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

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Two high-yielding strategies for the synthesis of 4*H*-anthra[1,2-*b*]pyran antibiotics have been developed giving access to novel antitumor agent **24** (ED_{50} 1.5 μM) and to (*S*)-espicufolin (**3**). A key step for the assembly of the tetracyclic 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione skeleton is the nucleophilic addition of an aryl lithium species onto an aldehyde which allows the introduction of either an ynone or 1,3-diketo side chain, serving as precursors for an acid-catalysed cyclisation.

Introduction

Anthrapyran antibiotics represent a broad class of natural products which can be isolated from various terrestrial and marine *Streptomyces* sp. strains as secondary metabolites. These compounds comprise a characteristic 4*H*-anthra[1,2-*b*]-pyran-4,7,12-trione nucleus **1** (Fig. 1). Furthermore, they show versatile and potent biological activities making them an attractive synthetic target. For example, the pluramycin antibiotics,[1,2] first described in 1956 by Umezawa *et al.*,[3] are known for their strong anticancer activities, due to a specific alkylation at *N*-7 of the guanine base in DNA. Pluramycin antibiotics have amino sugars typically attached at C-8 and C-10 positions, which play a major role in sequence recognition during intercalation of the planar tetracyclic chromophore into DNA.[4] There are also many anthrapyrans known lacking the amino sugars but nonetheless exhibiting interesting biological activites. Rohr and Salas *et al.*[5] have shown significant antitumor activity (*e.g.* IC_{50} 12.9 μg mL^{-1}, lung carcinoma cells A549) of premithramycinone H (**2**, Fig. 1), a hybrid natural product[6] which was discovered during biosynthetic investigations of the aureolic acid antibiotic mithramycin and that has recently been synthesised by Krohn and Vitz.[7] In contrast, espicufolin (**3**), which has been isolated from a *Streptomyces* sp. cu39 strain by Seto *et al.*,[8] possesses remarkable neuronal cell protecting properties, displaying an inhibitory activity against glutamic acid toxicity.[9]

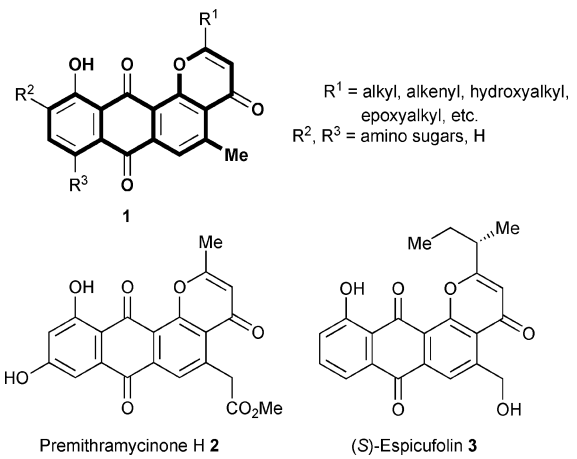

Fig. 1 Common structural core **1** of 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione natural products, premithramycinone H (**2**) and (*S*)-espicufolin (**3**).

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† Electronic supplementary information (ESI) available: performance and conditions of the HTCFA (cytotoxicity) test, general and full experimental procedures and analytical data for compounds **5–7**, **9–10**, **16–20**, **31–34** and **36–41**. See DOI: 10.1039/b700838d

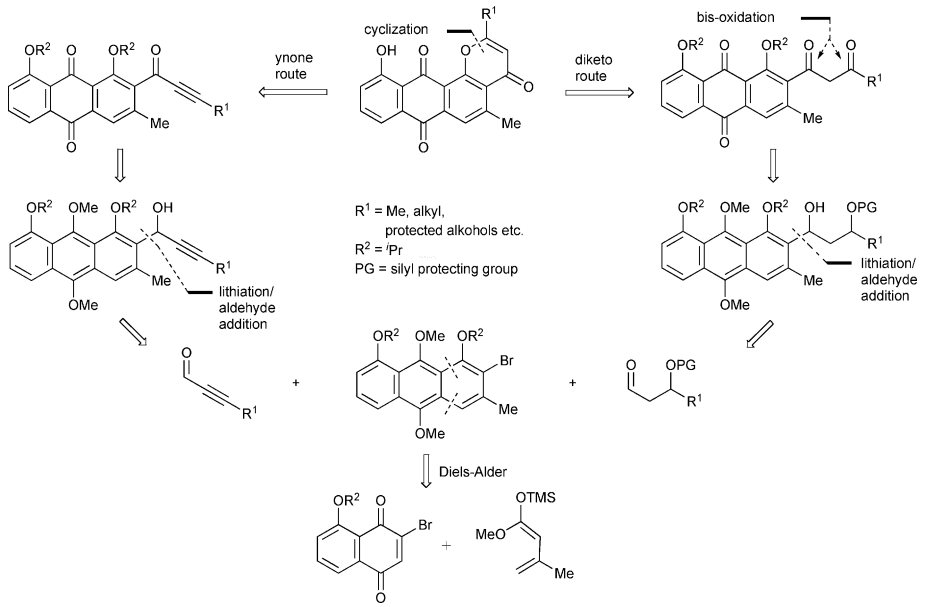
Despite the multitude of isolated compounds from the anthrapyran class, few procedures for their synthesis have so far been reported. In 1979, Hauser and Rhee[10,11] were successful in synthesising the kidamycinone methyl ether, whereas 20 years later Uno and coworkers accomplished the total synthesis of (*S*)-espicufolin (**3**).[12,13] In addition, an elegant access to the aglycons of altromycins and kidamycin has been reported by McDonald and Fei.[14] Recently, we described the first enantioselective total synthesis of the antiherpetic anthrapyran AH-1763 IIa[15] and of the antibiotic γ-indomycinone.[16]

Herein we report in full our novel strategies for the assembly of anthrapyrans and their application in the course of the total synthesis of (*S*)-espicufolin (**3**). The retrosynthetic analysis (Scheme 1) envisions as the first disconnection the cleavage of the pyrone ring moiety leading to either an anthraquinone with a 1,3-diketo[7] or ynone side chain which are both suitable for a final ring closure.[12,13,17] The introduction of the side chains was planned to be realised by a nucleophilic attack of an aryl lithium species derived from a bromodimethoxyanthracene onto the appropriate aldehyde. In turn, the anthracene derivative should be accessible by a Diels–Alder reaction of a juglone derivative and a silylketene acetal, followed by bromination of the resulting anthraquinone and final reductive methylation.

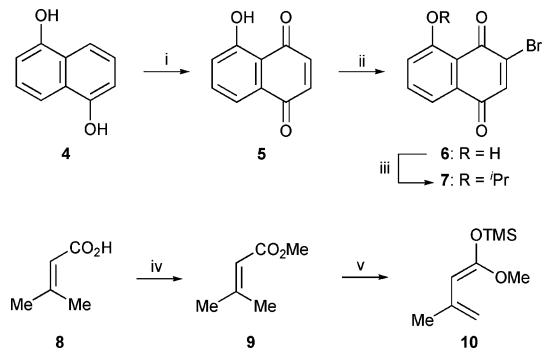
Results and discussion

Synthesis of anthrapyran 24

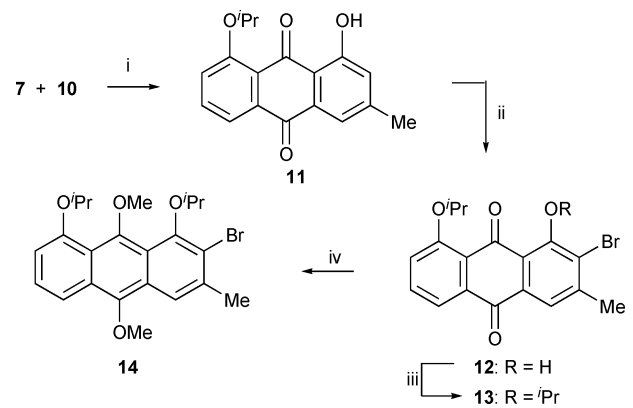
The synthesis commences from commercially available 1,5-dihydroxynaphthalene (**4**) which was oxidised with air in the presence of $Cu^{I}Cl$ to yield juglone (**5**) in 55% yield (Scheme 2).[18,19] Regioselective bromination of **5** was accomplished using a known



Scheme 1 Key stages in the retrosynthetic analysis of the anthrapyran core structure.



Scheme 2 *Reagents and conditions*: (i) CuCl, air, CH_3CN, 20 °C (55%); (ii) (a) Br_2, HOAc, 20 °C, 15 min, (b) EtOH, reflux, 10 min (80%); (iii) *i*PrI, Ag_2O, $CHCl_3$, 20 °C, 36 h, (iv) MeOH, cat. H_2SO_4, reflux, 16 h (92%); (v) LDA, THF, −78 °C, 2 h then TMSCl, −78 °C, 1.5 h, −78 °C → 20 °C, 1.5 h (94%).



