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Journal:	*The Journal of Organic Chemistry*
Manuscript ID	jo-2020-02638k.R2
Manuscript Type:	Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Mies, Thomas; Imperial College, Chemistry White, Andrew; Imperial College London, Department of Chemistry Parsons, Philip; Imperial College London, Department of Chemistry Barrett, Anthony; Imperial College London, Department of Chemistry

Biomimetic Syntheses of Analogs of Hongoquercin A and B by Late-Stage Derivatization

Thomas Mies, Andrew J. P. White, Philip J. Parsons, and Anthony G. M. Barrett*

Department of Chemistry, Imperial College, Molecular Sciences Research Hub, White City Campus, Wood Lane, London W12 0BZ, England.

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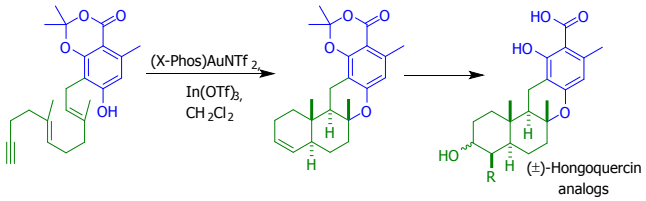
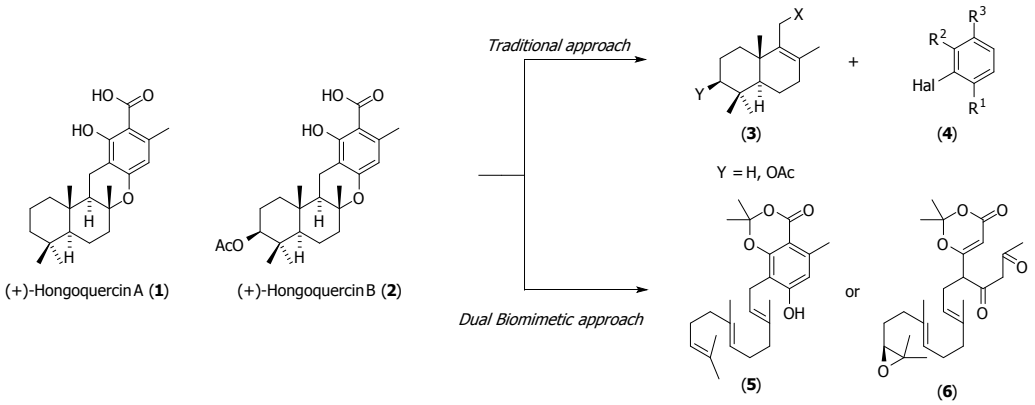


ABSTRACT

The hongoquercins are tetracyclic meroterpenoid natural products with the *trans-transoid* decalin-dihydrobenzopyran ring system, which display a range of different bioactivities. In this study, the syntheses of a range of hongoquercins using gold catalyzed enyne cyclization reactions and further derivatization are described. The parent enyne resorcylate precursors were synthesized biomimetically from the corresponding dioxinone keto ester *via* regioselective acylation, Tsuji-Trost allylic decarboxylative rearrangement and aromatization. The dioxinone keto ester **12** was prepared in 6 steps from geraniol using allylic functionalization and alkyne synthesis.

