Supplementary Material for Organic & Biomolecular Chemistry

ELECTRONIC SUPPLEMENTARY MATERIAL

New strategies for the synthesis of anthrapyran antibiotics: discovery of a novel antitumor agent and total synthesis of (*S*)-espicufolin

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Human Tumor Colony Forming Ability (HTCF) Test:

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 of line A549 were sown in triplicate in 6 multiwell plates at concentrations of 10^2, 10^3 and 10^4 cells per cavity. Culture medium was removed by suction after cultivating 24 h and the cells were washed with the incubation medium Ultraculture (UC, serum-free special medium, Cambrex Bioproducts). Next, 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 were 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 days 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:

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

General and experimental procedures and analytical data for compounds 5–7, 9–10, 16–20 and 36–41:

General: All reactions were performed in flame-dried glassware under an atmosphere of argon. Solvents were dried and purified according to the method defined by Perrin and Armarego.[1] 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 silica gel 60 from Merck with particle size 0.063–0.200 mm for normal pressure and 0.020–0.063 mm for flash chromatography (P = pentane). Melting points were recorded on a Mettler FP61 and are uncorrected. IR spectra were determined on a Bruker Vektor 22, UV-VIS spectra on a Perkin-Elmer Lambda 2, and mass spectra on 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 either on a Varian VXR-200 MHz or Varian UNITY-300 MHz. ^{13}C-NMR spectra were recorded at 50 or 75 MHz. Spectra were taken at room temperature in deuterated 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.

5-Hydroxy-1,4-naphthoquinone (juglone, 5). A suspension of freshly recrystallised CuCl (12.0 g, 0.121 mol) in acetonitrile (500 mL) was placed in a 4 L three-neck 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 (**4**, 30.0 g, 0.187 mol) in acetonitrile (500 mL) was added with vigorous stirring at 20 °C in the dark over 30 min. Afterwards, another amount of CuCl (12.0 g, 0.121 mol) was added followed by the addition of **4** (30.0 g, 0.187 mol) in acetonitrile (500 mL) over 30 min. This procedure was carried out again with the same amount of reactants (CuCl, 12.0 g, 0.121 mol; **4**, 30.0 g, 0.187 mol in 500 mL acetonitrile). The resulting mixture was stirred for 8 h and then the solvent was removed under reduced pressure. The crude product was purified in a Soxhlet extractor with *n*-heptane (1.6 L) as solvent to afford **5** (53.7 g, 55 %) as orange-red needles, Rf 0.34 (P–EtOAc, 8:1); mp 154 °C (Found: C, 69.09; H, 5.49. $C_{10}H_6O_3$ requires C, 68.97; H, 3.47%); λ_{max} (CH_3CN)/nm 207.5 (lg ε/dm^3 mol^{-1} cm^{-1} 4.508), 248.5 (4.128) and 420.0 (3.540); ν_{max} (KBr)/cm^{-1} 3386, 3070, 1665, 1644, 1600, 1486, 1451, 1364, 1338, 1290 and 1226; δ_H (300 MHz, $CDCl_3$) 11.91 (1 H,

s, OH), 7.69–7.60 (2 H, m, 7-H, 8-H), 7.29 (1 H, dd, *J* 7.3 and 2.5, 6-H) and, 6.96 (2 H, s, 2-H, 3-H); δ_C (75.5 MHz, $CDCl_3$) 190.2, 184.2, 161.4, 139.5, 138.59, 136.5, 131.7, 124.4, 119.1 and 114.9; *m/z* (EI) 174.0 (100%, $[M]^+$), 146.0 (10%, $[M - CO]^+$) and 118 (36%, $[M - C_2O_2])^+$.

3-Bromo-5-hydroxy-1,4-naphthoquinone (3-bromojuglone, 6). A suspension of juglone (**5**, 12.0 g, 68.9 mmol) in acetic acid (180 mL) was treated in the dark at 20 °C with bromine (68.9 mmol, 3.60 mL). After stirring for 15 min, the reaction mixture was poured onto ice. The resultant slurry was stirred for 10 min after which the dibrominated intermediate was filtered off under reduced pressure. The pale-orange solid was washed with a little amount of ice-water and then immediately treated with ethanol (80 mL) and stirred for 10 min under reflux using a pre-heated oil bath. The mixture was cooled down to 20 °C and the red precipitate was filtered off under reduced pressure. The residue was washed with a small amount of cold ethanol and then subjected to silica gel flash chromatography (CH_2Cl_2). Concentration of the appropriate fractions *in vacuo* furnished 3-bromojuglone (**6**, 14.0 g, 80 %) as an orange solid, Rf 0.46 (P–EtOAc, 8:1); mp 168 °C (Found: C, 47.72; H, 2.05. $C_{10}H_5BrO_3$ requires C, 47.46; H, 1.99%); λ_{max} (CH_3CN)/nm 212.0 (lg ε/dm^3 mol^{-1} cm^{-1} 4.462), 247.5 (3.705), 282.0 (4.041) and 426.5 (3.515); ν_{max} (KBr)/cm^{-1} 3421, 3051, 1655,1630, 1582, 1487, 1458, 1363, 1291, 1275 and 1214; δ_H (300 MHz, $CDCl_3$) 11.73 (1 H, s, OH), 7.68 (1 H, t, *J* 7.4, 7-H), 7.64 (1 H, dd, *J* 7.4 and 2.0, 8-H), 7.50 (s, 1 H, 2-H), 7.31 (1 H, dd, *J* 7.4, 2.0, 6-H); δ_C (75.5 MHz, $CDCl_3$) 182.8, 181.6, 162.0, 141.2, 139.3, 137.2, 131.6, 124.7, 119.9 and 113.9; *m/z* (EI) 253.9, 251.9 (100%, $[M]^+$), 173.0 (50%, $[M - Br]^+$) and 145.0 (46%, $[M - Br - CO]^+$); (EI) 251.9422. $C_{10}H_5BrO_3$ requires 251.9422.

