A Diels–Alder Reaction for the Total Synthesis of the Novel Antibiotic Antitumor Agent Mensacarcin

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Dedicated to Professor Horst Kessler on the occasion of his 65th birthday

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The antibiotic mensacarcin (**1**), which contains nine stereogenic centers and two epoxy functionalities, is a novel antitumor agent that was first isolated from the culture broth of *Streptomyces* sp. Gö C4/4 found in a soil sample next to the northern cafeteria of the University of Göttingen. For the synthesis of **1** and related structurally simplified analogs, a Diels–Alder reaction of *O*-methyljuglone (**11**) and the tetrasubstituted 1,3-butadiene **22** was performed to give the cycloadduct *rac*-**28**, which was transformed into the epoxides *rac*-**31** and *rac*-**33**. The cytotoxicity of *rac*-**33** is only 53 times lower than the much more complex **1**.

Introduction

Chemotherapy is a fundamental approach for the treatment of cancer, and the majority of clinically employed antitumor agents are natural products or related compounds. Thus, the search for new, naturally occurring anticancer agents and the synthesis of these compounds is an important objective in organic chemistry. Moreover, preparing analogs and partial structures allows us to study their structure–activity relationship. To improve their selectivity these compounds can be used in a disguized form as prodrugs for antibody-directed enzyme prodrug therapy (ADEPT) or as conjugates with monoclonal antibodies.[1]

In 1998 Zeeck and coworkers[2] isolated a novel anthracene derivative **1** from the culture broth of *Streptomyces* sp. Gö C4/4, which was found in a soil sample close to the northern cafeteria (mensa) of the University of Göttingen. This compound, called mensacarcin, has a similar anticancer potency as the clinically used doxorubicin (**2**; Figure 1); it is a rather unique compound containing nine stereogenic centers and two epoxide moieties. Natural products with an anthracene skeleton are well known for their bioactivity such as antiviral, antifungal, antitumor, and antibiotic activity,[3–6] neuronal cell protecting properties,[7] IL-4 signal transduction inhibition,[8] and herbicidal activity.[9]

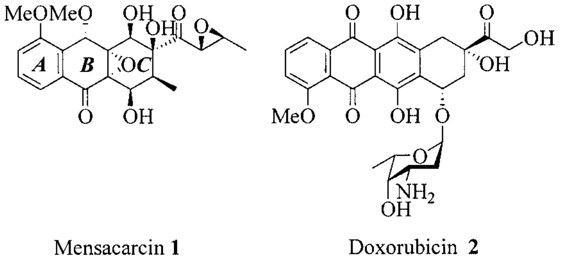
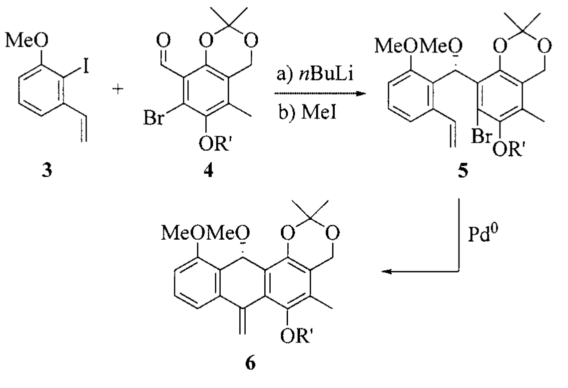


Figure 1. Structures of mensacarcin (**1**), doxorubicin (**2**).

Most general strategies for the synthesis of the carbocyclic framework of these anthracene derivatives uses Diels–Alder reactions.[10–12] Another approach, which has recently been developed by us, is based on two disconnections in



Scheme 1. Synthesis of the mensacarcin skeleton **6** via a Pd-catalyzed transformation.

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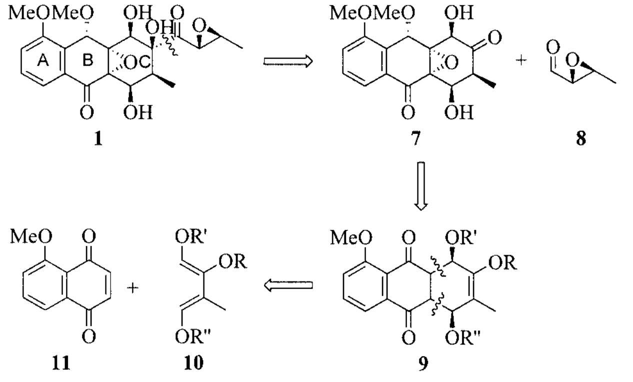
ring B and employs an addition of a metal-organic species obtained from **3** to the aldehyde **4** to give **5**.[13] The latter can easily be transformed into **6** by a Pd-catalyzed arylation (Scheme 1).

Here we describe the synthesis of the core skeleton of **1** by the cycloaddition of a naphthoquinone and a tetrasubstituted 1,3-butadiene as dienophile. The research includes investigations on the structural features responsible for the interesting cytotoxic properties of mensacarcin (**1**) by preparing a monoepoxide and determination of its ED_{50} on human bronchial carcinoma cells of line A549.

Results and Discussion

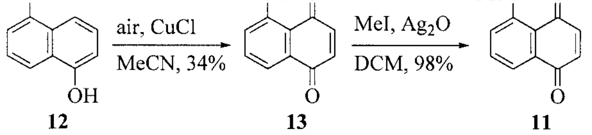
Synthesis

The composition of the skeleton of mensacarcin (**1**) is based on two disconnections of the C ring and an assembly of the C ring by a Diels–Alder reaction of *O*-methyljuglone (**11**) and the tetrasubstituted 1,3-butadiene **10** was envisaged as the key step (Scheme 2).



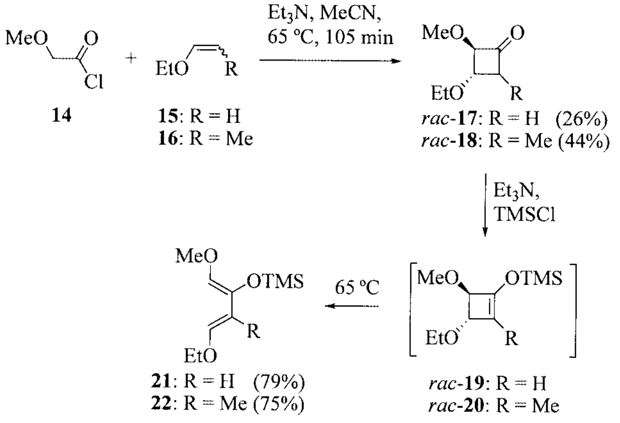
Scheme 2. Retrosynthetic analysis of mensacarcin (**1**).

For the synthesis of **11** 1,5-dihydroxynaphthalene (**12**) was oxidized with air in the presence of CuCl in the dark to give juglone (**13**), which was subsequently methylated with methyl iodide in the presence of silver(I) oxide to afford *O*-methyljuglone (**11**; Scheme 3).[14]



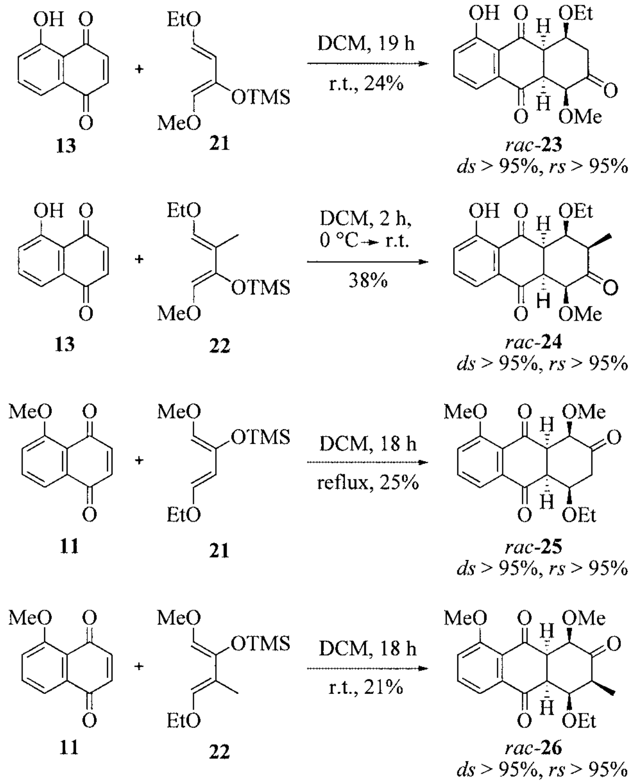
Scheme 3. Synthesis of juglone (**13**) and *O*-methyljuglone (**11**).