INTRODUCTION

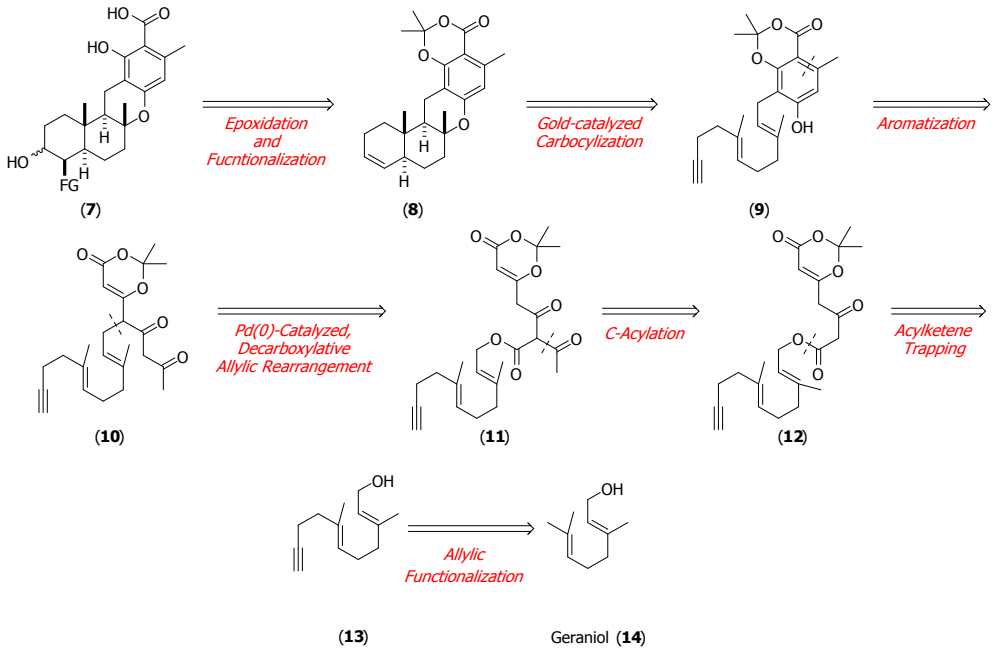
Meroterpenoids are natural products that are biosynthesized via two different pathways, such as the polyketide pathway for the arene moiety and the terpene pathway.[1] A sub-group of the meroterpenoids are natural products that incorporate a sesquiterpene unit and these include the hongoquercins. These natural products have attracted attention, not only due to the synthetic challenges with the 4 continuous stereocenters and highly substituted arene scaffold, but also in consequence of their biological activities that include inhibition of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[2] Abbanat's proposed mechanism of antibiotic action for hongoquercins (**1**) and (**2**) involves binding and disruption of the bacterial membrane. Hongoquercin A (**1**) showed higher biological activity than hongoquercin B (**2**) in both studies. Previous syntheses of the hongoquercins have used a coupling reaction between the arene entity, such as aryl halide **4** and an allylic functionalized decalin **3**.[3] The Barrett group has also reported two syntheses of hongoquercin A and B, which employed a dual-biomimetic polyketide and terpene polyene cyclization strategy with either early terpene **6** or late stage terpene **5** remote functionalization (Scheme 1).[4] In order to enhance the structural diversity of analogs of the hongoquercins, we now report the application of gold-catalyzed 1,5-enyne cycloisomerization reactions and post-cyclization modification to convert dienyne-resorcylates into a small library of novel (±)-hongoquercins. The dienyne-resorcylates were in turn synthesized using diketo-dioxinone chemistry[5] with modified terpenoid starting materials derived from geraniol.



Scheme 1. Known retrosynthetic strategies for hongoquercin A and B.

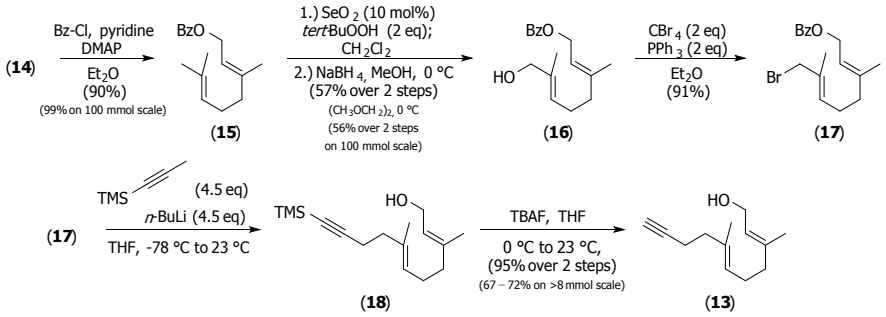
RESULTS AND DISCUSSION

The retrosynthetic analysis for the hongoquercin analogs **7** is outlined in Scheme 2. Thus, the key intermediate **8** should be available from dienyne **9** by gold-catalyzed carbocyclization, a process reported by Michelet, Toste and Echavarren, amongst others.[6] Dienyne **9** should, in turn, be available from the sequential *C*-acylation of keto-ester **12**,[7] palladium-catalyzed decarboxylative allylic rearrangement[8] to give diketo-dioxinone **10** and aromatization[5] to produce resorcylate **9**. Dienynol **13**, which should be available from geraniol (**14**), could then be easily converted into the key dienynol ester **12** using ketene generation and trapping.[5,7,9]