Scheme 3 *Reagents and conditions*: (i) (a) benzene, 20 °C, 8 h, (b) SiO_2, CH_2Cl_2, 20 °C, 24 h then removal of solvent (94%); (ii) NBS, cat. iPr_2NH, CH_2Cl_2, 20 °C, 9 h (97%); (iii) *i*PrI, Cs_2CO_3, acetone–DMF (3 : 1), reflux, 16 h (94%); (iv) (a) $Na_2S_2O_4$, cat. TBABr, THF–H_2O, 20 °C, 25 min, (b) KOH, H_2O, 20 °C, 15 min, (c) Me_2SO_4, 20 °C, 12 h (98%).

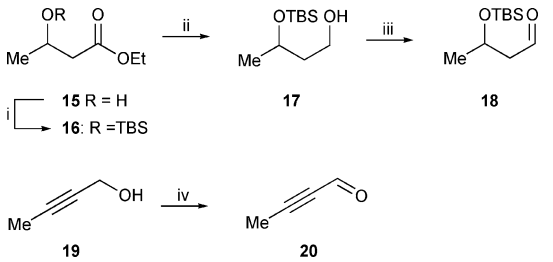
procedure furnishing isomeric pure 3-bromojuglone (**6**) in 80% yield.[20] The OH group was protected utilizing Ag^{I}_2O and *i*PrI to deliver isopropyl ether **7** in nearly quantitative yield.[21] Starting from 3,3-dimethylacrylic acid (**8**) a classical acid-catalysed conversion into the corresponding methyl ester followed by treatment with LDA and TMSCl gave the desired 1-methoxy-3-methyl-1-trimethylsiloxy-1,3-butadiene (**10**)[22] in very high yield.

With **7** and **10** in hand, we next turned our focus to the subsequent Diels–Alder reaction applying the strategy of Brassard and Savard.[22] To our delight, the addition of diene **10** to the 3-bromojuglone derivative **7** in benzene provided the cycloaddition product, which was converted in 94% yield into the thermodynamically more stable chrysophanol-8-isopropyl ether **11** using silica gel as a mild source of acid (Scheme 3).‡ As a special feature, this reaction proceeds with excellent regioselectivity and without the unwanted formation of the 1-methyl ether derivative, a major side-product in Brassard's synthesis. The use of NBS in dichloromethane in the presence of catalytic amounts of a secondary amine allowed, due to the strong *ortho*-directing effect of the hydroxyl group, the regioselective bromination of anthraquinone **11**.[23] Thus, **12**, whose structure was unambiguously deduced from HMBC-^{1}H-NMR experiments, could be isolated in 97% yield. To complete the synthesis of the building block **14**, we protected the remaining phenolic hydroxyl group as its isopropyl ether **13** in 94% yield by treatment with *i*PrI and Cs_2CO_3 in a mixture of acetone and DMF.[24] Finally, protection of the quinone moiety was accomplished by reductive methylation using aq. sodium dithionite to furnish the air-sensitive hydroquinone, which underwent methylation upon treatment with KOH and dimethylsulfate to obtain the dimethoxyanthracene **14** in an excellent overall yield.

The synthesis of aldehyde **18** was achieved from commercially available β-hydroxy ester **15** which was first protected as TBS ether

‡ The use of toluene instead of benzene in the Diels–Alder reaction led to the desired product in slightly lower yields.

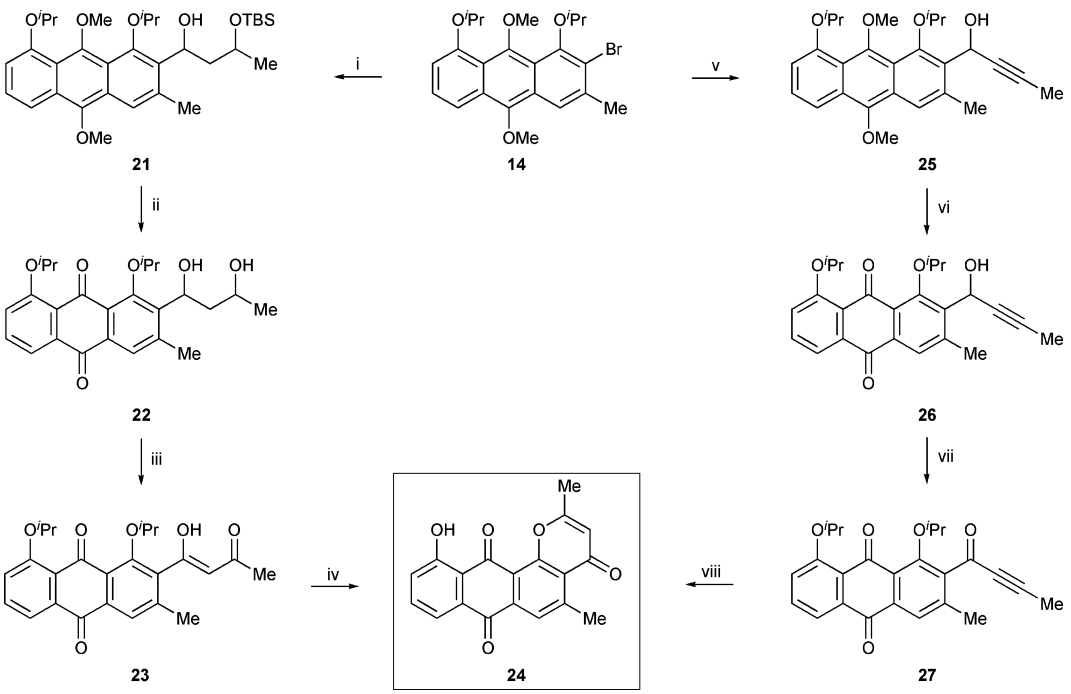
16 applying standard conditions (Scheme 4).[25] The reduction of the ester moiety using lithium borohydride in THF afforded the corresponding primary alcohol **17** in good yield.[26] Oxidation was carried out under Parikh–Doering conditions which led to the formation of required aldehyde **18** in 86% yield.[27] Manganese dioxide was the appropriate agent for the oxidation of propargylic alcohol **19** providing the aldehyde **20** which serves as an alternative unit for the implementation of the side chain.



Scheme 4 *Reagents and conditions*: (i) TBSCl, imidazole, cat. DMAP, DMF, 20 °C, 18 h, (100%); (ii) $LiBH_4$, THF, reflux, 3 h (80%); (iii) SO_3·py, Hünig-base, DMSO, 0 °C, 1 h (86%); (iv) MnO_2, CH_2Cl_2, 20 °C, 18 h (67%).

Having effectively synthesised building blocks **14**, **18** and **20**, we next considered the coupling of these intermediates. The conversion of **14** to the corresponding lithium derivative could be carried out *via* bromine lithium exchange using *n*BuLi at low temperature. This reaction was observed to proceed very fast (0.5–1 min), so it was important to add the aldehyde **18** immediately after generation of the organolithium compound to avoid the formation of the corresponding debrominated compound as side product (Scheme 5). Following this strategy, the alcohol **21** could be afforded in 89% yield as a nearly 1 : 1-mixture of the two possible diastereomers. Oxidative demethylation of the anthracene derivative **21** using $Ag^{II}O$–HNO_3[28] and subsequent TBS-deprotection with TBAF after a short work-up procedure furnished the anthraquinone **22** in an excellent yield over two steps. The bis-oxidation of the 1,3-diol unit was accomplished in a single step using Dess–Martin periodinane.[29] Thus, the desired 1,3-diketo compound **23** could be obtained in remarkable 80% yield. It is of great importance to mention that only old batches of Dess–Martin reagent led to a satisfying conversion, a phenomenon which has been already described by Schreiber and Meyer.[30] However, when freshly prepared Dess–Martin reagent was used, the reaction could efficiently be accelerated by adding catalytic amounts of water. For the final conversion of the 1,3-diketone into the pyranone moiety we assumed that deprotection of the isopropyl ethers and the following cyclisation–condensation reaction could be achieved in a domino-like procedure[31] under acidic conditions. Hence, simply heating of **23** in the presence of catalytic amounts of sulfuric acid in conc. acetic acid gave after only 5 min reaction time the desired cyclised product **24** in excellent yield.