For the Diels–Alder reaction with **11** we used two different 1,3-butadienes, namely **21** and the new 1,3-butadiene **22**, which already contains the methyl group necessary for the synthesis of mensacarcin (**1**). 1,3-Butadienes of type **21** and **22** can be synthesized by the Danishefsky method;[15] however, this procedure has the disadvantage that it leads to mixtures of (*E*)- and (*Z*)-stereoisomers. We therefore used an electrocyclic ring-opening of the silyl enol ether of the cyclobutanones **17** and **18** (Scheme 4).[16] The necessary compounds **17** and **18** were prepared by a [2+2] cycloaddition of ethyl vinyl ether (**15**) and *cis*/*trans* ethyl propenyl ether (**16**), respectively, to the methoxyketene obtained from **14**. The stereochemistry of the cyclobutanones can partially be controlled by varying the reaction conditions since Scheeren has shown that cyclobutanones of type **17** isomerize to the *trans* diastereomer under basic conditions. After adding triethylamine to the reaction mixture **17** and **18** were obtained in 26% and 44% yield, respectively. Transformation of **17** and **18** into the corresponding TMS enol ethers **19** and **20** was achieved by treatment with TMSCl in the presence of Et_3N; the compounds, however, were not isolated but heated up to 60 °C and 65 °C, respectively, to give the desired 1,3-butadienes **21** and **22**. This procedure gives only mediocre overall yields but it is straightforward and leads to **21** and **22** as single diastereomers; furthermore, the yield of the desired **22** (33%) is nearly twice as high as for **21**. However, as expected, the tetrasubstituted 1,3-butadiene **22** is less stable than the corresponding trisubstituted compound **21**.



Scheme 4. Synthesis of the 1,3-butadienes **21** and **22**.

We then investigated the Diels–Alder reaction of juglone **13** and *O*-methyljuglone (**11**) with the two 1,3-butadienes **21** and **22**. The two main problems concerning the cycloaddition are the regio- and the stereoselectivity. Reaction of juglone **13** with the dienes **21** and **22** at 20 °C led to the cycloadducts **23** and **24** in 24% and 38% yield, respectively (Scheme 5). Under these conditions, the primarily formed compounds containing an TMS enol ether moiety are not stable, but are cleaved to give the corresponding anthracenes containing a carbonyl functionality. The stereochemistry in **23** and **24** correlates with the configuration of the two double bonds in the employed 1,3-butadienes. Since the Diels–Alder reaction is a disrotatory suprafacial process and proceeds usually with high *endo* selectivity, the two substituents at C-1 and C-4 should have a *cis* orientation to each other and an *anti* orientation towards the neighboring hydrogens. Moreover, the results show that the methyl group in diene **22** compared to **21** seems not to have any influence on the regioselectivity in the cycloaddition step. However, both products **23** and **24** present the wrong regiochemistry with respect to mensacarcin (**1**). The dominating factor for the regiochemical control in these Diels–Alder reactions with normal electron demand is the chelated phenolic hydroxyl group, which reduces the electron density of the neighboring carbonyl group in **13**. As a consequence, the coefficients at C-2 and C-3 of the LUMO of juglone become quite different, resulting in a high degree of regioselectivity. Blocking the free phenolic hydroxyl group by methylation leads to a change of the coefficients, resulting in the inversion of regioselectivity necessary for the synthesis of mensacarcin (**1**).[17]



Scheme 5. Study of the regioselectivity of the cycloaddition with **11** and **13**.

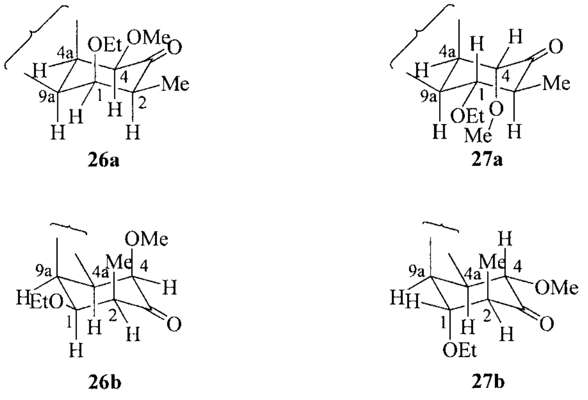
Thus, the cycloaddition of *O*-methyljuglone **11** with the dienes **21** and **22** yielded the racemic cycloadducts **25** and **26**, respectively, with an excellent diastereo- and regioselectivity.

The regio- and relative stereochemistry of the products were analyzed according to the work of Stoodley by comparing the coupling constants of the ^{1}H NMR spectra (Table 1).[18]

Table 1. Coupling constants [Hz] of the signals for the C ring protons of the cycloadduct **26**.

$J_{2,4}$	$J_{4,4a}$	$J_{4a,9a}$	$J_{9a,1}$	$J_{1,2}$	$J_{2,3\text{–Me}}$
1.2	5.6	5.6	2.8	3.6	6.7

For compound **26** two possible conformers (**a** and **b**) could exist (Scheme 6). In addition, we included in our discussion the two possible conformers **a** and **b** of the possible diastereomer **27**, which could be formed by an *exo*-cycloaddition. For the conformers **27a** and **27b**, with a *trans*-diaxial orientation of 1-H and 2-H and of 4-H and 4a-H, respectively, we should expect coupling constants of J = 8–12 Hz for the corresponding resonances, which were not found in the spectra. The long-range coupling of J = 1.2 Hz between 2-H and 4-H suggests a W-coupling, which requires an equatorial-like orientation of these protons. This is only consistent with the conformer **26b**. The coupling constants of about J = 3–6 Hz between 4-H/4a-H, 4a-H/9a-H, 9a-H/1-H, and 1-H/2-H correspond to a synclinal orientation, which requires an axial-like arrangement of the methoxy and the methyl group. This is in agreement with a *syn* orientation of the ethoxy, methoxy, and methyl groups. The carbonyl group at C-3 flattens the C ring so that the methyl and the methoxy group probably have a pseudo-axial arrangement; the six-membered C ring should therefore exist as a twisted chair. The final proof of the structure of **26** was achieved by X-ray analysis, which also shows the W-orientation of the two hydrogens 2-H and 4-H, as proposed in the conformer **26b** (Figure 2).



Scheme 6. The four possible conformers of the C ring of the cycloaddition product **26** and the possible diastereomer **27**.

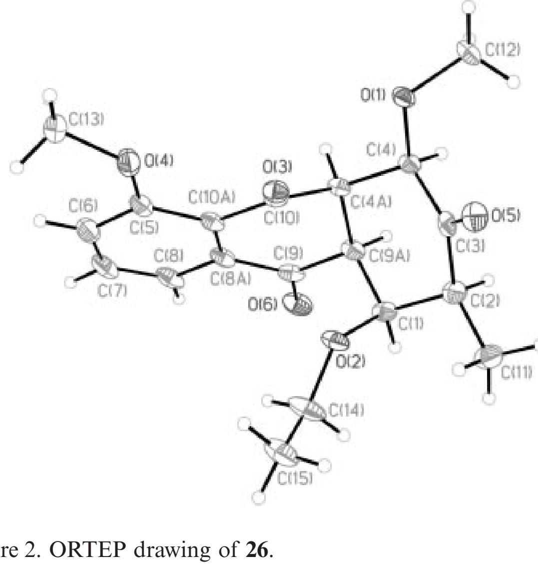
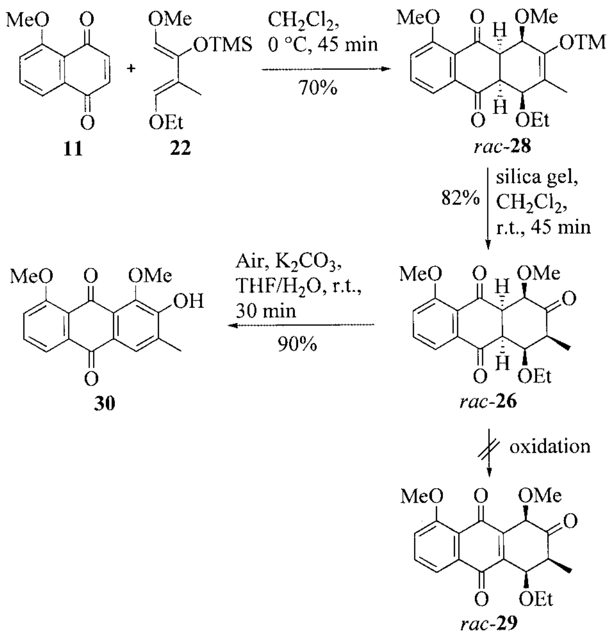


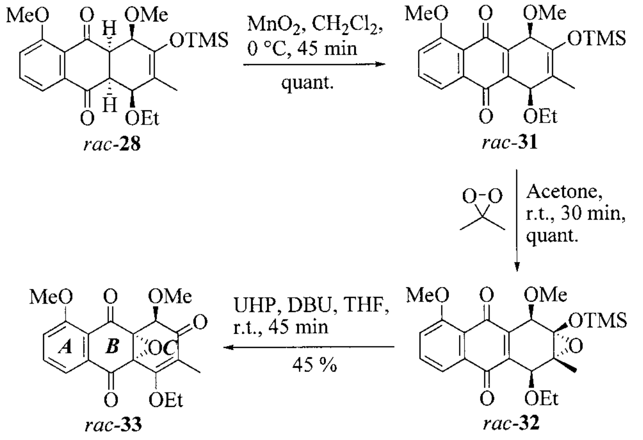
Figure 2. ORTEP drawing of **26**.