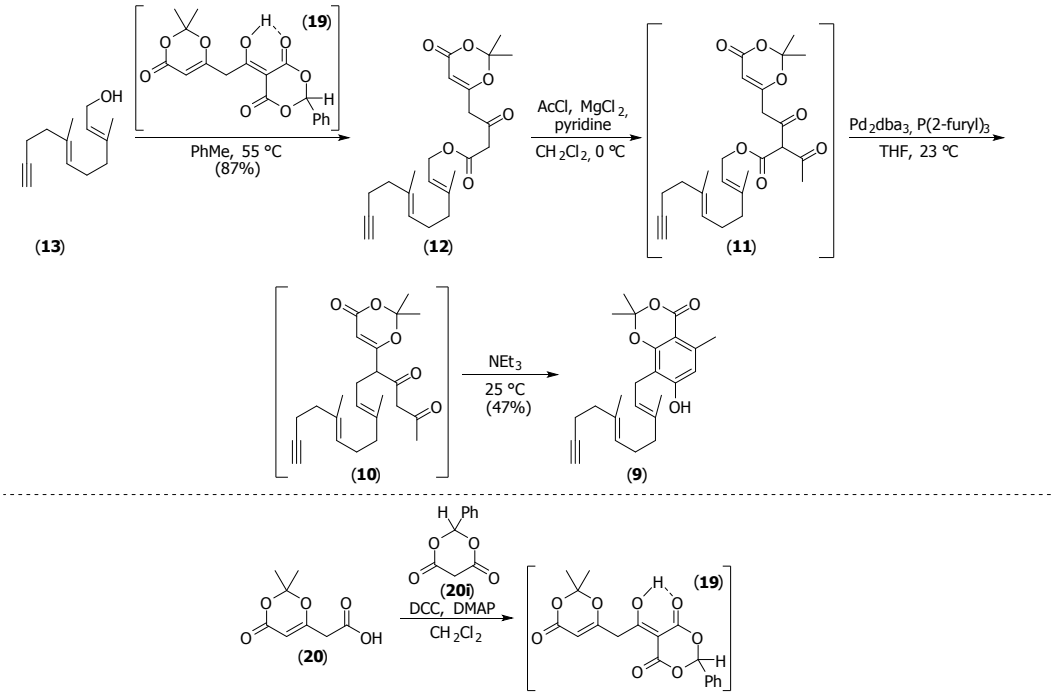
Scheme 2: Retrosynthetic analysis.

Protection of geraniol (**14**) as its benzoate ester **15** (96%)[10] and subsequent allylic oxidation using selenium dioxide and *t*-butyl hydroperoxide (56% on 40 mmol scale)[11] gave alcohol **16** which was converted into allylic bromide **17** under Appel conditions[12] (91%). Subsequent reaction of bromide **17** with 3-trimethylsilyl-1-prop-2-ynyllithium[13] gave the acetylene **18**, which was desilylated using tetrabutylammonium fluoride to give the key *trans, trans*-dienynol **13** (70% from bromide **17**) (Scheme 3).



