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Synthesis of the BCD-Ring Substructure of Granaticin A

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The BCD-ring substructure of granaticin A was synthesised following a new approach for the construction of the naphthoquinone moiety. The 2-oxabicyclo[2.2.2]oct-5-ene substructure was accessible stereoselectively using a Sharpless asymmetric dihydroxylation and a diastereoselective ketone reduction in combination with Yoshii's route. The naphthoquinone B-ring was prepared by addition of an aryllithium intermediate to an anhydride followed by a Friedel–Crafts cyclisation mediated by $AlCl_3$ and $Mg(OTf)_2$. The success of the Friedel–Crafts cyclisation relied on the conversion of the ketone-carboxylic acid into a lactone acetal.

Introduction

The pyrano-naphthoquinone granaticin A (Figure 1) was named after the red garnet-like crystals that were obtained after isolation of the natural product from *Streptomyces olivaceus*.[1] The structure of granaticin A was elucidated by UV, IR, and NMR spectroscopic analysis in combination with ozonolytic degradation, and was confirmed by X-ray crystallography of the triacetyl-monoiodoacetyl derivative.[2,3] Some examples of structurally related natural products are known, such as the rhodinoside of granaticin A, called granaticin B, and dihydro-granaticin.[4,5] Granaticin A shows antibiotic activity against Gram positive bacteria,[6] antitumor activity in mice with P388 lymphatic leukemia, and cytotoxicity against KB cells (ED_{50} 1.6 μg/mL).[7]

Granaticin A contains a rare 2-oxabicyclo[2.2.2]oct-5-ene substructure. The only other natural product incorporating this structural motif is sarubicin A (Figure 1) .[8] As shown by Floss et al., the biosynthetic origin of the 2-oxabicyclo[2.2.2]oct-5-ene structural feature is glucose, which is converted into 2,6-dideoxy-4-keto-dTDP-glucose and then attached to the hydroquinone precursor.[9] The pyranolactone substructure of granaticin A is also present in many other natural products such as nanaomycin D (Figure 1).[10]

Several stereoselective synthetic routes have been developed for the synthesis of the AB-ring substructure, with most of them using an oxa-Pictet–Spengler reaction for the construction of the pyranolactone.[11] The Yoshii group successfully achieved the stereoselective synthesis of the 2-oxabicyclo[2.2.2]oct-5-ene substructure that culminated in the first and only total synthesis of racemic granaticin A,[12] followed by the synthesis of the enantiomerically pure natural product.[13] A new stereoselective synthesis of the BCD-ring substructure of granaticin A is presented in this paper.

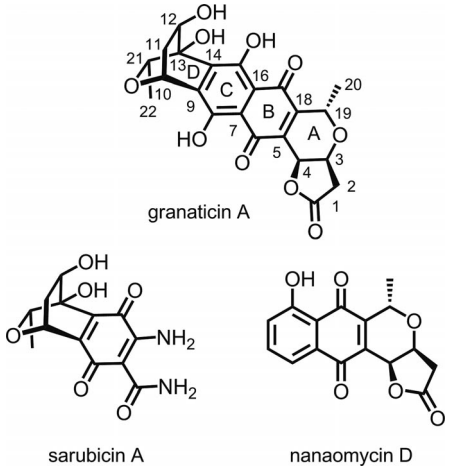

Figure 1. Structures of granaticin A, sarubicin A, and nanaomycin D.

Results and Discussion

A comparison between the key step used by Yoshii and that used in this paper for the construction of the BCD-ring substructure is shown in Scheme 1. Following Kraus's method, Yoshii used a benzannulation[14] of cyanophthalide **2** and Michael acceptor **3** to assemble the molecular skeleton of granaticin A (**1**).[12,13] The presence of the enone in Michael acceptor **3** allowed the introduction of the lactone ring to be postponed to the end of the synthesis. Our syn-

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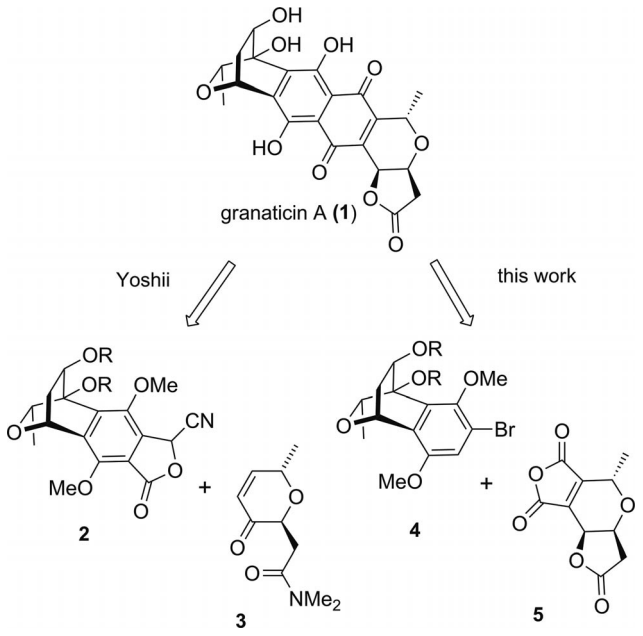
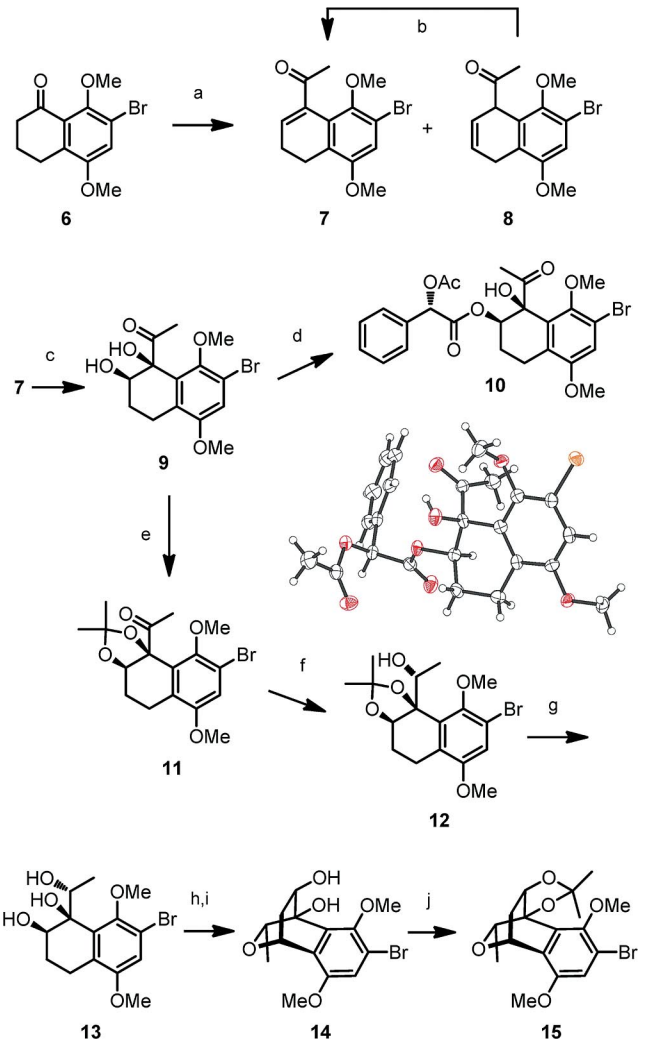
thetic plan involved the addition of an organometallic intermediate generated from bromide **4** to anhydride **5**. A subsequent Friedel–Crafts type cyclisation would lead to the closure of the B-ring. Regioselective attack on unsymmetrical anhydrides has precedent in related systems.[15] The identification of suitable conditions for the bromine–metal exchange and the investigation of the annulation with a symmetrical anhydride are important steps towards the realisation of our strategy, and the results are reported here.



Scheme 1. Different key steps for the construction of the granaticin skeleton.