The yield of the cycloaddition of **11** with **22** to give **26** was rather low and, in addition, the further transformation of the carbonyl moiety in **26** turned out to be difficult. We therefore performed the Diels–Alder reaction at low temperature to allow the isolation of the primarily formed cycloadduct. Indeed, reaction of **11** and **22** at 0 °C for 45 min gave the desired cycloadduct in 70% yield. Mild treatment of **28** (silica gel) afforded the ketone **26** in 82% yield. Unfortunately, oxidation of **26** under many different conditions did not lead to the desired compound **29** necessary for the B ring epoxidation,[19] but to the fully aromatized anthraquinone **30** (Scheme 7). Evidently acidic or basic conditions have to be avoided. Thus, the tendency of this type of molecules to undergo aromatization to form anthraquinones is very high.[20,21]



Scheme 7. Attempted synthesis of **29**.

Due to the described problems an alternative route was applied starting with the primarily formed Diels–Alder product **28**, which indeed could be oxidized without aromatization. The best results were achieved by using activated manganese dioxide in dichloromethane to give the naphthoquinone **31** in quantitative yield (Scheme 8).[22] However, a cleavage of the silyl enol ether in **31** to obtain the corresponding ketone necessary for the subsequent introduction of the side chain could not be achieved under standard conditions with diluted hydrochloric acid, PTSA, montmorillorite K-10, or silica gel; instead aromatization occurred again. Due to the poor stability of **31**, direct epoxidation of the B=C double bond was then tried by treatment with *m*CPBA, H_2O_2, or *t*BuOOH, but only the anthraquinone **30** was isolated.[23] However, much to our delight, with dimethyldioxirane as epoxidizing agent the C ring epoxide **32** could be obtained in quantitative yield.[24] Finally, the double bond between the B and C ring in **32** could also be epoxidized with the urea-hydroperoxide complex (UHP) to give **33** using the Julia–Colonna method for α,β-unsaturated ketones (Scheme 8).[25] We assume that in **32** and **33** the epoxide moieties have the α-orientation, which means that the epoxidation should have taken place from the less-hindered side. In both cases a single diastereomer is formed as a racemic mixture.



Scheme 8. Synthesis of **33** containing the three-membered-ring skeleton of mensacarcin and the *endo*-epoxide moiety.

Cytotoxicity Tests

The cytotoxicity of compound **33** was studied compared to that of mensacarcin **1** and the clinically used doxorubicin **2** by in vitro growth inhibition of human lung carcinoma cells of line A549. The adherent cells were sown in different numbers and, after incubation with different concentrations of the compounds, the numbers of formed colonies were counted. Comparing the bioactivity through the ED_{50} values for the relative colony-forming rates, we observed that the clinically used doxorubicin **2** is the most bioactive of the tested compounds (45 nM), mensacarcin (**1**) is approximately 35 times less active than **2**, and compound **33** is about 54 times less active than **1** (Figure 3). The only small decrease in cytotoxicity of the simplified three-membered ring skeleton analog **33** compared to mensacarcin (**1**) suggests that the epoxide moiety between ring B and C is important for the bioactivity of mensacarcin (**1**).

Experimental Section

General Remarks: Reactions were usually performed in preheated glassware under an atmosphere of argon. Dry solvents were prepared according to standard procedures. Commercial reagents were used without further purification. Anhydrous sodium sulfate was used for drying solutions. 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. Semi-preparative HPLC was carried out on a Kromasil 100 RP-C18 (250 × 20 mm, 7 µm) column, with the following gradient $MeOH/H_2O$ (60:40→100:0) over 30 min, flow 12 mL min^{-1}, with a Jasco-HPLC unit PU87 and a Jasco detector UV-2075 at 251 nm. Solvents used were HPLC grade and the probes were filtered through a 0.22 µm teflon membrane filter.

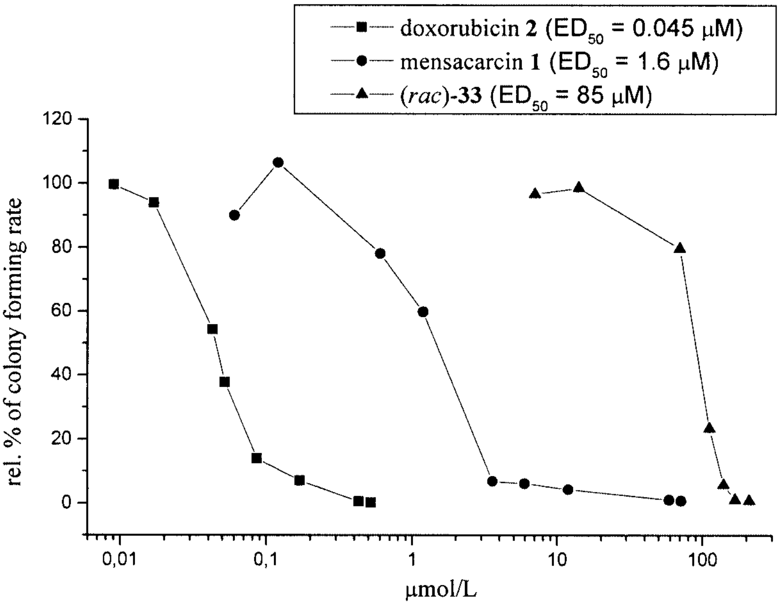


Figure 3. Growth inhibition and ED_{50} values (μM) of the in vitro cytotoxicity of mensacarcin (**1**), doxorubicin (**2**), and **33** against the human bronchial carcinoma cell line A549.

Melting points were recorded on a Mettler FP61 and are uncorrected. IR spectra were determined on a Bruker IFS25, UV/Vis spectra on a Perkin–Elmer Lambda 2 or Lambda 9, and mass spectra on a Varian MAT 311A and Varian MAT 731 for HRMS. ^{1}H NMR spectra were recorded with either a Varian VXR-200 MHz, Varian UNITY-300 MHz or Bruker AMX-300 MHz spectrometer and ^{13}C NMR spectra at 75 MHz. Spectra were taken at room temperature in deuterated solvents as indicated, using the solvent peak as internal standard.

5-Hydroxy-1,4-naphthoquinone (Juglone, 13): A suspension of CuCl (12.0 g, 0.12 mol) in acetonitrile (500 mL) was placed in a 2-L, three-necked flask fitted with a mechanical stirrer and a gas inlet tube and a strong current of air was bubbled through it. A suspension of 1,5-dihydroxynaphthalene (**12**; 30.0 g, 0.19 mol) in acetonitrile (500 mL) was added with vigorous stirring at room temperature in the dark over 30 min, and the resultant mixture stirred for 7 h. The mixture was filtered, washed with acetonitrile, and the solvent removed under reduced pressure. The crude product was purified in a Soxhlet extractor with *n*-heptane as solvent to afford **13** (11.1 g, 34%) as orange-red needles. M.p. 154–161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96 (s, 2 H, 2-H, 3-H), 7.29 (dd, J = 6.3, 2.9 Hz, 1 H, 6-H), 7.64 (m, 2 H, 7-H, 8-H), 12.01 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 114.92 (C-4a), 119.13 (C-6), 124.47 (C-8), 131.70 (C-8a), 138.62 (C-7), 136.54, 139.56 (C-2, C-3), 161.40 (C-5), 184.22, 190.25 (C-1, C-4) ppm. MS (70 eV, EI): *m*/*z* (%) = 174.1 (100) [M$^+$], 158.1 (4), 146.1 (8), 118.1 (22), 92.0 (16), 63.0 (10). HRMS: *m*/*z* (M$^+$, $C_{10}H_6O_3$): calcd. 174.0317; found 174.0317.