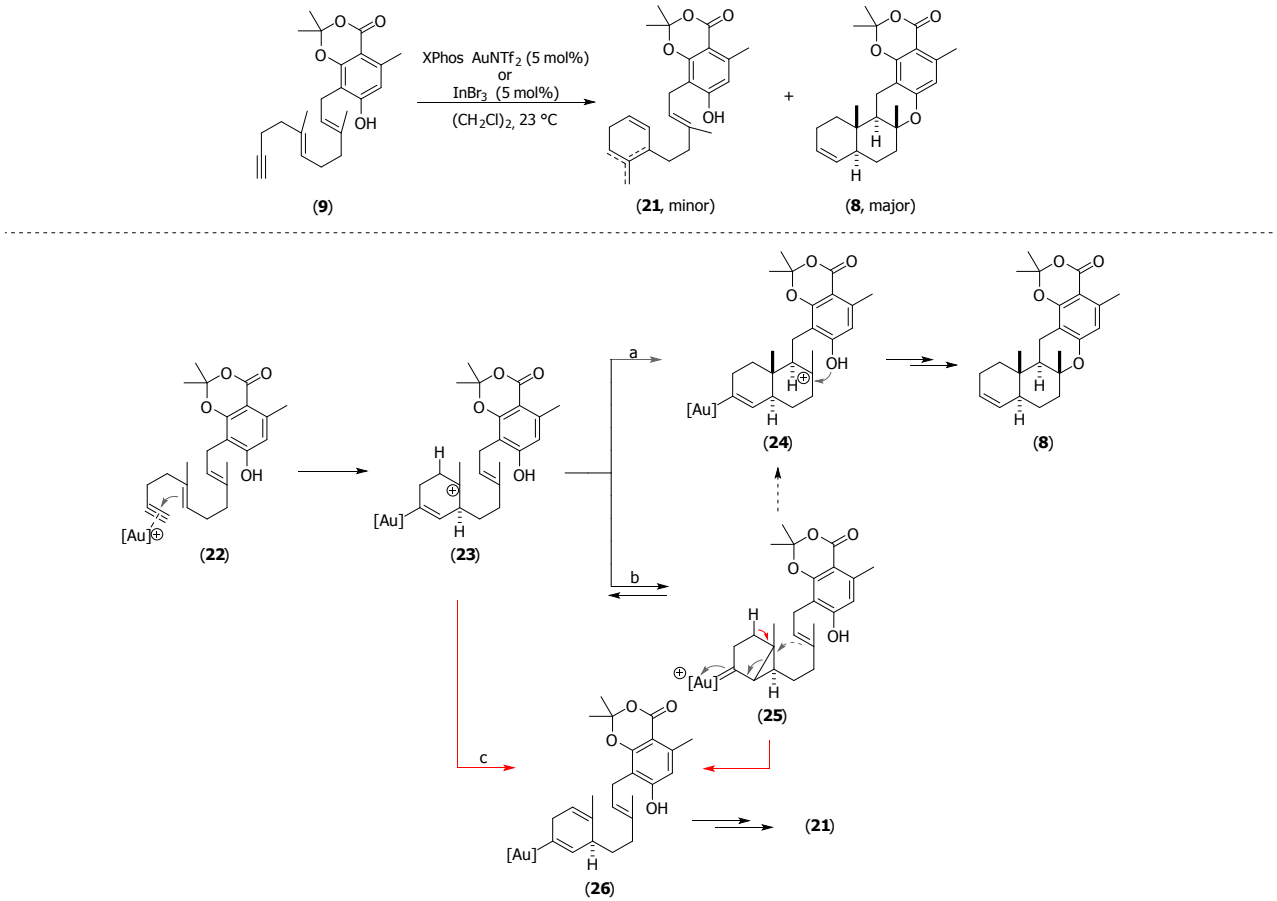
Scheme 3: Synthesis of the 1,5-enyne allylic alcohol **13**.

Dioxinone carboxylic acid **20** activation and homologation by DCC-mediated coupling with the Meldrum's acid derivative **20i** gave dioxane-4,6-dione keto dioxanone **19**, which following literature precedent,[7] gave the highly electrophilic dioxinone acyl ketene regioselectively upon heating at 55 °C. Trapping *in situ* with dienynol **13** gave the 1,5-enyne *β*-keto ester **12** in good yield (87%). Subsequent magnesium chloride mediated regioselective C-acylation, palladium(0) catalyzed decarboxylative allylic migration and aromatization of the intermediate diketo-dioxinone **10** gave the 1,5-enyne resorcylate **9** (47% over 2 steps) (Scheme 4).



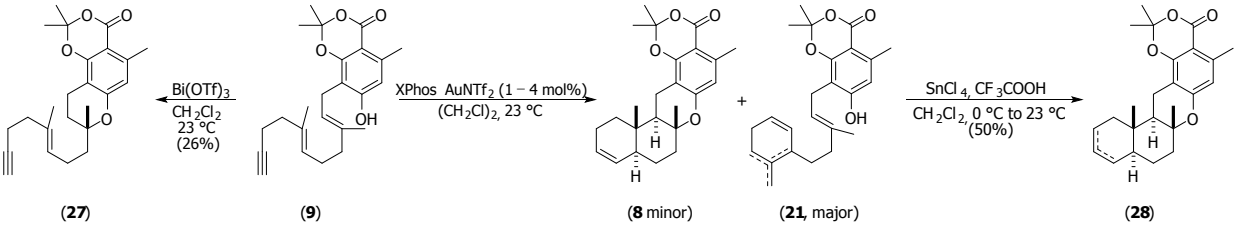
Scheme 4: Synthesis of the resorcylate dienyne **9**.