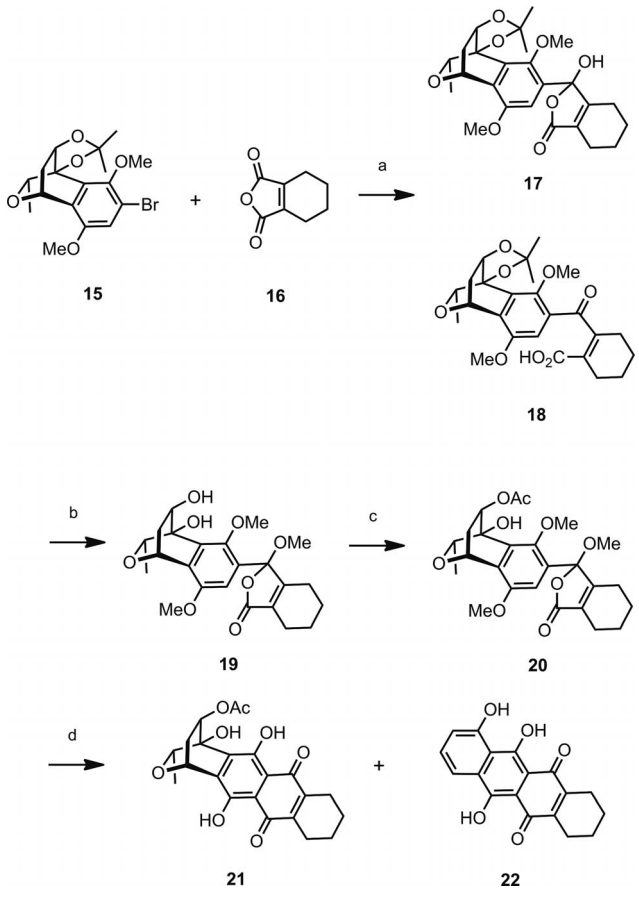
Enantiopure aryl bromide **4** was synthesised from bromotetralone **6**, which is available from *p*-dimethoxybenzene and succinic anhydride in 52% yield over six steps (Scheme 2).[16] The reaction of ketone **6** with (1-ethoxyvinyl)lithium,[12] which was transmetallated to the less basic organocerium reagent, provided the corresponding tertiary alcohol, which gave, after acid cleavage of the enol ether and elimination of water, α,β-unsaturated ketone **7**, together with β,γ-unsaturated ketone **8**. Compound **7** could be obtained in pure form by crystallisation. The by-product (i.e., **8**) was converted into **7** by treatment with DBU (1,8-diazabicycloundec-7-ene). Sharpless asymmetric dihydroxylation of alkene **7** with commercially available AD-mix-β gave diol **9**, with only 21% *ee*.[17] The enantioselectivity could be increased to 76% *ee* by using $(DHQD)_2Pyr$ as a chiral ligand. After recrystallisation of diol **9**, enantiopure material (95% *ee*) was obtained. The enantioselectivity of the dihydroxylation was determined by NMR analysis of the (*S*)-*O*-acetylmandelic ester (i.e., **10**) derived from compound **9**. The absolute configuration of compound **10** was determined by X-ray crystallography (Scheme 2).[18] After conversion of diol **9** into acetonide **11**, a substrate-controlled reduction of the ketone group was achieved. DIBAl-H in THF at –78 °C gave alcohol **12** with 97:3 diastereoselectivity.[19] The use of L-Selectride or borane–THF complex gave similarly good selectivities in this reduction step, whereas the use of $NaBH_4$ in MeOH led to a ratio of only 86:14.



Scheme 2. Stereoselective synthesis of aryl bromide **15** and X-ray structure of ester **10**. Reagents and conditions: a) ethyl vinyl ether, *t*BuLi, THF, –78 °C, $CeCl_3$, 0 °C, **6** at –78 °C; **7**: 87%, and **8**: 10%; b) DBU, CH_2Cl_2, 40 °C; c) $(DHQD)_2Pyr$, $K_3Fe(CN)_6$, $NaHCO_3$, methanesulfonamide, $K_2OsO_4{\cdot}2H_2O$, *t*BuOH/H_2O, 0 °C, 3 d, 96% (76% *ee*), after recrystallisation from EtOAc/*n*-heptane, 79%, (95% *ee*); d) (*S*)-(+)-α-acetoxyphenylacetic acid, DMAP, DCC, CH_2Cl_2, 20 °C, 79%; e) acetone, cat. H_2SO_4, reflux, 97%; f) DIBAl-H (diisobutylaluminium hydride), THF, –78 °C, 93%; g) HCl (10% in MeOH), 20 °C, 14 h, 86%; h) NBS, AIBN, CCl_4, 45 min, reflux; i) $AgClO_4$, THF, 20 °C, 15 min, 87% over two steps; j) *p*TsOH, 2,2-dimethoxypropane, THF, 20 °C, 91%.

Upon cleavage of the acetonide under acidic conditions, triol **13** was obtained. Benzylic bromination of **13** according to Yoshii[12] and subsequent Ag^I-initiated intramolecular Williamson reaction resulted in the formation of the desired 2-oxabicyclo[2.2.2]oct-5-ene derivative (i.e., **14**). After acetonide-protection of the diol, aryl bromide **15** was available for the intended bromine–metal exchange reaction.

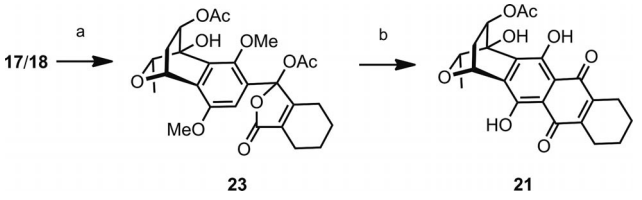
Cyclohexyl maleic anhydride **16** was chosen as substrate for the coupling studies (Scheme 3).[20] Bromine–lithium exchange of aryl bromide **15** was not straightforward, since the high reactivity of the aryllithium species led to a considerable amount of the protonated by-product. The optimal reaction conditions for the bromine–lithium exchange were found to be a reaction time of 10 min at –60 °C. After addition of anhydride **15**, a mixture of hemiacetal **17** and ketocarbocylic acid **18** was obtained in 64% yield. Transmetallation of the aryllithium intermediate to give a magnesium species did not improve the yield (55%). Treatment of the **17/18** mixture with oxalyl chloride followed by the addition of methanol gave, via the keto-acid chloride, mixed acetal **19** (as a 1:1 epimeric mixture). The acetonide was cleaved to reveal the diol in this step. Attempts to close the B-ring to form the naphthoquinone by a Friedel–Crafts reaction were unsuccessful in the presence of the free diol. Therefore, monoacetate **20** was prepared and used for the cyclisation studies. The Friedel–Crafts cyclisation[21] of mixed acetal **20** with $AlCl_3$ in nitromethane at 60 °C produced the desired naphthoquinone (i.e., **21**) together with anthraquinone **22**.



Scheme 3. Synthesis of naphthoquinone **21**. Reagents and conditions: a) *n*BuLi, THF, –60 °C, 10 min, then **16**, –78 °C, 20 min, 64%; b) oxalyl chloride, 20 °C, then MeOH, 0 °C, 74%; c) Ac_2O, DMAP, 20 °C, 91%; d) $AlCl_3$, $MeNO_2$, 60 °C, 30 min; **21**: 21%, and **22**: 18%.

The formation of compound **22** indicates the instability of the 2-oxabicyclo[2.2.2]oct-5-ene substructure under acidic conditions. Both aryl methyl ethers were cleaved under the cyclisation conditions. If the cyclisation occurs after the ether cleavage, an intramolecular acyl shift followed by a Fries rearrangement could also give a mechanistic explanation for the formation of **21**. Attempts to conduct the Friedel–Crafts cyclisation under protic conditions (HF, H_2SO_4, H_3PO_4, TFA, Nafion-H) were unsuccessful, and led to elimination side-reactions in the cyclohexyl ring.[22]

The mixture of hemiacetal **17** and ketocarbocylic acid **18** could be converted into acetate **23**, which proved to be a suitable precursor for the Friedel–Crafts reaction (Scheme 4). The use of 5 equiv. $AlCl_3$ in combination with 2 equiv. $Mg(OTf)_2$ in 1,3-dichlorobenzene was found to give optimal results for the formation of naphthoquinone **21**.



