DOI: 10.1002/chem.200700823

Total Synthesis of the Proposed Structure of the Anthrapyran Metabolite δ-Indomycinone

Lutz F. Tietze,* Ramakrishna Reddy Singidi, and Kersten M. Gericke[a]

Dedicated to Professor Klaus Müllen on the occasion of his 60th birthday

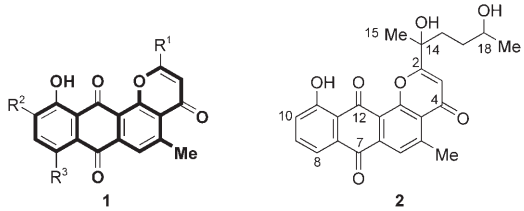
Abstract: The first total synthesis of the proposed structure of δ-indomycinone has been accomplished. The key steps involve the Diels–Alder reaction of a bromonaphthoquinone (**6**) and 1-methoxy-3-methyl-1-trimethylsiloxy-1,3-butadiene (**7**) to access the anthraquinone skeleton, representing a common building block of other naturally occurring anthraquinone antibiotics, regioselective bromination of anthraquinone (**14**) and a highly diastereoselective alkylation of enantiomerically pure dioxolanone **8**. The reported synthetic approach has the advantage of high yields, excellent selectivity and a remarkable general applicability for the total synthesis of other anthrapyran natural products. The spectroscopic data obtained for the synthetic compounds **2** and **36** are not in agreement with those reported for the natural product, and therefore revision of the assigned structure is required.

Keywords: antibiotics · cycloaddition · natural products · total synthesis

Introduction

Pluramycin antibiotics[1] containing the 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione nucleus **1** (Figure 1) to which amino sugars such as angolosamine and vancosamine are typically attached by C-glycosidic linkage at C-8 and C-10, are found to have versatile and strong antimicrobial and anticancer activities. These antibiotics, first described in 1956 by Umezawa et al.,[2] are most commonly isolated from terrestrial *Streptomyces* sp.; however, δ-indomycinone (**2**), also containing the skeleton **1**, has recently been obtained by Laatsch et al.[3] as a new member of the pluramycin family from the culture broth of a marine actinomycete identified as *Streptomyces* sp. (strain B 8300)[3] along with the known β-indomycinone.[4] In contrast to the normal pluramycin antibiotics, the indomycinones lack the amino sugar moieties attached to the chromophore. It was mentioned that the newly isolated compound exhibits antimicrobial activity against *B. subtilis*[3] and as well as antioxidative properties in a test carried out using the DPPH method.[5]

Thus, the observation of strong biological activities of anthrapyran antibiotics and the possibility of their application in the treatment of various diseases such as cancer as well as bacterial and viral infections should have made them attractive synthetic targets. However, from the synthetic point of view the anthrapyran antibiotics were rather neglected thus far and only a few approaches can be found in literature.[6] A general access to anthrapyran antibiotics, especially those with stereogenic centers in the side chain, has only recently been accomplished within the total synthesis of the anthrapyran natural products AH-1763 IIa,[7] γ-indomycinone,[8a–c] and (*S*)-espicufolin.[8d]



R^1 = alkyl, alkenyl, hydroxyalkyl, epoxyalkyl, etc.
R^2, R^3 = amino sugars, H

Figure 1. Structural core of 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione natural products (**1**) and proposed structure of δ-indomycinone (**2**).

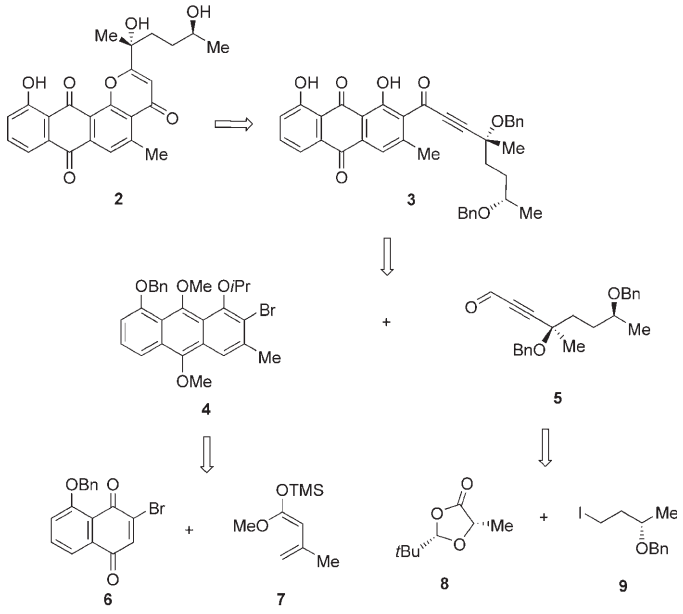
[a] Prof. L. F. Tietze, Dr. R. R. Singidi, Dr. K. M. Gericke
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität, Tammannstrasse 2
37077 Göttingen (Germany)
E-mail: ltietze@gwdg.de

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

The constitution of δ-indomycinone was established by spectroscopic methods, but its relative as well as absolute configuration in the side chain remained unknown. For that reason, a total synthesis was necessary, not only to determine the absolute and relative stereochemistry of the compound, but also to provide material for further biological studies. In our continuous efforts toward the total synthesis and structure determination of anthrapyran antibiotics, herein, we disclose our approach toward the first enantioselective total synthesis and structure determination of (14*R*,18*S*)-δ-indomycinone (**2**) and its (14*R*,18*R*)-diastereomer (**36**).

Results and Discussion

The retrosynthetic analysis of (14*R*,18*S*)-δ-indomycinone (**2**) is outlined in Scheme 1. The first disconnection in the pyrone ring moiety envisions an intramolecular 6-*endo*-digonal cyclization of ynone derivative **3**, which in turn should result from a nucleophilic attack of an aryllithium species generated from the bromodimethoxyanthracene derivative **4** onto the propargylic aldehyde **5**.

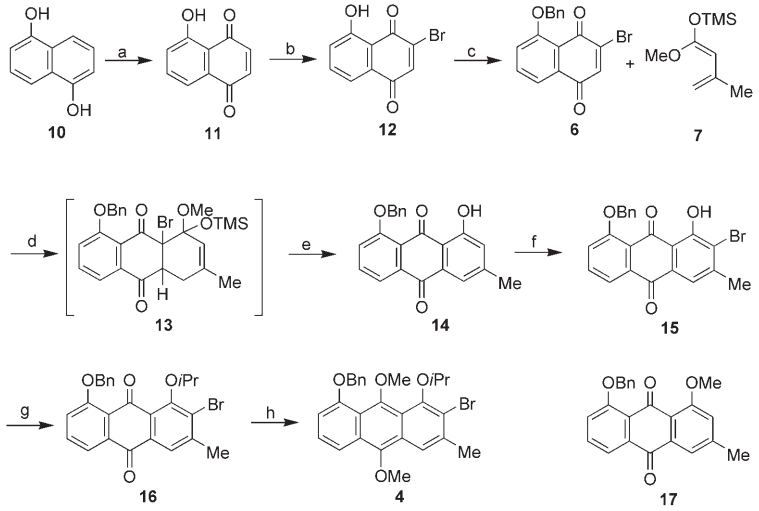


Scheme 1. Retrosynthetic analysis of (14*R*,18*S*)-δ-indomycinone (**2**).

The desired dimethoxyanthracene derivative **4** was divided into two fragments **6** and **7**, which were planned to be coupled by a Diels–Alder cycloaddition. Finally, the propargylic aldehyde **5** should be accessible by the usage of a stereoselective alkylation employing the enantiopure dioxolanone **8** and alkyl iodide **9**.

The first step of our synthesis was the $Cu^{I}Cl$-mediated air oxidation of commercially available 1,5-dihydroxynaphthalene **10** (Scheme 2) yielding the naphthoquinone natural product juglone (**11**).[9,10] Regioselective bromination[11] of the latter was carried out using a literature-known procedure to give 3-bromojuglone (**12**) as a pure isomer, which was protected under mild conditions utilizing Ag^{I}_2O and benzyl bromide to furnish the desired benzyl ether of 3-bromojuglone (**6**).[12] A Diels–Alder reaction of a naphthoquinone such as **6** and a diene such as 1-methoxy-3-methyl-1-trimethylsiloxy-1,3-butadiene (**7**)[13] was chosen for the straightforward construction of chrysophanol-8-benzyl ether (**14**), a strategy which has been developed by Brassard and Savard.[13] Thus, addition of diene **7** to the 3-bromojuglone derivative **6** in benzene yielded the cycloaddition product **13**, which was converted without further isolation into the thermodynamically more stable anthraquinone derivative **14** by treatment with silica gel as mild acid. The regioselectivity of this step was controlled by the bromine atom of the dienophil which directed the carbon–carbon bond formation during the Diels–Alder reaction.[14] This method turned out to be operationally simple and suitable for scaled up preparations of anthraquinone building block **14**, which represents a common precursor of other naturally occurring anthraquinone antibiotics. The yield of this two-step procedure could be improved up to 94% yield, without observing the possible formation of *O*-methyl ether **17**, a major side product in Brassard's protocol. The following regioselective bromination of anthraquinone **14** was feasible using NBS in the presence of a catalytic amount of a secondary amine[15] by taking advantage of the strong *ortho*-directing effect of the hydroxyl group under these conditions. Hence, the monobromoanthraquinone (**15**) could be obtained in nearly quantitative yield (96%). The regioselectivity of both the bromination and the Diels–Alder reaction was unambiguously deduced from HMBC ^{1}H NMR experiments. To complete the synthesis of the building block **4** a protection of both the hydroxyl group and the quinone moiety was necessary. Following an orthogonal protecting-group strategy the hydroxyl group of bromoanthraquinone (**15**) was converted into the corresponding isopropyl ether **16** in 90% yield by treatment with *i*PrI and Cs_2CO_3 in a mixture of acetone and *N*,*N*-dimethylformamide.[16] Finally, the reductive methylation[17] of the quinone was realized using aqueous sodium dithionite to furnish the air- and light-sensitive hydroquinone, which underwent methylation by subsequent treatment with KOH and dimethylsulfate to obtain the air- and light-sensitive dimethoxyanthracene (**4**) in an excellent overall yield of 90%. The use of two different protecting groups in the building block **4** has the advantage over the corresponding building block with two isopropyl ether moieties[7] that deprotection of the less activated A-ring as one of the last steps should not cause any problems.