3-Bromo-5-isopropoxy-[1,4]naphthoquinone (7). To a mixture of 3-bromojuglone (**6**, 1.46 g, 5.77 mmol) and silver(I) oxide (2.67 g, 11.5 mol) in $CHCl_3$ (70 mL) was added 2-iodopropane (1.73 mL, 17.3 mmol) and the resulting suspension was stirred for 24 h at 20 °C. Then, additional silver(I) oxide (1.33 g, 5.77 mmol) and 2-iodopropane (0.58 mL, 5.77 mmol) was added and stirring was continued for another 12 h (TLC-control). The mixture was filtered trough a plug of celite® and the filter cake was rinsed carefully with CH_2Cl_2. After removal of the solvent under reduced pressure, the crude product was subjected to silica gel flash chromatography (CH_2Cl_2). Concentration of the appropriate fractions *in vacuo* afforded

naphthoquinone **7** (1.69 g, 99 %) as a yellow solid, Rf 0.38 (P–EtOAc, 4:1); mp 73 °C (Found: C, 52.75; H, 3.96. $C_{13}H_{11}BrO_3$ requires C, 52.91; H, 3.76%); λ_{max} (CH_3CN)/nm 211.5 (lg ε/dm^3 mol^{-1} cm^{-1} 4.533), 258.0 (4.033), 277.0 (4.106) and 407.0 (3.558); ν_{max} (KBr)/cm^{-1} 3046, 2978, 2932, 1668, 1612, 1598, 1581, 1467, 1436, 1376, 1309, 1293, 1275 and 1205; δ_H (300 MHz, $CDCl_3$) 7.72–7.62 (2 H, m, 7-H, 8-H), 7.44 (1 H, s, 2-H), 7.31 (1 H, dd, *J* 7.4 and 2.3, 6-H), 4.74 (1 H, sept., *J* 6.0, OC*H*(CH_3)$_2$) and 1.47 (6 H, d, *J* 6.0, 2 × CH_3); δ_C (75.5 MHz, $CDCl_3$) 182.6, 175.9, 159.1, 142.8, 138.2, 135.2, 134.0, 120.8, 119.3, 72.27 and 21.93; *m/z* (EI) 296.1 (12%, $[M]^+$), 294.1 (10%, $[M]^+$), 254.0 (100%, $[M - C_3H_6]^+$), 252.1 (97%, $[M - C_3H_6]^+$), 173.1 (84%, $[M - C_3H_6 - Br]^+$) and 145.1 (56%, $[M - C_3H_6 - Br - CO]^+$); Found (ESI) $[M + H]^+$ 294.99662. $C_{13}H_{11}BrO_3 + H^+$ requires 294.99643.

Methyl 3-methylbut-2-enoate (9). 3-Methyl-but-2-enoic acid (**8**, 70.0 g, 0.700 mol) in MeOH (260 mL) was treated with a catalytically amount of conc. H_2SO_4 (4.0 mL) and then stirred for 16 h under reflux. Afterwards, H_2O (500 mL) was added to the reaction mixture, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 120 mL). The combined organic phases were washed subsequently with half-saturated aqueous $NaHCO_3$ solution (300 mL) and H_2O (400 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was distilled over a 10 cm Vigreux-column to afford the ester **9** (73.7 g, 92 %) as a colourless liquid, *R*f 0.50 (P–Et_2O, 20:1); bp 135 °C; (Found: C, 63.31; H, 9.11. $C_6H_{10}O_2$ requires C, 63.14; H, 8.83%), λ_{max} (CH_3CN)/nm 215.5 (lg ε/dm^3 mol^{-1} cm^{-1} 4.102); ν_{max} (film)/cm^{-1} 2951, 1723, 1662, 1448, 1379, 1351, 1281 and 1233; δ_H (300 MHz, $CDCl_3$) 5.68 (1 H, m$_c$, 2-H), 3.68 (3 H, s, OCH_3), 2.17 (3 H, d, *J* 1.1, (*E*)-3-CH_3) and 1.90 (3 H, d, *J* 1.1, (*Z*)-3-CH_3); δ_C (50.3 MHz, $CDCl_3$) 167.1, 156.7, 115.6, 50.71, 27.33 and 20.13; *m/z* (EI) 114.2 (33%, $[M]^+$), 99.1 (4%, $[M - CH_3]^+$), 83.1 (100% $[M - CH_3O]^+$) and 55.1 (58%, $[C_2H_7]^+$).

1-Methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene (10). A solution of diisopropyl-amine (60.8 mL, 0.434 mol) in THF (300 mL) was treated with stirring at −78 °C dropwise with *n*BuLi (174 mL, 0.434 mol, 2.5 M in *n*-hexane) during 1 h. The mixture was warmed within 2 h to 20 °C, cooled again to −78 °C, and then ester **9** (45.0 g, 0.395 mol) was added dropwise over 30 min. After being stirred for 1.5 h, TMSCl (60.5 mL, 0.473 mol) in THF