Scheme 4. Synthesis of naphthoquinone **21**. Reagents and conditions: a) *p*-TsOH, CH_2Cl_2, 20 °C, 3 h, then Ac_2O, pyridine, DMAP, 20 °C, 99%; b) $AlCl_3$, $Mg(OTf)_2$, 1,3-dichlorobenzene, 60 °C, 30 min, 31%.

Conclusions

In summary, the synthesis of the BCD-ring substructure of granaticin A was accomplished. The 2-oxabicyclo[2.2.2]-oct-5-ene substructure was stereoselectively accessible using a Sharpless asymmetric dihydroxylation, a diastereoselective ketone reduction, and a benzylic bromination/Williamson reaction, as implemented by Yoshii. The naphthoquinone moiety was formed by reaction of an aryllithium intermediate prepared by bromine–lithium exchange and a symmetrical anhydride, followed by a Friedel–Crafts cyclisation mediated by $AlCl_3$ and $Mg(OTf)_2$. To achieve a successful Friedel–Crafts cyclisation, it was ncessary to convert the ketone-carboxylic acid into a lactone acetal. This new route should be applicable to the synthesis of granaticin A as well as its derivatives, which would enable structure–activity relationship studies and allow the exploration of this intriguing natural product scaffold.

Experimental Section

General Methods: All air-sensitive reactions were carried out under argon with anhydrous solvents in dried glassware. All solvents were dried according to standard procedures, or were bought dry (Sigma–Aldrich). Reagents were used as purchased. Flash chromatography was performed on silica gel (0.04–0.063 mm/Fluka Analytical). Analytical TLC was carried out on aluminium-coated silica gel 60 F254. Optical rotations were measured at the sodium D line with a 1 dm path length and 1 mL cell. NMR spectra were

recorded with Bruker DPX-400 or DRX-500 spectrometers using partially deuterated solvents as internal standards. Coupling constants (*J*) are given in Hz, and chemical shifts (δ) in ppm. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, m = multiplet. IR spectra were recorded with a Bruker IFS 200 spectrometer. Mass spectra were recorded with a Qstar pulstar I instrument from Applied Biosystems, or on a Finnigan LTQ-FT instrument from Thermo Fisher Science.

1-(7-Bromo-5,8-dimethoxy-3,4-dihydronaphthalen-1-yl)ethanone (7) and 1-(7-Bromo-5,8-dimethoxy-1,4-dihydronaphthalen-1-yl)ethanone (8): Ethyl vinyl ether (29.26 g, 405.6 mmol) was dissolved in dry THF (100 mL) under an atmosphere of argon. The solution was cooled to –78 °C, and *t*BuLi (179 mL, 304.4 mmol) was added. The yellow mixture was stirred for 1 h at 0 °C until a colourless solution was observed. This solution was poured into a suspension of $CeCl_3$ (50.00 g, 202.8 mmol) in dry THF (150 mL) at –78 °C, which had been stirred for 12 h under an atmosphere of argon beforehand. Finally, bromotetralone **6** (6.20 g, 21.74 mmol) in dry THF (50 mL) was added to the suspension, and the resulting mixture was stirred for 2 h at –78 °C. The reaction was stopped by the addition of H_2O (50 mL), and the mixture was stirred for 10 min at room temperature, filtered, and washed with EtOAc (3× 200 mL). The organic phase was washed with HCl (5% aq.) and dried with Na_2SO_4, and the solvents were removed under reduced pressure. The resulting oil was dissolved in EtOAc (10 mL), and HCl (10% aq.; 180 mL) was added. The mixture was heated at reflux for 36 h, and was then allowed to cool to room temperature. The aqueous phase was extracted with EtOAc (5× 100 mL), and the combined organic extracts were washed with $NaHCO_3$ solution and dried with Na_2SO_4, and the solvents were removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:9) to give an isomeric mixture, which could then be separated by crystallisation (EtOAc/*n*-heptane) to give enone **7** (5.89 g, 18.92 mmol, 87%) as colourless crystals (m.p. 128–129 °C), and a mixture of **7** and **8** (9:1, 0.68 g, 2.17 mmol, 10%) as colourless oil. Data for **7**: R_f = 0.76 (EtOAc/*n*-hexane, 1:1). IR (film): $\tilde{\nu}$ = 2959, 2937, 2894, 2826, 1682, 1612, 1458, 1403, 1212, 977, 824, 761, 657 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, $COCH_3$), 2.26 (dd, *J* = 4.9, 7.8 Hz, 2 H, 3-H), 2.67 (t, *J* = 7.8 Hz, 2 H, 4-H), 3.54 (s, 3 H, 8-OMe), 3.81 (s, 3 H, 5-OMe), 6.43 (t, *J* = 4.9 Hz, 1 H, 2-H), 7.01 (s, 1 H, 6_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6 (C-4), 22.1 ($COCH_3$), 28.8 (C-3), 56.2 (5-OMe), 61.8 (8-OMe), 114.5 (C_{Ar}-7), 115.4 (C_{Ar}-6), 126.0 (C_{Ar}-4a), 128.2 (C_{Ar}-8a), 133.3 (C-2), 140.3 (C-1), 146.8 (C_{Ar}-8), 153.2 (C_{Ar}-5), 202.7 ($COCH_3$) ppm. HRMS (ESI): calcd. for $C_{14}H_{15}BrO_3$ $[M + Na]^+$ 333.0102; found 333.0097.

Data for **8**: R_f 0.76 (EtOAc/*n*-heptane, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, $COCH_3$), 3.15–3.38 (m, 2 H, 4-H), 3.37 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 4.47–4.48 (m, 1 H, 1-H), 5.78–5.81 (m, 1 H, 3-H), 6.07–6.11 (m, 1 H, 2-H), 6.94 (s, 1 H, 6_{Ar}-H) ppm.

The β,γ-enone (i.e., **8**) could be isomerised into enone **7** by adding CH_2Cl_2 and DBU (4 equiv.) under an atmosphere of argon. The solution was stirred at 40 °C overnight. H_2O was added to the solution, and the aqueous phase was extracted with EtOAc (3× 50 mL). The combined organic extracts were washed with brine and dried with Na_2SO_4, and the solvents were removed under reduced pressure. The crude product was dissolved in a mixture of EtOAc/*n*-heptane and cooled to 0 °C to give solid enone **7**.

1′-[(1*S*,2*R*)-7-Bromo-1,2-dihydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-naphthalen-1-yl]ethanone (9): $(DHQD)_2Pyr$ (837 mg, 0.95 mmol), $K_3Fe(CN)_6$ (9.35 g, 28.40 mmol), $NaHCO_3$ (2.39 g, 28.40 mmol), K_2CO_3 (3.93 g, 28.40 mmol), methanesulfonamide (900 mg, 9.46 mmol), and $K_2OsO_4{\cdot}2H_2O$ (35 mg, 0.10 mmol) were added to a stirred solution of enone **7** (2.94 g, 9.46 mmol) in H_2O (90 mL) and *t*BuOH (90 mL) at 0 °C. The reaction mixture was stirred for 3 d at a constant temperature. After completion of the reaction, $NaHSO_4$ (10 mg) and H_2O (50 mL) were added. The aqueous layer was extracted with EtOAc (5× 100 mL), and the combined organic layers were washed with an aq. $NaHCO_3$ solution and dried with Na_2SO_4, and the solvents were removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 0:1 to 1:1) to give diol **9** (13.14 g, 9.08 mmol, 96%, 76% *ee*) as a colourless solid. Diol **9** was crystallised from EtOAc/*n*-heptane to give the racemic compound as colourless crystals (628.4 mg, 1.82 mmol, 19%, m.p. ***rac*-9**: 159–160 °C), and the enantiomerically pure compound in the filtrate (2.47 g, 7.16 mmol, 79%, 95% *ee*). Data for **9**: m.p. 67–69 °C. R_f = 0.31 (EtOAc/*n*-hexane, 1:1). $[\alpha]_D^{24}$ = +0.24 (*c* = 1.03, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3411, 2940, 2839, 1710, 1577, 1466, 1229, 1056, 1017, 952, 907, 768, 704 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.93–2.08 (m, 2 H, 3-H), 2.13 (s, 3 H, $COCH_3$), 2.53 (ddd, *J* = 6.6, 12.4, 18.4 Hz, 1 H, 4-H), 2.99 (ddd, *J* = 1.5, 5.6, 18.2 Hz, 1 H, 4-H), 3.68 (s, 3 H, 8-OMe), 3.81 (s, 3 H, 5-OMe), 3.89 (dd, *J* = 3.0, 12.1 Hz, 1 H, 2-H), 4.95 (s, 1 H, OH), 6.99 (s, 1 H, 6_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.1 (C-4), 23.4 ($COCH_3$), 26.2 (C-3), 56.0 (5-OMe), 61.6 (8-OMe), 71.2 (C-2), 78.8 (C-1), 114.4 (C_{Ar}-7), 115.0 (C_{Ar}-6), 127.5 (C_{Ar}-4a), 132.2 (C_{Ar}-8a), 148.5 (C_{Ar}-8), 154.0 (C_{Ar}-5), 206.8 ($COCH_3$) ppm. HRMS (ESI): calcd. for $C_{14}H_{18}BrO_5$ $[M + Na]^+$ 367.0157; found 367.0152.