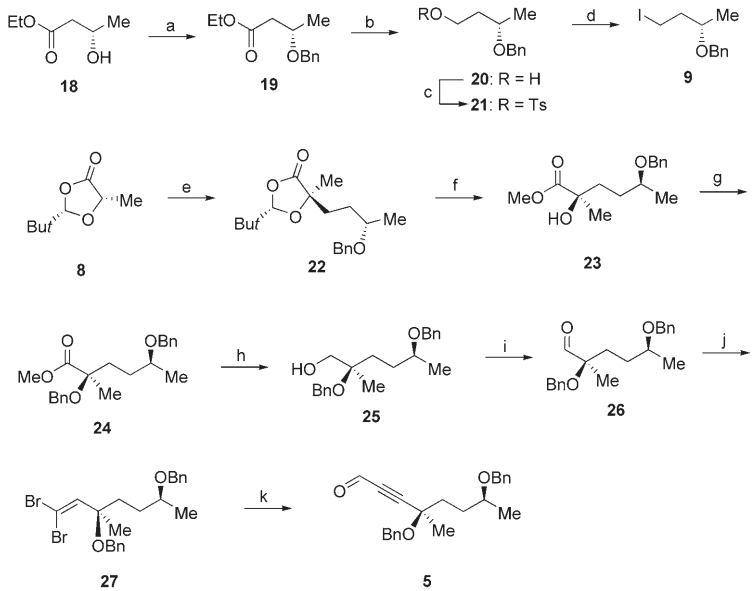
As outlined in Scheme 3, our synthesis of the propargylic aldehyde **5** started from commercially available (*S*)-3-hydroxybutanoic acid. Treatment of the β-hydroxy ester **18** with benzyl 2,2,2-trichloroacetimidate under acidic conditions[18] afforded benzyl ether **19**. Reduction of the ester moiety in **19** with $LiAlH_4$ yielded the primary alcohol **20** in 92% yield and its tosylation[19] utilizing TosCl and pyridine



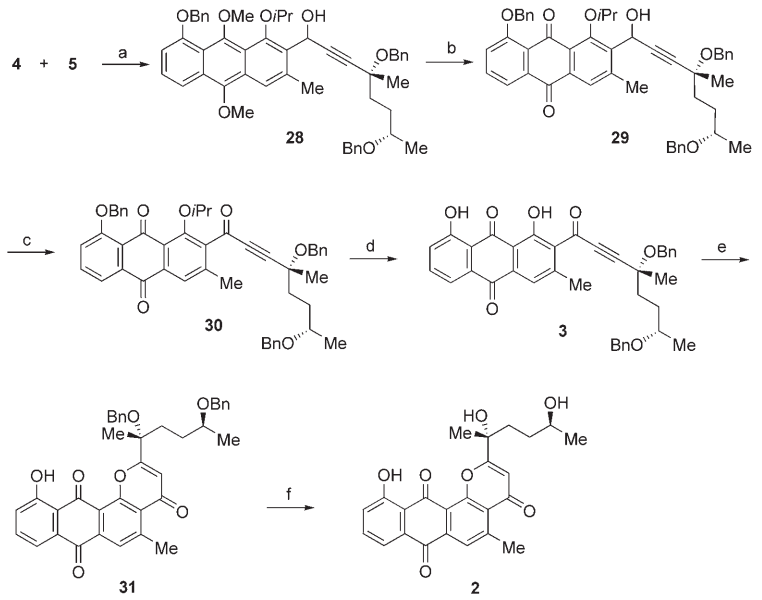
Scheme 2. a) O_2, $Cu^{I}Cl$, CH_3CN, RT, 8 h, 55%; b) 1) Br_2, AcOH, RT, 10 min, 2) EtOH, reflux, 15 min, 80%; c) $Ag^{II}O$, BnBr, CH_2Cl_2, RT, 24 h, 99%; d) benzene, RT, 6 h; e) SiO_2, CH_2Cl_2, RT, 24 h, 94% overall yield for two steps; f) NBS, cat. iPr_2NH, CH_2Cl_2, RT, 12 h, 96%; g) Cs_2CO_3, *i*PrI, acetone/DMF 3:1, reflux, 12 h, 90%; h) $Na_2S_2O_4$, TBABr, KOH, H_2O, $DMSO_4$, THF, RT, 8 h, 90%.

furnished the tosylate **21**, which was transformed into the alkyl iodide **9** in 86% overall yield over two steps by treatment with NaI.[19] Our attention was next turned to the diastereoselective alkylation of the enantiomerically pure dioxolanone **8**[20] using LDA with alkyl iodide **9**. Generation of the lithium enolate derived from dioxolanone **8** employing LDA followed by addition of the alkyl iodide **9** cleanly provided coupling product **22** in excellent 96% yield with high diastereoselectivity (94%).[20,21] The structure was assigned to the product **22** based on literature precedent.[20] It is worthwhile to note that deprotonation of **8** using bases such as LiHMDS, KHMDS and NaHMDS followed by treatment with the iodide **9** did not yield the desired product **22**; only starting material was recovered under these conditions. The transesterification[22] of dioxolanone **22** with sodium methoxide in absolute methanol followed by benzyl protection of the resulting tertiary alcohol **23** gave methyl ester **24**. Reduction of the latter using $LiAlH_4$ delivered the primary alcohol **25**. The following oxidation utilizing the very mild IBX[23] reagent gave the aldehyde **26** in 90% yield, which was subjected to a Corey–Fuchs homologation[24] affording vinyl dibomide **27** in 86% yield. Subsequent treatment of vinyl dibromide **27** with *n*BuLi followed by formylation with *N*,*N*-dimethylformamide furnished the desired propargylic aldehyde **5** in 82% yield.[25]

With building blocks **4** and **5** in hand, we next turned our attention to the coupling of these intermediates. After conversion of **4** to the lithium derivative by bromine lithium exchange using *n*BuLi at low temperature, the subsequent reaction with propargylic aldehyde **5** proceeded smoothly to give the corresponding alcohol **28** in 80% yield (Scheme 4) as a mixture of both possible diastereomers in a ratio of 1:1 according to ^1H and ^{13}C NMR spectra of the product. The missing selectivity at this point has no further consequence since the formed stereogenic alcohol is later removed by oxidation to the corresponding ketone. It was important to add aldehyde **5** immediately after generation of the organolithium compound to avoid the formation of the debrominated compound as side product. Oxidative demethylation of anthracene derivative **28** using $Ag^{II}O/HNO_3$[26] yielded anthraquinone derivative **29** in 90% yield, which was subsequently subjected to IBX oxidation[23] to afford ynone derivative **30** in 95% yield. The



Scheme 3. a) Benzyl trichloroacetimidate, cat. TfOH, cyclohexane/CH_2Cl_2 2:1, RT, 1 h, 87%; b) $LiAH_4$, THF, 0°C, 30 min, 92%; c) TsCl, pyridine, DMAP, 0°C, 5 h; d) NaI, $NaHCO_3$, acetone, RT, 24 h, 86%; e) LDA, THF, −78 to 0°C, 4 h, 96%; f) NaOMe, MeOH, 0°C, 2 h, 88%; g) BnBr, NaH, cat. TBAI, THF, 0°C to RT, 12 h, 92%; h) $LiAH_4$, THF, 0°C, 30 min, 96%; i) IBX, CH_2Cl_2, DMSO, RT, 4 h, 90%; j) PPh_3, CBr_4, Zn, CH_2Cl_2, RT, 12 h, 86%; k) *n*BuLi, THF, DMF, −78 to 0°C, 6 h, 82%.



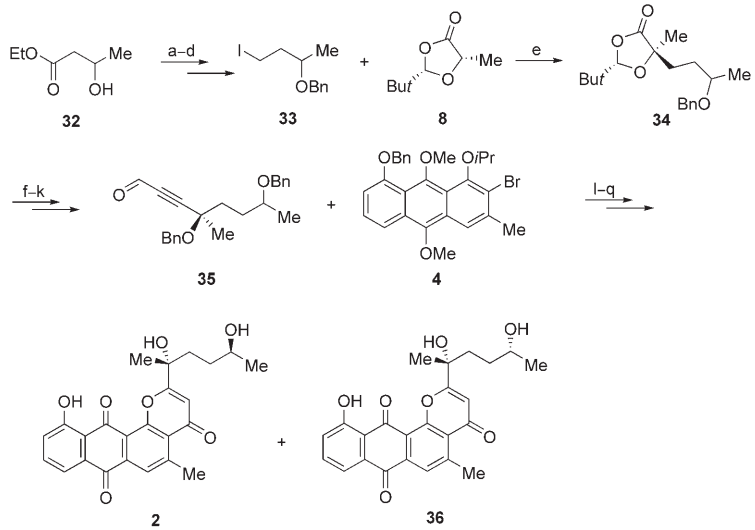
Scheme 4. a) *n*BuLi, THF, −78 °C, 10 min, 80 %; b) $Ag^{II}O$, dioxane, 4 N HNO_3, RT, 30 min, 90 %; c) IBX, CH_2Cl_2, DMSO, RT, 4 h, 95 %; d) AcOH, cat. H_2SO_4, 55 °C, 30 min, 86 %; e) Cs_2CO_3, acetone, 0 to 5 °C, 30 min, 42 %; f) $TiCl_4$, CH_2Cl_2, −78 to −20 °C, 2 h, 80 %.

planned approach was to remove the isopropyl protecting group at the anthraquinone moiety and perform the ring closure under acidic conditions in a domino process.[27] However, treatment of a solution of **30** in acetic acid at 55 °C with a catalytic amount of sulfuric acid led to cleavage of the benzyl and isopropyl ethers at the anthraquinone to give **3**, but a cyclization was not observed under these conditions. Moreover, raising the temperature and increasing the reaction time did not lead to a cyclization but induced an elimination of the benzyloxy group in the side chain. Finally, the pyron ring construction could be achieved under basic conditions. Thus, treatment of compound **3** in acetone with Cs_2CO_3 yielded compound **31** in 42 % yield via an intramolecular 6-*endo*-digonal cyclization.[28] The pyrone ring construction in compound **31** was unambiguously deduced from HMBC ^{1}H NMR experiments. The final step in the synthesis of (14*R*,18*S*)-δ-indomycinone (**2**) was the removal of the benzyl protecting groups which were effected in 80 % yield by treatment of **31** with $TiCl_4$ in CH_2Cl_2 at −78 °C and then slow warming up to −20 °C.[15d]

Unfortunately, comparison of the ^{1}H NMR spectroscopic data of synthetic (14*R*,18*S*)-δ-indomycinone (**2**) with those reported for the isolated δ-indomycinone revealed that they were not identical. It should be noted that due to the low solubility of the synthetic compound **2** in $CDCl_3$ it was difficult to obtain ^{13}C NMR spectroscopic data in $CDCl_3$ for comparison. A careful examination of the chemical shifts of the synthetic and natural product revealed that 2-H and 18-H of (14*R*,18*S*)-δ-indomycinone (**2**) resonate at $\delta =$ 6.62 and 3.88–3.96 ppm, respectively, whereas the reported data for these protons in the isolated compound are $\delta = 6.30$ and 3.22 ppm.