Reaction of dienyne **9** with a range of gold catalysts produced two compounds: the fully cyclized resorcylate **8** and the partially cyclized material **21**.[6a] Cyclization using XPhos $AuNTf_2$[6i] (5 mol %) in 1,2-dichloroethane proceeded with a better overall conversion (combined yields >80%) as well as providing greater selectivity favoring the required pentacyclic product **8** (Scheme 5). This is in accord with the fact that XPhos is a sterically less demanding ligand and renders the Au^+-species more alkynophilic.[14] Initial coordination of $[Au]^+$ to the alkyne provides complex **22** which gives rise to the formation of the 6-membered ring in complex **23** and the derived tertiary carbocation is then available for classical cationic cyclisation (path a). Alternatively, as postulated by Echavarren,[6d] activation of the acetylene by $[Au]^+$ as intermediate **22** promotes cyclization *via* intermediate **23** and rearrangement to the cyclopropyl-gold-carbene **25** (path b) that can undergo ring opening to produce carbocations **23** or **24**, which undergo classical terpene cyclisation. On the other hand, removal of an α-proton next to the carbocation **23** or cleavage of the cyclopropyl-gold-carbene **25** gives triene **26**, which will lead to the formation of the partially cyclized material **21** (path c). The structure of the pentacyclic product **8** was confirmed as having the rigid *trans-trans*-ring stereochemistry by an X-ray single crystal structure determination.



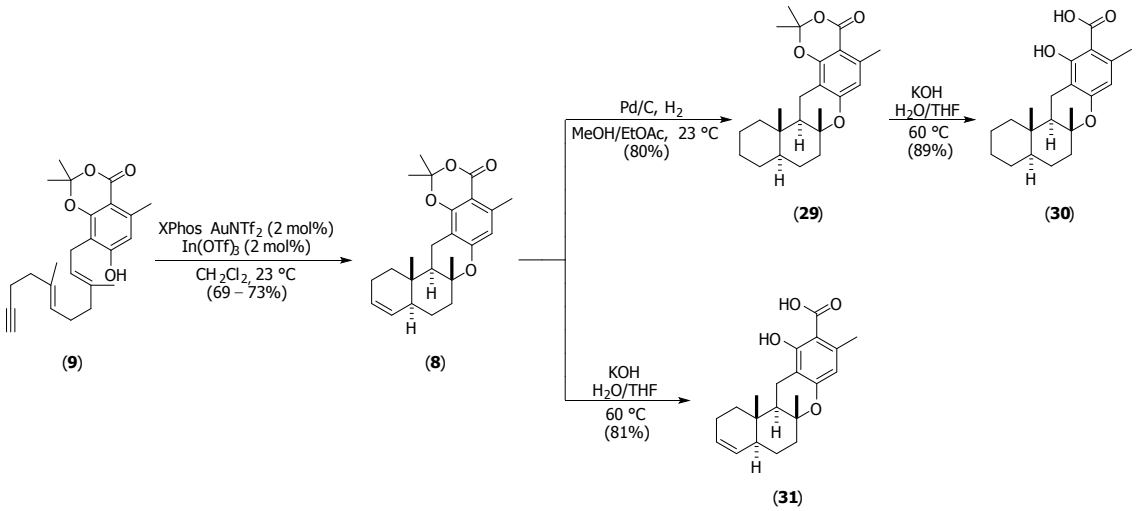
Scheme 5: Dienyne cyclization to produce hongoquercin alkene **8** and proposed mechanism.

The use of other Lewis acids, amongst others indium bromide or bismuth triflate, gave the pentacyclic product **8** in inferior yields (58%) or gave chromane **27** (26%) (Scheme 6). In addition, upon scale up and also with lower gold-catalyst loadings (1-4 mol %), cyclization to produce the pentacyclic product **8** was slow and proceeded in inferior yield (16%) with formation of the partially cyclized compounds **21** (47%) as the major products (Scheme 6). Reactions in alternative solvents (diethyl ether, dichloromethane or toluene) did not improve the efficiency of full cyclization. Such partial cyclization is a common observation in cationic polyene cyclizations.[15] Reaction of the dienyne **21** with a Lewis acid enhanced Brønsted acid catalyst, stannic chloride with trifluoroacetic acid,[4b, 15b, 15c] also did not provide high yields of the pentacyclic product **28** (50%) and more so as a mixture of isomers.[6f]



Scheme 6: Cyclization with dual catalysis.