Encouraged by these results, we next investigated the alternative route to **24** *via* introduction of the ynone side chain (Scheme 5). Using the same conditions as for the synthesis of **21** but replacing aldehyde **18** by compound **20**, we could isolate the desired coupling product **25** in 73% yield. Reoxidation of the latter into anthraquinone **26** was again realised by utilising $Ag^{II}O$–HNO_3 in high yield. Dess–Martin reagent was again found to be appropriate for the oxidation of the benzylic alcohol moiety



Scheme 5 *Reagents and conditions*: (i) *n*BuLi, **17**, THF, −78 °C → 20 °C, 1 h (89%); (ii) (a) AgO, 4N HNO_3, dioxane, 20 °C, 10 min, (b) TBAF·3H_2O, THF, 0 °C → 20 °C, 30 min (97%); (iii) DMP, CH_2Cl_2, 0 °C → 20 °C, 3 h (80%); (iv) HOAc, cat. H_2SO_4, reflux, 5 min (97%); (v) *n*BuLi, **19**, THF, −78 °C → 20 °C, 1 h (73%); (vi) AgO, 4N HNO_3, dioxane, 20 °C, 10 min (88%); (vii) DMP, CH_2Cl_2, 0 °C → 20 °C, 4.5 h (98%); (viii) HOAc, cat. H_2SO_4, reflux, 40 min (95%).

into the ynone side chain affording compound **27** in 98% yield. For the final deprotection–6-*endo-dig* cyclisation we first tested the previously established HOAc–cat.H_2SO_4 conditions. Although the conversion was in comparison to the 1,3-diketo system significantly slower (40 min), the yield of the anthrapyran **24** was again nearly quantitative.

Antitumor activity

Due to the significant antitumor activity of both premithramycinone H (**2**) and compound **28** synthesised by Krohn (IC_{50} 8.8 μM, cell line A-431, P-glycoprotein, 3 days exposition) (Fig. 2),[7] we were highly interested in the biological properties of anthrapyran **24**. The cytotoxicity was studied by *in vitro* growth inhibition of human lung carcinoma cells of line A549. The adherent cells were sown in different numbers and, after incubation with different concentrations of the compound, the numbers of formed colonies were counted. Using this methodology we observed a remarkably low IC_{50} value of 1.5 μM for the relative colony-forming rate of **24**, therefore turning it into a potential lead structure for continuing pharmacological investigations.

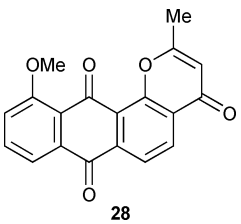
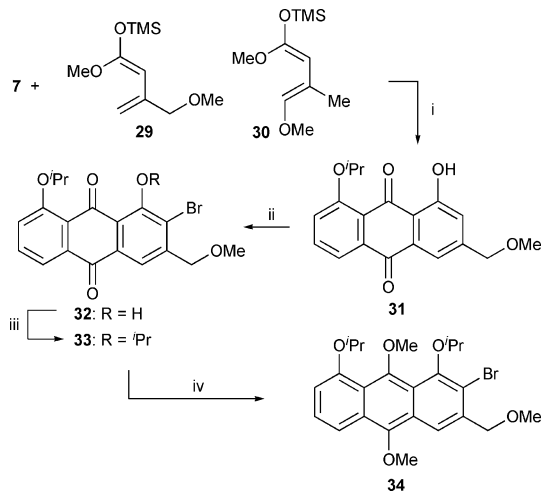


Fig. 2 Krohn's anthrapyran **28** with antitumor properties.

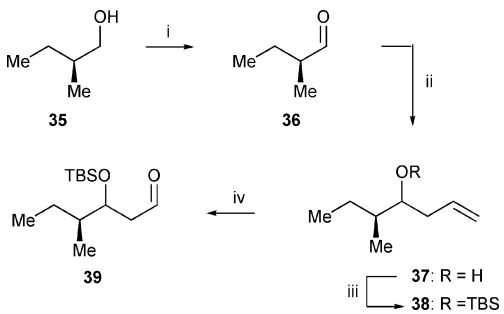
Synthesis of (*S*)-espicufolin (3)

Having successfully synthesised the anthrapyran **24** by utilizing two simple and highly efficient strategies, we were also interested to demonstrate the general synthetic value by applying these novel methodologies in the course of the synthesis of a more complex structure. As a target molecule, we chose (*S*)-espicufolin (**3**), which exhibits a stereogenic centre in the side chain and in addition, a benzylic alcohol functionality on the anthraquinone moiety. We planned to introduce this alcohol group protected as its methyl ether in the beginning of the synthesis *via* Diels–Alder reaction using an appropriate diene. Therefore, we tried to synthesise diene **29** (Scheme 6) starting from methyl 3,3-dimethylacrylate (**9**) employing a literature-known procedure.[32] Unfortunately, we only obtained a complex mixture of diene **29** and **30** together with their double bond isomers, a result which has already been observed by Brassard *et al.* [33] Due to a lower steric demand of trisubstituted diene **29** in comparison to tetrasubstituted diene **30**, we assumed a higher reactivity of **29** during the Diels–Alder cycloaddition. As a consequence, we decided to use the mixture of the dienes in the following step. Thus, the reaction of naphthoquinone **7** and the mixture of dienes **29** and **30** afforded, after aromatisation of the cycloadduct by the use of silica gel, the desired anthraquinone **31** in 50% yield (based on **7**). The amine-catalysed bromination furnished compound **32** in 97% yield, whereas the formation of the isopropyl ether derivative **33** could be realised in 94% yield. Finally, reductive methylation provided the desired anthracene **34** in nearly quantitative yield.



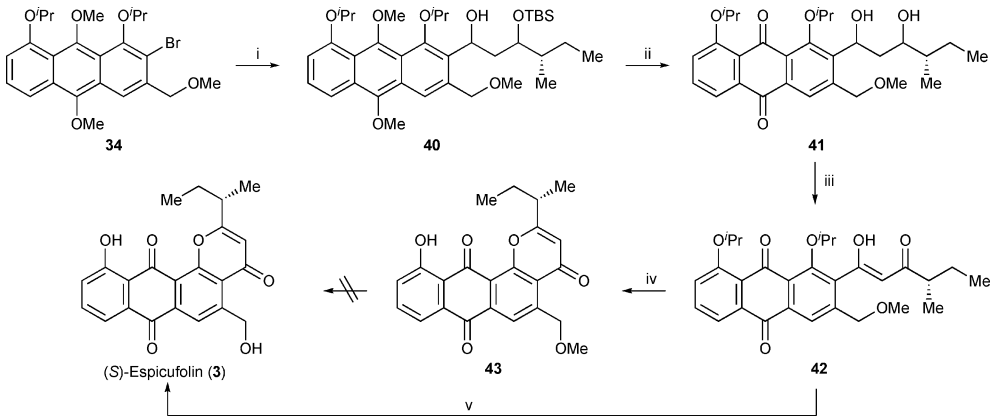
Scheme 6 *Reagents and conditions*: (i) (a) benzene, reflux, 6 h, (b) SiO_2, CH_2Cl_2, 20 °C, 24 h then removal of solvent (50%); (ii) NBS, cat. iPr_2NH, CH_2Cl_2, 20 °C, 4.5 h (97%); (iii) *i*PrI, Cs_2CO_3, acetone–DMF (3:1), reflux, 16 h (94%); (iv) (a) $Na_2S_2O_4$, cat. TBABr, THF–H_2O, 20 °C, 25 min, (b) KOH, H_2O, 20 °C, 15 min, (c) Me_2SO_4, 20 °C, 12 h (99%).

The synthesis of the enantiopure coupling partner **39** commences from commercially available (*S*)-2-methyl-butanol (**35**) which was first oxidised to the corresponding aldehyde **36** in 79% yield using Swern-conditions (Scheme 7).[34] Further addition of allylmagnesium bromide provided homoallyl alcohol **37** in 68% yield as a nearly 1 : 1 mixture of the two possible diastereoisomers. Since one of the stereogenic centres was planned to be destroyed *via* oxidation at a later stage of the synthesis, both diastereoisomers were used as a mixture for the following steps. However, due to their high volatility they were immediately transformed into the TBS-ether **38** using TBSOTf and 2,6-lutidine. Finally, cleavage of the terminal double bond utilising a one-pot osmium tetroxide–sodium periodate oxidation led to the formation of the desired aldehyde **39** in 77% yield.[35] Due to its high sensitivity, the latter was directly used within the following coupling reaction.



Scheme 7 *Reagents and conditions*: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → 20 °C, 2.5 h (79%); (ii) allylmagnesium bromide, Et_2O, −78 °C, 30 min (68%); (iii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min (80%); (iv) (a) cat. OsO_4, NMO, *t*-BuOH–THF–H_2O, 20 °C, 2 h, (b) $NaIO_4$, 20 °C, 45 min (77%).