(50 mL) was added dropwise during 1.5 h and then the mixture was warmed to 20 °C over 1.5 h. The solvent was removed under reduced pressure and the slurry suspended with pentane (300 mL), filtered through a sintered glass fritted funnel (porosity 3), and concentrated *in vacuo*. The crude product was distilled under reduced pressure over a 10 cm Vigreux-column to afford the butadiene **10** (69.2 g, 94 %) as a colourless liquid, *R*f 0.41 (P–Et_2O, 19:1); bp 35 °C (0.4 mmHg); λ_{max} (CH_3CN)/nm 214.5 (lg ε/dm^3 mol^{-1} cm^{-1} 3.400); ν_{max} (film)/cm^{-1} 3080, 2963, 2841, 1655, 1607, 1444, 1413, 1372, 1352, 1307, 1254 and 1211; δ_H (300 MHz, $CDCl_3$) 4.78 (1 H, br d, *J* 2.8, (*Z*)-4-H), 4.54 (1 H, m_c, (*E*)-4-H), 4.26 (1 H, s, 2-H), 3.57 (3 H, s, OCH_3), 1.93 (3 H, m_c, 3-CH_3) and 0.23 (9 H, s, Si(CH_3)$_3$); δ_C (75.5 MHz, $CDCl_3$) 173.4, 140.3, 107.4, 80.47, 54.97, 23.62 and 0.36; *m/z* (EI) 186.2 (12%, $[M]^+$) and 171.2 (4%, $[M - CH_3]^+$), 89.1 (18%), 82.1 (100%), 73.1 (42%, $[C_3H_9Si]^+$).

(3*RS*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-butyric acid ethylester (16). A solution of 3-hydroxy-butyric acid ethylester (**15**, 2.66 mL, 20.0 mmol), imidazole (3.40 g, 50.0 mmol), and a catalytically amount of DMAP (50 mg) in DMF (100 mL) was treated at 20 °C with TBSCl (4.52 g, 30.0 mmol). After being stirred for 16 h, the reaction mixture was poured into H_2O (500 mL) and then extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was subjected to silica gel flash chromatography (P–Et_2O, 50:1 → 20:1) and concentration of the appropriate fractions *in vacuo* afforded ester **16** (4.92 g, 100%) as a colourless liquid, (Found: C, 58.69; H, 10.42. $C_{12}H_{26}O_3Si$ requires C, 58.49; H, 10.63%), λ_{max} (CH_3CN)/nm 216.5 (lg ε/dm^3 mol^{-1} cm^{-1} 2.413); ν_{max} (film)/cm^{-1} 2958, 2931, 2858, 1739, 1473, 1377, 1301 and 1256; δ_H (300 MHz, $CDCl_3$) 4.25 (1 H, m_c, 3-H), 4.09 (2 H, m_c, $CO_2CH_2CH_3$), 2.44 (1 H, dd, *J* 14.6 and 8.0, 2-H_a), 2.33 (1 H, dd, *J* 14.6 and 5.4, 2-H_b), 1.23 (3 H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.16 (3 H, d, *J* 6.1, 4-H_3), 0.83 (9 H, s, $SiC(CH_3)_3$, TBS), 0.03 (3 H, s, Si(CH_3)$_2$, TBS) and 0.01 (3 H, s, Si(CH_3)$_2$, TBS); δ_C (75.5 MHz, $CDCl_3$) 171.7, 65.84, 60.24, 44.94, 25.70, 23.91, 17.93, 14.17, –4.53 and –5.07; *m/z* (ESI) 269.0 (80%, $[M + Na]^+$).

(3*RS*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-butan-1-ol (17). A solution of ester **16** (2.46 g, 10.0 mmol) in THF (15 mL) was treated at 20 °C dropwise during 5 min with a solution of $LiBH_4$ (5.50 mL, 11.0 mmol, 2 M in THF). After being stirred for 3 h under reflux, the

reaction mixture was diluted with Et_2O (30 mL) at 0 °C and then treated dropwise during 10 min with a saturated aqueous solution of NH_4Cl (1.00 mL). After additional stirring for 30 min, the mixture was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjecting the crude material to silica gel flash chromatography (P–Et_2O, 20:1 → 2:1) and concentration of the appropriate fractions *in vacuo* afforded alcohol **17** (1.65 g, 80%) as a colourless liquid, *R*f 0.14 (P–Et_2O, 4:1); (Found: C, 58.87; H, 11.61. $C_{10}H_{24}O_2Si$ requires C, 58.77; H, 11.84%); ν_{max} (film)/cm^{-1} 3358, 2957, 2931, 2858, 1651, 1473, 1376 and 1256; δ_H (300 MHz, $CDCl_3$) 4.07 (1 H, m_c, 3-H), 3.86–3.76 (1 H, m, 1-H_a), 3.74–3.64 (1 H, m, 1-H_b), 2.58 (1 H, br s, OH, disappears after H/D-exchange with D_2O), 1.82–1.69 (1 H, m, 2-H_a), 1.66–1.54 (1 H, m, 2-H_b), 1.17 (3 H, d, *J* 6.4, 4-H_3), 0.87 (9 H, s, $SiC(CH_3)_3$, TBS), 0.07 (3 H, s, $Si(CH_3)_2$, TBS) and 0.06 (3 H, s, $Si(CH_3)_2$, TBS); δ_C (75.5 MHz, $CDCl_3$) 68.40, 60.48, 40.38, 25.77, 23.39, 17.92, –4.37 and –5.00; *m/z* (ESI) 205.0 (100%, $[M + H]^+$), Found (ESI) $[M + H]^+$ 205.16177. $C_{10}H_{24}O_2Si + H^+$ requires 205.16183, $[M + Na]^+$ 227.14379. $C_{10}H_{24}O_2Si + Na^+$ requires 227.14378.