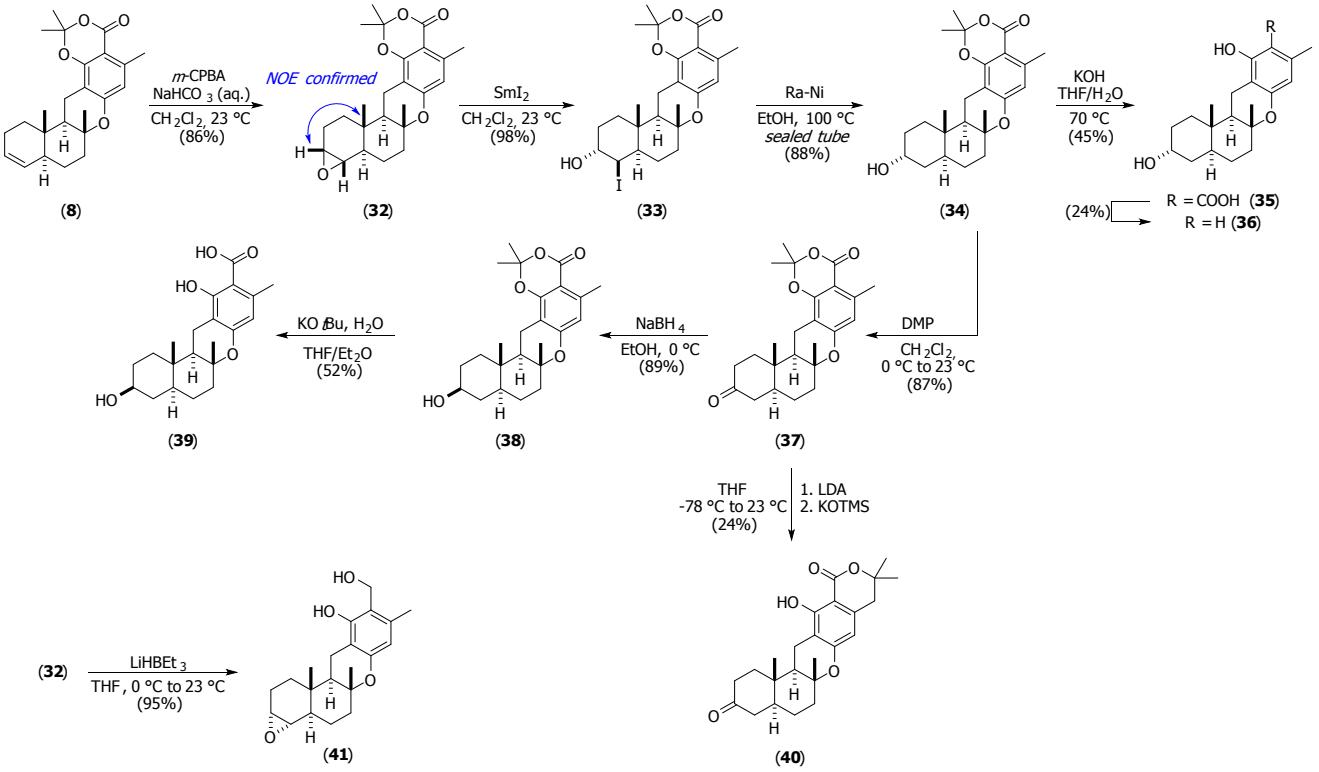
To avoid this issue of olefin isomerization, dual gold(I) and Lewis acid catalysis was examined. Thus, reaction using XPhos $AuNTf_2$ (2 mol%) and indium triflate (2 mol %) gave the pentacyclic product **8** as the major product (69–73%) with only traces of the partially cyclized trienes **21** (Scheme 7). The exact role of indium triflate remains unclear, however we speculate it helps in stabilizing intermediates **23** or **25** to favor cyclization over elimination. To the best of our knowledge, such a dual catalysts system has not been reported for dienyne cyclizations.[16] Subsequent hydrogenation of the pentacyclic product **8** over palladium on carbon (80%) followed by saponification gave resorcylic acid **30** in excellent yield (89%). Alternatively, saponification of the pentacyclic product **8** gave resorcylic acid **31** in good yields (81%).