5-Methoxy-1,4-naphthoquinone (*O*-Methyljuglone, 11): Methyl iodide (7.0 mL, 12 mmol) was added to a mixture of juglone **13** (10.0 g, 57 mmol) and silver(I) oxide (10.0 g, 46 mol) in DCM (180 mL) and stirred for 20 h at room temperature. Then, methyl iodide (2.9 mL, 46 mmol) and silver(I) oxide (10.6 g, 46 mol) were added again and the reaction mixture stirred for another 3 h at room temperature (TLC control). This mixture was then filtered through Celite, washed with DCM, and the solvent removed under reduced pressure. Column chromatography (DCM) afforded **11** (10.7 g, 98%) as orange needles. M.p. 184–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, OCH_3), 6.85 (s, 2 H, 2-H, 3-H), 7.30 (dd, J = 7.1, 1.8 Hz, 1 H, 6-H), 7.67 (dd, J = 7.9, 7.1 Hz, 1 H, 7-H), 7.72 (dd, J = 7.9, 1.8 Hz, 1 H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.45 (OCH_3), 117.90 (C-6), 119.13 (C-8), 119.66 (C-4a), 133.99 (C-8a), 134.96 (C-2), 136.17 (C-7), 140.85 (C-3), 159.58 (C-5), 184.32, 185.16 (C-1, C-4) ppm. MS (70 eV, EI): *m*/*z* (%) = 188.1 (100) [M$^+$], 174.1 (20), 159.1 (18), 130 (16), 104 (18), 76 (20), 63 (12). HRMS: *m*/*z* (M$^+$, $C_{11}H_8O_3$): calcd. 188.0473; found 188.0473.

2-Methoxyethanoyl Chloride (14): Thionyl chloride (71 mL, 0.97 mol) was added dropwise over 15 min to a solution of 2-methoxyethanoic acid (50 mL, 0.65 mol) and DMF (1.0 mL). After heating under reflux for 2.5 h, the mixture was distilled through a 20 cm Vigreux column to give **14** (58.5 g, 83%) as a pale-yellow liquid. B.p. 105–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.40 (s, 3 H, OCH_3), 4.30 (s, 2 H, CH_2) ppm.

3-Ethoxy-2-methoxycyclobutanone (17): Triethylamine (165 mL, 1.18 mol) was added to a solution of ethyl vinyl ether (**15**; 131 mL, 1.36 mol) in acetonitrile (400 mL). The mixture was cooled to 0 °C and **14** (100 mL, 1.09 mol) was added dropwise over 15 min. Next, the reaction mixture was placed in a pre-warmed oil bath at 65–70 °C and stirred for 105 min. The solvent was removed under reduced pressure (20 mbar) and the slurry re-suspended in diethyl ether, filtered through Celite, and the solvent removed under reduced pressure (15 mbar). The crude product was distilled to afford **17** (42 g, 26%) as a colorless oil. B.p. 40–51 °C (0.115 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7 Hz, 3 H, OCH_2CH_3), 2.93–2.76 (m, 2 H, $4H_2$), 3.51 (s, 3 H, OCH_3), 3.53–3.65 (m, 2 H, OCH_2CH_3), 4.09–4.13 (m, 1 H, 3-H), 4.52 (m, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0 (OCH_2CH_3), 45.4 (C-4), 58.2 (OCH_3), 65.9 (OCH_2CH_3), 70.2 (C-3), 94.6 (C-2), 203.3 (C-1) ppm. MS (70 eV, EI): *m*/*z* (%) = 144.1 (4) [M$^+$, $C_7H_{12}O_3$], 102.1 (72), 99.0 (20), 85.0 (20), 74.0 (88), 71.0 (52), 45.0 (100).

3-Ethoxy-2-methoxy-4-methylcyclobutanone (18): Triethylamine (70 mL, 0.50 mol) was added to a solution of ethyl 1-(*E*/*Z*)propenyl ether (**16**; 50 g, 0.58 mol) in acetonitrile (170 mL). The mixture was cooled to 0 °C and **14** (43 mL, 0.47 mol) was added dropwise over

15 min. Next, the reaction mixture was placed in a pre-warmed oil bath at 65–70 °C and stirred for 105 min. The solvent was removed under reduced pressure (20 mbar) and the slurry re-suspended in diethyl ether, filtered through Celite, and the solvent evaporated in vacuo (15 mbar). The crude product was distilled to give a *cis/trans* mixture of **18** (33 g, 44%) as a colorless oil. B.p. 32–36 °C/0.15 mbar. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 1.22 (d, J = 7.1 Hz, 3 H, 4-$\mathrm{CH_3}$), 1.27 (t, J = 7.1 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 2.97 (m, 1 H, 4-H), 3.47 (s, 3 H, $\mathrm{OCH_3}$), 3.61 (dq, J = 7.1, 1.0 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 3.65 (m, 1 H, 3-H), 4.48 (m, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 11.6 ($\mathrm{CH_3}$), 15.2 ($\mathrm{OCH_2}C\mathrm{H_3}$), 51.8 (C-4), 58.3 ($\mathrm{OCH_3}$), 65.8 ($\mathrm{O}C\mathrm{H_2CH_3}$), 77.5 (C-3), 92.8 (C-2), 206.7 (C-1) ppm. MS (70 eV, EI): m/z (%) = 158.1 (4) [M$^+$], 102.1 (80), 85.0 (80), 74.0 (100), 58.0 (42), 45.1 (32), 41.1 (30). HRMS: m/z (M$^+$, $\mathrm{C_8H_{14}O_3}$): calcd. 158.0943; found 158.0943.

(1*Z*,3*E*)-4-Ethoxy-1-methoxy-2-(trimethylsilanyloxy)butadiene (21): Triethylamine (23.2 mL, 166 mmol) and then, dropwise, TMSCl (9.9 mL, 78 mmol) were added to a solution of cyclobutanone **17** (8.0 g, 55.5 mmol) in acetonitrile (40 mL). Next, the mixture was placed in a pre-warmed oil bath at 60 °C and stirred for 14 h (TLC control). The solvent was removed under reduced pressure (20 mbar), the slurry was re-suspended in diethyl ether containing 2% triethylamine (re-suspension in *n*-hexane is also possible), filtered through Celite, and the solvent removed under reduced pressure (20 mbar). The crude product was distilled (avoiding overheating) to give **21** (9.5 g, 79%) as a slightly reddish oil. B.p. 44–48 °C/0.30 mbar. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 0.20 [s, 9 H, $\mathrm{Si(CH_3)_3}$], 1.27 (t, J = 7.0 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 3.53 (s, 3 H, $\mathrm{OCH_3}$), 3.74 (q, J = 7.0 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.21 (d, J = 12.2 Hz, 1 H, 3-H), 5.47 (s, 1 H, 1-H), 6.51 (d, J = 12.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 0.20 [$\mathrm{Si(CH_3)_3}$], 14.7 ($\mathrm{OCH_2}C\mathrm{H_3}$), 56.3 ($\mathrm{OCH_3}$), 65.3 ($\mathrm{O}C\mathrm{H_2CH_3}$), 101.5 (C-3), 103.5(C-1), 132.8 (C-2), 145.3 (C-4) ppm. MS (70 eV, EI): m/z (%) = 216 (5) [M$^+$, $\mathrm{C_{10}H_6O_3Si}$], 201 (5), 189 (3), 157 (5), 133 (50), 99 (8), 89 (12), 73 (100).

(1*Z*,3*E*)-4-Ethoxy-1-methoxy-3-methyl-2-(trimethylsilanyloxy)butadiene (22): Triethylamine (36.7 mL, 263 mmol) and then, dropwise, TMSCl (15.7 mL, 124 mmol) were added to a solution of cyclobutanone **18** (13.8 g, 87 mmol) in acetonitrile (63 mL). Next, the mixture was placed in a pre-warmed oil bath at 65 °C and stirred for 2.5 h (TLC control). The solvent was removed under reduced pressure (20 mbar), the slurry was re-suspended in diethyl ether containing 2% triethylamine (re-suspension in *n*-hexane is also possible), filtered through Celite, and the solvent removed under reduced pressure (20 mbar). The crude product was distilled (avoiding overheating) to give **22** (15 g, 75%) as a slightly reddish oil. B.p. 40–42 °C/0.115 mbar. ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 0.17 [s, 9 H, $\mathrm{Si(CH_3)_3}$], 1.24 (t, J = 7.0 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.60 (d, J = 1.2 Hz, 3 H, $\mathrm{CH_3}$), 3.55 (s, 3 H, $\mathrm{OCH_3}$), 3.81 (q, J = 7.0 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.57 (s, 1 H, 1-H), 6.30 (d, J = 1.2 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 0.30 [$\mathrm{Si(CH_3)_3}$], 9.33 ($\mathrm{CH_3}$), 15.32 ($\mathrm{OCH_2}C\mathrm{H_3}$), 59.43 ($\mathrm{OCH_3}$), 67.92 ($\mathrm{O}C\mathrm{H_2CH_3}$), 109.87 (C-3), 129.55 (C-1), 135.30 (C-2), 142.01 (C-4) ppm. IR (film): $\tilde{\nu}$ = 3402, 2958, 2901, 2830, 1783, 1729, 1636, 1445, 1386, 1362, 1250, 1195, 1103, 1008, 994, 947, 956, 926 cm^{-1}. UV ($\mathrm{CHCl_3}$): $\lambda_{\max}$ (log ε) = 258.5 (4.044) ppm. MS (70 eV, EI): m/z (%) = 230.1 (16) [M$^+$], 186.1 (20), 143.0 (8), 133.0 (92), 73.0 (100), 69.0 (16), 45.0 (8). HRMS: m/z (M$^+$, $\mathrm{C_{11}H_{22}O_3Si}$): calcd. 230.1338; found 230.1338.