(1*S*,2*R*)-1-Acetyl-7-bromo-1-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl (2′*S*)-(Acetyloxy)(phenyl)acetate (10): Diol **9** (25.3 mg, 0.07 mmol) was dissolved in CH_2Cl_2 (5 mL), and (*S*)-(+)-α-acetoxyphenylacetic acid (17.1 mg, 0.09 mmol) and a catalytic amount of DMAP (ca. 1 mg, 0.12 mmol) were added. The solution was cooled to 0 °C in an ice-bath, and DCC (18.2 mg, 0.09 mmol) was added portionwise. The reaction mixture was warmed to room temp. and was stirred for 14 h. The solid urea was removed by filtration through silica and washed with EtOAc (2× 10 mL), and the solvent was removed from the filtrate under reduced pressure. The crude product was crystallised from EtOAc/*n*-heptane at –4 °C to give ester **10** (35.4 mg, 0.07 mmol, 79%) as a colourless solid (m.p. 186 °C). R_f = 0.56 (EtOAc/*n*-hexane, 1:1). $[\alpha]_D^{23}$ = +73.7 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3492, 2940, 1754, 1736, 1720, 1216, 1040, 739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.81–1.86 (m, 1 H, 3-H), 2.07 (s, 3 H, $COCH_3$), 2.10 (dd, *J* = 6.1, 12.8 Hz, 1 H, 3-H) 2.18 (s, 3 H, $COOCH_3$), 2.56 (ddd, *J* = 6.4, 12.2, 18.6 Hz, 1 H, 4-H), 2.95 (dd, *J* = 4.9, 18.3 Hz, 1 H, 4-H), 3.66 (s, 3 H, 8-OMe), 3.78 (s, 3 H, 5-OMe), 4.71 (s, 1 H, OH), 5.17 (dd, *J* = 3.7, 12.2 Hz, 1 H, 2-H), 5.81 (s, 1 H, 2′-H), 6.99 (s, 1 H, 6_{Ar}-H), 7.40–7.46 (m, 5 H, $2'_{Ar}$-H, $3'_{Ar}$-H, $4'_{Ar}$-H, $5'_{Ar}$-H, $6'_{Ar}$-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7 ($COOCH_3$), 21.9 (C-3), 22.7 (C-4), 23.4 ($COCH_3$), 56.0 (5-OMe), 61.7 (8-OMe), 74.1 (C-2′), 74.7 (C-2), 77.7 (C-1), 114.7 (C_{Ar}-7), 115.1 (C_{Ar}-6), 126.8 (C_{Ar}-4a), 127.7 (C_{Ar}-4′′), 129.0 (C_{Ar}-3′′, C_{Ar}-5′), 129.5 (C_{Ar}-2′′, C_{Ar}-6′′), 131.8 (C_{Ar}-8a), 133.4 (C-1′′), 148.2 (C_{Ar}-8), 154.0 (C_{Ar}-5), 168.4 (COO), 170.4 ($COOCH_3$), 204.9 (CO) ppm. HRMS (ESI): calcd. for $C_{24}H_{25}BrO_8$ $[M + Na]^+$ 543.0631; found 543.0629.

1-[(3a*R*,9b*S*)-8-Bromo-6,9-dimethoxy-2,2-dimethyl-4,5-dihydronaphtho[1,2-*d*][1,3]dioxol-9b(3a*H*)-yl]ethanone (11): Diol **9** (1.04 g, 3.01 mmol) was dissolved in dry acetone (15 mL), and a catalytic amount of conc. sulfuric acid (0.02 mL, 0.38 μmol) was added dropwise. The solution was heated under reflux (80 °C) for 3 h. After cooling to room temperature, $NaHCO_3$ (saturated aq.; 50 mL) was added. The aqueous phase was extracted with EtOAc

(5× 30 mL). The combined organic extracts were washed with brine and dried with Na_2SO_4, and the solvents were removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:4) to give protected diol **11** (1.12 g, 2.91 mmol, 97%) as a colourless solid (m.p. 122 °C). R_f = 0.81 (EtOAc/*n*-hexane, 1:1). $[\alpha]_D^{24}$ = –136.2 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2979, 2940, 1713, 1579, 1463, 1225, 1080, 1018, 653 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.13 (s, 3 H, 2-CH_3), 1.55 (s, 3 H, 2-CH_3), 1.79–1.86 (m, 1 H, 4-H), 2.23 (d, *J* = 14.0 Hz, 1 H, 4-H), 2.46 (s, 3 H, $COCH_3$), 2.51–2.58 (m, 1 H, 5-H), 2.80 (dd, *J* = 3.7, 17.1 Hz, 1 H, 5-H), 3.78 (s, 3 H, 9-OMe), 3.86 (s, 3 H, 6-OMe), 4.20 (d, *J* = 1.8 Hz, 1 H, 3a-H), 6.91 (s, 1 H, 7_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7 (C-5), 23.2 (C-4), 25.6 ($COCH_3$), 27.1 (2-CH_3), 27.7 (2-CH_3), 56.0 (6-OMe), 61.6 (9-OMe), 74.7 (C-3a), 85.6 (C-9b), 110.3 (C-2), 113.5 (C_{Ar}-8), 114.3 (C_{Ar}-7), 127.3 (C_{Ar}-5a), 133.7 (C_{Ar}-9a), 149.2 (C_{Ar}-9), 153.0 (C_{Ar}-6), 209.5 ($COCH_3$) ppm. HRMS (ESI): calcd. for $C_{17}H_{21}BrO_5$ $[M + Na]^+$ 407.0470; found 407.0473.

(1′*R*)-1-[(3a*R*,9b*R*)-8-Bromo-6,9-dimethoxy-2,2-dimethyl-4,5-dihydronaphtho[1,2-*d*][1,3]dioxol-9b(3a*H*)-yl]ethanol (12): Ketone **11** (1.40 g, 3.63 mmol) was dissolved in dry THF (80 mL). The solution was cooled to –78 °C, and DIBAl-H (54.40 mL, 54.40 mmol) was added by syringe, keeping the temperature below –70 °C. The mixture was stirred for 1 h at constant temperature. The reaction was stopped by the addition of H_2O (5 mL) with vigorous stirring at 0 °C. The ice-bath was removed, and the reaction mixture was warmed to room temperature. The solid was removed by filtration, and washed with EtOAc (5× 20 mL). The solvent of the filtrate was removed under reduced pressure to give alcohol **12** (1.36 g, 3.52 mmol, 97%) as a colourless solid in sufficient purity for the next step. An analytically pure sample was obtained by column chromatography on silica gel (EtOAc/*n*-hexane, 1:4) to give the product as a yellow solid in 93% yield (m.p. 92–93 °C). R_f = 0.36 (EtOAc/*n*-hexane, 1:4). $[\alpha]_D^{24}$ = +49.8 (*c* = 1.09, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3482, 2983, 2938, 1574, 1463, 1394, 1253, 1226, 1207, 857 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.1 Hz, 3 H, CHOH-CH_3), 1.12 (s, 3 H, 2-CH_3), 1.47 (s, 3 H, 2-CH_3), 1.83–1.91 (m, 1 H, 4-H), 2.26–1.31 (m, 1 H, 4-H), 2.55 (m, 1 H, 5-H), 2.84 (dd, *J* = 4.6, 17.2 Hz, 1 H, 5-H), 3.78 (s, 3 H, 9-OMe), 3.82 (s, 3 H, 6-OMe), 4.64 (s, 1 H, 3a-H), 4.97 (q, *J* = 7.1 Hz, 1 H, 1′-H), 6.95 (s, 1 H, 7_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4 (CHOH-CH_3, C-5), 24.1 (C-4), 27.4 (2-CH_3), 28.2 (2-CH_3), 55.9 (6-OMe), 62.0 (9-OMe), 66.8 (C-1′), 71.5 (C-3a), 84.3 (C-9b), 108.0 (C-2), 114.2 (C_{Ar}-8), 115.6 (C_{Ar}-7), 127.4 (C_{Ar}-5a), 132.4 (C_{Ar}-9a), 150.7 (C_{Ar}-9), 153.0 (C_{Ar}-6) ppm. HRMS (ESI): calcd. for $C_{17}H_{23}BrO_5$ $[M + Na]^+$ 409.0627; found 409.0623.