For that reason we synthesized the other possible diastereomer **36** as a mixture with **2** in order to compare again the analytical data. Thus, (14*R*,18*S*)-δ-indomycinone (**2**) and (14*R*,18*R*)-δ-indomycinone (**36**; Scheme 5) were prepared starting from racemic β-hydroxy ester **32** following the synthetic route established for the synthesis of (14*R*,18*S*)-δ-indomycinone (**2**).

As expected, the ^{1}H NMR data of the diastereomer (14*R*,18*R*)-δ-indomycinone (**36**) were different from those



Scheme 5. a) Benzyl trichloroacetimidate, cat. TfOH, cyclohexane/CH_2Cl_2 2:1, RT, 1 h, 87 %; b) $LiAlH_4$, THF, 0 °C, 30 min, 92 %; c) TsCl, pyridine, DMAP, 0 °C, 5 h; d) NaI, $NaHCO_3$, acetone, RT, 24 h, 86 %; e) LDA, THF, −78 to 0 °C, 4 h, 90 %; f) NaOMe, MeOH, 0 °C, 2 h, 88 %; g) BnBr, NaH, TBAI, THF, 0 °C to RT, 12 h, 92 %; h) $LiAlH_4$, THF, 0 °C, 30 min, 96 %; i) IBX, CH_2Cl_2, DMSO, RT, 2 h, 90 %; j) PPh_3, CBr_4, Zn, CH_2Cl_2, RT, 12 h, 86 %; k) *n*BuLi, THF, DMF, −78 to 0 °C, 3 h, 82 %; l) *n*BuLi, THF, −78 °C, 10 min, 80 %; m) $Ag^{II}O$, dioxane, 4 N HNO_3, RT, 30 min, 90 %; n) IBX, CH_2Cl_2, DMSO, RT, 4 h, 95 %; o) AcOH, cat. H_2SO_4, 55 °C, 30 min, 84 %; p) Cs_2CO_3, acetone, 0 to 5 °C, 30 min, 42 %; q) $TiCl_4$, CH_2Cl_2, −78 to −20 °C, 2 h, 75 %.

found for **2**, but they also did not match with the signals published for the proposed natural δ-indomycinone (**2**). Thus, 2-H and 18-H in **36** resonate at $\delta = 6.67$ and 4.03–4.14 ppm, respectively (see the Supporting Information for NMR spectra), whereas signals at $\delta = 6.30$ and 3.22 ppm, respectively, were reported for the natural compound.

Since the comparison of the ^{1}H NMR data published for the isolated δ-indomycinone with those of the two possible diastereomers (14*R*,18*S*)-δ-indomycinone (**2**) and (14*R*,18*R*)-δ-indomycinone (**37**) unequivocally demonstrated that neither of them are consistent with the data reported for the natural product, we have to presume that the isolated compound does not have the proposed structure **2**.

Conclusion

In summary, based on the unambiguous synthesis of the two possible diastereomers **2** and **36** having the proposed constitution of δ-indomycinone it is concluded that the originally anticipated structure for the natural product is untenable and that structural revision will be necessary. The strategy for the synthesis of the proposed structure of δ-indomycinone presented here can easily be adopted for the synthesis of other pluramycin antibiotics described in the literature, and furthermore it also allows the preparation of unnatural analogues with possibly higher biological activity.

Experimental Section

General: All reactions were performed in flame-dried glassware under an atmosphere of argon and the reactants were introduced by syringe. Solvents were dried and purified according to the method defined by Perrin and Armarego.[29] 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. 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 (KBr pellets or films), UV/Vis spectra on a Perkin-Elmer Lambda 2 (CH_3CN), and mass spectra on a Finnigan MAT 95, and a Bioapex fourier transformation ion cyclotron resonance mass spectrometer for ESI-HRMS. ^{1}H NMR spectra were recorded either on a Varian Mercury 300, Unity 300 or Inova 600 spectrometer. ^{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 or TMS as internal standard. Elemental analysis was performed at the Mikroanalytisches Labor des Institutes für Organische und Biomolekulare Chemie der Universität Göttingen.

Compound 11: A suspension of freshly recrystallized 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 **10** (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 **10** (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; **10**, 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 **11** (53.7 g, 55 %) as orange-red needles.[9,10] M.p. 154 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.91$ (s, 1H, OH), 7.69–7.60 (m, 2H, 7-H, 8-H), 7.29 (dd, $J = 7.3$, 2.5 Hz, 1H, 6-H), 6.96 ppm (s, 2H, 2-H, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 190.2$, 184.2, 161.4, 139.5, 138.59, 136.5, 131.7, 124.4, 119.1, 114.9 ppm; IR (KBr): $\tilde{\nu} = 3386$, 3070, 1665, 1644, 1600, 1486, 1451, 1364, 1338, 1290, 1226 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 207.5 (4.508), 248.5 (4.128), 420.0 nm (3.540); MS (EI, 70 eV): *m*/*z* (%): 174.0 (100) $[M]^+$, 146.0 (10) $[M-CO]^+$, 118 (36) $[M-C_2O_2]^+$; elemental analysis calcd (%) for $C_{10}H_6O_3$ (174.15): C 68.97, H 3.47; found: C 69.09, H 3.38.

Compound 12: A suspension of juglone **11** (12.0 g, 68.9 mmol) in acetic acid (180 mL) was treated in the dark at 25 °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 **12** (14.0 g, 80 %) as an orange solid. M.p. 168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.73$ (s, 1H, OH), 7.68 (t, $J = 7.4$ Hz, 1H, 7-H), 7.64 (dd, $J = 7.4$, 2.0 Hz, 1H, 8-H), 7.50 (s, 1H, 2-H), 7.31 ppm (dd, $J = 7.5$, 2.0 Hz, 1H, 6-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 182.8$, 181.6, 162.0, 141.2, 139.3, 137.2, 131.6, 124.7, 119.9, 113.9 ppm; IR (KBr): $\tilde{\nu} = 3421$, 3051, 1655, 1630, 1582, 1487, 1458, 1363, 1291, 1275, 1214 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 212.0 (4.462), 247.5 (3.705), 282.0 (4.041), 426.5 nm (3.515); MS (EI, 70 eV): *m*/*z* (%): 253.9, 251.9 (100) $[M]^+$, 173.0 (50) $[M-Br]^+$, 145.0 (46) $[M-Br-CO]^+$; HRMS (EI): *m*/*z*: calcd for $C_{10}H_5BrO_3$: 251.9422; found: 251.9422; elemental analysis calcd (%) for $C_{10}H_5BrO_3$ (253.05): C 47.46, H 1.99; found: C 47.72, H 2.05.

Compound 6: Benzylbromide (0.47 mL, 4.00 mmol) was added to a mixture of 3-bromojuglone **12** (506 mg, 2.00 mmol) and silver(I) oxide (684 mg, 4.00 mmol) in CH_2Cl_2 (13 mL) and the resulting suspension was stirred for 12 h at 25 °C. Then, additional silver(I) oxide (342 mg, 2.00 mmol) and benzylbromide (0.23 mL, 2.00 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 **6** (672 mg, 98 %) as a yellow solid. M.p. 107 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.73$ (dd, $J = 7.8$, 1.0 Hz, 1H, 8-H), 7.66 (t, $J = 8.1$ Hz, 1H, 7-H), 7.58 (br d, $J = 7.8$ Hz, 2H, 2 × *o*-Ph-H), 7.46–7.30 (m, 5H, *p*-Ph-H, 6-H, 2 × *m*-Ph-H, 2-H), 5.29 ppm (s, 2H, CH_2Ph); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 182.5$, 176.0, 159.2, 142.6, 138.3, 135.6, 135.4, 133.9, 128.7, 128.0, 126.7, 119.7, 119.6, 119.0, 70.95 ppm; IR (KBr): $\tilde{\nu} = 3063$, 2923, 1671, 1583, 1452, 1310, 1281, 1204, 1149, 1026 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 238.0 (4.108), 277.0 (4.058), 347.0 (3.334), 402.5 nm (3.496); MS (EI, 70 eV): *m*/*z* (%): 344.0, 342.0 (14) $[M]^+$, 91.0 (100) $[C_7H_7]^+$; elemental analysis calcd (%) for $C_{17}H_{11}BrO_3$ (343.17): C 59.50, H 3.23; found: C 59.25, H 3.09.