The lithium-mediated coupling of bromoanthracene **34** and aldehyde **39** again proceeded very smoothly delivering the required product **40** in 93% yield as a complex mixture of diastereoisomers (Scheme 8). The following oxidative demethylation of anthracene derivative **40** utilizing $Ag^{II}O$–HNO_3 and subsequent



Scheme 8 *Reagents and conditions*: (i) *n*BuLi, **39**, THF, −78 C → 20 °C, 1 h (93%); (ii) (a) AgO, 4N HNO_3, dioxane, 20 °C, 10 min, (b) TBAF·$3H_2O$, THF, 0 °C → 20 °C, 30 min (85%); (iii) DMP, cat. H_2O, CH_2Cl_2, 0 °C → 20 °C, 1 h (77%); (iv) HOAc, cat. H_2SO_4, reflux, 5 min (97%); (v) (a) HOAc, cat. H_2SO_4, reflux, 1 h, (b) NaOMe, MeOH, 20 °C, 1 h, then IR-120 (23% over 2 steps).

TBS-deprotection using TBAF led to the formation of 1,3-diol **41** in a combined yield of 85%. Afterwards, the bis-oxidation into the 1,3-diketo compound **42** could be realised in 77% yield *via* Dess–Martin oxidation with water as additive. The acid-catalysed cyclisation procedure was again very simple and highly efficient. Thus, exposure of 1,3-diketone **42** to catalytic amounts of sulfuric acid in boiling acetic acid triggered the pyranone formation to afford anthrapyran **43** in excellent 97% yield. To complete the total synthesis of (*S*)-espicufolin (**3**) we only had to cleave the remaining methyl ether as the final step. Many attempts to complete this transformation using different Lewis-acids or aqueous hydrogen chloride turned out to be ineffective. Finally, we observed that a prolonged reaction time (1 h) during the cyclisation step led to a partial transformation of the methyl ether **43** into the corresponding acetate (**43**: OAc instead of OMe) due to the presence of acetic acid. Unfortunately, further increase of the reaction time led to complete decomposition of the starting material. However, the acetate group could be removed by solvolysis according to Zemplén using catalytic amounts of sodium methoxide in methanol.[36] In the end, (*S*)-espicufolin (**3**) could be obtained by acidic work up with ion exchange resin IR-120 in 23% yield over both reaction steps. All physical data for the synthetic sample of **3** were in good agreement with those reported in literature.[8,9,12,13] Despite the low yield in the last transformation, the above outlined reaction sequence represents an overall yield of 2.7% and only 13 steps starting from 1,3-dihydroxynaphthalene **4**, the most efficient and shortest access to (*S*)-espicufolin (**3**) reported to date.

Conclusions

The present work reveals the efficient construction of the 4*H*-anthra[1,2-*b*]pyran ring system by two different cyclisation strategies. We have shown that the side chain units of the required cyclisation precursors could be easily introduced *via* a nucleophilic addition of an aryl lithium species onto an appropriate aldehyde. Thus, we obtained the novel anthrapyran **24**; its biological investigation revealed a remarkable antitumor activity, in very high yield. The versatility of this methodology was also demonstrated by the synthesis of the more complex (*S*)-espicufolin (**3**), thus disclosing a general method for the construction of other anthrapyran natural products and their analogues.

Experimental

Electronic supplementary material

Details about the performance and conditions of the HTCFA (cytotoxicity) test, general and full experimental procedures and analytical data for compounds **5–7**, **9–10**, **16–20** and **36–41** have been deposited as ESI.†

Synthesis of anthrapyran 24

1-Hydroxy-8-isopropoxy-3-methylanthraquinone (11). To a solution of juglone derivative **7** (840 mg, 2.85 mmol) in benzene (40 mL) was added, at 0 °C dropwise with stirring, diene **10** (1.59 g, 8.55 mmol) within 10 min. After being stirred for 1 h at 0 °C, the mixture was warmed to 20 °C and stirring was continued for an additional 7 h. Afterwards, 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 **11** (7.94 g, 2.68 mmol, 94%) as a yellow solid, R_f 0.44 (P–EtOAc, 4 : 1); mp 163 °C; (Found: C, 72.69; H, 5.49. $C_{18}H_{16}O_4$ requires C, 72.96; H, 5.44%); λ_{max} (CH_3CN)/nm 192.5 (lgε/dm^3 mol^{-1} cm^{-1} 4.446), 224.0 (4.580), 257.5 (4.351) and 413.5 (3.963); ν_{max} (KBr)/cm^{-1} 2979, 1670, 1638, 1585, 1491, 1441, 1384, 1368, 1321, 1286, 1270, 1239 and 1208; δ_H (300 MHz, $CDCl_3$) 13.07 (1 H, s, 8-OH), 7.92 (1 H, dd, *J*7.8 and 1.4, 5-H), 7.67 (1 H, t, *J*7.8, 6-H), 7.56 (1 H, d, *J*1.1, 4-H), 7.34 (1 H, brd, *J*7.8, 7-H), 7.07 (1 H, d, *J*1.1, 2-H), 4.74 (1 H, sept., *J*6.0, C*H*(CH_3)$_2$), 2.43 (3 H, s, Ar–CH_3) and 1.50 (6 H, d, *J*6.0, CH(C*H*$_3$)$_2$); δ_C (75.5 MHz, $CDCl_3$) 188.2, 183.1, 162.6, 159.5, 147.2, 135.9, 135.1, 132.3, 124.5, 121.8, 121.6, 120.1, 119.8, 115.0, 72.66, 22.07 and 22.00; *m*/*z* (EI) 296.1 (22%, $[M]^+$), 254.0 (100%, $[M - C_3H_6]^+$), 250.0 (47%, $[M - C_2H_4O_2]^+$) and 222.0 (37%, $[M - C_2H_4O_2 - CO]^+$);

Found (ESI) $[M + H]^+$ 297.11235. $C_{18}H_{16}O_4 + H^+$ requires 297.11214.

2-Bromo-1-hydroxy-8-isopropoxy-3-methylanthraquinone (12). A solution of anthraquinone **11** (1.50 g, 5.60 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 (1.35 g, 7.59 mmol) in CH_2Cl_2 (60 mL) was added dropwise during 10 min. After being stirred for 6 h (TLC-control), additional NBS (450 mg, 2.53 mmol) was added and stirring was continued for another 3 h. Afterwards, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed subsequently with aqueous 0.2N 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 **12** (1.85 g, 97%) as an orange solid, R_f 0.47 (P–EtOAc, 4 : 1); mp 228 °C; (Found: C, 57.64; H, 4.24. $C_{18}H_{15}BrO_4$ requires C, 57.62; H, 4.03%); λ_{max} (CH_3CN)/nm 195.0 (lgε/dm^3 mol^{-1} cm^{-1} 4.409), 228.5 (4.535), 262.0 (4.410), 286.5 (4.011) and 416.5 (4.013); ν_{max} (KBr)/cm^{-1} 2978, 1673, 1636, 1582, 1480, 1440, 1383, 1366, 1344, 1299, 1263 and 1237; δ_H (300 MHz, $CDCl_3$) 13.93 (1 H, s, 8-OH), 7.92 (1 H, dd, *J*8.1 and 1.0, 5-H), 7.70 (1 H, t, *J*8.1, 6-H), 7.64 (1 H, s, 4-H), 7.35 (1 H, brd, *J*8.1, 7-H), 4.75 (1 H, sept., *J*6.0, C*H*(CH_3)$_2$), 2.54 (3 H, s, Ar–CH_3) and 1.50 (6 H, d, *J*6.0, CH(C*H*$_3$)$_2$); δ_C (75.5 MHz, $CDCl_3$) 187.9, 182.5, 159.7, 159.2, 147.1, 135.6, 135.6, 130.5, 121.6, 121.5, 121.3, 2 × 120.0, 115.2, 72.79, 24.14 and 22.06; *m*/*z* (EI) 376.0, 374.0 (26%, $[M]^+$) and 334.0, 332.0 (100%, $[M - C_3H_6]^+$); Found (ESI) $[M + H]^+$ 375.02267. $C_{18}H_{15}BrO_4 + H^+$ requires 375.02265.