(1*SR*,4*SR*,4a*RS*,9a*SR*)-4-Ethoxy-5-hydroxy-1-methoxy-2-oxo-3,4,4a,9a-tetrahydro-1*H*-9,10-anthraquinone (23): Diene **21** (2.5 g, 11.6 mmol) was added to a solution of **13** (1.0 g, 5.7 mmol) in DCM (77 mL) and the reaction mixture stirred for 19 h at room temperature. The solvent was removed under reduced pressure and the crude product was stored at –18 °C under argon overnight. The solid formed was re-suspended in diethyl ether and filtered to afford **23** (430 mg, 24%) as pale beige crystals. M.p. > 170 °C (dec.). ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$): δ = 0.65 (t, J = 7.0 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 2.61 (ddd, J = 14.5, 3.5, 1.0 Hz, 1 H, 3-H$_a$), 2.90 (dd, J = 14.5, 3.5 Hz, 1 H, 3-H$_b$), 3.02 (dd, J = 9.0, 7.0 Hz, 1 H, $\mathrm{OC}H_a\mathrm{HCH_3}$), 3.42 (dd, J = 9.0, 7.0 Hz, 1 H, $\mathrm{OCH}H_b\mathrm{CH_3}$), 3.49 (s, 3 H, $\mathrm{OCH_3}$), 3.55 (dd, J = 6.0, 3.0 Hz, 1 H, 4a-H), 3.85 (dd, J = 6.0, 6.0 Hz, 9a-H), 3.92 (dd, J = 6.0, 1.0 Hz, 1 H, 1-H), 4.19 (q, J = 3.0 Hz, 1 H, 4-H), 7.15 (dd, J = 8.0, 1.3 Hz, 1 H, 6-H), 7.40 (dd, J = 7.3, 1.7 Hz, 1 H, 8-H), 7.57 (dd, J = 8.0, 7.3 Hz, 1 H, 7-H), 11.81 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 14.2 ($\mathrm{OCH_2}C\mathrm{H_3}$), 43.7 (C-3), 51.3 (C-9a), 54.1 (C-4a), 59.3 ($\mathrm{OCH_3}$), 64.9 ($\mathrm{O}C\mathrm{H_2CH_3}$), 78.3 (C-4), 82.2 (C-1), 117.4 (C-8), 118.3 (C-10a), 122.4 (C-5), 137.0 (C-7), 138.1 (C-8a), 161.3 (C-5), 191.1 (C-9), 202.0 (C-2, C-10) ppm. IR (KBr): $\tilde{\nu}$ = 2934, 1727, 1706, 1645, 1454, 1331, 1258, 1240, 1137, 1102, 1018 cm^{-1}. UV ($\mathrm{CHCl_3}$): $\lambda_{\max}$ (log ε) = 194.0 (4.182), 229.0 (4.323), 262.0 (3.698), 346.0 (3.700) ppm. MS (70 eV, EI): m/z (%) = 318.1 (32) [M$^+$], 288.1 (18), 240.1 (56), 218.1 (40), 173.1 (34), 159.1 (12), 144.1 (44), 102.1 (28), 89.1 (100), 72.0 (32), 61.0 (62), 45.0 (22). HRMS: m/z (M$^+$, $\mathrm{C_{17}H_{18}O_6}$): calcd. 318.1103; found 318.1103.

(1*SR*,4*SR*,4a*RS*,9a*SR*)-4-Ethoxy-5-hydroxy-1-methoxy-3-methyl-2-oxo-3,4,4a,9a-tetrahydro-1*H*-9,10-anthraquinone (24): Diene **22** (213 mg, 0.93 mmol) was added at 0 °C to a solution of juglone (**13**; 64 mg, 0.37 mmol) in DCM (4.9 mL) and the reaction left to warm to room temperature over 2 h while stirring. The solvent was removed under reduced pressure and the crude product was stored at –18 °C under argon overnight. The solid formed was re-suspended in diethyl ether and filtered to afford **24** (47 mg, 38%) as pale-yellow crystals. M.p. > 150 °C (dec.). ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$): δ = 0.48 (t, J = 7.0 Hz, 3 H, $\mathrm{OCH_2C}H_3$),1.16 (d, J = 6.9 Hz, 3 H, $\mathrm{CH_3}$), 2.71 (m, 1 H, 3-H), 2.82 (dq, J = 9.4, 7.0 Hz, 1 H, $\mathrm{OC}H_a\mathrm{HCH_3}$), 3.21 (dq, J = 9.4, 7.0 Hz, 1 H, $\mathrm{OCH}H_b\mathrm{CH_3}$), 3.56 (s, 1 H, $\mathrm{OCH_3}$), 3.59 (m, 1 H, 4a-H), 3.92 (m, 1 H, 1-H), 3.94 (m, 1 H, 1a-H), 4.07 (br. t, J = 2.6 Hz, 1 H, 4-H), 7.18 (dd, J = 8.4, 0.9 Hz, 1 H, 6-H), 7.46 (dd, J = 7.5, 0.9 Hz, 1 H, 8-H), 7.62 (dd, J = 8.4, 7.5 Hz, 1 H, 7-H), 12.01 (s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 10.18 ($\mathrm{CH_3}$), 14.27 ($\mathrm{OCH_2}C\mathrm{H_3}$), 48.96 (C-3), 51.46 (C-9a), 55.82 (C-4a), 59.65 ($\mathrm{OCH_3}$), 69.81 ($\mathrm{O}C\mathrm{H_2CH_3}$), 82.89 (C-1), 84.95 (C-4), 191.30 (C-9), 117.52 (C-8), 117.75 (C-10a), 122.28 (C-6), 137.57 (C-7), 138.07 (C-8a), 161.62 (C-5), 202,76, 202.84 (C-2, C-10) ppm. IR (KBr): $\tilde{\nu}$ = 2979, 1724, 1642, 1454, 1334, 1240, 1136, 1071 cm^{-1}. UV ($\mathrm{CHCl_3}$): $\lambda_{\max}$ (log ε) = 194.0 (8.136), 229.5 (8.250), 347.0 (7.645) ppm. MS (70 eV, EI): m/z (%) = 332.3 (26) [M$^+$], 302.3 (24), 284.2 (16), 254.2 (100), 218.2 (20), 158.2 (14), 89.1 (52), 61.0 (32), 45.0 (10). HRMS: m/z (M$^+$, $\mathrm{C_{18}H_{20}O_6}$): calcd. 332.1260; found 332.1260.

(1*RS*,4*RS*,4a*RS*,9a*SR*)-1-Ethoxy-4,5-dimethoxy-3-oxo-1,2,4a,9a-tetrahydro-4*H*-9,10-anthraquinone (25): Diene **21** (79 mg, 0.37 mmol) was added to a solution of *O*-methyljuglone (**11**; 33 mg, 0.18 mmol) in DCM (2.4 mL) and the reaction mixture stirred for 18 h under reflux. The solvent was removed under reduced pressure and the crude product was stored at –18 °C under argon overnight. The solid formed was re-suspended in diethyl ether and filtered to afford **25** (15 mg, 25%) as pale beige crystals. M.p. > 165 °C (dec.). ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$): δ = 0.82 (t, J = 7.0 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 2.60 (dd, J = 14.5, 3.5 Hz, 1 H, 2-H$_a$), 3.05 (dd, J = 14.5, 5.1 Hz, 1 H, 2-H$_b$), 3.15 (m, 1 H, $\mathrm{OC}H_a\mathrm{HCH_3}$), 3.42 (s, 3 H, 4-$\mathrm{OCH_3}$), 3.50 (m, 2 H, $\mathrm{OCH}H_b\mathrm{CH_3}$, 9a-H), 3.72 (dd, J = 6.0, 4.6 Hz, 4a-H), 3.85 (d, J = 4.6 Hz, 1 H, 4-H), 3.90 (s, 3 H, 5-$\mathrm{OCH_3}$), 4.10 (m, 1 H, 1-H), 7.22 (dd, J = 7.5, 1.4 Hz, 1 H, 6-H), 7.58 (dd, J = 7.8, 7.5 Hz, 1 H, 7-H), 7.66 (dd, J = 7.8, 1.4 Hz, 1 H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.56 (OCH_2CH_3), 64.98 (OCH_2CH_3), 43.05 (C-2), 52.33 (C-9a), 52.77 (C-4a), 56.46 (5-OCH_3), 59.16 (4-OCH_3), 78.12 (C-1), 82.99 (C-4), 117.57 (C-6), 118.47 (C-8), 126.0 (C-10a), 133.87 (C-7), 137.85 (C-8a), 158.31 (C-5), 191.41 (C-10), 195.20 (C-9), 203.09 (C-3) ppm. IR (KBr): $\tilde{\nu}$ = 2931, 1731, 1693, 1585, 1469, 1285, 1129, 1083, 1016 cm^{-1}. UV ($CHCl_3$): λ_{max} (log ε) = 225.5 (8.265), 331.5 (7.559) ppm. MS (70 eV, EI): m/z (%) = 332.2 (26) [M$^+$], 302.2 (20), 286.2 (40), 254.2 (20), 232.2 (52), 190.2 (40), 144.1 (36), 115.1 (24), 89.1 (100), 61.0 (54), 45.0 (16). HRMS: m/z (M$^+$, $C_{18}H_{20}O_6$): calcd. 332.1260; found 332.1260.