Compound 14: Diene **7** (1.10 g, 5.88 mmol) was added at 0 °C dropwise with stirring within 10 min to a solution of juglone derivative **6** (672 mg, 1.96 mmol) in benzene (19 mL). After being stirred for 1 h at 0 °C, the mixture was warmed to 20 °C and stirring was continued for additional 5 h. Afterwards, the reaction mixture was poured onto silica gel (40 g), CH_2Cl_2 (200 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 **14** (633 mg, 94 %) as a yellow solid. M.p. 218 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 13.03$ (s, 1H, OH), 7.93 (m, $J = 7.6$, 0.8 Hz, 1H, 5-

H), 7.65 (t, $J=8.2$ Hz, 1H, 6-H), 7.60 (s, 1H, 4-H), 7.57 (m, 2×*o*-Ph-H), 7.43 (t, $J=7.3$ Hz, 2H, 2×*m*-Ph-H), 7.38–7.30 (m, 2H, 7-H, *p*-Ph-H), 7.08 (s, 1H, 2-H), 5.33 (s, 2H, OCH_2Ph), 2.42 ppm (s, 3H, Ar-CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=188.2$, 182.9, 162.7, 159.7, 147.4, 136.1, 135.9, 135.3, 132.4, 128.7, 128.0, 126.7, 124.5, 121.5, 120.4, 118.0, 119.9, 115.1, 71.22, 22.0 ppm; IR (KBr): $\tilde{\nu}=3035$, 1672, 1638, 1585, 1489, 1.444, 1365, 1301, 1271, 1240, 1205 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 192.5 (4.721), 223.0 (4.469), 257.0 (4.258), 412.5 nm (3.834); MS (EI, 70 eV): *m*/*z* (%): 344.3 (42) $[M]^+$, 91.1 (100) $[C_7H_7]^+$; HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{16}O_4$+H^+: 345.11214; found: 345.11219; elemental analysis calcd (%) for $C_{22}H_{16}O_4$+Na^+: 367.09408; found: 367.09419.

Compound 15: A solution of anthraquinone **14** (633 mg, 1.84 mmol) in CH_2Cl_2 (25 mL) was treated at 25 °C with a catalytic amount of diisopropylamine (6 drops) and then a solution of NBS (480 mg, 2.70 mmol) in CH_2Cl_2 (20 mL) was added dropwise during 10 min. After being stirred for 8 h (TLC control), additional NBS (81 mg, 0.46 mmol) was added and stirring was continued for another 4 h. Afterwards, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed subsequently with aqueous 0.2 N HCl (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 **15** (730 mg, 96 %) as an orange solid. M.p. 238 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.95 (s, 1H, OH), 7.95 (d, $J=7.6$ Hz, 1H, 5-H), 7.73–7.66 (m, 2H, 6-H, 4-H), 7.61–7.55 (m, 2H, 2×*o*-Ph-H), 7.47–7.31 (m, 4H, 7-H, 2×*m*-Ph-H, *p*-Ph-H), 5.37 (s, 2H, OCH_2Ph), 2.56 ppm (s, 3H, Ar-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=187.99$, 182.44, 159.85, 159.23, 147.33, 136.25, 135.83, 135.81, 135.58, 130.46, 128.76, 128.11, 126.65, 121.68, 120.91, 120.52, 120.43, 120.23, 120.04, 115.20, 71.15, 24.20 ppm; IR (KBr): $\tilde{\nu}=2869$, 1670, 1633, 1582, 1479, 1442, 1382, 1365, 1263, 1240, 1188, 1139, 1055, 1010 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 228.5 (4.476), 261.5 (4.385), 416.0 nm (3.976); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{15}BrO_4$+H^+: 423.01541; found: 423.01538.

Compound 16: A solution of anthraquinone **15** (730 mg, 1.72 mmol) in a mixture of acetone (57 mL) and DMF (17 mL) was treated subsequently at 20 °C with Cs_2CO_3 (1.68 g, 5.16 mmol) and 2-iodopropane (0.34 mL, 3.44 mmol). After being stirred for 12 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 (150 mL) and washed subsequently with aqueous 2 M Na_2CO_3 (100 mL) and brine (100 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 **16** (719 mg, 90 %) as a yellow solid. M.p. 165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.88$–7.83 (m, 2H, 4-H, 5-H), 7.67–7.60 (m, 3H, 6-H, 2×*o*-Ph-H), 7.45–7.29 (m, 4H, 7-H, 2×*m*-Ph-H, *p*-Ph-H), 5.29 (s, 2H, OCH_2Ph), 4.52–4.39 (m, 1H, OCH(CH_3)$_2$), 2.56 (s, 3H, Ar-CH_3), 1.38 ppm (d, $J=6.2$ Hz, 6H, OCH-(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=183.27$, 182.32, 158.0, 154.71, 145.04, 136.30, 134.85, 134.02, 132.53, 130.53, 128.49, 127.82, 127.16, 126.83, 126.71, 123.54, 119.73, 119.36, 79.44, 70.90, 24.47, 22.28 ppm; IR (KBr): $\tilde{\nu}=2973$, 1672, 1583, 1498, 1446, 1352, 1312, 1291, 1233, 1102, 788 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 263.0 (4.453), 372.5 nm (3.792); HRMS (ESI): *m*/*z*: calcd for $C_{25}H_{21}BrO_4$ + H^+: 465.06960; found: 465.06987.

Compound 4: A solution of anthraquinone **16** (719 mg, 1.54 mmol) and tetra-*n*-butylammonium bromide (148 mg, 0.46 mmol) in THF (22 mL) was treated at 20 °C with a solution of $Na_2S_2O_4$ (1.60 g 9.24 mmol) in H_2O (4 mL) and stirred for 25 min. Afterwards, a solution of KOH (1.98 g, 35.0 mmol) in H_2O (2 mL) was added (the yellow solution turned into deep-red) and stirring was continued for additional 15 min. After addition of dimethyl sulfate (1.5 mL), the reaction mixture was stirred for 8 h (the solution turned back into yellow) and then poured into H_2O (50 mL). The resulting solution was extracted with CH_2Cl_2 (3×50 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 anthracene **4** (681 mg, 1.38 mmol, 90 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.89$ (s, 1H, 4-H), 7.85 (d, $J=$ 8.4 Hz, 1H, 5-H), 7.70–7.65 (m, 2H, 2×*m*-Ph-H), 7.47–7.33 (m, 4H, 6-H, 2×*o*-Ph-H, *p*-Ph-H), 6.87 (d, $J=8.4$ Hz, 1H, 7-H), 5.28 (s, 2H, OCH_2Ph), 4.79–4.68 (m, 1H, OCH(CH_3)$_2$), 4.05 (s, 3H, OMe), 3.74 (s, 3H, OMe), 2.63 (s, 3H, Ar-CH_3), 1.22–1.47 ppm (br s, 6H, OCH(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=156.20$, 150.47, 149.37, 147.22, 137.37, 135.97, 128.39, 127.67, 127.56, 127.21, 126.06, 125.77, 120.28, 120.01, 119.32, 117.65, 115.14, 106.54, 78.07, 71.43, 63.87, 62.72, 24.76, 22.05 ppm; HRMS (ESI): calcd for $C_{27}H_{27}BrO_4$ + H^+: 495.11655; found: 495.11674.

Compound 20: A solution of ester **19** (772 mg, 3.48 mmol) in THF (4 mL) was added at 0 °C to a stirred suspension of $LiAH_4$ (128 mg, 3.48 mmol) in THF (12 mL) and stirring was continued at the same temperature for 30 min. The reaction mixture was diluted with diethyl ether and quenched by adding ice. The reaction mixture was passed through a small pad of Celite and the filtrate evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography using 20 % EtOAc/pentane to yield the alcohol **20** (576 mg, 92 %) as viscous oil. $[\alpha]_D^{20}=+18.6$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.59$–7.08 (m, 5H, Ph), 4.63 (d, $J=11.7$ Hz, 1H, C-3-OCH_aPh), 4.43 (d, $J=11.7$ Hz, 1H, C-3-OCH_bPh), 3.86–3.60 (m, 3H, 1-H_2, 3-H_1), 2.79–2.30 (br s, 1H, OH), 1.83–1.68 (m, 2H, 2-H_2), 1.24 ppm (d, $J=6.8$ Hz, 3H, 4-H_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=138.28$, 128.44, 127.70, 127.66, 74.61, 70.38, 60.84, 38.65, 19.29 ppm; IR (KBr): $\tilde{\nu}=1453$, 1376, 1279, 1054 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 251.0 (2.628), 256.5 (2.622), 261.5 nm (2.586); MS (EI, 70 eV): *m*/*z* (%): 181.1 (16) $[M+H]^+$, 179.1 (43), 123.1 (25), 107.1 (100), 105.0 (50), 79.0 (30).

Compound 21: *p*TsCl (912 mg, 4.80 mmol) was added at 0 °C to a stirred solution of **20** (576 mg, 3.20 mmol) in pyridine (5 mL), and the mixture was stirred at 0 °C for 5 h. After addition of crashed ice, the resulting mixture was stirred vigorously for 10 min, poured into ice water, and then extracted with Et_2O. The extracts were washed successively with water, cold 1 N HCl solution, water, sat. $NaHCO_3$ solution, water, and brine and concentrated to yield the tosylate **21** (1.00 g), which was used without further purification in the next step. $[\alpha]_D^{20}=+40.0$ ($c=1.3$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.78$ (d, $J=8.9$ Hz, 2H, 2×*m*-Tol-H), 7.34–7.21 (m, 7H, Ph, 2×*o*-Tol-H), 4.50 (d, $J=11.4$ Hz, 1H, C-3-OCH_aPh), 4.26 (d, $J=11.4$ Hz, 1H, C-3-OCH_bPh), 4.21–4.09 (m 2H, 1-H_2), 3.69–3.58 (m, 1H, 3-H_1), 2.40 (s, 3H, Tol-CH_3), 1.85–1.79 (m, 2H, 2-H_2), 1.17 ppm (d, $J=6.1$ Hz, 3H, 4-H_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=$ 144.69, 138.38, 132.95, 129.80, 128.30, 127.87, 127.55, 127.52, 70.93, 70.60, 67.56, 36.14, 21.59, 19.46 ppm; IR (KBr): $\tilde{\nu}=1356$, 1179, 939, 887, 555 cm^{-1}; UV (CH_3CN): (lg ε) = 257.5 (2.971), 272.5 (2.802), 261.5 nm (2.990); MS (EI, 70 eV): *m*/*z* (%): 334.2 (8) $[M]^+$, 250.1 (6), 172.1 (35), 155.1 (18), 91.1 (100).