2-Bromo-1,8-diisopropoxy-3-methylanthraquinone (13). A solution of anthraquinone **12** (1.80 g, 4.80 mmol) in a mixture of acetone (90 mL) and DMF (30 mL) was treated subsequently at 20 °C with Cs_2CO_3 (4.69 g, 14.4 mmol) and 2-iodopropane (0.96 mL, 9.60 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 (150 mL) and washed subsequently with aqueous 2M 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 **13** (1.88 g, 94%) as a yellow solid, R_f 0.49 (P–EtOAc, 4 : 1); mp 163 °C; (Found: C, 60.33; H, 4.84. $C_{21}H_{21}BrO_4$ requires C, 60.44; H, 5.07%); λ_{max} (CH_3CN)/nm 222.5 (lgε/dm^3 mol^{-1} cm^{-1}4.468), 263.0 (4.457) and 370.5 (3.766); ν_{max} (KBr)/cm^{-1} 2978, 1681, 1580, 1464, 1440, 1380, 1348, 1309, 1277, 1260 and 1238; δ_H (300 MHz, $CDCl_3$) 7.84 (1 H, d, *J* 0.6, 4-H), 7.79 (1 H, dd, *J*8.0 and 0.8, 5-H), 7.60 (1 H, t, *J*8.0, 6-H), 7.30 (1 H, dd, *J*8.0 and 0.8, 7-H), 4.66 (1 H, sept., *J*6.2, C*H*(CH_3)$_2$), 4.41 (1 H, sept., *J*6.2, C*H*(CH_3)$_2$), 2.54 (3 H, s, Ar–CH_3), 1.44 (6 H, d, *J*6.2, CH(C*H*$_3$)$_2$) and 1.40 (6 H, d, *J*6.2, CH(C*H*$_3$)$_2$); δ_C (75.5 MHz, $CDCl_3$) 183.4, 182.4, 157.6, 154.6, 144.7, 135.0, 133.6, 132.6, 130.2, 127.7, 125.9, 123.4, 122.0, 119.2, 79.69, 72.71, 24.40, 22.26 and 22.02; *m*/*z* (ESI) 856.8 (100%, 2 × M + Na^+); Found (ESI) $[M + H]^+$ 417.06965. $C_{21}H_{21}BrO_4$ + H^+ requires 417.06960. $[M + Na]^+$ 439.05166. $C_{21}H_{21}BrO_4 + Na^+$ requires 439.05154.

2-Bromo-1,8-diisopropoxy-9,10-dimethoxy-3-methylanthracene (14). A solution of anthraquinone **13** (8.53 g, 20.4 mmol) and tetra-*n*-butylammonium bromide (3.29 g, 10.2 mmol) in THF (300 mL) was treated at 20 °C with a solution of $Na_2S_2O_4$ (21.3 g 122 mmol) in H_2O (150 mL) and stirred for 25 min. Afterwards, a solution of KOH (34.5 g, 0.614 mol) in H_2O (100 mL) was added (the yellow solution turned into deep-red) and stirring was continued for an additional 15 min. After addition of dimethyl sulfate (20 mL), the reaction mixture was stirred for 12 h (the solution turned back into yellow) and then poured into H_2O (600 mL). The resulting solution was extracted with CH_2Cl_2 (3 × 250 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 **14** (8.94 g, 98%) as a yellow oil, R_f 0.49 (P–EtOAc, 20 : 1); (Found: C, 61.50; H, 5.84. $C_{23}H_{27}BrO_4$ requires C, 61.75; H, 6.08%); λ_{max} (CH_3CN)/nm 202.5 (lgε/dm^3 mol^{-1} cm^{-1} 4.361), 229.5 (4.112), 269.5 (4.986), 363.0 (3.736), 381.5 (4.011), 400.5 (3.904) and 423.0 (3.768); ν_{max} (KBr)/cm^{-1} 2977, 2931, 1616, 1556, 1510, 1449, 1417, 1396, 1352, 1305, 1288 and 1255; δ_H (300 MHz, $CDCl_3$) 7.88 (1 H, d, *J* 1.0, 4-H), 7.83 (1 H, dd, *J*8.8 and 0.9, 5-H), 7.35 (1 H, dd, *J*8.8 and 7.5, 6-H), 6.82 (1 H, brd, *J*7.5, 7-H), 4.67 (2 H, sept., *J*5.9, 2 × C*H*(CH_3)$_2$), 4.04 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 2.63 (3 H, d, *J* 1.0, Ar–CH_3), 1.47 (6 H, d, *J*5.9, C-8-OCH(C*H*$_3$)$_2$) and 1.36 (6 H, brs, C-1-OCH(C*H*$_3$)$_2$); δ_C (75.5 MHz, $CDCl_3$) 154.8, 150.4, 149.2, 147.2, 135.7, 127.8, 125.8, 125.8, 2 × 120.2, 119.9, 117.6, 115.1, 109.9, 77.92, 71.87, 63.65, 62.65, 24.73, 22.16 and 21.90; *m*/*z* (EI) 448.0, 446.0 (14%, $[M]^+$); Found (ESI) $[M + H]^+$ 447.11673. $C_{23}H_{27}BrO_4 + H^+$ requires 447.11655. $[M + Na]^+$ 469.09849. $C_{23}H_{27}BrO_4 + Na^+$ requires 469.09870.

(1*RS*, 3*RS*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-1-(1,8-diisopropoxy-9,10-dimethoxy-3-methylanthracene-2-yl)-butan-1-ol (21). A solution of anthracene **14** (1.03 g, 3.30 mmol) in THF (30 mL) was treated at −78 °C dropwise during 1 min with *n*BuLi (1.01 mL, 2.53 mmol, 2.5M in *n*-hexane). After being stirred for 30 s, aldehyde **18** (699 mg, 3.45 mmol) in THF (5 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 (100 mL). Afterwards, 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 material was subjected to silica gel flash chromatography (P–EtOAc, 20 : 1 → 10 : 1) and concentration of the appropriate fractions *in vacuo* afforded a diastereomeric mixture (dr ≈ 1 : 1) of alcohol **21** (1.17 g, 89%) as a yellow foam, R_f 0.35 (P–EtOAc, 10 : 1); (Found: C, 69.21; H, 8.58. $C_{33}H_{50}O_6Si$ requires C, 69.43; H, 8.83%); λ_{max} (CH_3CN)/nm 202.0 (lgε/dm^3 mol^{-1} cm^{-1} 4.380), 229.0 (4.107), 267.0 (4.996), 362.5 (3.731), 380.5 (3.896), 398.0 (3.896) and 420.5 (3.742); ν_{max} (KBr)/cm^{-1} 3499, 2972, 2930, 2857, 1556, 1510, 1451, 1420, 1394, 1359, 1281 and 1255; mixture of two diastereoisomers: δ_H (300 MHz, $CDCl_3$) 7.88 (1 H, dt, *J* 8.7 and 1.0, 5′-H), 7.73 (0.5 H, d, *J*1.0, 4′-H), 7.71 (0.5 H, d, *J*1.0, 4′-H),

7.31 (1 H, dd, *J*8.7 and 7.6, 6′-H), 6.80 (1 H, d, *J*7.6, 7′-H), 5.71–5.54 (1 H, m, 1-H), 4.71–4.51 (2 H, m, 2 × OC*H*(CH_3)$_2$), 4.38–4.23 (1 H, m, C-3), 4.03 (1.5 H, s, OCH_3), 4.02 (1.5 H, s, OCH_3), 3.96 (1 H, brs, OH, disappears after H/D-exchange with D_2O), 3.77 (1.5 H, s, OCH_3), 3.76 (1.5 H, s, OCH_3), 2.70 (1.5 H, brs, Ar–CH_3), 2.62 (1.5 H, d, *J*0.8Hz, Ar–CH_3), 2.43–2.29 (0.5 H, m, 2-H_a), 2.18 (0.5 H, m_c, 2-H_a), 1.82–1.68 (1 H, m, 2-H_b), 1.45 (9 H, m_c, C-8′-OCH(CH_3)$_2$, C-1′-OCH(CH_3)$_2$), 1.29 (3 H, t, *J*6.6, 4-H_3), 1.10 (3 H, brs, C-1′-OCH(CH_3)$_2$), 0.95 (4.5 H, s, SiC(CH_3)$_3$, TBS), 0.94 (4.5 H, s, SiC(CH_3)$_3$, TBS) and 0.20, 0.16, 0.12 (6 H, 3 × s, Si(CH_3)$_2$, TBS); δ_C (150.8 MHz, $CDCl_3$) 154.8, 154.8, 149.7, 149.5, 146.8, 135.2, 135.0, 127.7, 127.6, 126.4, 126.3, 125.3, 125.3, 119.7, 119.7, 118.8, 118.8, 118.7, 118.4, 115.3, 115.2, 110.3, 110.0, 76.41, 72.09, 71.99, 66.45, 63.16, 63.06, 62.57, 62.55, 46.36, 46.31, 46.11, 25.90, 23.90, 23.81, 22.23, 22.17, 22.06, 21.99, 21.79, 21.72, 21.60, 21.52, 21.29, 18.04, 18.02, −4.03, −4.58, −4.68 and −4.78; *m*/*z* (EI) 570.4 (100%, $[M]^+$), 552.4 (42%, $[M - H_2O]^+$) and 420.3 (46%, $[M - H_2O - OTBS]^+$); Found (ESI) $[M + Na]^+$ 593.32685. $C_{33}H_{50}O_6Si + Na^+$ requires 593.32689. $[M + K]^+$ 609.30082. $C_{33}H_{50}O_6Si + K^+$ requires 609.30082.