(1*R*,2*R*)-7-Bromo-1[(1′*R*)-1-hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-1,2-diol (13): Alcohol **12** (679 mg, 1.97 mmol) was dissolved in HCl (10% in MeOH; 15 mL), and was stirred for 14 h at room temperature. $NaHCO_3$ (saturated aq.; 50 mL) was added slowly to the reaction mixture at 0 °C. The aqueous phase was extracted with EtOAc (5× 50 mL). The combined organic extracts were washed with brine (50 mL) and dried with Na_2SO_4, and the solvents were removed under reduced pressure. The remaining crude product was purified by column chromatography on silica gel (EtOAc/*n*-heptane, 0:1 to 1:1) to give triol **13** (565 mg, 1.69 mmol, 86%) as a colourless solid (m.p. 124–125 °C). R_f = 0.30 (EtOAc/*n*-heptane, 1:1). $[\alpha]_D^{24}$ = +373.9 (*c* = 1.06, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3364, 2936, 2837, 1573, 1461, 1422, 1223, 959, 890, 819, 711 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.25 (br. s, 1 H, OH), 1.81–1.95 (m, 2 H, 3-H), 2.43 (ddd, *J* = 6.3, 8.3, 18.2 Hz, 1 H, 4-H), 2.87 (dt, *J* = 6.1, 18.2 Hz, 1 H, 4-H), 3.78 (s, 3 H, 5-OMe), 3.94 (s, 3 H, 8-OMe), 4.19 (dd, *J* = 3.5, 8.6 Hz, 1 H, 2-H), 4.78 (q, *J* = 6.6 Hz, 1 H, 1′-H), 6.95 (s, 1 H, 6_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5 (CH_3), 21.2 (C-4), 25.0 (C-3), 55.9 (5-OMe), 62.5 (8-OMe), 69.2 (C-2), 73.8 (C-1′), 76.8 (C-1), 114.1 (C_{Ar}-6), 115.2 (C_{Ar}-7), 127.6 (C_{Ar}-4a), 133.5 (C_{Ar}-8a), 150.5 (C_{Ar}-8), 153.4 (C_{Ar}-5) ppm. HRMS (ESI): calcd. for $C_{14}H_{19}BrO_5$ $[M + Na]^+$ 369.0314; found 369.0314.

(1*R*,3*R*,4*S*,9*R*)-6-Bromo-5,8-dimethoxy-9-methyl-2,3-dihydro-1,4-(epoxymethano)naphthalene-3,4(1*H*)-diol (14): Triol **13** (828 mg, 2.39 mmol) was dissolved in dry CCl_4 (30 mL), and NBS (510 mg, 2.87 mmol) and a catalytic amount of AIBN (5 mg, 0.03 mmol) were added. The solution was heated under reflux for 45 min. The solution was cooled to 0 °C, and was washed with $NaHSO_3$ (1% aq.; 20 mL) and brine (20 mL). The aqueous phases were extracted with CH_2Cl_2 (2× 20 mL). The combined organic phases were dried with Na_2SO_4, and the solvents were removed under reduced pressure. The crude product was dissolved in dry THF (10 mL), and dry $AgClO_4$ (495 mg, 2.39 mmol) was added at room temperature under an atmosphere of nitrogen. The reaction was quenched after 15 min by the addition of brine (20 mL), and the aqueous phase was extracted with EtOAc (4× 20 mL). The combined organic phases were dried with Na_2SO_4, and the solvents were removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/*n*-heptane, 1:2) to give oxabicyclic diol **14** (722 mg, 2.09 mmol, 87%) as a colourless solid (m.p. 62 °C). R_f = 0.37 (EtOAc/*n*-heptane, 1:1). $[\alpha]_D^{24}$ = –168.4 (*c* = 0.95, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3448, 2970, 2933, 2887, 1582, 1474, 1220, 1039, 813, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.1 Hz, 3 H, 9-CH_3), 1.43 (dt, *J* = 1.8, 1.9, 14.5 Hz, 1 H, 2_{endo}-H), 2.69 (ddd, *J* = 3.8, 8.7, 14.3 Hz, 1 H, 2_{exo}-H), 3.76 (q, *J* = 6.01 Hz, 1 H, 9-H), 3.79 (s, 3 H, 8-OMe), 3.93 (s, 3 H, 5-OMe), 4.00 (dd, *J* = 2.3, 8.8 Hz, 1 H, 3-H), 5.12 (dd, *J* = 1.8, 3.8 Hz, 1 H, 1-H), 7.03 (s, 1 H, 7_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7 (9-CH_3), 37.1 (C-2), 56.1 (8-OMe), 62.7 (C-1), 63.3 (5-OMe), 70.7 (C-3), 72.5 (C-9), 79.5 (C-4), 114.9 (C_{Ar}-7), 116.3 (C_{Ar}-6), 127.5 (C_{Ar}-8a), 128.4 (C_{Ar}-4a), 149.3 (C_{Ar}-5), 149.9 (C_{Ar}-8) ppm. HRMS (ESI): calcd. for $C_{14}H_{17}BrO_5$ $[M + Na]^+$ 367.0157; found 367.0153.

(3a*R*,5*S*,9b*R*,10*R*)-8-Bromo-6,9-dimethoxy-2,2,10-trimethyl-4,5-dihydro-3a*H*-5,9b-(epoxymethano)naphtho[1,2-*d*][1,3]dioxole (15): Diol **14** (474 mg, 1.37 mmol) and *p*TsOH (7.10 mg, 0.04 mmol) were dissolved in dry THF (20 mL). The solution was cooled to 0 °C, and 2-methoxypropane (347 mg, 4.81 mmol) was added. The reaction mixture was stirred at room temperature for 12 h, and then the solution was treated with $NaHCO_3$ (saturated aq.; 50 mL). The aqueous phase was extracted with EtOAc (4× 20 mL), and the combined organic extracts were washed with brine, and dried with Na_2SO_4. The solvents were removed under reduced pressure. The crude residue was purified by chromatography on silica gel (EtOAc/*n*-heptane, 1:9) to give bromide **15** (477 mg, 1.24 mmol, 91%) as a colourless solid (m.p. 50–52 °C). R_f = 0.69 (EtOAc/*n*-heptane, 1:1). $[\alpha]_D^{23}$ = +5.8 (*c* = 1.38, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2987, 2934, 2901, 2887, 1473, 1291, 219, 1115, 1045, 991, 839, 757 cm^{-1}. ^1H NMR (400 MHz, [D_4]methanol): δ = 0.74 (d, *J* = 6.6 Hz, 3 H, 10-CH_3), 1.38 (dd, *J* = 6.3, 12.9 Hz, 1 H, 4_{endo}-H), 1.52 (s, 3 H, 2-CH_3), 1.56 (s, 3 H, 2-CH_3), 2.69 (ddd, *J* = 5.1, 9.1, 14.2 Hz, 1 H, 4_{exo}-H), 3.73 (s, 3 H, 6-OMe), 3.81 (s, 3 H, 9-OMe), 4.00 (q, *J* = 6.4 Hz, 1 H, 10-H), 4.30 (dd, *J* = 6.1, 9.1 Hz, 1 H, 3a-H), 5.19 (d, *J* = 5.1 Hz, 1 H, 5-H), 7.20 (s, 1 H, 7_{Ar}-H) ppm. ^{13}C NMR (125 MHz, [D_4]-methanol): δ = 18.9 (10-CH_3), 27.0 (2-CH_3), 27.0 (2-CH_3), 34.2 (C-4), 56.7 (6-OMe), 62.0 (9-OMe), 65.4 (C-5), 78.2 (C-3a), 78.6 (C-10), 83.6 (C-9b), 115.3 (C-2), 115.9 (C_{Ar}-7), 119.9 (C_{Ar}-8), 129.3 (C_{Ar}-5a), 130.6 (C_{Ar}-9a), 149.8 (C_{Ar}-6), 150.3 (C_{Ar}-9) ppm.