Compound 9: A mixture of tosylate **21** (1.00 g), NaI (715 mg, 4.80 mmol) and $NaHCO_3$ (391 mg, 5.40 mmol) in dry acetone (10 mL) was stirred for 24 h at 20 °C. Afterwards, the solution was concentrated in vacuo and the residue was diluted with water and extracted with Et_2O. The extract was washed successively with water, 10 % $Na_2S_2O_3$ solution, water, brine and evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography using 10 % EtOAc/pentane to yield alkyl iodide **9** (800 mg, 86 % overall yield for two steps) as liquid. $[\alpha]_D^{20}=+67.3$ ($c=2.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.34$–7.24 (m, 5H, Ph), 4.50 (d, $J=11.3$ Hz, 1H, C-3-OCH_aPh), 4.43 (d, $J=11.3$ Hz, 1H, C-3-OCH_bPh), 3.70–3.56 (m, 1H, 3-H_1), 3.30–3.24 (m, 2H, 1-H_2), 1.05–2.92 (m, 2H, 2-H_2), 1.18 ppm (d, $J=6.4$ Hz, 3H, 4-H_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=138.71$, 128.53, 127.90, 127.73, 74.60, 70.80, 40.65, 18.93, 2.92 ppm; IR (KBr): $\tilde{\nu}=1453$, 1374, 1252, 1127, 1066, 734, 697 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 252.0 (2.871), 257.0 nm (2.869); MS (EI, 70 eV): *m*/*z* (%): 290.1 (14) $[M]^+$, 135.1 (30), 91.1 (100), 65.0(12).

Compound 22: *n*BuLi (2.5 M in hexane, 2.1 mL, 5.25 mmol) was added dropwise at −78 °C to a solution of diisopropyl amine (0.78 mL, 5.51 mmol) in THF (35 mL). After 10 min, the white slurry was warmed to −10 °C for 30 min. After the solution was cooled back to −78 °C, a solution of dioxolanone **8** (790 mg, 5.00 mmol) in THF (2 mL) was added dropwise to the solution. After 40 min, a solution of alkyl iodide **9**

(727 mg, 2.50 mmol) in THF (2 mL) was added dropwise. After 30 min, the reaction was warmed slowly to −10 °C over 3 h and quenched by the addition of a sat. aq. NH_4Cl solution. The aqueous layer was extracted with Et_2O and the organic layer washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel chromatography using 25% EtOAc/pentane to yield compound **22** (768 mg, 96%) as a liquid. $[\alpha]_D^{20} = +39.7$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.32 (m, 5H, Ph), 5.17 (s, 1H, C*H*-*t*Bu), 4.54 (d, $J = 11.3$ Hz, 1H, C-6-OCH_aPh), 4.44 (d, $J = 11.3$ Hz, 1H, C-6-OCH_bPh), 3.58–3.47 (m, 1H, 6-H_1), 1.99–1.90 (m, 1H, 4-H_a), 1.75–1.59 (m, 3H, 4-H_b, 5-H_2), 1.43 (s, 3H, 3-H_3), 1.21 (d, $J = 6.0$ Hz, 3H, 7-H_3), 0.94 ppm (s, 9H, *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.71$, 138.72, 128.33, 127.59, 127.48, 108.30, 79.61, 74.31, 70.33, 34.51, 31.89, 30.37, 23.29, 22.50, 19.44 ppm; IR (KBr): $\tilde{\nu} =$ 2965, 1796, 1376, 1075, 982, 736 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 252.0 (2.341), 258.0 (2.341), 263.5 nm (2.292); HRMS (ESI): calcd for $C_{19}H_{28}O_4 + H^+$: 321.20604; found: 321.20603.

Compound 34: Compound **34** was prepared from the dioxolanone **8** and alkyl iodide **33** following the procedure described for the preparation of the compound **22**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.24$–7.38 (m, 10H, 2×Ph), 5.17 (s, 1H, C*H*-*t*Bu), 5.14 (s, 1H, C*H*-*t*Bu), 4.54 (d, $J = 11.3$ Hz, 2H, 2×C-6-OCH_aPh), 4.44 (d, $J = 11.3$ Hz, 2H, 2×C-6-OCH_aPh), 3.57–3.48 (m, 2H, 2×6-H_1), 2.01–1.88 (m, 2H, 2×4-H_a), 1.79–1.52 (m, 6H, 2×4-H_b, 2×5-H_2), 1.43 (s, 6H, 2×3-H_3), 1.21 (d, $J = 6.0$ Hz, 6H, 2×7-H_3), 0.98–0.90 ppm (m, 18H, 2×*t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.82$, 175.75, 138.68, 128.33, 127.60, 127.57, 127.49, 108.39, 108.30, 79.75, 79.61, 74.29, 74.19, 70.31, 34.53, 34.51, 31.92, 31.89, 30.41, 30.35, 23.27, 22.63, 22.50, 19.51, 19.43 ppm.

Compound 23: Sodium methoxide (5.5 M in methanol, 0.52 mL, 2.88 mmol) was added at 0 °C to a stirred solution of **22** (768 mg, 2.40 mmol) in absolute methanol (4.8 mL), and the mixture was stirred at 0 °C for 2 h before quenching by the addition of ice. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel chromatography using 30% EtOAc/pentane to yield compound **23** (561 mg, 88%) as a liquid. $[\alpha]_D^{20} = +0.8$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.32 (m, 5H, Ph), 4.55 (d, $J = 11.5$ Hz, 1H, C-6-OCH_aPh), 4.44 (d, $J = 11.5$ Hz, 1H, C-6-OCH_bPh), 3.76 (s, 3H, OCH_3), 3.57–3.47 (m, 1H, 6-H_1), 2.0–1.89 (m, 1H, 4-H_a), 1.72–1.58 (m, 3H, 4-H_b, 5-H_2), 1.41 (s, 3H, 3-H_3), 1.18 ppm (d, $J = 6.1$ Hz, 3H, 7-H_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.59$, 138.83, 128.29, 127.58, 127.41, 74.63, 74.45, 70.26, 52.69, 35.90, 30.54, 26.19, 19.44 ppm; IR (KBr): $\tilde{\nu} =$ 1732, 1454, 1213, 1069 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 253.5 (2.380), 257.5 (2.435), 263.0 nm (2.384); HRMS (ESI): *m*/*z*: calcd for $C_{15}H_{22}O_4 + H^+$: 267.15909; found: 267.15918.

Compound 24: Methyl ester **23** (561 mg, 2.11 mmol) dissolved in THF (2 mL) was added to a solution of the NaH (50% in paraffin oil, 200 mg, 4.22 mmol) in THF (3 mL). The reaction mixture was stirred at 0 °C for 30 min. To the above solution was added benzyl bromide (0.37 mL, 3.16 mmol) followed by tetra-*n*-butylammonium iodide (30 mg, 0.20 mmol). The reaction mixture was stirred at 25 °C for 12 h and quenched with aq. saturated $NaHCO_3$. The layers were separated and the organic layer was washed successively with water, brine and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to afford the crude product which was purified by column chromatography on silica gel using 10% EtOAc/pentane to yield **24** (690 mg, 92%) as a liquid. $[\alpha]_D^{20} = +7.8$ ($c = 1.8$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.40–7.25 (m, 10H, 2×Ph), 4.55 (d, $J = 11.7$ Hz, 1H, C-6-OCH_aPh), 4.48–4.42 (m, 3H, C-6-OCH_bPh, C-2-OCH_2Ph), 3.75 (s, 3H, OCH_3), 3.57–3.46 (m, 1H, 6-H_1), 2.08–1.96 (m, 1H, 4-H_a), 1.87–1.76 (m, 1H, 4-H_b), 1.65–1.57 (m, 2H, 5-H_2), 1.50 (s, 3H, 3-H_3), 1.20 ppm (d, $J = 6.4$ Hz, 3H, 7-H_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.80$, 138.98, 128.27, 128.24, 127.54, 127.50, 127.37, 127.34, 80.31, 74.75, 70.26, 66.62, 51.94, 34.48, 30.25, 21.64, 19.58 ppm; IR (KBr): $\tilde{\nu} =$ 1739, 1453, 1092, 697 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 252.5 (2.588), 257.5 (2.661), 263.5 nm (2.588); HRMS (ESI): calcd for $C_{22}H_{28}O_4 + H^+$: 357.20604; found: 357.20604 $[M+H]^+$.

Compound 25: A solution of ester **24** (690 mg, 1.94 mmol) in THF (4 mL) was added at 0 °C to a stirred suspension of $LiAH_4$ (143 mg, 3.88 mmol) in THF (6 mL) and stirring was continued at the same temperature for 30 min. The reaction mixture was diluted with Et_2O and quenched by adding ice. The reaction mixture was passed through a small pad of Celite and the filtrate evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography using 25% EtOAc/pentane to yield alcohol **25** (610 mg, 96%) as viscous oil. $[\alpha]_D^{20} = +11.7$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$–7.25 (m, 10H, 2×Ph), 4.58 (d, $J = 11.4$ Hz, 1H, C-6-OCH_aPh), 4.46–4.42 (m, 3H, C-6-OCH_bPh, C-2-OCH_2Ph), 3.58–3.45 (m, 3H, 6-H_1, 1-H_2), 2.05–1.99 (m, 1H, 4-H_a), 1.83–1.72 (m, 1H, 4-H_b), 1.65–1.52 (m, 2H, 5-H_2), 1.24 (s, 3H, 3-H_3), 1.21 ppm (d, $J = 6.4$ Hz, 3H, 7-H_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 139.05$, 138.84, 128.39, 128.33, 127.64, 127.46, 127.41, 127.38, 77.58, 75.06, 70.37, 67.23, 63.59, 30.74, 30.48, 2026, 19.57 ppm; IR (KBr): $\tilde{\nu} =$ 2968, 1651, 1453, 1067 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 252.0 (2.463), 257.5 (2.563), 263.0 nm (2.476); HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{28}O_3 + H^+$: 329.21111; found: 329.21104.