(1*RS*, 3*RS*)-2-(1,3-Dihydroxy-butyl)-1,8-diisopropoxy-3-methylanthraquinone (22). A solution of anthracene **21** (770 mg, 1.35 mmol) in 1,4-dioxane (60 mL) was treated at 20 °C with silver(II) oxide (835 mg, 6.74 mmol) and stirred for 5 min until a suspension was formed. Afterwards, 4N 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·3H_2O (852 mg, 2.70 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 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, 4 : 1 → 1 : 1) and concentration of the appropriate fractions *in vacuo* afforded a diastereomeric mixture (dr ≈ 1 : 1) of anthraquinone **22** (565 mg, 97%) as a yellow foam, R_f 0.17 (diastereomer 1), 0.24 (diastereomer 2) (P–EtOAc, 1 : 1); λ_{max} (CH_3CN)/nm 222.0 (lgε/dm^3 mol^{-1} cm^{-1} 4.491), 261.5 (4.403) and 373.0 (3.747); ν_{max} (KBr)/cm^{-1} 3443, 2975, 2931, 2857, 1674, 1584, 1463, 1442, 1384, 1309 and 1275; mixture of two diastereoisomers: δ_H (300 MHz, $CDCl_3$) 7.77 (1 H, d, *J*7.9, 5-H), 7.59 (1 H, d, *J*7.9, 6-H), 7.72 (1 H, s, 4-H), 7.28 (1 H, d, *J*7.9, 7-H), 5.60–5.51 (1 H, m, 1′-H), 4.67 (1 H, sept., *J*6.0, C-8-OC*H*(CH_3)$_2$), 4.53–4.31 (1 H, m, C-1-OC*H*(CH_3)$_2$), 4.31–3.66 (3 H, m, 3′-H, 2 × OH), 2.57 (1.5 H, s, Ar–CH_3), 2.53 (1.5 H, s, Ar–CH_3), 2.28–2.04 (1 H, m, 2′-H_a), 1.80–1.56 (1 H, m, 2′-H_b), 1.47–1.37 (9 H, m, C-8-OCH(CH_3)$_2$, C-1-OCH-(CH_3)$_2$) and 1.34–1.20 (6 H, m, 4′-H_3, C-1-OCH(CH_3)$_2$); δ_C (75.5 MHz, $CDCl_3$) 184.2, 184.0, 183.3, 157.2, 157.1, 154.8, 154.6, 143.0, 142.6, 142.2, 141.6, 135.1, 135.0, 133.5, 132.7, 132.5, 127.0, 126.9, 126.1, 126.0, 124.6, 124.3, 121.5, 121.4, 119.0, 78.76, 78.27, 72.44, 72.39, 70.43, 68.78, 67.11, 65.27, 44.15, 43.65, 23.64, 23.32, 22.42, 22.05, 21.99, 20.79 and 20.63; *m*/*z* (DCI) 870.8 (1%, 2 × $[M + NH_4]^+$), 444.4 (12%, $[M + NH_4]^+$) and 427.4 (100%, $[M + H]^+$); Found (ESI) $[M + H]^+$ 427.21152. $C_{25}H_{30}O_6 + H^+$ requires 427.21152.

2-(1-Hydroxy-3-oxo-but-1-enyl)-1,8-diisopropoxy-3-methylanthraquinone (23). A solution of anthraquinone **22** (300 mg, 0.703 mmol) in CH_2Cl_2 (70 mL) was treated at 0 °C with Dess–Martin periodinane (1.19 g, 2.81 mmol) and stirred for 4.5 h (if the conversion was too slow, one drop of H_2O was added). Afterwards, the reaction mixture was directly subjected to silica gel (containing 4% NaH_2PO_4) flash chromatography (CH_2Cl_2) and concentration of the appropriate fractions *in vacuo* afforded a enol–ketone mixture (~10 : 1) of anthraquinone **23** (238 mg, 80%) as a yellow oil, R_f 0.27 (P–EtOAc, 4 : 1); λ_{max} (CH_3CN)/nm 222.0 (lgε/dm^3 mol^{-1} cm^{-1} 4.472), 261.5 (4.455) and 373.5 (3.829); ν_{max} (KBr)/cm^{-1} 3331, 2978, 2931, 1676, 1585, 1463, 1441, 1383, 1312, 1277 and 1230; δ_H (300 MHz, $CDCl_3$) enol: 15.5 (1 H, brs, enol-OH), 7.85–7.70 (2 H, m, 5-H, 4-H), 7.60 (1 H, t, *J*8.2, 6-H), 7.30 (1 H, brd, *J*8.2, 7-H), 5.85 (1 H, s, 2′-H), 4.66 (1 H, sept., *J*6.1, OC*H*(CH_3)$_2$), 4.27 (1 H, sept., *J*6.1, OC*H*(CH_3)$_2$), 2.41 (3 H, s, Ar-CH_3), 2.16 (3 H, s, 4′-H_3), 1.44 (6 H, d, *J*6.1, CH(CH_3)$_2$) and 1.28 (6 H, d, *J*6.1, CH(CH_3)$_2$); ketone: 4.09 (2H, s, 2′-CH_2) and 2.30 (3H, s, 4′-H_3) (the other signals are covered); δ_C (50.3 MHz, $CDCl_3$) enol: 190.6, 187.7, 183.5, 182.7, 157.6, 154.8, 142.2, 139.1, 135.0, 134.4, 133.6, 127.4, 126.0, 123.7, 122.2, 119.3, 103.8, 79.68, 72.74, 59.02, 22.12, 22.02, 20.01 and 24.70; ketone: 133.9, 124.4, 119.4, 80.02, 77.20 and 59.02 (the other signals are covered); *m*/*z* (ESI) 423.2 ($[M + H]^+$); Found (ESI) $[M + H]^+$ 423.18009. $C_{25}H_{26}O_6 + H^+$ requires 423.18022.

(1*RS*)-1-(1,8-Diisopropoxy-9,10-dimethoxy-3-methylanthracene-2-yl)-but-2-yn-1-ol (25). A solution of anthracene **14** (500 mg, 1.12 mmol) in THF (20 mL) was treated at −78 °C dropwise during 1 min with *n*BuLi (0.51 mL, 1.29 mmol, 2.5M in *n*-hexane). After being stirred for 1 min, aldehyde **20** (305 mg, 4.48 mmol) in THF (4 mL) was added quickly. Stirring was continued for 10 min at −78 °C until the reaction was warmed to 20 °C during 1 h. The reaction mixture was treated with sat. NH_4Cl (5 mL), stirred for 5 min and then poured into H_2O (50 mL). Next, the resulting solution was extracted with CH_2Cl_2 (3 × 30 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, 9 : 1 → 4 : 1) and concentration of the appropriate fractions *in vacuo* afforded alcohol **25** (359 mg, 73%) as a yellow oil, R_f 0.25 (P–EtOAc, 6 : 1); λ_{max} (CH_3CN)/nm 202.0 (lgε/dm^3 mol^{-1} cm^{-1} 4.364), 229.0 (4.093), 267.5 (5.003), 362.0 (3.735), 380.0 (3.999), 398.0 (3.891) and 420.0 (3.740); ν_{max} (KBr)/cm^{-1} 3454, 2974, 2930, 1617, 1556, 1512, 1450, 1420, 1394, 1359 and 1256; δ_H (300 MHz, $CDCl_3$) 7.83 (1 H, dd, *J* 8.6 and 0.5, 5′-H), 7.80 (1 H, s, 4′-H), 7.34 (1 H, dd, *J* 8.6 and 7.3, 6′-H), 6.82 (1 H, d, *J*7.3, 7′-H), 6.26 (1 H, brs, OH), 4.71–4.52 (2 H, m, 2 × OC*H*(CH_3)$_2$), 4.04 (3 H, s, OMe), 3.79 (3 H, s, OMe), 2.78 (3 H, brs, Ar–CH_3), 1.87 (3 H, d, *J*2.0, 4-H_3), 1.58–1.01 (12 H, m, C-1′-OCH(CH_3)$_2$, C-8′-OCH(CH_3)$_2$); δ_C (75.5 MHz, $CDCl_3$) 154.8, 150.4, 2 × 150.1, 146.9, 129.9, 128.0, 126.6, 125.6, 119.9, 118.8, 115.2, 109.9, 109.7, 82.05, 77.34, 77.20, 71.91, 63.36, 62.57, 53.41, 22.79, 22.65, 22.53, 22.41, 22.32, 22.28, 22.01, 21.91, 21.66, 20.70 and 3.79; *m*/*z* (ESI) 459.2 ($[M + Na]^+$) and 419.2 ($[M + H - H_2O]^+$); Found (ESI)

$[M + Na]^+$ 459.21420. $C_{27}H_{32}O_5 + Na^+$ requires 459.21420. $[M + H - H_2O]^+$ 419.22169. $C_{27}H_{32}O_5 + H^+ - H_2O$ requires 419.22169.

