 1377, 1262, 1213, 1163, 1060, 1036, 934, 888, 837, 785, 770, 749, 647, 567, 428 cm^{-1}. UV (MeOH): λ_{max} (lgε) = 226.5 (4.451), 259.0 (4.430), 290.0 (4.010), 428.0 nm (4.039). MS (ESI): *m*/*z* (%) = 886.9 (100) [2×M + Na]$^+$, 455.1 (5) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{21}H_{20}O_{10}$ + H$^+$: 455.09487; found: 455.09491; calcd. for 2×$C_{21}H_{20}O_{10}$ + Na$^+$: 887.20051; found: 887.20052.

Synthesis of 1,7-Dihydroxy-6-methylanthraquinone (2)

7-Hydroxy-1-methoxy-6-methylanthraquinone (18): A solution of the naphthoquinone **16** (1.00 g, 5.31 mmol) in CH_2Cl_2 (60 mL) was treated at 0 °C dropwise within 10 min with diene **17** (3.66 g, 15.9 mmol). After being stirred for 3.5 h at 20 °C the reaction mixture was concentrated in vacuo. The residue was dissolved in THF (100 mL), 2 N HCl (30 mL) was added and the mixture was heated under reflux for 20 h. Afterwards, the solution was poured on ice and the yellow precipitate was filtered off. The residue was washed with ice-cold EtOAc (3×30 mL) and dried in vacuo to furnish the pure anthraquinone **18** (1.31 g, 92%) as a pale yellow solid. R_f = 0.28 (pentane/EtOAc, 1:1); m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3306, 2943, 2839, 1662, 1599, 1581, 1511, 1470, 1446, 1350, 1312, 1278, 1240 cm^{-1}. UV (CH_3CN): λ_{max} (lgε) = 212.5 (4.457), 269.5 (4.559), 364.5 nm (3.897). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.24 (s, 3 H, Ar-CH_3), 3.92 (s, 3 H, OCH_3), 7.45 (s, 1 H, 8-H), 7.50 (dd, *J* = 7.2, 2.0 Hz, 1 H, 2-H), 7.71–7.81 (m, 2 H, 3-H, 4-H), 7.83 (s, 1 H,

5-H), 10.9 (br. s, 1 H, 7-OH) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]-DMSO): δ = 15.88, 56.23, 111.1, 118.4, 118.7, 120.7, 123.9, 129.1, 130.8, 134.8, 135.1, 135.2, 159.8, 161.4, 181.1, 181.3 ppm. MS (EI, 70 eV): *m*/*z* (%) = 268.2 (100) [M]$^+$, 239.2 (31). HRMS (EI): calcd. for $C_{16}H_{12}O_4$: 268.0736; confirmed. $C_{16}H_{12}O_4$ (268.26): calcd. C 71.64, H 4.51; found C 71.41, H 4.44.

1,7-Dihydroxy-6-methylanthraquinone (2): A suspension of the anthraquinone **18** (200 mg, 0.746 mmol) in HOAc (20 mL) was treated with a 30% solution of HBr in HOAc (15 mL). After being stirred for 1.5 h at 100 °C additional HBr solution (5 mL) was added and the reaction mixture was stirred for another 30 min. Afterwards, the solution was poured on ice and the yellow precipitate was filtered off. The residue was washed with ice-cold EtOAc (3 × 10 mL) and dried in vacuo to furnish the pure anthraquinone **2** (182 mg, 96%) as a yellow solid. R_f = 0.34 (pentane/EtOAc, 4:1); m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3299, 1652, 1638, 1572, 1463, 1430, 1358, 1344, 1306, 1249 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 211.5 (4.393), 273.5 (4.547), 382.0 nm (3.847). ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 2.20 (s, 3 H, Ar-CH$_3$), 7.21 (dd, *J* = 7.2, 1.0 Hz, 1 H, 2-H), 7.40 (s, 1 H, C-8), 7.53 (dd, *J* = 7.6, 0.8 Hz, 1 H, 4-H), 7.67 (t, *J* = 8.0 Hz, 1 H, 3-H), 7.74 (s, 1 H, 5-H), 10.9 (br. s, 1 H, 7-OH), 12.4 ppm (br. s, 1 H, 1-OH) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]-DMSO): δ = 16.07, 111.0, 115.6, 118.5, 123.2, 124.8, 129.7, 132.4, 132.4, 133.2, 136.7, 161.2, 180.3, 188.1 ppm. MS (EI, 70 eV): 254.0 (100) [M]$^+$, 226.1 (19) [M – CO]$^+$. HRMS (ESI): calcd. for $C_{15}H_{10}O_4$ + H$^+$: 255.06519; found: 255.06535. $C_{15}H_{10}O_4$ (254.24): C 70.86, H 3.96; found: C 70.59, H 4.14.

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