(3*RS*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-butyraldehyde (18): A solution of alcohol **17** (613 mg, 3.00 mmol), diisopropylethyl amine (2.48 mL, 15.0 mmol), and DMSO (2.13 mL, 30.0 mmol) in CH_2Cl_2 (30 mL) was treated at 0 °C with SO_3·Py (1.19 g, 7.50 mmol) and stirred for 1 h. Afterwards, the reaction mixture was diluted with CH_2Cl_2 (70 mL), washed with a saturated aqueous solution of $NaHCO_3$ (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude material was subjected to silica gel flash chromatography (P–Et_2O, 20:1 → 10:1) and concentration of the appropriate fractions *in vacuo* afforded aldehyde **18** (523 mg, 86%) as a colourless liquid, which was directly used within in the next step, *R*f 0.35 (P–Et_2O, 10:1); ν_{max} (film)/cm^{-1} 2957 , 2931, 2858, 2721, 1729, 1473, 1376, 1256 and 1218; δ_H (300 MHz, $CDCl_3$) 9.76 (1 H, t, *J* 2.5, CHO), 4.32 (1 H, m_c, 3-H), 2.52 (1 H, ddd, *J* 15.7, 7.1 and 2.5, 2-H_a), 2.43 (1 H, ddd, *J* 15.7, 5.0 and 2.2, 2-H_b), 1.21 (3 H, d, *J* 6.2, 4-H_3), 0.83 (9 H, s, $SiC(CH_3)_3$, TBS), 0.04 (3 H, s, $Si(CH_3)_2$, TBS), 0.03 (3 H, s, $Si(CH_3)_2$, TBS); δ_C (75.5 MHz, $CDCl_3$) 202.2, 64.50, 52.94, 25.68, 24.14, 17.91, –4.42, –5.00; *m/z* (DCI) 405.4 (2%, $[2 \times M + H]^+$), 220.2 (100%, $[M + NH_4]^+$) and 203.2 (48%, $[M + H]^+$).

But-2-ynal (20). A solution of but-2-ynol (**19**, 6.00 g, 85.6 mmol) in CH_2Cl_2 (300 mL) was treated at 20 °C with MnO_2 (74.4 g, 0.86 mol) and stirred for 18 h. The reaction mixture was filtered through a plug of celite® and the filter cake was rinsed carefully with CH_2Cl_2. After removal of the solvent *via* distillation over a Vigreux-column (30 cm) the crude material was distilled to afford the aldehyde **20** (3.93 g, 67%) as pale yellow liquid, bp 105−108 °C; δ_H (300 MHz, $CDCl_3$) 9.16 (1 H, m_c, CHO), 2.09 (3 H, s, 4-CH_3); δ_C (50.3 MHz, $CDCl_3$) 177.3, 95.16, 80.87 and 4.24; *m/z* (EI) 68.1 (30%, $[M]^+$) and 67.1 (100%, $[M - H]^+$).

1-Hydroxy-8-isopropoxy-3-methoxymethylanthraquinone (31). To a solution of juglone derivative **7** (2.00 g, 6.78 mmol) in benzene (40 mL) was added at 20 °C dropwise a mixture of diene 29 and 30 (4.40 g, 20.3 mmol) within 10 min. After being stirred for 1 h, the mixture was heated under reflux for 3 h, additional diene 29 and 30 (2.93 g, 13.6 mmol) was added and stirring was continued for further 3 h. Next, the reaction mixture was poured onto silica gel (50 g), CH_2Cl_2 (250 mL) was added, and then the suspension was stirred for 24 h. After removing the solvent under reduced pressure, the silica gel was eluted carefully with CH_2Cl_2/MeOH (10:1) and the combined organic fractions were concentrated *in vacuo* to afford the crude product. This material was subjected to silica gel flash chromatography (CH_2Cl_2) and concentration of the appropriate fractions *in vacuo* furnished anthraquinone **31** (1.11 g, 50%) as a yellow solid, Rf 0.35 (P–EtOAc, 4:1); mp 160 °C (Found: C, 69.93; H, 5.75. $C_{19}H_{18}O_5$ requires C, 69.93; H, 5.56%); λ_{max} (CH_3CN)/nm 224.5 (lg ε/dm^3 mol^{-1} cm^{-1} 4.609), 257.0 (4.341) and 413.0 (3.964); ν_{max} (KBr)/cm^{-1} 2972, 2930, 2824, 1672, 1640, 1585, 1488, 1440, 1377, 1318, 1301, 1262 and 1240; δ_H (300 MHz, $CDCl_3$) 13.08 (1 H, s, 8-OH), 7.91 (1 H, dd, *J* 7.3 and 0.9, 5-H), 7.71−7.64 (2 H, m, 4-H, 6-H), 7.34 (1 H, br d, *J* 8.2, 7-H), 7.26 (1 H, d, *J* 0.7, 2-H), 4.75 (1 H, sept., *J* 5.8, C*H*$(CH_3)_2$), 4.51 (2 H, s, C*H*$_2$OCH$_3$), 3.45 (3 H, s, OCH_3) and 1.50 (6 H, d, *J* 5.8, CH(C*H*$_3$)$_2$); δ_C (75.5 MHz, $CDCl_3$) 188.2, 182.7, 162.7, 159.5, 147.2, 135.8, 135.2, 132.7, 122.3, 121.6, 121.4, 120.0, 117.1, 116.2, 73.40, 72.58, 58.59 and 22.02; *m/z* (EI) 326.2 (22%, $[M]^+$) and 254.1 (100%, $[M - C_3H_7 - CHO]^+$); Found (ESI) $[M + H]^+$ 327.12271. $C_{19}H_{18}O_5 + H^+$ requires 327.12270.