Compound 26: A solution of **25** (610 mg, 1.86 mmol) in CH_2Cl_2 (6 mL) was added to a stirred solution of IBX (625 mg, 2.23 mmol) in DMSO (1.5 mL). The reaction mixture was stirred at 25 °C for 4 h and quenched by the addition of an aq. sat. $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the organic layer washed with aq. sat. $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel chromatography using 15% EtOAc/pentane to yield compound **26** (548 mg, 90%) as a liquid. $[\alpha]_D^{20} = +30.4$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.64$ (s, 1H, CHO), 7.35–7.23 (m, 10H, 2×Ph), 4.55 (d, $J = 11.6$ Hz, 1H, C-6-OCH_aPh), 4.44 (s, 2H, C-2-OCH_2Ph), 4.41 (d, $J = 11.6$ Hz, 1H, C-6-OCH_bPh), 3.56–3.44 (m, 1H, 6-H_1), 1.99–1.88 (m, 1H, 4-H_a), 1.73–1.52 (m, 3H, 4-H_b, 5-H_2), 1.57 (s, 3H, 3-H_3), 1.19 ppm (d, $J = 6.2$ Hz, 3H, 7-H_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 204.92$, 138.82, 138.22, 128.39, 128.30, 127.65, 127.54, 127.40, 82.45, 74.56, 70.27, 66.09, 30.54, 29.61, 19.43, 18.32 ppm; IR (KBr): $\tilde{\nu} = 1715$, 1453, 1065 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 247.5 (2.710), 251.5 (2.736), 257.0 nm (2.717); MS (EI, 70 eV): *m*/*z* (%): 326.3 (6) $[M]^+$, 164.1 (40), 107.1 (40), 91.1 (100), 43.1 (18); HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{26}O_3 + NH_4^+$: 344.22202; found: 344.22201.

Compound 27: Ph_3P (880 mg, 3.36 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C to a stirred mixture of CBr_4 (1.12 g, 3.36 mmol) and zinc (218 mg, 3.36 mmol) in CH_2Cl_2 (2 mL) and stirring was continued at 25 °C for 60 min. After cooling back to 0 °C a solution of the aldehyde **26** (548 mg, 1.68 mmol) in CH_2Cl_2 (4 mL) was added. The reaction mixture was stirred at 25 °C for 12 h and then diluted with pentane with vigorous stirring. A precipitate is formed which was removed by filtration through florisil. The filtrate was evaporated under reduced pressure to afford the crude product which was purified by chromatography using 10% EtOAc/pentane to yield compound **27** (700 mg, 86%) as a liquid. $[\alpha]_D^{20} = +4.0$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.25 (m, 10H, 2×Ph), 6.66 (s, 1H, 2-H_1), 4.57 (d, $J = 11.6$ Hz, 1H, C-3-OCH_aPh), 4.47–4.39 (m, 3H, C-3-OCH_bPh, C-7-OCH_2Ph), 3.58–3.46 (m, 1H, 7-H_1), 2.08–1.97 (m 1H, 5-H_a), 1.82–1.57 (m, 3H, 5-H_b, 6-H_2), 1.48 (s, 3H, 4-H_3), 1.21 ppm (d, $J = 6.3$ Hz, 3H, 8-H_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 142.47, 138.95, 138.81, 128.31, 128.29, 127.56, 127.46, 127.39, 127.31, 88.25, 79.38, 74.79, 70.28, 64.75, 34.73, 30.03, 23.19, 19.59 ppm; IR (KBr): $\tilde{\nu} =$ 1453, 1066, 734 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 247.5 (2.887), 251.5 (2.904), 257.0 nm (2.892); HRMS (ESI): *m*/*z*: calcd for $C_{22}H_{26}Br_2O_2 + NH_4^+$: 498.06378; found: 498.06388.

Compound 5: *n*BuLi (2.5 M in hexane, 1.20 mL, 3.02 mmol) was added at −78 °C to a stirred solution of compound **27** (700 mg, 1.44 mmol) in dry THF (5.5 mL). After being warmed to −20 °C over 2 h, the mixture was recooled to −78 °C and DMF (0.10 mL) was added. After being gradually warmed to 25 °C over 4 h, the mixture was quenched by the addition of aq. sat. NH_4Cl solution. The reaction mixture was diluted with diethyl ether and washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography. Elution with 15% EtOAc/pentane provided product **5** (410 mg, 82%) as a liquid.

$[\alpha]_D^{20} = +5.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.25$ (s, 1H, CHO), 7.36–7.26 (m, 10H, 2×Ph), 4.68–4.56 (m, 3H, C-8-OCH_aPh, C-4-OCH_2Ph), 4.44 (d, $J = 12.1$ Hz, 1H, C-8-OCH_bPh), 3.60–3.49 (m, 1H, 8-H$_1$), 2.08–1.95 (m 1H, 6-H$_a$), 1.91–1.66 (m, 3H, 6-H$_b$, 7-H$_2$), 1.58 ppm (s, 3H, 5-H$_3$), 1.22 (d, $J = 6.4$ Hz, 3H, 9-H$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.41$, 138.87, 138.27, 128.35, 128.31, 127.60, 127.57, 127.55, 127.43, 97.45, 84.95, 74.52, 73.59, 70.34, 66.77, 37.0, 31.05, 25.65, 19.63 ppm; IR (KBr): $\tilde{\nu} = 1669$, 1454, 1068, 697 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 257.0 nm (3.006); MS (EI) m/z (%): 351.4 (6) $[M]^+$, 270.2 (25), 179.2 (68), 99.1 (20), 91.1 (100); HRMS (ESI): m/z: calcd for $C_{23}H_{26}O_3 + H^+$: 351.19547; found: 351.19559.

Compound 28: To a stirred solution of compound **4** (247 mg, 0.50 mmol) in THF (3 mL) at −78 °C was added *n*BuLi (2.5 M in hexane, 0.24 mL, 0.60 mmol) followed by propargylic aldehyde **5** (230 mg, 0.60 mmol) dissolved in THF (1 mL). Stirring was continued at −78 °C for 10 min and the reaction was quenched by the addition of aq. sat. NH_4Cl solution. The reaction mixture was diluted with CH_2Cl_2 and washed with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography. Elution with 20% EtOAc/pentane provided product **28** (305 mg, 0.40 mmol, 80%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$–7.73 (m, 4H, 2×6′-H, 2×4′-H), 7.66 (d, $J = 7.4$ Hz, 2H, 2×5′-H), 7.45–7.14 (m, 30H, 6×Ph), 6.85 (d, $J = 7.4$ Hz, 2H, 2×7′-H), 6.59–6.18 (brs, 2H, 2×1-H), 5.30–5.19 (brs, 4H, 2×C-8′-OCH_2Ph), 4.66–4.34 (m, 10H, 2×OCH(CH$_3$)$_2$, 2×C-4-OCH_2Ph, 2×C-8-OCH_2Ph), 4.01 (s, 6H 2×OMe), 3.69 (s, 6H, 2×OMe), 3.55–3.43 (m, 2H, 2×8-H), 2.86–2.68 (brs, 6H, 2×Ar-CH$_3$), 1.96–1.65 (m, 8H, 2×6-H, 2×7-H), 1.59–1.12 ppm (m, 24H, 2×5-H$_3$, 2×9-H$_3$, 2×C-1′-OCH(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.33$, 150.57, 146.99, 139.12, 139.03, 139.0, 137.48, 128.37, 128.24, 128.22, 128.19, 127.86, 127.65, 127.53, 127.51, 127.31, 127.29, 127.23, 127.20, 125.74, 119.09, 119.02, 115.18, 106.38, 87.20, 77.20, 74.83, 73.77, 71.43, 70.19, 70.17, 66.31, 63.60, 62.62, 37.51, 31.16, 26.32, 26.29, 20.76, 19.69 ppm; IR (KBr): $\tilde{\nu} = 2930$, 1617, 1556, 1452, 1357 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 362.5 (3.731), 380.0 (3.995), 397.0 (3.897), 419.0 nm (3.738); HRMS (ESI): calcd for $C_{50}H_{54}O_7 + H^+$: 784.42078; found: 784.42045.

Compound 29: To a stirred solution of compound **28** (305 mg, 0.40 mmol) in dioxane (8 mL) was added AgO (247 mg, 2.0 mmol) followed by 4 N HNO_3 until the silver oxide has completely dissolved. The resulting solution was stirred for 30 min and then diluted with CH_2Cl_2. The organic layer was washed with water, brine, dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude product which was purified by silica gel chromatography using 35% EtOAc/pentane to yield compound **29** (265 mg, 90%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.85$–7.76 (m, 4H, 2×5′-H, 2×4′-H), 7.65–7.58 (m, 4H, 2×7′-H, 2×6′-H), 7.44–7.17 (m, 30H, 6×Ph), 6.28 (s, 2H, 2×1-H), 5.27 (s, 4H, 2×C-8′-OCH_2Ph), 4.61–4.29 (m, 10H, 2×OCH(CH$_3$)$_2$, 2×C-4-OCH_2Ph, 2×C-8-OCH_2Ph), 3.56–3.45 (m, 2H, 2×8-H), 3.16–3.04 (brs, 2H, 2×OH), 2.68 (s, 6H, 2×Ar-CH$_3$), 1.95–1.63 (m, 8H, 2×6-H, 2×7-H), 1.49–1.10 ppm (m, 24H, 2×5-H$_3$, 2×9-H$_3$, 2×C-1′-OCH(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 183.26$, 183.23, 157.91, 154.60, 144.27, 139.77, 139.74, 138.92, 138.91, 138.90, 138.87, 136.32, 134.91, 133.96, 133.50, 128.47, 128.24, 128.23, 128.20, 127.83, 127.53, 127.39, 127.37, 127.34, 127.33, 127.26, 126.74, 126.50, 124.88, 119.61, 119.39, 87.56, 87.54, 84.54, 84.46, 79.23, 74.73, 74.71, 73.63, 70.90, 70.18, 66.24, 66.22, 58.13, 37.43, 37.39, 31.13, 31.10, 26.23, 26.20, 22.42, 22.28, 20.52, 20.50, 19.66 ppm; IR (KBr): $\tilde{\nu} = 2928$, 1672, 1585, 1453, 1277 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 260.5 (4.446), 375.5 nm (3.783); HRMS (ESI): calcd for $C_{48}H_{48}O_7 + H^+$: 737.34728; found: 737.34718.