HRMS (ESI): calcd. for $C_{17}H_{21}BrO_5$ [M + Na]$^+$ 407.0470; found 407.0464.

3-[(3a*R*,5*R*,9b*S*,10*R*)-6,9-Dimethoxy-2,2,10-trimethyl-4,5-dihydro-3a*H*-5,9b-(epoxymethano)naphtho[1,2-*d*][1,3]dioxol-8-yl]-3′-hydroxy-4′,5′,6′,7′-tetrahydro-2′-benzofuran-1(3*H*)-one (17) and (3a*R*,5*R*,9b*S*,10*R*)-2[[6,9-Dimethoxy-2,2,10-trimethyl-4,5-dihydro-3a*H*-5,9b-(epoxymethano)naphtho[1,2-*d*][1,3]dioxol-8-yl]carbonyl]-cyclohex-1′-ene-1′-carboxylic Acid (18): Bromide **15** (1.31 g, 3.40 mmol) was dissolved in dry THF (50 mL) under an atmosphere of argon. The solution was cooled to –78 °C, and *n*BuLi (1.63 mL, 4.08 mmol) was added. After 4 min, the solution was warmed to –60 °C for 4 min, and was then cooled back down to –78 °C. A solution of anhydride **16** (621 mg, 4.08 mmol) in dry THF (10 mL) was added quickly. After stirring for 30 min, the solution was warmed to room temperature and was poured into a sat. aq. NH_4Cl solution. The aqueous phase was extracted with EtOAc (5× 20 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, and filtered, and the solvents were evaporated under reduced pressure. The crude residue was purified by chromatography on silica gel (EtOAc/*n*-heptane, 0:1 to 1:1) to give a mixture acid **17** and lactone **18** (1.01 g, 2.19 mmol, 64%) as a colourless oil. R_f = 0.41 (EtOAc/*n*-hexane, 1:1). $[\alpha]_D^{23}$ = –17.5 (*c* = 1.27, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2973, 2933, 1734, 1474, 1383, 1221, 1116, 1044, 988, 741, 509 cm^{-1}. ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 0.81 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.33 (dd, *J* = 6.4, 13.1 Hz, 1 H, 4-H), 1.47 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.66–2.25 (m, 8 H, 3′-H, 4′-H, 5′-H, 6-H), 2.69 (ddd, *J* = 4.9, 9.2, 13.1 Hz, 1 H, 4-H), 3.56 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 4.01 (q, *J* = 6.5 Hz, 1 H, 10-H), 4.28 (dd, *J* = 6.1, 9.2 Hz, 1 H, 3a-H), 5.23 (d, *J* = 4.9 Hz, 1 H, 5-H), 7.49 (s, 1 H, 7_{Ar}-H) ppm. The acid/lactone mixture showed a complex ^{13}C NMR spectrum, which was not assigned. Complete ^{13}C NMR characterisation was possible for the subsequent compound **19**. HRMS (ESI): calcd. for $C_{25}H_{30}O_8$ [M + Na]$^+$ 481.1838; found 481.1836.

(1*R*,3*R*,4*S*,9*R*)-3′-[3,4-Dihydroxy-5,8-dimethoxy-9-methyl-1,2,3,4-tetrahydro-1,4-(epoxymethano)naphthalen-6-yl]-3′-methoxy-4′,5′,6′,7′-tetrahydro-2′-benzofuran-1′(3*H*)-one (*rac*-19): The mixture of *rac*-**17** and *rac*-**18** (150 mg, 0.33 mmol) was dissolved in oxalyl chloride (5 mL) at room temperature, and the solution was stirred for 30 min. The solvent was then removed under reduced pressure. The crude residue was dissolved in MeOH (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, and was stirred for 15 min. The solvent was removed under reduced pressure. The crude product was dissolved in EtOAc (20 mL), and H_2O (30 mL) was added. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3× 50 mL). The combined organic extracts were dried with Na_2SO_4. The solvents were removed under reduced pressure. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 99:1) to give mixed acetal *rac*-**19** (103 mg, 0.24 mmol, 74%) as a colourless solid, as a separable 1:1 mixture of two diastereomers. R_f (diastereomer 1) = 0.11 (EtOAc/*n*-hexane, 1:1). IR (film): $\tilde{\nu}$ = 3479, 2929, 2851, 1765, 1452, 1390, 1217, 1076, 1042, 1007, 917, 869 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, diastereomer 1): δ = 0.68 (d, *J* = 6.1 Hz, 3 H, 9-CH_3), 1.48 (dd, *J* = 2.0, 14.2 Hz, 1 H, 2-H), 1.63–1.72 (m, 5 H, 4′-H, 5′-H, 6′-H), 2.06–2.10 (m, 1 H, 7′-H) 2.33 (m, 2 H, 6′-H), 2.73 (ddd, *J* = 4.0, 8.8, 14.4 Hz, 1 H, 2-H), 3.35 (s, 3 H, OMe), 3.72 (q, *J* = 6.1 Hz, 1 H, 9-H), 3.83 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 4.02–4.04 (m, 1 H, 3-H), 5.16 (br. s, 1 H, 1-H), 5.44 (s, 1 H, OH), 7.21 (s, 1 H, 7_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, diastereomer 1): δ = 16.2 (9-CH_3), 20.1 (C-6′), 21.6 (C-4′, C-5′), 22.2 (C-7′), 37.2 (C-2), 50.6 (OMe), 55.9 (OMe), 62.7 (C-1), 66.6 (OMe), 70.5 (C-3), 72.7 (C-9), 79.6 (C-4), 107.0 (C-3′), 109.8 (C_{Ar}-7), 128.3 (C_{Ar}-4a), 128.6 (C_{Ar}-6), 129.3 (C_{Ar}-8a), 129.4 (C-7a′), 149.7 (C_{Ar}-8), 150.6 (C_{Ar}-5), 160.5 (C-3a′), 171.4 (C-1′) ppm. R_f (diastereomer 2) = 0.09 (EtOAc/*n*-hexane, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$, diastereomer 2): δ = 0.88 (d, *J* = 6.1 Hz, 3 H, 9-CH_3), 1.39 (d, *J* = 14.15 Hz, 1 H, 2-H), 1.60–1.72 (m, 5 H, 4′-H, 5′-H, 6′-H), 2.16–2.19 (m, 1 H, 7′-H) 2.33 (m, 2 H, 6′-H), 2.67–2.74 (m, 1 H, 2-H), 3.33 (s, 3 H, OMe), 3.78–3.80 (m, 1 H, 9-H), 3.77 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.97 (m, 1 H, 3-H), 5.16 (br. s, 1 H, 1-H), 5.44 (s, 1 H, OH), 7.18 (s, 1 H, 7_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, diastereomer 2): δ = 17.0 (9-CH_3), 20.0 (C-6′), 21.5 (C-5′), 21.6 (C-4′) 22.6 (C-7′), 37.2 (C-2), 50.6 (OMe), 56.0 (OMe), 62.7 (C-1), 66.0 (OMe), 71.3 (C-3), 72.5 (C-9), 79.6 (C-4), 106.9 (C-3′), 109.7 (C-7), 128.3 (C_{Ar}-4a), 128.9 (C_{Ar}-6), 129.3 (C_{Ar}-8a), 129.7 (C-7a′), 149.5 (C_{Ar}-8), 150.9 (C_{Ar}-5), 161.3 (C-3a′), 171.3 (C-1′) ppm. HRMS (ESI): calcd. for $C_{23}H_{28}O_8$ [M + Na]$^+$ 455.1682; found 455.1682.