(1*RS*,4*RS*,4a*RS*,9a*SR*)-1-Ethoxy-4,5-dimethoxy-2-methyl-3-oxo-1,2,4a,9a-tetrahydro-4*H*-9,10-anthraquinone (26): Diene **22** (1.2 g, 5.3 mmol) was added to a solution of **11** (400 mg, 2.1 mmol) in DCM (28 mL) and the reaction mixture stirred for 3.5 h at room temperature. The solvent was removed under reduced pressure and the crude product was stored at –18 °C under argon overnight. The solid formed was re-suspended in diethyl ether and filtered to afford **26** (125 mg, 21%) as pale beige crystals. M.p. > 185 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.50 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.11 (d, J = 6.7 Hz, 3 H, CH_3), 2.70 (ddq, J = 6.7, 3.6, 1.2 Hz, 1 H, 2-H), 2.89 (dq, J = 9.4, 7.0 Hz, 1 H, OCH_aHCH_3), 3.20 (dq, J = 9.4, 7.0 Hz, 1 H, $OCHH_bCH_3$), 3.50 (dd, J = 5.6, 2.8 Hz, 1 H, 9a-H), 3.53 (s, 3 H, 4-OCH_3), 3.81 (dd, J = 5.6, 1.2 Hz, 1 H, 4-H), 3.84 (s, 3 H, 5-OCH_3), 3.93 (dd, J = 5.6, 5.6 Hz, 1 H, 4a-H), 4.12 (dd, J = 3.6, 2.8 Hz, 1 H, 1-H), 7.21 (dd, J = 8.4, 0.8 Hz, 1 H, 6-H), 7.56 (dd, J = 8.4, 7.7 Hz, 1 H, 7-H), 7.67 (dd, J = 7.7, 0.8 Hz, 1 H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.11 (CH_3), 10.16 (OCH_2CH_3), 48.72 (C-2), 53.29 (C-4a), 55.44 (C-9a), 56.46 ($PhOCH_3$), 59.71 (OCH_3), 69.66 (OCH_2CH_3), 82.95 (C-4), 85.23 (C-1), 118.36 (C-6), 118.57 (C-8), 126.62 (C-10a), 133.34 (C-7), 136.33 (C-8a), 157.93 (C-5), 190.80 (C-10), 196.56 (C-9), 203.01 (C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3428, 2979, 2937, 2902, 1731, 1686, 1586, 1267, 1200, 1139, 1072, 1047, 1034 cm^{-1}. UV (MeCN): λ_{max} (log ε) = 226.0 (4.305), 330.0 (3.604). $[\alpha]_D^{20} \approx 0.0$ (c = 0.5, $CHCl_3$). MS (70 eV, EI): m/z (%) = 346.2 (10) [M$^+$], 316.1 (32), 300.1 (20), 273.1 (20), 245.1 (32), 230.1 (100), 189.1 (24), 156.1 (30), 89.1 (96), 61.0 (38). HRMS: m/z (M$^+$, $C_{19}H_{22}O_6$): calcd. 332.1260; found 332.1260.

X-ray Structure Determination of 26:[26] $C_{12}H_{14.67}O_4$, M_r = 222.90, monoclinic, space group $P2_1/c$, a = 14.279(3), b = 12.628(3), c = 9.352(2) Å, β = 91.957(5)°, V = 1685.3(7) Å^3, Z = 6, $D_{calcd.}$ = 1.318 Mg m^{-3}, F(000) = 712, T = 103(2) K. Bruker SMART 6000 (Cu-K_α), absorption coefficient = 0.820 mm^{-1}, crystal size $0.20 \times 0.10 \times 0.02$ mm^3, 2469 independent reflections collected, theta range for data collection 3.10 to 59.86°, $-15 \le h \le 15$, $0 \le k \le 14$, $0 \le l \le 10$. Structure solved by full-matrix least-squares refinement on F^2 and 230 parameters. Refinement converged: final R indices [$I > 2\sigma(I)$]: $R_1(F)$ = 0.0635, wR_2 = 01591; R indices (all data): R_1 = 0.0792, wR_2 = 0.1714. Goodness-of-fit on F^2 = 1.065. Largest diff. peak and hole: 0.282 and –0.458 e Å^{-3}, Figure 2 shows the molecular structure of **26**. Programs used: SHELXTL.[27]

(1*RS*,4*RS*,4a*RS*,9a*SR*)-1-Ethoxy-4,5-dimethoxy-2-methyl-3-(trimethylsilyloxy)-1,4,4a,9a-tetrahydro-9,10-anthraquinone (28): Diene **22** (4.9 g, 21 mmol) was added to a solution of **11** (1.6 g, 8.5 mmol) in DCM (110 mL) and the reaction mixture was stirred for 45 min at 0 °C (TLC control). The solvent was removed under reduced pressure, some *n*-hexane was added, and the crude product was stored at –18 °C under argon overnight. The solid formed was resuspended in *n*-hexane, filtered, washed first with *n*-hexane and then quickly with an ice-cold mixture of *n*-hexane and diethyl ether (5:1) at 0 °C to afford **28** (2.5 g, 70%) as pale beige crystals. M.p. > 118 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.28 [s, 9 H, $Si(CH_3)_3$], 0.78 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.69 (br. d, J = 1.4 Hz, 3 H, CH_3), 3.26 (s, 3 H, 4-OCH_3), 3.28 (m, 1 H, OCH_aHCH_3), 3.36 (m, 2 H, $OCHH_bCH_3$, 9a-H), 3.55 (m, 1 H, 4a-H), 3.77 (m, 1 H, 4-H), 3.92 (s, 3 H, 5-OCH_3), 3.99 (br. d, J = 4.5 Hz, 1 H, 1-H), 7.20 (dd, J = 7.7, 1.8 Hz, 1 H, 6-H), 7.59 (br. d, J = 7.7, 1 H, 8-H), 7.61 (dd, J = 7.7, 7.7 Hz, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.14 [$Si(CH_3)_3$], 14.29 (CH_3), 15.37 (OCH_2CH_3), 49.87 (C-4a), 51.03 (C-9a), 56.51 (5-OCH_3), 59.49 (4-OCH_3), 67.67 (OCH_2CH_3), 77.59 (C-4), 78.69 (C-1), 114.89 (C-2), 117.16 (C-6), 118.42 (C-8), 126.20 (C-10a), 133.86 (C-7), 138.87 (C-8a), 145.35 (C-3), 158.47 (C-5), 193.37 (C-10), 196.21(C-9) ppm. MS (70 eV, EI): m/z (%) = 418.3 (3) [M$^+$], 403.3 (2), 373.3 (4), 230.2 (100), 179.1 (8), 73.0 (28). HRMS: m/z (M$^+$, $C_{22}H_{30}O_6Si$): calcd. 418.1812; found 418.1812.

Hydrolysis of 28: Silica gel (approx. 50 g) was added to a solution of **28** (600 mg, 1.4 mmol) in DCM (150 mL) and stirred for 45 min at room temperature (TLC control). The mixture was filtered through a sintered glass filter and washed with cold DCM. Then, the silica gel was eluted with DCM/MeOH (75:25) to afford the aromatized product **30** (64 mg, 15%) as a yellow solid and afterwards with DCM/MeOH (50:50) to afford **26** (405 mg, 82%) as a pale beige solid.