Compound 30: Compound **29** (265 mg, 0.36 mmol) in CH_2Cl_2 (2.5 mL) was added to a stirred solution of IBX (120 mg, 0.43 mmol) in DMSO (0.5 mL). The mixture was stirred at 20 °C for 4 h and quenched by addition of an aq. saturated $Na_2S_2O_3$ solution. The aq. layer was extracted with CH_2Cl_2 and the organic layer washed with aq. saturated $NaHCO_3$ solution, water, brine, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained crude product was purified by silica gel chromatography using 25% EtOAc/pentane to yield compound **30** (250 mg, 95%) yield as a viscous oil. $[\alpha]_D^{20} = -13.8$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.83$ (dd, $J = 7.6$, 1.2 Hz, 1H, 5′-H), 7.79 (s, 1H, 4′-H), 7.65–7.59 (m, 2H, 7′-H, 6′-H), 7.41–7.15 (m, 15H, 3×Ph), 5.27 (s, 2H, C-8′-OCH_2Ph), 4.60–4.37 (m, 5H, OCH(CH$_3$)$_2$, C-4-OCH_2Ph, C-8-OCH_2Ph), 3.56–3.49 (m, 1H, 8-H), 2.38 (s, 3H, Ar-CH$_3$), 1.05–2.93 (m, 1H, 6-H$_a$), 1.89–1.62 (m, 3H, 6-H$_b$, 7-H$_2$), 1.56 (s, 3H. 5-H$_3$), 1.30–1.24 (m, 6H, C-1′-OCH(CH_3)$_2$), 1.18 ppm (d, $J = 6.3$ Hz, 3H, 9-H$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 183.22$, 182.07, 180.76, 158.15, 155.68, 141.69, 141.49, 138.92, 138.43, 136.35, 134.87, 134.03, 128.50, 128.25, 127.85, 127.66, 127.57, 127.39, 127.34, 126.71, 126.56, 124.02, 119.94, 119.52, 96.82, 85.76, 79.20, 77.20, 74.55, 73.83, 71.00, 70.21, 66.88, 36.86, 30.92, 25.57, 22.26, 19.64 ppm; IR (KBr): $\tilde{\nu} = 2929$, 1673, 1585, 1453, 1280, 1063 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 258.5 (4.399), 379.0 nm (3.773); HRMS (ESI): m/z: calcd for $C_{48}H_{46}O_7 + H^+$: 735.33163; found: 735.33168.

Compound 3: H_2SO_4 (0.01 mL) was added at 25 °C to a stirred solution of compound **30** (250 mg, 0.34 mmol) in AcOH (2 mL) and stirring was continued at 55 °C for 30 min. The mixture was diluted with CH_2Cl_2 and the organic layer washed with water and brine. Drying over Na_2SO_4 and evaporation of the solvent under reduced pressure afforded the crude product which was purified by silica gel chromatography using 15% EtOAc/pentane to yield compound **3** (174 mg, 86%) as a viscous oil. $[\alpha]_D^{20} = -13.8$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (dd, $J = 7.6$, 1.2 Hz, 1H, 5′-H), 7.71–7.60 (m, 2H, 6′-H, 4′-H), 7.37–7.13 (m, 11H, 7′-H, 2×Ph), 4.66 (d, $J = 11.0$ Hz, 1H, C-4-OCH_aPh), 4.60 (d, $J = 11.0$ Hz, 1H, C-4-OCH_bPh), 4.51 (d, $J = 11.7$ Hz, 1H, C-8-OCH_aPh), 4.40 (d, $J = 11.7$ Hz, 1H, C-8-OCH_bPh), 3.59–3.48 (m, 1H, 8-H), 2.44 (s, 3H, Ar-CH$_3$), 1.06–2.48 (m, 7H, 6-H$_2$ 7-H$_2$, 5-H$_3$), 1.19 ppm (d, $J = 6.1$ Hz, 3H, 9-H$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 192.28$, 181.22, 178.35, 162.51, 160.41, 146.71, 138.81, 138.41, 137.38, 133.93, 133.62, 133.25, 128.26, 128.23, 127.53, 127.43, 127.39, 127.37, 127.25, 124.91, 121.97, 120.21, 115.64, 114.22, 96.87, 85.49, 85.49, 74.46, 73.96, 70.19, 66.84, 36.91, 30.93, 25.58, 20.45, 19.65 ppm; IR (KBr): $\tilde{\nu} = 1734$, 1455, 1384, 1160, 1067 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 257.5 (4.385), 320.0 (3.922), 425.5 nm (3.867); HRMS (ESI): m/z: calcd for $C_{38}H_{34}O_7 + H^+$: 603.23742; found: 603.23748.

Compound 31: Cs_2CO_3 (78 mg, 0.24 mmol) was added at 0 °C To a stirred solution of compound **3** (120 mg, 0.20 mmol) in acetone (1.5 mL). The reaction mixture was brought to 15 °C over 30 min, then diluted with diethyl ether and filtered through a small pad of Celite. The filtrate was evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography using 20% EtOAc/pentane to provide compound **31** (48 mg, 42%) as a viscous oil. $[\alpha]_D^{20} = +29.7$ ($c = 0.32$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 12.93$–12.84 (brs, 1H, C-11-OH), 8.03 (s, 1H, 6′-H), 7.80 (dd, $J = 7.6$, 1.2 Hz, 1H, 8′-H), 7.66 (t, $J = 7.6$ Hz, 1H, 9′-H), 7.39–7.09 (m, 11H, 10′-H, 2×Ph), 6.64 (s, 1H, 3-H), 4.58 (d, $J = 11.7$ Hz, 1H, C-14-OCH_aPh), 4.55 (d, $J = 11.7$ Hz, 1H, C-14-OCH_bPh), 4.47 (d, $J = 12.1$ Hz, 1H, C-18-OCH_aPh), 4.36 (d, $J = 12.1$ Hz, 1H, C-18-OCH_bPh), 3.54–3.47 (m, 1H, 18-H), 3.0 (s, 3H, Ar-CH$_3$), 2.38–2.32 (m, 1H, 16-H_a), 2.16–2.08 (m, 1H, 16-H_b), 1.80 (s, 3H, 15-H$_3$), 1.67–1.46 (m, 2H, 17-H$_2$), 1.16 ppm (d, $J = 6.1$ Hz, 3H, 19-H$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 187.07$, 181.88, 179.22, 170.48, 162.56, 156.28, 149.76, 138.79, 138.21, 136.31, 135.95, 132.22, 128.14, 127.48, 127.28, 127.25, 127.06, 126.43, 125.62, 125.27, 119.79, 119.29, 116.76, 111.13, 78.67, 74.52, 70.18, 64.73, 33.91, 30.36, 24.23, 22.52, 19.50 ppm; IR (KBr): $\tilde{\nu} = 2927$, 1673, 1454, 1269 cm^{-1}; UV (CH_3CN): λ_{max} (lg ε) = 257.5 (4.271), 419.0 nm (3.763); MS (ESI): m/z: 625.2 $[M+Na]^+$, 601.3 $[M+H]^+$; HRMS (ESI): m/z: calcd for $C_{38}H_{34}O_7 + H^+$: 603.23773; found: 603.2380.

Compound 2: $TiCl_4$ (1 M in CH_2Cl_2, 0.30 mL, 0.30 mmol) was added at −78 °C to a stirred solution of compound **31** (36 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) and the mixture was allowed to warm to −20 °C over 2 h. Then, the mixture was diluted with CH_2Cl_2, washed successively with 1 M HCl, water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography on silica gel using 5% MeOH/CH_2Cl_2 to yield compound **2** (20 mg, 80%) as yellow solid. $[\alpha]_D^{20} = +18.6$ ($c = 0.22$ in DMSO); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 12.84$ (s, 1H, C-11-OH), 8.08 (s, 1H, 6-H), 7.83 (dd, $J = 7.8$, 1.2 Hz, 1H, 8-H), 7.69 (t, $J = 7.8$ Hz, 1H, 9-

H), 7.36 (dd, $J=7.8$, 1.2 Hz, 1H, 10-H), 6.62 (s, 1H, 3-H), 3.96–3.88 (m, 1H, 18-H), 3.03 (s, 3H, Ar-CH_3), 2.34–2.25 (m, 1H, 16-H_a), 1.14–2.65 (m, 3H, 16-H_b, 17-H_2), 1.70 (s, 3H, 15-H_3), 1.23 ppm (d, $J=6.6$ Hz, 3H, 19-H_3); ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta=12.71$ (s, 1H, C-11-OH), 7.95 (s, 1H, 6-H), 7.79 (t, $J=7.8$ Hz, 1H, 9-H), 7.70 (dd, $J=7.8$, 1.2 Hz, 1H, 8-H), 7.41 (dd, $J=8.2$, 1.2 Hz, 1H, 10-H), 6.48 (s, 1H, 3-H), 5.56 (s, 1H, C-14-OH), 4.27 (d, $J=4.8$ Hz, 1H, C-18-OH), 3.57–3.50 (m, 1H, 18-H), 2.91 (s, 3H, Ar-CH_3), 2.20–2.12 (m, 1H, 16-H_a), 1.83–1.75 (m, 1H, 16-H_b), 1.62 (s, 3H, 15-H_3), 1.56–1.42 (m, 2H, 17-H_2), 1.01 ppm (d, $J=6.1$ Hz, 3H, 19-H_3); ^{13}C NMR (150 MHz, [D$_6$]DMSO): $\delta=186.89$, 181.32, 178.30, 173.98, 161.33, 155.53, 148.26, 136.60, 135.75, 132.09, 125.49, 124.65, 124.62, 119.72, 118.65, 116.69, 108.83, 72.35, 65.97, 36.57, 32.91, 27.11, 23.34, 23.31 ppm; IR (KBr): $\tilde{\nu}=1734$, 1455, 1384, 1160, 1067 cm^{-1}, UV (CH_3CN): λ_{max} (lg ε) = 238.5 (4.041), 266.0 (3.780), 415.5 nm (3.253); MS (EI, 70 eV): m/z (%): 422.2 (20) $[M]^+$, 349.2 (60), 324.2 (28), 281.1 (100), 99.1 (45), 43.1 (22); HRMS (ESI): m/z: calcd for $C_{24}H_{22}O_7 + H^+$: 423.14383; found: 423.14398.