(1*R*,3*R*,4*S*,9*R*)-4-Hydroxy-5,8-dimethoxy-6-(1′-methoxy-3-oxo-1′,3′,4′,5′,6′,7′-hexahydro-2′-benzofuran-1′-yl)-9-methyl-1,2,3,4-tetrahydro-1,4-(epoxymethano)naphthalen-3-yl Acetate (*rac*-20): Diol *rac*-**19** (229 mg, 0.50 mmol) was dissolved in Ac_2O (3.00 mL) and pyridine (6.00 mL) at room temperature. A catalytic amount of DMAP was added, and the solution was stirred overnight. The solvent was removed under reduced pressure after addition of *n*-hexane and the crude product was dissolved in EtOAc (20 mL), and H_2O (30 mL) was added. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3× 50 mL). The combined organic extracts were dried with Na_2SO_4. The solvents were removed under reduced pressure. The crude residue was purified by chromatography on silica gel (EtOAc/*n*-heptane, 1:4) to give acetate *rac*-**20** (99.7 mg, 0.21 mmol, 91%) as a colourless solid, as a separable 1:1 mixture of two diastereomers (m.p. 91–93 °C). R_f = 0.36 (EtOAc/*n*-heptane, 1:9). IR (film): $\tilde{\nu}$ = 3493, 2936, 2860, 1765, 1738, 1473, 1377, 1335, 1235, 1130, 1073, 1046, 1006, 964, 734 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, diastereomer 1): δ = 0.70 (d, *J* = 6.1 Hz, 3 H, 9-CH_3), 1.45 (dd, *J* = 2.0, 14.7 Hz, 1 H, 2-H), 1.62–1.74 (m, 5 H, 4′-H, 5′-H, 6′-H), 1.91 (s, 3 H, Ac), 2.08–2.09 (m, 1 H, 4′-H), 2.35 (m, 2 H, 7′-H), 2.86 (ddd, *J* = 3.5, 8.8, 14.9 Hz, 1 H, 2-H), 3.35 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.82–3.85 (m, 1 H, 9-H), 3.86 (s, 3 H, OMe), 5.04 (dd, *J* = 2.0, 8.6 Hz, 1 H, 3-H), 5.17 (s, 1 H, 1-H), 5.20 (s, 1 H, OH), 7.28 (s, 1 H, 7_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, diastereomer 1): δ = 16.3 (9-CH_3), 20.0 (C-5′), 21.2 (Ac), 21.6 (C-6′, C-7′), 22.3 (C-4′), 37.3 (C-2), 50.4 (OMe), 55.9 (OMe), 62.4 (C-1), 66.0 (OMe), 72.7 (C-3), 72.9 (C-9), 77.0 (C-4, overlapping solvent signal), 106.8 (C-1′), 109.8 (C_{Ar}-7), 128.4 (C_{Ar}-4a), 128.9 (C_{Ar}-6), 129.1 (C_{Ar}-8a), 129.5 (C-3a′), 149.7 (C_{Ar}-8), 149.9 (C_{Ar}-5), 160.5 (C-7a′), 170.5 ($COOCH_3$), 171.4 (C-3′) ppm. ^{1}H NMR (400 MHz, $CDCl_3$, diastereomer 2): δ = 0.92 (d, *J* = 6.1 Hz, 3 H, 9-CH_3), 1.36 (dd, *J* = 2.0, 14.8 Hz, 1 H, 2-H), 1.62–1.75 (m, 5 H, 4′-H, 5′-H, 6′-H), 1.85 (s, 3 H, Ac), 2.08–2.09 (m, 1 H, 4′-H), 2.35 (m, 2 H, 7′-H), 2.78–2.86 (m, 1 H, 2-H), 3.35 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 3.82–3.85 (m, 1 H, 9-H), 3.84 (s, 3 H, OMe), 5.00 (dd, *J* = 2.0, 8.6 Hz, 1 H, 3-H), 5.14 (s, 1 H, OH), 5.18 (s, 1 H, 1-H), 7.20 (s, 1 H, 7_{Ar}-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, diastereomer 2): δ = 17.1 (9-CH_3), 20.1 (C-5′), 21.2 (Ac), 21.6 (C-6′, C-7′), 22.6 (C-4′), 37.1 (C-2), 50.4 (OMe), 56.0 (OMe), 62.5 (C-1), 65.8 (OMe), 72.3 (C-3), 74.0 (C-9), 77.1 (C-4, overlapping solvent signal) 107.3 (C-1′), 109.6 (C_{Ar}-7), 128.6 (C_{Ar}-4a), 129.1 (C_{Ar}-6), 129.5 (C_{Ar}-8a, C-3a′), 149.4 (C_{Ar}-8), 150.4 (C_{Ar}-5), 160.8 (C-7a′), 170.4 ($COOCH_3$), 171.2 (C-3′) ppm. HRMS (ESI): calcd. for $C_{25}H_{30}O_9$ [M + Na]$^+$ 497.1788; found 497.1784.

(1*R*,3*R*,4*S*,13*R*)-4,5,12-Trihydroxy-13-methyl-6,11-dioxo-1,2,3,4,6,7,8,9,10,11-decahydro-1,4-(epoxymethano)tetracen-3-yl Acetate (*rac*-21) and 1,6,11-Trihydroxy-7,8,9,10-tetrahydrotetra-

cene-5,12-dione (22): Acetate *rac*-**20** (30.0 mg, 0.06 mmol) was dissolved in dry nitromethane (1 mL) under an atmosphere of argon, and this solution was added by syringe to a tube containing dry $AlCl_3$ (42.2 mg, 0.32 mmol), which was sealed with a Teflon® cap. The reaction mixture was heated under microwave irradiation at 60 °C for 30 min. After cooling to room temperature, the reaction mixture was decomposed with oxalic acid solution (5% (w/w) aq.; 20 mL). The aqueous phase was extracted with EtOAc (5× 20 mL). The combined organic extracts were dried with Na_2SO_4. The solvents were removed under reduced pressure. The remaining crude product was purified by chromatography on silica gel (CH_2Cl_2/CH_3CN = 1:0 to 9:1) to give the cyclised product *rac*-**21** (5.30 mg, 0.013 mmol, 21%) as a red solid (m.p. > 300 °C) and **22** (3.35 mg, 0.011 mmol, 18%) as a red solid (m.p. > 300 °C).

Data for *rac*-**21**: R_f 0.42 (CH_2Cl_2/CH_3CN, 95:5). IR (film): $\tilde{\nu}$ = 3526, 2927, 2855, 1742, 1644, 1596, 1455, 1407, 1354, 1229, 1137, 1058, 1022, 777 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.1 Hz, 3 H, 13-CH_3), 1.47 (d, J = 15.0 Hz, 1 H, 2-H), 1.78 (m, 4 H, 7-H, 10-H), 1.95 (s, 3 H, Ac), 2.65 (m, 4 H, 8-H, 9-H), 2.88 (ddd, J = 3.4, 8.6, 15.0 Hz, 1 H, 2-H), 3.93 (q, J = 6.1 Hz, 1 H, 13-H), 5.10 (d, J = 6.7 Hz, 1 H, 3-H), 5.26 (s, 1 H, 1-H), 5.77 (s, 1 H, OH), 12.79 (s, 1 H, OH), 13.43 (s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.8 (13-CH_3), 21.1 (C-7, C-10, Ac), 23.1 (C-8, C-9), 36.6 (C-2), 62.0 (C-1), 73.0 (C-3, C-13), 77.9 (C-4), 110.8 (C_{Ar}-11a), 111.0 (C_{Ar}-5a), 134.6 (C_{Ar}-4a), 140.0 (C_{Ar}-12a), 145.0 (C_{Ar}-6a), 145.9 (C_{Ar}-10a), 156.1 (C_{Ar}-12), 160.8 (C_{Ar}-5), 170.6 (COO), 183.3 (C_{Ar}-11), 184.1 (C_{Ar}-6) ppm. HRMS (ESI): calcd. for $C_{22}H_{22}O_8$ $[M + Na]^+$ 437.1212; found 437.1211.