3-Hydroxy-4,5-dimethoxy-2-methyl-9,10-anthraquinone (30): M.p. > 155 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (br. d, J = 0.8 Hz, 3 H, CH_3), 4.03 (s, 3 H, 5-OCH_3), 4.04 (s, 3 H, 4-OCH_3), 6.73 (s, 1 H, OH), 7.30 (dd, J = 8.4, 1.2 Hz, 1 H, 6-H), 7.66 (dd, J = 8.4, 7.5 Hz, 7-H), 7.88 (dd, J = 7.5, 1.2 Hz, 1 H, 7-H), 7.89 (s, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.18 (CH_3), 56.69 (5-OCH_3), 62.38 (4-OCH_3), 117.62 (C-6), 119.22 (C-8), 122.81, 125.56 (C-4a, C-10a), 125.81 (C-1), 130.28, 135.25 (C-8a, C-9a), 134.40 (C-7), 136.02 (C-2), 145.55 (C-3), 153.85 (C-4), 159.73 (C-5), 182.73, 186.01 (C-9, C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3320, 2941, 1580, 1468, 1316, 1276, 1235, 978 cm^{-1}. UV ($CHCl_3$): λ_{max} (log ε) = 213.0 (4.406), 269.0 (4.481), 367.0 (3.865) ppm. MS (70 eV, EI): m/z (%) = 298.2 (100), [M$^+$], 283.2 (84), 280.2 (46), 268.2 (38), 255.1 (32), 181.1 (16), 139.1 (20), 76.0 (18),63.0 (12). HRMS: m/z (M$^+$, $C_{17}H_{14}O_5$): calcd. 298.0841; found 298.0841.

(1*RS*,4*RS*)-1-Ethoxy-4,5-dimethoxy-2-methyl-3-(trimethylsilyloxy)-1,4-dihydro-9,10-anthraquinone (31): MnO_2 (4.0 g, 46 mmol) was added to a solution of **28** (1.0 g, 2.4 mmol) in DCM (200 mL). The reaction mixture was stirred for 15 min at room temperature (TLC control). After filtration through a sintered glass filter the solvent was removed under reduced pressure to afford **31** (1.0 g, 100%) as a brown oil, which was used in the following steps without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.25 [s, 9 H, $Si(CH_3)_3$], 1.05 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.79 (s, 3 H, CH_3), 3.35 (m, 1 H, OCH_aHCH_3), 3.53 (m, 1 H, $OCHH_bCH_3$), 3.55 (s, 3 H, 4-OCH_3), 3.98 (s, 3 H, 5-OCH_3), 4.75 (m, 1 H, 1-H), 5.05 (d, J = 2.0 Hz, 1 H, 4-H), 7.30 (dd, J = 8.3, 1.0 Hz, 1 H, 6-H), 7.66 (dd, J = 8.3, 7.6 Hz, 1 H, 7-H), 7.76 (dd, J = 7.6, 1.0 Hz, 1 H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.85 [$Si(CH_3)_3$], 13.42 (CH_3), 15.72 (OCH_2CH_3), 56.55 (5-OCH_3), 58.95 (4-OCH_3), 61.82 (OCH_2CH_3), 70.12, 71.41 (C-1, C-4), 114.63 (C-2), 117.61 (C-6), 119.17 (C-8), 134.31, 134.32, (C-4a, C-10a), 134.92 (C-7), 139.91 (C-8a), 143.36 (C-9a), 145.82 (C-3), 159.52 (C-5), 182.79, 183.76 (C-9, C-10) ppm. MS (70 eV, EI): m/z (%) = 416.1 (24) [M$^+$], 371.0 (100), 340.0 (52), 325.0 (24), 298.0 (16), 230.1 (80), 147.0 (60), 73.0 (38). HRMS: m/z (M$^+$, $C_{22}H_{28}O_6Si$): calcd. 416.1655; found 416.1655.

(1*SR*,2*RS*,3*RS*,4*RS*)-2,3-Epoxy-1-ethoxy-4,5-dimethoxy-2-methyl-1,2,3,4-tetrahydro-9,10-anthraquinone (32): A freshly prepared solution of dimethyldioxirane (0.1 M in acetone, approx. 75 mL) was added to the naphthoquinone **31** (1.3 g, 3.1 mmol). After stirring for 30 min at room temperature in the dark, the reaction mixture was dried with sodium sulfate and the solvent removed under reduced pressure to afford **32** (1.4 g, 100%) as a red-brown oil, which was used in the following step without further purification. ^{1}H NMR (200 MHz, C_6D_6): δ = 0.26 [s, 9 H, $Si(CH_3)_3$], 1.01 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.59 (s, 3 H, CH_3), 3.21 (s, 3 H, 4-OCH_3), 3.56 (dq, J = 8.7, 6.9 Hz, 1 H, OCH_aHCH_3), 3.66 (s, 3 H, 5-OCH_3), 3.87 (dq, J = 8.7, 6.9 Hz, 1 H, $OCHH_bCH_3$), 5.07 (s, 1 H, 1-H), 5.29 (s, 1 H, 4-H), 6.39 (br. d, J = 8.3 Hz, 1 H, 6-H), 6.93 (dd, J = 8.8, 7.6 Hz, 1 H, 7-H), 7.72 (dd, J = 7.6, 0.7 Hz, 1 H, 8-H) ppm. ^{13}C NMR (50 MHz, C_6D_6): δ = 1.30 [$Si(CH_3)_3$], 13.6 (CH_3), 15.8 (OCH_2CH_3), 55.6 (4-OCH_3), 59.6 (5-OCH_3), 62.3 (C-2), 66.7 (OCH_2CH_3), 72.9 (C-4), 73.1 (C-1), 85.2 (C-3), 117.6 (C-6), 118.8 (C-8), 127.8 (C-10a), 134.3 (C-7), 134.5, 137.2, 142.2 (C-4a, C-8a, C-9a), 159.7 (C-5), 182.2, 185.1 (C-9, C-10) ppm. MS (70 eV, EI): m/z (%) = 432.2 (12) [M$^+$], 400.2 (32), 340.1 (20), 315.1 (100), 255.1 (40), 183.1 (12), 89.0 (8), 73.0 (54). HRMS: m/z (M$^+$, $C_{22}H_{28}O_7Si$): calcd. 432.1604; found 432.1604.

(4*RS*,4a*RS*,9a*SR*)-4a,9a-Epoxy-1-ethoxy-4,5-dimethoxy-2-methyl-3-oxo-4*H*-9,10-anthraquinone (33): DBU (0.36 mL, 2.4 mmol) and then THF (10 mL) were added to the urea-hydroperoxide complex (UHP; 280 mg, 3.0 mmol) and the mixture was stirred for 5 min at room temperature.[24] Afterwards, a solution of the epoxide **32** (1.04 g, 2.41 mmol) in THF (30 mL) was added quickly and the mixture stirred for an additional 45 min at room temperature. The reaction was quenched by addition of water and the mixture extracted three times with DCM. The combined organic phases were washed with water until the aqueous phase was colorless, then with brine and dried with sodium sulfate; the solvent was removed under reduced pressure to afford crude **33** (737 mg, 89%) as a brown oil. Subsequent semi-preparative HPLC separation gave the pure product in 45% yield. M.p. > 65 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.51 (s, 3 H, CH_3), 3.64 (dq, J = 6.9, 6.9 Hz, 2 H, OCH_2CH_3), 3.82 (s, 3 H, 4-OCH_3), 3.93 (s, 3 H, 5-OCH_3), 4.14 (s, 1 H, 4-H), 7.27 (d, J = 6.8 Hz, 1 H, 6-H), 7.66 (dd, J = 7.3, 6.8 Hz, 1 H, 7-H), 7.71 (d, J = 7.3 Hz, 1 H, 8-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.36 (OCH_2CH_3), 20.53 (CH_3), 56.50 (5-OCH_3), 61.45 (4-OCH_3), 69.40 (OCH_2CH_3), 75.79, 75.89 (C-4a, C-9a), 82.09 (C-4), 118.26 (C-6), 119.44 (C-8), 124.554 (C-10a), 129.53 (C-2), 134.57 (C-8a), 135.09 (C-7), 150.71 (C-1), 158.38 (C-5), 186.19 (C-10), 191.82 (C-9), 193.14 (C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3416, 2979, 2939, 1704, 1586, 1446, 1284, 1226, 1095, 1042 cm^{-1}. UV (MeCN): λ_{max} (log ε) = 227.0 (4.173), 249.0 (4.216), 347.5 (3.791) ppm. MS (70 eV, EI):-m/z (%) = 358.3 (3) [M$^+$], 301.2 (16), 287.2 (16), 274.2 (100), 231.1 (60), 203.1 (24), 187.1 (8), 44.1 (16). HRMS: m/z (M$^+$, $C_{19}H_{18}O_7$): calcd. 358.1053; found 358.1053.