(1*RS*)-2-(1-Hydroxy-but-2-ynyl)-1,8-diisopropoxy-3-methyl-anthraquinone (26). A solution of anthracene **25** (380 mg, 0.870 mmol) in 1,4-dioxane (30 mL) was treated at 20 °C with silver(II) oxide (553 mg, 4.47 mmol) and stirred for 5 min until a suspension was formed. Next, 4N HNO_3 solution (6 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 (150 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 crude material was subjected to silica gel flash chromatography (CH_2Cl_2, CH_2Cl_2–EtOAc, 20 : 1 → 4 : 1) and concentration of the appropriate fractions *in vacuo* afforded alcohol **26** (312 mg, 88%) as a yellow foam, R_f 0.53 (P–EtOAc, 2 : 1); λ_{max} (CH_3CN)/nm 222.5 (lgε/dm^3 mol^{-1} cm^{-1} 4.556), 260.5 (4.471) and 373.0 (3.795); ν_{max} (KBr)/cm^{-1} 3462, 2976, 2930, 1674, 1584, 1463, 1442, 1384, 1307, 1276 and 1236; δ_H (300 MHz, $CDCl_3$) 7.78 (1 H, dd, *J* 8.0 and 0.5, 5-H), 7.76 (1 H, s, 4-H), 7.59 (1 H, t, *J* 8.0, 6-H), 7.29 (1 H, d, *J*8.0, 7-H), 6.04 (1 H, brd, *J*2.2, 1′-H), 4.66 (1 H, sept., *J*6.2, C*H*(CH_3)$_2$), 4.43 (1 H, sept., *J*6.2, C*H*(CH_3)$_2$), 3.47 (1 H, brs, OH), 2.65 (3 H, s, Ar–CH_3), 1.83 (3 H, d, *J*2.2, 4-H_3), 1.48–1.40 (9 H, m, C-1-OCH(C*H*$_3$)$_2$, C-8-OCH(C*H*$_3$)$_2$) and 1.33 (3 H, d, *J*6.2, C-1-OCH(C*H*$_3$)$_2$); δ_C (75.5 MHz, $CDCl_3$) 2 × 183.4, 157.4, 154.6, 143.4, 140.0, 135.1, 133.5, 133.2, 127.0, 126.1, 124.5, 121.8, 119.2, 82.29, 79.09, 78.49, 72.64, 58.90, 22.43, 22.04, 21.99, 20.39 and 3.67; *m*/*z* (ESI) 429.2 ($[M + Na]^+$) and 407.2 ($[M + H]^+$); Found (ESI) $[M + H]^+$ 407.18518. $C_{25}H_{26}O_5$+H^+ requires 407.18530. $[M + Na]^+$ 429.16718. $C_{25}H_{26}O_5 + Na^+$ requires 429.16725.

1,8-Diisopropoxy-3-methyl-2-(1-oxo-but-2-ynyl)anthraquinone (27). A solution of anthraquinone **26** (280 mg, 0.689 mmol) in CH_2Cl_2 (30 mL) was treated at 20 °C with Dess–Martin periodinane (438 mg, 1.03 mmol) and stirred for 3 h. Afterwards, the reaction mixture was simultaneously treated with sat. $NaHCO_3$ (5 mL) and 1M $Na_2S_2O_3$ (5 mL) and stirred for 15 min until the solution became clear. The reaction mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 30 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) and concentration of the appropriate fractions *in vacuo* afforded ketone **27** (274 mg, 98%) as a yellow solid, R_f 0.24 (P–EtOAc, 4 : 1); mp 126 °C; λ_{max} (CH_3CN)/nm 222.0 (lgε/dm^3 mol^{-1} cm^{-1} 4.552), 260.0 (4.435) and 376.0 (3.799); ν_{max} (KBr)/cm^{-1} 2976, 2931, 2203, 1678, 1653, 1585, 1465, 1440, 1384, 1312, 1280 and 1228; δ_H (300 MHz, $CDCl_3$) 7.82–7.77 (2 H, m, 4-H, 5-H), 7.61 (1 H, t, *J*7.9, 6-H), 7.31 (1 H, d, *J*7.9, 7-H), 4.67 (1 H, sept., *J*6.2, C*H*(CH_3)$_2$), 4.40 (1 H, sept., *J*6.2, C*H*(CH_3)$_2$), 2.40 (3 H, s, Ar–CH_3), 2.08 (3 H, d, *J*2.2, 4′-H_3), 1.44 (3 H, d, *J*6.2, CH(C*H*$_3$)$_2$) and 1.33 (3 H, d, *J*6.2, CH(C*H*$_3$)$_2$); δ_C (75.5 MHz, $CDCl_3$) 183.3, 182.5, 181.5, 157.6, 155.0, 141.9, 140.9, 134.9, 134.5, 133.6, 127.0, 125.7, 123.7, 122.1, 119.2, 94.52, 81.29, 79.36, 72.68, 22.05, 21.97, 19.40 and 4.58; *m*/*z* (EI) 404.3 (30%, $[M]^+$), 361.2 (15%, M-$C_3H_7^+$), 320.2 (100%) and 304.2 (50%); Found (ESI) $[M + H]^+$ 405.16955. $C_{25}H_{24}O_5 + H^+$ requires 405.16965.

11-Hydroxy-2,5-dimethyl-1-oxa-benzo[*a*]anthracen-4,7,12-trion (24).

Procedure A. A solution of anthraquinone **23** (100 mg, 0.237 mmol) in conc. acetic acid (10 mL) was treated with a catalytic amount of conc. H_2SO_4 (10 drops) and stirred for 5 min under reflux. The reaction mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to silica gel filtration (CH_2Cl_2, CH_2Cl_2–EtOAc, 10 : 1) and concentration of the appropriate fractions *in vacuo* afforded the target compound **24** (74 mg, 97%) as a yellow solid.

Procedure B. A solution of anthraquinone **27** (120 mg, 0.297 mmol) in conc. acetic acid (10 mL) was treated with a catalytic amount of conc. H_2SO_4 (10 drops) and stirred for 40 min under reflux. The reaction mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to silica gel filtration (CH_2Cl_2, CH_2Cl_2–EtOAc, 10 : 1) and concentration of the appropriate fractions *in vacuo* afforded the target compound **24** (90 mg, 95%) as a yellow solid, R_f 0.17 (P–EtOAc, 4 : 1); mp 271 °C; (Found: C, 71.45; H, 4.03. $C_{19}H_{12}O_5$ requires C, 71.25; H, 3.78%), λ_{max} (CH_3CN)/nm 203.5 (lgε/dm^3 mol^{-1} cm^{-1} 4.365), 238.5 (4.678) and 266.0 (3.934); ν_{max} (KBr)/cm^{-1} 2925, 1652, 1626, 1586, 1465, 1453, 1386, 1344, 1311 and 1272; δ_H (300 MHz, $CDCl_3$) 12.79 (1 H, s, OH), 8.00 (1 H, s, 6-H), 7.78 (1 H, dd, *J*8.0 and 1.1, 8-H), 7.65 (1 H, t, *J*8.0, 9-H), 7.33 (1 H, d, *J*8.0 and 1.1, 10-H), 6.24 (1 H, s, 3-H), 2.99 (3 H, s, Ar–CH_3) and 2.51 (3 H, s, 2-CH_3); δ_C (75.5 MHz, $CDCl_3$) 187.1, 181.8, 178.9, 165.8, 162.5, 156.6, 149.7, 136.3, 135.8, 132.1, 126.2, 125.6, 125.3, 119.5, 119.2, 116.7, 112.8, 24.19 and 20.12; *m*/*z* (EI) 320.1 (100%, $[M]^+$); (EI) 320.0685. $C_{19}H_{12}O_5$ requires 320.0685.