2-Bromo-1-hydroxy-8-isopropoxy-3-methoxymethylanthraquinone (32). A solution of anthraquinone **31** (1.55 g, 4.76 mmol) in CH_2Cl_2 (60 mL) was treated at 20 °C with a catalytic amount of diisopropyl amine (10 drops) and then a solution of NBS (1.27 g, 7.14 mmol) in

CH_2Cl_2 (60 mL) was added dropwise during 10 min. After being stirred for 3 h (TLC-control), additional NBS (423 mg, 2.38 mmol) was added and stirring was continued for another 1.5 h. Next, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed subsequently with 0.2 N HCl solution (250 mL) and H_2O (250 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was subjected to silica gel flash chromatography (CH_2Cl_2) and concentration of the appropriate fractions *in vacuo* afforded anthraquinone **32** (1.85 g, 96%) as an orange solid, *R*f 0.37 (P–EtOAc, 4:1); mp 198 °C; (Found: C, 56.08; H, 4.35. $C_{19}H_{17}BrO_5$ requires C, 56.31; H, 4.23%); λ_{max} (CH_3CN)/nm 229.0 (lg ε/dm^3 mol^{-1} cm^{-1} 4.583), 261.0 (4.411), 286.0 (4.007) and 416.5 (4.036); ν_{max} (KBr)/cm^{-1} 2977, 2935, 1671, 1635, 1582, 1481, 1441, 1407, 1339, 1302, 1290, 1261 and 1235; δ_H (300 MHz, $CDCl_3$) 13.91 (1 H, s, 8-OH), 7.91 (1 H, dd, *J* 7.7 and 0.9, 5-H), 7.88 (1 H, s, 4-H), 7.70 (1 H, t, *J* 7.7, 6-H), 7.35 (1 H, br d, *J* 7.7, 7-H), 4.76 (1 H, sept., *J* 6.2, C*H*(CH_3)$_2$), 4.58 (3 H, s, C*H*$_2$OCH_3), 3.54 (3 H, s, OCH_3) and 1.51 (6 H, d, *J* 6.2, CH(C*H*$_3$)$_2$); δ_C (75.5 MHz, $CDCl_3$) 188.0, 182.2, 159.7, 158.7, 146.5, 135.7, 135.6, 130.9, 121.4, 121.2, 120.1, 118.3, 117.3, 116.2, 73.73, 72.72, 59.03 and 22.02; *m/z* (EI) 406.2, 404.2 (56%, $[M]^+$), 364.1, 362.1 (35%, $M - C_3H_6]^+$), 334.1, 332.1 (100%, $[M - C_3H_6 - CO]^+$) and 283.2 (70%, $[M - Br]^+$); Found (ESI) $[M + H]^+$ 405.03310. $C_{19}H_{17}BrO_5$ requires 405.03321.

2-Bromo-1,8-diisopropoxy-3-ethoxymethylanthraquinone (33). A solution of anthraquinone **32** (1.70 g, 4.20 mmol) in a mixture of acetone (120 mL) and DMF (40 mL) was treated subsequently at 20 °C with Cs_2CO_3 (3.91 g, 12.6 mmol) and 2-iodopropane (0.84 mL, 8.40 mmol). After being stirred for 16 h under reflux, the reaction mixture was filtered through a plug of celite®. The filter cake was rinsed carefully with CH_2Cl_2 and then the combined organic phases were concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and washed subsequently with aqueous 2 M Na_2CO_3 (150 mL) and brine (150 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was subjected to silica gel flash chromatography (CH_2Cl_2, CH_2Cl_2–EtOAc, 40:1) and concentration of the appropriate fractions *in vacuo* afforded anthraquinone **33** (1.76 g, 94%) as a yellow solid, *R*f 0.40 (P–EtOAc, 4:1); mp 123 °C; λ_{max} (CH_3CN)/nm 223.5 (lg ε/dm^3 mol^{-1} cm^{-1} 4.554), 262.5 (4.518) and 370.0 (3.855); ν_{max} (KBr)/cm^{-1} 2970, 2930, 2822, 1676, 1584, 1469, 1445, 1405, 1382, 1307, 1278 and 1236; δ_H (300 MHz, $CDCl_3$) 8.10 (1 H, s, 4-H), 7.80 (1 H, dd, *J* 8.0 and 1.0, 5-H), 7.61

(1 H, t, *J* 8.0, 6-H), 7.30 (1 H, br d, *J* 8.0, 7-H), 4.67 (1 H, sept., *J* 6.2, C*H*$(CH_3)_2$), 4.58 (3 H, s, CH_2OCH_3), 4.41 (1 H, sept., *J* 6.2, C*H*$(CH_3)_2$), 3.54 (3 H, s, OCH_3), 1.44 (6 H, d, *J* 6.2, CH(CH_3)$_2$) and 1.41 (6 H, d, *J* 6.2, CH(CH_3)$_2$); δ_C (75.5 MHz, $CDCl_3$) 183.2, 182.4, 157.5, 154.3, 144.2, 135.0, 133.7, 133.0, 128.7, 126.8, 125.7, 121.7, 121.0, 119.1, 79.88, 73.93, 72.59, 58.95, 22.23 and 21.99, *m/z* (ESI) 916.8 (100%, $[2 \times M + Na]^+$) and 469.1 (10%, $[M + Na]^+$); Found (ESI) $[M + H]^+$ 447.08002. $C_{22}H_{23}BrO_5 + H^+$ requires 447.08016.