Data for **22**: R_f 0.91 (CH_2Cl_2/MeOH, 9:1). IR (film): $\tilde{\nu}$ = 3357, 2922, 2853, 1659, 1445, 1393, 1289, 1237, 1194, 1162, 827, 775, 705 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.83 (m, 4 H, 8-H, 9-H), 2.78 (m, 4 H, 7-H, 10-H), 7.27 (d, 1 H, 2_{Ar}-H), 7.67 (dd, J = 7.9 Hz, 1 H, 3_{Ar}-H), 7.86 (d, J = 7.4 Hz, 1 H, 4_{Ar}-H), 12.32 (s, 1 H, OH), 12.85 (s, 1 H, OH), 13.67 (s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (C-8, C-9), 23.9 (C-7, C-10), 108.9 (C_{Ar}-5a, C-11a), 116.1 (C_{Ar}-12a), 119.0 (C_{Ar}-4), 124.01 (C_{Ar}-2), 133.6 (C_{Ar}-4a), 136.4 (C_{Ar}-3), 139.5 (C_{Ar}-10a), 140.0 (C_{Ar}-6a), 156.7 (C_{Ar}-11, C_{Ar}-6) 162.3 (C_{Ar}-1), 185.7 (C-5, C-12) ppm. HRMS (ESI): calcd. for $C_{18}H_{14}O_5$ $[M + Na]^+$ 333.0739; found 333.0733.

(1*R*,3*R*,4*S*,9*R*)-1′-[3-Acetoxy-4-hydroxy-5,8-dimethoxy-9-methyl-1,2,3,4-tetrahydro-1,4-(epoxymethano)naphthalen-6-yl]-3′-oxo-1′,3′,4′,5′,6′,7′-hexahydro-2-benzofuran-1′-yl Acetate (23): A mixture of **17** and **18** (242 mg, 0.53 mmol) was dissolved in CH_2Cl_2 (10 mL), and *p*TsOH (7.0 mg, 0.04 mmol) was added. The solution was stirred at room temperature. After 3 h, a mixture of pyridine (6 mL) and Ac_2O (2 mL) was added, together with a catalytic amount of DMAP, and the mixture was stirred at room temperature overnight. The solution was poured into ice-water, and extracted with EtOAc (4× 20 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and evaporated under reduced pressure with *n*-heptane (3× 50 mL). The crude product was purified by chromatography on silica gel (EtOAc/*n*-heptane, 1:9) to give acetate **23** (264 mg, 0.526 mmol, 99%) as a colourless oil, as an inseparable ca. 1:1 mixture of two diastereomers. R_f = 0.34 (EtOAc/*n*-heptane, 1:9). IR (film): $\tilde{\nu}$ = 3502, 2925, 2855, 1772, 1739, 1463, 1372, 1233, 1206, 1044, 1008, 910, 867, 731, 447 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, diastereomer 1): δ = 0.71 (d, J = 6.1 Hz, 3 H, CH_3), 1.39 (d, J = 14.7 Hz, 1 H, 2-H), 1.52–1.77 (m, 5 H, 5′-H, 6′-H, 7′-H), 1.88 (s, 3 H, OAc), 2.18 (s, 3 H, OAc), 2.22–2.32 (m, 3 H, 4′-H, 7′-H), 2.77–2.83 (m, 1 H, 2-H), 3.80 (s, 3 H, OMe), 3.80–3.84 (m, 1 H, 9-H), 3.88 (s, 3 H, OMe), 5.00 (t, J = 7.02 Hz, 1 H, 3-H), 5.12 (s, 1 H, 1-H), 5.17 (s, 1 H, OH), 6.88 (s,1 H, 7-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, diastereomer 1): δ = 16.3 (CH_3), 20.0 (C-7′), 21.0 (Ac), 21.2 (C-6′), 21.5 (C-5′), 21.8 (Ac), 22.2 (C-4′), 37.0 (C-2), 55.7 (OMe), 62.2 (C-1), 65.9 (OMe), 72.6 (C-9), 72.9 (C-3), 77.4 (C-4), 104.9 (C-1′), 108.2 (C-7), 127.8 (C-6), 128.2 (C-4a), 129.1 (C-8a), 129.3 (C-3a′), 149.5 (C-8), 149.5 (C-5), 160.4 (C-7a′), 167.6 ($COOCH_3$), 170.3 (C-3′), 170.4 ($COOCH_3$) ppm. ^1H NMR (500 MHz, $CDCl_3$, diastereomer 2): δ = 0.82 (d, J = 6.1 Hz, 3 H, CH_3), 1.39 (d, J = 12.2 Hz, 1 H, 2-H), 1.52–1.77 (m, 5 H, 5′-H, 6′-H, 7′-H), 1.85 (s, 3 H, OAc), 2.16 (s, 3 H, OAc), 2.22–2.32 (m, 3 H, 4′-H, 7′-H), 2.77–2.83 (m, 1 H, 2-H), 3.78 (s, 3 H, OMe), 3.80–3.84 (m, 1 H, 9-H), 3.87 (s, 3 H, OMe), 5.00 (t, J = 7.0 Hz, 1 H, 3-H), 5.08 (s, 1 H, OH), 5.12 (s, 1 H, 1-H), 6.88 (s, 1 H, 7-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, diastereomer 2): δ = 16.6 (CH_3), 20.1 (C-7′), 21.0 (Ac), 21.2 (C-6′), 21.6 (C-5′), 21.9 (Ac), 22.9 (C-4′), 36.9 (C-2), 55.8 (OMe), 62.3 (C-1), 65.6 (OMe), 72.4 (C-9), 73.3 (C-3), 77.0 (C-4), 105.3 (C-1′), 108.1 (C-7), 128.1 (C-6), 128.4 (C-4a), 129.1 (C-8a), 129.5 (C-3a′), 149.4 (C-8), 149.9 (C-5), 161.1 (C-7a), 167.6 ($COOCH_3$), 170.4 (C-3′), 170.5 ($COOCH_3$) ppm. HRMS (ESI): calcd. for $C_{26}H_{30}O_{10}$ $[M + Na]^+$ 525.1737; found 525.1735.

(1*R*,3*R*,4*S*,13*R*)-4,5,12-Trihydroxy-13-methyl-6,11-dioxo-1,2,3,4,6,7,8,9,10,11-decahydro-1,4-(epoxymethano)tetracen-3-yl Acetate (21): Acetate **23** (18.8 mg, 0.04 mmol) was dissolved in dry 1,3-dichlorobenzene (1 mL) under an atmosphere of argon, and was transferred by syringe to a tube, which was sealed with a Teflon® cap, containing dry $AlCl_3$ (25.0 mg, 0.19 mmol) and $Mg(OTf)_2$ (24.2 mg, 0.08 mmol). The reaction mixture was heated under microwave irradiation at 75 °C for 15 min. After cooling to room temperature, the reaction mixture was treated with oxalic acid solution (5% (w/w) aq.; 20 mL). The aqueous phase was extracted with EtOAc (5× 20 mL). The combined organic extracts were dried with Na_2SO_4. The solvents were removed under reduced pressure. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/CH_3CN = 1:0 to 9:1) to give cyclised product **21** (4.7 mg, 0.012 mmol, 31%) as a red solid (m.p. > 300 °C). $[\alpha]_D^{22}$ = –0.9 (c = 1.00, $CHCl_3$).

The analytical data matched the data found for the same compound prepared from **20**.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all new compounds.

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[18] Supplementary crystallographic data for **10** has been deposited in the Cambridge Crystallographic Data Centre and allocated deposition number CCDC-895132.
[19] The stereochemical assignment of alcohol **12** was possible after the next step by comparison of the NMR spectroscopic data for triol **13** with the reported data from Yoshii (ref.[12]).
[20] The reactions shown in Scheme 3 were performed in the racemic series.
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