Total synthesis of (*S*)-espicufolin (3)

2-(4*S*)-(1-Hydroxy-4-methyl-3-oxo-hex-1-enyl)-1,8-diisopropoxy-3-methoxymethylanthraquinone (42). A solution of anthraquinone **41** (190 mg, 0.381 mmol) in CH_2Cl_2 (50 mL) was treated at 0 °C with Dess–Martin periodinane (1.19 g, 1.52 mmol) and stirred for 0.5 h. Afterwards, a drop of H_2O was added and the solution was warmed to 20 °C. Next, another amount of Dess–Martin periodinane (600 mg, 0.760 mmol) was added and stirring was continued for 30 min. The reaction mixture was then directly subjected to silica gel flash chromatography (CH_2Cl_2 + 5% EtOAc + 1% HOAc) and concentration of the appropriate fractions *in vacuo* afforded an enol–ketone mixture (~6 : 1) of anthraquinone **42** (145 mg, 77%) as a yellow oil, R_f 0.53 (P–EtOAc, 4 : 1); $[\alpha]_D^{20}$ +12.3° (*c* = 1.0, $CHCl_3$); λ_{max} (CH_3CN)/nm 221.0 (lgε/dm^3 mol^{-1} cm^{-1} 4.430), 260.0 (4.398) and 370.5 (3.815); ν_{max} (KBr)/cm^{-1} 3337, 3097, 2973, 2930, 1680, 1586, 1460, 1384, 1371, 1305, 1278 and 1228; δ_H (300 MHz, $CDCl_3$) enol: 15.5 (1 H, brs, enol-OH), 8.13 (1 H, s, 4-H), 7.81 (1 H, brd, *J*7.2, 5-H), 7.61 (1 H, t, *J*8.3, 6-H), 7.31 (1 H, brd, *J*8.3, 7-H), 5.92 (1 H, s, 2′-H), 4.68 (1 H, sept., *J*6.1, OC*H*(CH_3)$_2$), 4.55 (2 H, s, CH_2OCH$_3$), 4.28 (1 H, sept., *J*6.7, OC*H*(CH_3)$_2$), 3.42 (3 H, s, OCH_3), 2.33 (1 H, m_c, 4′-H), 1.81–1.63 (1 H, m, 5′-H_a), 1.60–1.40 (1 H, m, 5′-H_b), 1.44 (6 H, d, *J*2.8, C-8-OCH(C*H*$_3$)$_2$), 1.28 (3 H, d, *J*2.8, C-1-OCH(C*H*$_3$)$_a$), 1.26 (3 H, d, *J*2.8, C-1-OCH(C*H*$_3$)$_b$), 1.20

(3 H, d, *J*7.0, 1″-H_3) and 0.95 (3 H, t, *J*7.6, 6′-H_3); ketone: 8.02 (1 H, s, 4-H), 4.53 (2 H, s, CH_2OCH_3), 3.41 (3 H, s, OCH_3) and 2.64 (1 H, m_c, 4′-H) (the other signals are covered); δ_C (75.5 MHz, $CDCl_3$) enol: 196.5, 188.1, 183.2, 182.7, 157.6, 154.7, 142.8, 138.0, 135.0, 134.9, 133.7, 128.7, 125.9, 122.0, 121.2, 119.3, 102.7, 79.73, 72.61, 71.35, 58.79, 43.66, 27.13, 22.12, 22.11, 22.00, 17.23 and 11.78; ketone: 29.65, 25.31, 22.22 and 14.98 (the other signals are covered); *m*/*z* (ESI) 1010.9 (100%, [2 × M + Na]$^+$), 517.1 (70%, [M + Na]$^+$) and 1009.1 (26%, [2 × M − 2 × H + Na]$^-$), 493.1 (100%, [M − H]$^-$); Found (ESI) [M + H]$^+$ 495.23818. $C_{29}H_{34}O_7$ + H$^+$ requires 495.23773.

(*S*)-2-(2-Methyl-propyl)-11-hydroxy-5-methoxymethyl-1-oxa-benzo[*a*]anthracen-4,7,12-trion (43). A solution of anthraquinone **42** (35.0 mg, 70.8 μmol) in conc. acetic acid (5 mL) was treated with conc. H_2SO_4 (5 drops) and stirred for 5 min under reflux. The reaction mixture was poured into H_2O (30 mL) and sat. NaCl (30 mL) was added. After extraction with CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to silica gel filtration (CH_2Cl_2 + 2% EtOAc + 0.5% HOAc) and concentration of the appropriate fractions *in vacuo* afforded the target compound **43** (27 mg, 97%) as a yellow solid, R_f 0.51 (P–EtOAc, 4 : 1); $[\alpha]_D^{20}$ +2.0° (*c* = 1.0, $CHCl_3$); λ_{max} (CH_3CN)/nm 206.5 (lgε/dm^3 mol^{-1} cm^{-1} 4.370), 238.5 (4.683), 266.0 (4.350) and 416.0 (3.914); ν_{max} (KBr)/cm^{-1} 2979, 2932, 1673, 1651, 1582, 1556, 1453, 1390, 1373, 1298, 1271 and 1218; δ_H (300 MHz, $CDCl_3$) 12.9 (1 H, s, OH), 8.57 (1 H, s, 6-H), 7.79 (1 H, dd, *J*7.9 and 1.0, 10-H), 7.66 (1 H, t, *J*7.9, 9-H), 7.33 (1 H, dd, *J*7.9, 1.0 Hz, 8-H), 6.26 (1 H, s, 3-H), 5.19 (2 H, s, CH_2OCH_3), 3.61 (3 H, s, OCH_3), 2.11 (1 H, m_c, 1′-H), 1.98 (1 H, m_c, 2′-H_a), 1.81 (1 H, m_c, 2′-H_b), 1.45 (3 H, d, *J*7.0, 1″-H_3) and 1.00 (3 H, t, *J*7.6, 3′-H_3); δ_C (75.5 MHz, $CDCl_3$) 187.4, 181.9, 179.3, 173.6, 162.7, 156.4, 150.4, 136.7, 136.5, 132.5, 125.3, 124.9, 120.3, 120.2, 119.6, 117.0, 111.2, 73.34, 59.26, 40.68, 27.56, 18.04 and 11.95; *m*/*z* (ESI) 806.7 (100%, [2 × M + Na]$^+$), 415.1 (30%, [M + Na]$^+$) and 805.2 (100%, [2 × M − 2 × H + Na]$^-$), 391.3 (20%, [M − H]$^-$); Found (ESI) [M + H]$^+$ 393.13316. $C_{23}H_{20}O_6$ + H$^+$ requires 393.13326. [M + Na]$^+$ 415.11513. $C_{23}H_{20}O_6$ + Na$^+$ requires 415.11521.

(*S*)-Espicufolin [((*S*)-2-(2-methyl-propyl)-11-hydroxy-5-hydroxy-methyl-6*a*,12*a*-dihydro-1-oxa-benzo[*a*]anthracen-4,7,12-trion)] (3). A solution of anthraquinone **42** (39 mg, 78.7 μmol) in conc. acetic acid (5 mL) was treated with conc. H_2SO_4 (15 drops) and stirred for 1 h under reflux. The reaction mixture was poured into H_2O (30 mL) and sat. NaCl (30 mL) was added. After extraction with CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to silica gel filtration (CH_2Cl_2 + 2% EtOAc + 0.5% HOAc) and concentration of the appropriate fractions *in vacuo* afforded a yellow solid (8.0 mg, 19 μmol). The latter was dissolved in MeOH (5 mL) and treated at 20 °C with NaOMe (7.2 μL, 38 μmol, 5.3 M in MeOH) (solution changed from yellow into red). After being stirred for 1 h the solution was treated with Amberlite® → IR-120 and the colour of the solution changed into yellow again. The solution was filtered and the residue was carefully washed with CH_2Cl_2 and MeOH. After evaporation of the solvents the residue was purified *via* silica gel flash chromatography (CH_2Cl_2 + 2% EtOAc + 0.5% HOAc) and concentration of the appropriate fractions *in vacuo* afforded (*S*)-espicufolin (**3**, 6.8 mg, 23% over two steps) as a yellow solid, R_f 0.22 (P–EtOAc, 7 : 3); $[\alpha]_D^{20}$ −5.0° (*c* = 0.2, $CHCl_3$); λ_{max} (CH_3CN)/nm 206.5 (lgε/dm^3 mol^{-1} cm^{-1} 4.338), 238.5 (4.644), 266.0 (4.319) and 416.0 (3.869); ν_{max} (KBr)/cm^{-1} 3472, 2965, 2929, 1681, 1649, 1625, 1584, 1554, 1459, 1392, 1344, 1314, 1300, 1275 and 1224; δ_H (300 MHz, $CDCl_3$) 12.8 (1 H, s, OH), 8.28 (1 H, s, 6-H), 7.83 (1 H, dd, *J*7.6 and 1.0, 8-H), 7.70 (1 H, t, *J*7.6, 9-H), 7.38 (1 H, dd, *J*8.4 and 1.0, 10-H), 6.39 (1 H, s, 3-H), 5.07 (2 H, s, CH_2OH), 4.67 (1 H, brs, OH), 2.80 (1 H, m_c, 1′-H), 1.99 (1 H, m_c, 2′-H_a), 1.83 (1 H, m_c, 2′-H_b), 1.45 (3 H, d, *J*7.0, 1″-H_3) and 1.00 (3 H, t, *J*7.5, 3′-H_3); δ_C (75.5 MHz, $CDCl_3$) 187.0, 181.5, 178.2, 172.5, 161.3, 155.6, 153.2, 136.6, 136.0, 132.1, 124.6, 124.0, 119.8, 118.7, 118.7, 110.5, 116.7, 62.19, 40.00, 26.68, 17.49 and 11.34; *m*/*z* (ESI) 379.1 (100%, [M + H]$^+$); Found (ESI) [M + H]$^+$ 379.11766. $C_{22}H_{18}O_6$ + H$^+$ requires 379.11761.

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