Compounds 2 and 36: A mixture of compound **2** and **36** was prepared from the compounds **35** and **4** following the procedure described for the synthesis of the compound **2**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=12.87$ (s, 1H, C-11-OH), 12.84 (s, 1H, C-11-OH), 8.08 (s, 2H, 2×6-H), 7.85–7.81 (m, 2H, 2×8-H), 7.73–7.63 (m, 2H, 2×9-H), 7.38–7.33 (m, 2H, 2×10-H), 6.67 (s, 1H, 3-H), 6.62 (s, 1H, 3-H), 4.14–4.03 (m, 1H, 18-H), 3.88–3.96 (m, 1H, 18-H), 3.03 (s, 6H, 2×Ar-CH_3), 2.36–2.23 (m, 2H, 2×16-H_a), 2.15–1.92 (m, 6H, 2×16-H_b, 2×17-H_2), 1.70 (s, 3H, 15-H_3), 1.68 (s, 3H, 15-H_3), 1.23 (d, $J=6.6$ Hz, 3H, 19-H_3), 1.19 ppm (d, $J=6.6$ Hz, 3H, 19-H_3); ^{1}H NMR (600 MHz, [D$_6$]DMSO): $\delta=12.72$–12.68 (br s, 2H, 2×C-11-OH), 7.95 (s, 2H, 6-H), 7.79 (t, $J=8.2$ Hz, 2H, 2×9-H), 7.70 (d, $J=8.2$ Hz, 2H, 2×8-H), 7.41 (d, $J=8.2$, 2H, 2×10-H), 6.48 (s, 2H, 2×3-H), 5.60 (s, 1H, C-14-OH), 5.56 (s, 1H, C-14-OH), 4.36 (d, $J=4.8$ Hz, 1H, C-18-OH), 4.27 (d, $J=4.8$ Hz, 1H, C-18-OH), 3.61–3.50 (m, 2H, 2×18-H), 2.91 (s, 6H, 2×Ar-CH_3), 2.21–2.10 (m, 2H, 2×16-H_a), 1.84–1.72 (m, 2H, 2×16-H_b), 1.62 (s, 3H, 15-H_3), 1.60 (s, 3H, 15-H_3), 1.58–1.42 (m, 4H, 2×17-H_2), 1.01 (d, $J=6.1$ Hz, 3H, 19-H_3), 0.99 ppm (d, $J=6.1$ Hz, 3H, 19-H_3).

Acknowledgements

The authors are grateful to the Fonds der Chemischen Industrie for supporting this work and R.R.S. thanks the Alexander von Humboldt Foundation for a post-doctoral grant.

[1] a) K. Eckardt in *Quinones and Other Carbocyclic Antitumor Antibiotics in Antitumor Compounds of Natural Origin: Chemistry and Biology, Vol. II* (Ed.: A. Aszalos), CRC Press, Boca Raoton, **1981**; b) U. Séquin, "The Antibiotics of the Pluramycin Group (4*H*-Anthra[1,2-*b*]pyran Antibiotics)" *in Prog. Chem. Org. Nat. Prod.*, *Vol. 50* (Ed.: L. Zechmeister), Springer, Wien, **1986**, pp. 58–122.

[2] T. Maeda, T. Takeuchi, K. Nitta, K. Yagishita, R. Utahara, T. Osato, M. Ueda, S. Kondo, Y. Okami, H. Umezawa, *J. Antibiot. Ser. A* **1956**, *9*, 75–81.

[3] M. A. Farooq Biabani, H. Laatsch, E. Helmke, H. Weyland, *J. Antibiot.* **1997**, *50*, 874–877.

[4] H. Brockmann, *Angew. Chem.* **1968**, *80*, 493; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 481.

[5] T. Takao, F. Kitatani, N. Watanabe, A. Yagi, K. Sakata, *Biosci. Biotechnol. Biochem.* **1994**, *58*, 1780–1783.

[6] a) F. M. Hauser, R. P. Rhee, *J. Am. Chem. Soc.* **1979**, *101*, 1628–1629; b) F. M. Hauser, R. P. Rhee, *J. Org. Chem.* **1980**, *45*, 3061–3068; c) H. Uno, K. Sakamoto, E. Honda, N. Ono, *Chem. Commun*, **1999**, 1005–1006; d) H. Uno, K. Sakamoto, E. Honda, K. Fukuhara, N. Ono, J. Tanaka, M. Sakanaka, *J. Chem. Soc. Perkin Trans. 1* **2001**, 229–238; e) K. Krohn, J. Vitz, *Eur. J. Org. Chem.* **2004**, 209–219; f) K. Krohn, A. Vidal, J. Vitz, B. Westermann, M. Abbas, I. Green, *Tetrahedron: Asymmetry* **2006**, *17*, 3051–3057; g) Z. Fei, F. E. McDonald, *Org. Lett.* **2005**, *7*, 3617–3620; h) D.-S. Hsu, T. Matsumoto, K. Suzuki, *Chem. Lett.* **2006**, *35*, 1016–1017.

[7] L. F. Tietze, K. M. Gericke, R. R. Singidi, *Angew. Chem.* **2006**, *118*, 7146–7150; *Angew. Chem. Int. Ed.* **2006**, *45*, 6990–6993.

[8] a) L. F. Tietze, R. R. Singidi, K. M. Gericke, *Org. Lett.* **2006**, *8*, 5873–5876; b) K. Krohn, H. T. Tran-Thien, J. Vitz, A. Vidal, *Eur. J. Org. Chem.* **2007**, 1905–1911; c) D. S. Hsu, T. Matsumoto, K. Suzuki, *Chem. Lett.* **2006**, *9*, 1016–1017; d) L. F. Tietze, K. M. Gericke, R. R. Singidi, I. Schuberth, *Org. Biomol. Chem.* **2007**, *5*, 1191–1200.

[9] a) G. Wurm, B. Goessler, *Arch. Pharm.* (Weinheim Ger.), **1987**, *320*, 564–566; b) L. F. Tietze, C. Güntner, K. M. Gericke, I. Schuberth, G. Bunkoczi, *Eur. J. Org. Chem.* **2005**, 2459–2467.

[10] The yield of this oxidizing step strongly depends on the quality of the 1,5-dihydroxynaphthaline (**10**) as well as on the purity of the copper(I) chloride. The 1,5-dihydroxynaphthaline (**10**) should be light-brown coloured (not black) whereas it is recommended to use freshly recrystallized copper(I) chloride having a pure white colour.

[11] a) T. Takeya, M. Kajiyama, C. Nakumara, S. Tobinaga, *Chem. Pharm. Bull.* **1999**, *47*, 209–219; b) A. S. Wheeler, B. Naiman, *J. Am. Chem. Soc.* **1922**, *44*, 2331–2334; c) R. H. Thomson, *J. Org. Chem.* **1948**, *13*, 377–383; d) R. L. Hannan, R. B. Barber, H. Rapoport, *J. Org. Chem.* **1979**, *44*, 2153–2158.

[12] a) H. Laatsch, *Liebigs Ann. Chem.* **1980**, *8*, 1321–1347; b) T. Takeya, M. Kajiyama, C. Nakumara, S. Tobinaga, *Chem. Pharm. Bull.* **1998**, *46*, 1660–1662.

[13] J. Savard, P. Brassard, *Tetrahedron* **1984**, *40*, 3455–3464.

[14] J. R. Grunwell, A. Karipides, C. T. Wigal, S. W. Heinzman, J. Parlow, J. A. Surso, L. Clayton, F. J. Fleitz, M. Daffner, J. E. Stevens, *J. Org. Chem.* **1991**, *56*, 91–95.

[15] a) S. Fujisaki, H. Eguchi, A. Omura, A. Okamoto, A. Nishida, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576–1579; b) K. Krohn, S. Bernhard, U. Floerke, N. Hayat, *J. Org. Chem.* **2000**, *65*, 3218–3222; c) K. C. Nicolaou, D. Gray, J. Tae, *Angew. Chem.* **2001**, *113*, 3791–3795; *Angew. Chem. Int. Ed.* **2001**, *40*, 3679–3683; d) G. Bringmann, D. Menche, J. Kraus, J. Mühlbacher, K. Peters, E.-M. Peters, R. Brun, M. Bezabih, B. M. Abegaz, *J. Org. Chem.* **2002**, *67*, 5595–5610.

[16] R. T. Winters, A. D. Sercel, H. D. Showalter, *Synthesis* **1988**, 712–714.

[17] P. Allevi, M. Anastasia, S. Bingham, P. Ciuffreda, A. Pierangela, *J. Chem. Soc. Perkin Trans. 1* **1998**, *3*, 575–582.

[18] G. E. Keck, J. A. Murry, *J. Org. Chem.* **1991**, *56*, 6606–6611.

[19] K. Mori, H. Watanabe, *Tetrahedron* **1984**, *40*, 229–303.

[20] D. Seebach, R. Naff, G. Calderari, *Tetrahedron* **1984**, *40*, 1313–1324.

[21] Diastereosectivity of the reaction is determined based on comparison of ^{1}H NMR and ^{13}C NMR spectra of compound **22** and **34**.

[22] G. C. Caldwell, M. K. Rupprecht, S. S. Bondy, A. A. Davis, *J. Org. Chem.* **1990**, *55*, 2355–2361.

[23] M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537–4538.

[24] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

[25] H. Ohno, M. Anzai, A. Toda, S. Ohishi, N. Fujii, T. Tetsuaki, Y. Takemoto, T. Ibuka, *J. Org. Chem.* **2001**, *66*, 4904–4914.

[26] a) C. D. Snyder, H. Rapoport, *J. Am. Chem. Soc.* **1972**, *94*, 227–231; b) F. M. Hauser, R. P. Rhee, *J. Org. Chem.* **1980**, *45*, 3061–3068.

[27] a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed.* **1993**, *32*, 131–163; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) L. F. Tietze, G. Brasche, K. M. Gericke, Domino Reactions in Organic Synthesis, Wiley-VCH, Weinheim, **2006**.

[28] M. A. Mzhel'skaya, A. A. Moroz, M. S. Shvartsberg, *Seriya Khimicheskaya* **1991**, *7*, 1469–1472.

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

Received: June 30, 2007
Published online: September 21, 2007