2-Bromo-1,8-diisopropoxy-9,10-dimethoxy-3-methoxy-methylanthracene (34). A solution of anthraquinone **33** (1.60 g, 3.58 mmol) and tetra-*n*-butylammonium bromide (346 mg, 1.07 mmol) in THF (60 mL) was treated at 20 °C with a solution of $Na_2S_2O_4$ (3.74 g, 21.5 mmol) in H_2O (25 mL) and stirred for 20 min. Next, a solution of KOH (4.62 g, 82.3 mmol) in H_2O (10 mL) was added (yellow solution turned into deep-reed) and stirring was continued for additional 15 min. After addition of dimethyl sulfate (5 mL) the reaction mixture was stirred for 12 h (solution turned back into yellow) and then poured into H_2O (150 mL). The resulting solution was extracted with CH_2Cl_2 (3×75 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was subjected to silica gel column filtration (CH_2Cl_2) and concentration of the appropriate fractions *in vacuo* afforded anthraquinone **34** (1.69 g, 99%) as a yellow oil, *R*f 0.41 (P–EtOAc, 10:1); λ_{max} (CH_3CN)/nm 203.0 (lg ε/dm^3 mol^{-1} cm^{-1} 4.330), 230.0 (4.120), 270.0 (4.959), 364.0 (3.744), 382.0 (4.014), 399.5 (3.887) and 422.0 (3.754); ν_{max} (KBr)/cm^{-1} 2978, 2932, 1616, 1556, 1511, 1451, 1396, 1352, 1305 and 1255; δ_H (300 MHz, $CDCl_3$) 8.09 (1 H, br s, 4-H), 7.86 (1 H, dd, *J* 8.6 and 0.7, 5-H), 7.37 (1 H, dd, *J* 8.6 and 7.3, 6-H), 6.85 (1 H, br d, *J* 7.3, 7-H), 4.76–4.60 (4 H, m, $2 \times$ C*H*$(CH_3)_2$, *C*H_2OCH), 4.06 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 3.57 (3 H, s, OCH_3), 1.47 (6 H, d, *J* 5.9, C-8-OCH(CH_3)$_2$) and 1.36 (6 H, br s, C-1-OCH(CH_3)$_2$); δ_C (75.5 MHz, $CDCl_3$) 154.8, 150.6, 149.2, 148.1, 134.7, 128.0, 125.9, 125.7, 120.7, 120.5, 117.0, 116.7, 115.2, 110.2, 78.06, 74.91, 71.88, 63.67, 62.86, 58.68, 22.04 and 21.88; *m/z* (ESI) 501.1 (100%, $[M + Na]^+$); Found (ESI) $[M + H]^+$ 477.12721. $C_{24}H_{29}BrO_5 + H^+$ requires 477.12711.

(*S*)-2-Methylbutyraldehyde (36). A solution of oxalyl dichloride (8.64 mL, 99.8 mmol) in CH_2Cl_2 (230 mL) was treated at −78 °C at the same time and within 45 min with a solution of DMSO (14.2 mL, 200 mmol) in CH_2Cl_2 (50 mL) and (*S*)-2-methyl-1-butanol (**35**, 9.86 mL,

90.8 mmol). After being stirred for 15 min, Et_3N (63.5 mL, 0.454 mol) was added dropwise within 15 min. After another 15 min at this temperature, the solution was warmed within 1 h to 20 °C. Afterwards, H_2O (500 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The combined organic phases were washed with 2%ic HCl and then with 5%ic Na_2CO_3 (50 mL). After drying over Na_2SO_4 and filtration, the solvent and dimethylsulfide were carefully removed *via* distillation using a Vigreux-column (30 cm). The residue was distilled using a 15 cm Vigreux-column to yield the aldehyde **36** (6.21 g, 79 %) as a colourless liquid, which was directly used within the next step, bp 90–92 °C; $[\alpha]_D^{20} = +37.6°$(*c* 1.4, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 9.63 (1 H, d, *J* 2.0, 1-H), 2.29 (1 H, m_c, 2-H), 1.75 (1 H, m_c, 3-H_a), 1.44 (1 H, m_c, 3-H_b), 1.10 (3 H, d, *J* 7.0, 1'-CH_3) and 0.96 (3 H, t, *J* 7.5, 4-H_3); δ_C (50.3 MHz, $CDCl_3$) 205.4, 47.73, 23.49, 12.83 and 11.33.

(5*S*)-5-Methyl-hept-1-ene-4-ol (37). A solution of aldehyde **36** (2.00 g, 23.2 mmol) in Et_2O (100 mL) was treated dropwise at −78 °C within 30 min with a solution of allylmagnesium bromide (25.5 mmol, 25.5 mL, 1.0 M solution in Et_2O) (1.19 g, 7.50 mmol) and stirred for 1 h. Afterwards, the reaction mixture was treated with a saturated aqueous solution of NH_4Cl (100 mL) and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic phases were dried over Na_2SO_4 and filtration, the solvent and dimethylsulfide were carefully removed *via* distillation using a Vigreux-column with CH_2Cl_2 (70 mL), washed (100 mL), dried ($MgSO_4$), filtetrated and concentrated under reduced pressure. The resulting crude material was subjected to silica gel flash chromatography (P–Et_2O, 20:1 → 50:1) and concentration of the appropriate fractions *in vacuo* afforded alcohol **37** (1.81 g, 68%) as a colourless liquid. Due to its high volatility it was directly used within in the next step, *R*f 0.36 (P–Et_2O, 5:1).