Cytotoxicity Tests: Human bronchial carcinoma cells of line A549 (ATCC CCL 185) were cultivated at 37 °C and 7.5% CO_2 in Dulbecco's modified Eagle's medium (DMEM, Biochrom) supplemented with fetal calf serum (10%, heat-inactivated for 30 min at 56 °C, GibcoBRL), $NaHCO_3$ (44 mM, Biochrom) and L-glutamine (4 mM, GibcoBRL). Adherent cells were sown in triplicate in six multiwell plates at concentrations of 10^2, 10^3, and 10^4 cells per cavity. The culture medium was removed by suction after cultivating for 24 h and the cells were washed with the incubation medium Ultraculture (UC, serum-free special medium, Cambrex Bioproducts). Next, the cells were incubated for 24 h in Ultraculture with solutions of the compounds to be tested at various concentrations freshly prepared in DMSO (VWR) and diluted with incubation medium to a final concentration of 1% DMSO in the wells. Control wells contained 1% DMSO. After 24 h of exposure, the test substance was removed by suction and the cells were washed with fresh medium. Cultivation was performed at 37 °C and 7.5% CO_2 in air for 12 d in culture medium. The medium was removed by suction, the colonies were dried, stained with Löffler's methylene blue (VWR), and counted macroscopically.

The relative colony forming rate was determined according to the following formula:

$$\text{relative colony forming rate [\%]} = \frac{(\text{number of colonies grown with test compound}) \times 100}{(\text{number of colonies grown in the control})}$$

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[1] a) T. W. Doyle, *Pharmacol. Ther.* **1999**, *83*, 67–123; b) L. F. Tietze, T. Feuerstein, *Aust. J. Chem.* **2003**, *56*, 841–854; c) L. F. Tietze, T. Feuerstein *Curr. Pharm. Des.* **2003**, *9*, 2155–2175.

[2] M. Arnold, Diploma thesis, University of Göttingen, **1998**.

[3] U. Séquin, *The Antibiotics of the Pluramycin Group (4H-Anthra[1,2-b]pyran Antibiotics)*, in *Prog. Chem. Org. Nat. Prod.* (Ed.: L. Zechmeister), Springer, Wien, New York, **1986**, vol. 50, pp. 58–122.

[4] F. Lombó, E. Künzel, L. Prado, A. F. Brana, K. U. Bindseil, J. Frevert, J. Bearden, C. Mendez, J. Salás, J. Rohr, *Angew. Chem. Int. Ed.* **2000**, *39*, 796–799.

[5] a) J. Rohr, R. Thiericke, *Nat. Prod. Rep.* **1992**, *9*, 103–107; b) K. Krohn, J. Rohr, *Top. Curr. Chem.* **1997**, *188*, 127–195.

[6] a) T. Noda, T. Take, M. Otani, K. Miyauchi, T. Watanabe, J. Abe, *Tetrahedron Lett.* **1968**, *9*, 6087–6090; b) A. Takenada, A. Furusake, T. Watanabe, T. Noda, T. Take, T. Watanabe, J. Abe, *Tetrahedron Lett.* **1968**, *9*, 6091–9605; c) T. Noda, T. Take, T. Watanabe, J. Abe, *Tetrahedron* **1970**, *26*, 1339–1348.

[7] J. S. Kim, K. Shin-Ya, J. Eishima, K. Furihata, H. Seto, *J. Antibiot.* **1996**, *49*, 947–948.

[8] M. Sakurai, J. Kohno, K. Yamamoto, T. Okuda, M. Nishio, K. Kawano, T. Ohnuki, *J. Antibiot.* **2002**, *55*, 685–692.

[9] K. L. Stevens, B.-U. Din, A. Ahmad, M. Ahmad, *Phytochem.* **1979**, *18*, 1579–1584.

[10] D. Larsen, R. Stoodley, *Tetrahedron* **1990**, *46*, 4711–4732.

[11] a) P. Preston, T. Winwick, M Morley, *J. Chem. Soc., Perkin Trans. 1* **1985**, 39–43; b) M. Carreño, A. Urbano, C. Vitta, *Chem. Eur. J.* **2000**, *6*, 906–913; c) D. Larsen, M. O'Shea, S. Brooker, *Chem. Commun.* **1996**, 203–204; d) R. Gupta, D. Jackson, R. Stoodley, D. Williams, *J. Chem. Soc., Perkin Trans. 1* **1985**, 525–533.

[12] a) K. Krohn, H. Markus, H. Kraemer, W. Frank, *Liebigs Ann. Chem.* **1988**, 1033–1041; b) K. Krohn, K. Tolkiehn, V. Lehne, H. Schmalle, H. Grützmacher, *Liebigs Ann. Chem.* **1985**, 1311–1328.

[13] L. Tietze, S. Stewart, M. Polomska, *Chem. Eur. J.* **2004**, *in press.*

[14] a) P. Contant, M. Haess, J. Riegl, M. Scalone, M. Visnik, *Synthesis* **1999**, 821–828; b) T. Masquelin, U. Hengartner, J. Streith, *Synthesis* **1995**, 780–786; c) H. Laatsch, *Liebigs Ann. Chem.* **1980**, 1321–1347.

[15] S. Danishefsky, C. Maring, *J. Am. Chem. Soc.* **1985**, *107*, 1269–1274.

[16] a) J. Stadlwieser, *Synthesis* **1985**, 490; b) W. D. Wulff, W. E. Bauta, R. W. Kaesler, P. J. Lankford, R. A. Miller, C. K. Mur-

ray, D. C. Yang, *J. Am. Chem. Soc.* **1990**, *112*, 3642–3659; c) R. W. Aben, H. W. Scheeren, *J. Chem. Soc., Perkin Trans. 1* **1979**, 3132–3138.

[17] H. Laatsch, *Liebigs Ann. Chem.* **1985**, 251–274.

[18] a) R. Gupta, D. Jackson, R. Stoodley, *J. Chem. Soc., Perkin Trans. 1* **1985**, 523–533; b) R. Guta, P. Harland, R. Stoodley, *Tetrahedron* **1984**, *40*, 4657–4667; c) R. Gupta, C. Raynor, R. Stoodley, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1773–1785.

[19] a) F. Fariña, P. Prados, *Tetrahedron Lett.* **1979**, *20*, 477–480; b) K. Krohn, H. Markus, J. P. Kraemer, W. Frank, *Liebigs Ann. Chem.* **1988**, 1033–1041; c) M. Frigerio, M. Santagostino, S. Sputore, G. Palmisano, *J. Org. Chem.* **1995**, *60*, 7272–7276; d) D. Larsen, R. Stoodley, *Tetrahedron* **1990**, *46*, 4711–4732.

[20] K. Krohn, K. Tolkiehn, *Chem. Ber.* **1979**, *112*, 3453–3471.

[21] S. Laugrand, A. Guingant, C. Chassagnard, J. d'Angelo, *J. Org. Chem.* **1988**, *53*, 1557–1560.

[22] D. Larsen, M. O'Shea, *J. Org. Chem.* **1996**, *61* ,5681–5683.

[23] a) W. Edwards, R. Gupta, C. Raynor, R. Stoodley, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1913–1918; b) W. Adam, A. Corma, T. Indrasena Reddy, M. Renz, *J. Org. Chem.* **1997**, *62*, 3631–3637; c) S. Takemura, A. Hirayama, J. Tokunaga, F. Kawamura, K. Inagaki, K. Hashimoto, M. Nakata, *Tetrahedron Lett.* **1999**, *40*, 7501–7505; d) P. Preston, T. Winwick, J. Morley, *J. Chem. Soc., Perkin Trans. 1* **1985**, 39–43; e) A. Rashid, G. Read, *J. Chem. Soc. (C)* **1967**, 1323–1325; f) D. Alickmann, R. Fröhlich, E. Wurthwein, *Org. Lett.* **2001**, *3*, 1527–1530; g) A. Davies, R. Sutcliffe, *J. Chem. Soc., Perkin Trans. 2* **1982**, 1483–1488; h) O. de Frutos, C. Atienza, A. Echavarren, *Eur. J. Org. Chem.* **2001**, 163–171.

[24] a) D. Larsen, M. O'Shea, *J. Org. Chem.* **1996**, *61*, 5681–5683; b) S. Cohen, R. Halcomb, *J. Org. Chem.* **2000**, *65*, 6145–6152.

[25] a) S. Colonna, A. Manfredi, R. Annunziata, N. Gaggero, *J. Org. Chem.* **1990**, *55*, 5862–5866; b) W. Adam, R. Curci, J. Edwards, *J. Am. Chem. Soc.* **1989**, *111*, 205–211; c) J. Allen, S. Bergeron, M. Griffiths, S. Mukherjee, S. Roberts, N. Williamson, L. Wu, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3171–3179.

[26] CCDC-253106 (for **26**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[27] Bruker (2002). SMART (Ver. 5.62), SAINT (Ver. 6.02), SHELXTL (Ver. 6.10) and SADABS (Ver. 2.03). Bruker AXS Inc., Madison, Wisconsin, USA.

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