***tert*-Butyldimethyl ((5S)-5-methylhept-1-en-4-yloxy) silane (38).** A solution of alcohol **37** (1.60 g, 14.1 mmol) and 2,6-lutidine (6.00 g, 6.52 mL, 56.0 mmol) was treated at 0 °C dropwise within 5 min with TBSOTf (6.67 g, 5.80 mL, 25.2 mmol). After being stirred for 30 min, the reaction mixture was washed with half-saturated aqueous NH_4Cl solution. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was subjected to silica gel flash chromatography (P) and concentration of the

appropriate fractions *in vacuo* afforded the desired product **38** (4.92 g, 100%) as a mixture of of diastereoisomers (*dr* ≈ 1.1:1) in form of a colourless liquid, *R*f 0.67 (diastereomer 1), 0.60 (diastereomer 2) (P); $[\alpha]_D^{20}$ +3.0° (*c* = 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3078, 2959, 2931, 1642, 1463, 1380, 1362 and 1254; δ_H (300 MHz, $CDCl_3$) 5.90–5.58 (1 H, m, 2-H), 5.07–4.04 (2 H, m, (*Z*)-1-H, (*E*)-1-H), 3.61–3.50 (1 H, m, 4-H), 2.22–2.09 (2 H, m, 3-H_b, 3-H_a), 1.53–1.32 (2 H, m, 5-H, 6-H_a), 1.16–0.99 (1 H, m, 6-H_b), 0.89–0.79 (15 H, m, SiC(CH_3)$_3$), 7-H_3, 1'-CH_3) and –0.03, –0.01 (6 H, m, Si(CH_3)$_2$, TBS); δ_C (75.5 MHz, $CDCl_3$) 136.3, 136.0, 116.3, 116.2, 75.70, 75.24, 40.03, 39.38, 38.92, 37.59, 25.90, 25.69, 25.54, 24.93, 18.15, 14.30, 13.54, 12.12, 12.00, –4.13, –4.26, –4.57, –4.60; *m/z* (DCI) 260.32 (10%, $[M + NH_4]^+$), 243.3 (100%, $[M + H]^+$).

(4S)-3-(*tert*-Butyldimethylsilyloxy)-4-methylhexanal (39). A solution of olefin (**38**) (1.21 g, 5.00 mmol) in *t*-BuOH (20 mL), THF (6.0 mL) and H_2O (1.7 mL) was treated at 20 °C with NMO (811 mg, 6.00 mmol) and OsO_4 (5.0 mol%, 63 mg, 2.53 mL, 0.250 mmol, 2.5%ic solution in *t*-BuOH). After being stirred for 2 h H_2O (8.5 mL) and $NaIO_4$ (3.21 g, 15.0 mmol) were added and stirring was continued for another 45 min. Afterwards, the reaction mixture was treated with saturated aqueous Na_2SO_3-solution (30 mL) and the mixture was stirred for 1 h at 20 °C. The reaction mixture was diluted with H_2O (100 mL) and then extracted with Et_2O (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was subjected to silica gel flash chromatography (P–Et_2O, 30:1 → 20:1) and concentration of the appropriate fractions *in vacuo* afforded aldehyde **39** (945 mg, 77 %) as a colourless oil. Due to its high sensitivity it was directly used within in the next step.

(*4S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-(1,8-diisoprop-oxy-9,10-dimethoxy-3-methoxymethyl-anthracene-2-yl)-4-methylhexan-1-ol (40). A solution of anthracene **34** (1.20 g, 2.51 mmol) in THF (30 mL) was treated at –78 °C dropwise during 1 min with *n*BuLi (1.15 mL, 2.89 mmol, 2.5 M in *n*-hexane). After being stirred for 1 min, aldehyde **39** (925 mg, 3.78 mmol) in THF (4 mL) was added quickly. Stirring was continued for 15 min at –78 °C, and then the reaction mixture was warmed to 20 °C during 1 h. The reaction mixture was treated with sat. NH_4Cl (10 mL), stirred for 5 min and then poured into H_2O (150 mL).

Afterwards, the resulting solution was extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to silica gel flash chromatography (P–EtOAc, 40:1 → 20:1) and concentration of the appropriate fractions *in vacuo* afforded a complex diastereomeric mixture (two major and one minor diastereoisomer) of alcohol **40** (1.51 g, 93%) as a yellow foam, *R*f 0.31 (diastereoisomer 1), 0.26 (diastereoisomer 2 and 3) (P–EtOAc, 10:1); λ_{max} (CH_3CN)/nm 202.0 (lg ε/dm^3 mol^{-1} cm^{-1} 4.431), 229.0 (4.139), 267.0 (5.002), 363.5 (3.798, sh), 381.5 (4.069), 397.0 (3.943) and 420.0 (3.777); ν_{max} (KBr)/cm^{-1} 2959, 2931, 1616, 1556, 1452, 1397, 1360 and 1264; δ_H (300 MHz, $CDCl_3$) diastereomer 1: 8.00 (1 H, br s, 4''-H), 7.84 (1 H, dd, *J* 8.6 and 0.7, 5''-H), 7.32 (1 H, dd, *J* 8.6 and 7.3, 6''-H), 6.83 (1 H, br d, *J* 7.3, 7''-H), 5.60 (1 H, m$_c$, 1-H), 4.90 (1 H, d, *J* 12.2, C*H*$_a$H$_b$OCH$_3$), 4.74 (1 H, d, *J* 12.2, CH$_a$*H*$_b$OCH$_3$), 5.71–5.54 (1 H, m, 1-H), 4.69–4.49 (2 H, m, 2 × OC*H*(CH$_3$)$_2$), 4.35 (1 H, br s, OH), 3.99–4.12 (4 H, m, OCH$_3$, 3-H), 3.76 (3 H, s, OCH$_3$), 3.48 (3 H, s, CH$_2$OC*H*$_3$), 2.07 (1 H, m$_c$, 2-H$_a$), 1.78–1.64 (2 H, m, 2-H$_b$, 4-H), 1.56–1.02 (14 H, m, 2 × OCH(C*H*$_3$)$_2$, 5-H$_b$, 5-H$_a$), 1.01–0.92 (12 H, m, SiC(C*H*$_3$)$_3$), 6-H$_3$), 0.88 (3 H, d, *J* 6.8, 1'-CH$_3$), 0.19, 0.10 (2 × 3 H, 2 × s, Si(C*H*$_3$)$_2$, TBS); δ_C (150.8 MHz, $CDCl_3$) diastereomer 1: 154.8, 149.7, 147.8, 134.1, 132.3, 127.7, 126.0, 125.5, 120.5, 119.3, 118.5, 115.3, 110.5, 77.20, 73.90, 72.65, 72.08, 66.33, 63.16, 62.81, 58.19, 40.58, 39.15, 26.05, 22.90, 22.17, 21.71, 18.11, 13.66, 12.26, –4.26 and –4.63; *m/z* (ESI) 1307.3 (100%, [2 × M + Na]$^+$) and 665.4 (89%, [M + Na]$^+$); Found (ESI) [M + Na]$^+$ 665.38453. $C_{37}H_{58}O_7Si$ + Na^+ requires 665.38440.

(1*RS*,3*RS*)-2-(1,3-Dihydroxy-butyl)-1,8-diisopropoxy-3-methylanthraquinone (41). A solution of a diastereomeric mixture of anthracene **40** (1.05 g, 1.63 mmol) in 1,4-dioxane (120 mL) was treated at 20 °C with silver(II) oxide (1.01 g, 8.15 mmol) and stirred for 5 min until a suspension was formed. Afterwards, 4 N HNO_3 (10 mL) was added dropwise within 5 min until the silver(II) oxide was completely dissolved. After being stirred for another 10 min, the reaction mixture was poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in THF (100 mL) and treated at 0 °C with a solution of TBAF·3 H_2O (1.03 g, 3.26 mmol) in THF (10 mL). The temperature was raised to 20 °C and stirring was continued for additional 30 min. The reaction was then poured into half-sat. NaCl (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic

layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to silica gel flash chromatography (CH_2Cl_2–EtOAc, 10:1 → 1:1) and concentration of the appropriate fractions *in vacuo* afforded a complex diastereomeric mixture (two major and one minor diastereoisomer) of anthraquinone **41** (693 mg, 85%) as a yellow foam, *R*f 0.25 (diastereomer 1), 0.16 (diastereomer 2 and 3) (P–EtOAc, 2:1); $[\alpha]_D^{20}$ –3.6° (*c* = 1.0, $CHCl_3$); λ_{max} (CH_3CN)/nm 193.0 (lg ε/dm^3 mol^{-1} cm^{-1} 4.489), 223.0 (4.517), 260.5 (4.418) and 371.5 (3.792); ν_{max} (KBr)/cm^{-1} 3451, 2973, 2932, 1676, 1584, 1464, 1383, 1276.; mixture of diastereoisomers: δ_H (300 MHz, $CDCl_3$) 8.00, 7.96, (1 H, s, 4-H), 7.78 (1 H, d, *J* 8.2, 5-H), 7.60 (1 H, t, *J* 8.2, 6-H), 7.29 (1 H, d, *J* 8.2, 7-H), 5.59–5.45 (1 H, m, 1'-H), 4.83 (1 H, d, *J* 12.0, C*H*$_a$H$_b$OCH$_3$), 4.73–4.60 (2 H, m, C*H*(CH$_3$)$_2$, CH$_a$*H*$_b$OCH$_3$), 4.53–4.33 (1 H, m, C*H*(CH$_3$)$_2$), 3.97–3.73 (1 H, m, 3'-H), 3.46, 3.45, 3.43 (3 H, s, CH$_2$OC*H*$_3$), 2.18–1.95 (1 H, m, 2'-H$_a$), 1.86–1.66 (1 H, m, 2'-H$_b$), 1.63–1.36 (10 H, m, C-8-OCH(C*H*$_3$)$_2$, C-1-OCH(C*H*$_3$)$_a$, 5'-H$_a$), 1.29 (3 H, d, *J* 6.0, C-1-OCH(C*H*$_3$)$_b$), 1.25–1.03 (1 H, m, 5'-H$_b$) and 0.97–0.85 (6 H, m, 6'-H$_3$, 1''-H$_3$); δ_C (75.5 MHz, $CDCl_3$) 183.9, 183.0, 157.2, 157.2, 154.7, 143.6, 142.7, 142.7, 141.6, 141.5, 141.02, 135.07, 133.68, 133.03, 132.72, 128.68, 128.7, 126.1, 126.0, 123.2, 123.2, 123.0, 121.3, 121.3, 121.3, 119.1, 78.95, 78.89, 78.52, 78.46, 76.48, 76.04, 72.80, 72.72, 72.55, 72.39, 72.02, 70.90, 70.85, 67.37, 67.31, 58.46, 58.31, 40.62, 40.45, 41.70, 40.53, 39.79, 38.69, 25.66, 25.27, 25.08, 25.00, 22.46, 22.42, 22.03, 22.00, 14.62, 14.35, 13.94, 13.89, 11.88, 11.73 and 11.69 (a few signals have a too weak intensity or are covered by other signals); *m/z* (ESI) 521.25 (36%, [M + Na]$^+$), 499.27 (100%, [M + H]$^+$); Found (ESI) [M + H]$^+$ 499.26914. $C_{29}H_{38}O_7$ + H$^+$ requires 499.26903. [M + Na]$^+$ 521.25097. $C_{29}H_{38}O_7$ + Na$^+$ requires 521.25097

[1] D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., Pentagon Press, Oxford, 1988.