Scheme 7: Dual catalyst system for the synthesis of analogs of hongoquercin A.

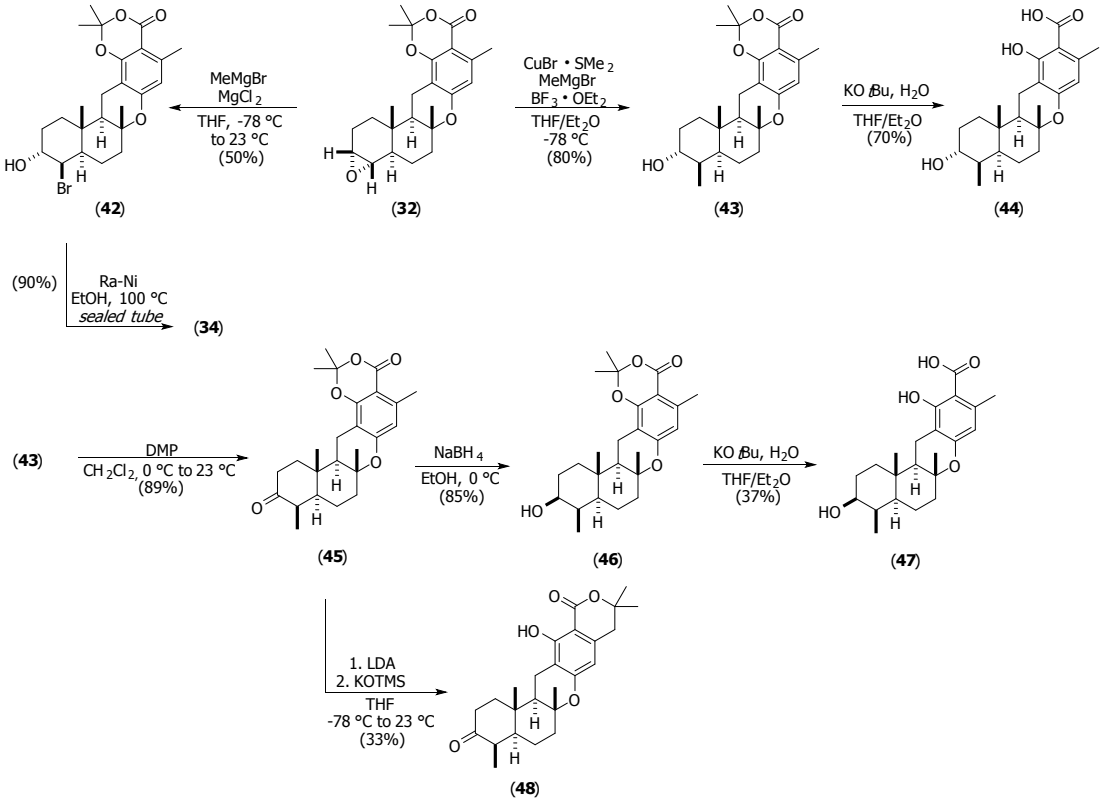
Further analogs of hongoquercin were synthesized from the pentacyclic product **8** (Scheme 8). Reaction with *m*-chloroperbenzoic acid gave the α-epoxide **32** (86%) and its stereochemistry was confirmed by nOe correlation experiments.[6g, 19a] Subsequent *trans*-diaxial ring opening with samarium(II) iodide in dichloromethane solution gave the iodo-alcohol **33** (98%) rather than any products derived from reduction.[18] Indeed, the same iodo-alcohol **33** (82%) was formed when epoxide **32** was allowed to react with samarium(II) iodide and triethylsilane. The structure and stereochemistry of the iodo-alcohol **33** were confirmed by X-ray crystallography. Reaction of iodo-alcohol **33** with Raney nickel[19] in ethanol gave alcohol **34** (88%). Attempts to reductively ring open epoxide **32** using lithium aluminum hydride[17] or lithium triethyl borohydride resulted in reductive cleavage of the dioxinone ring to produce the benzylic alcohol **41.**

Oxidation of alcohol **34** with Dess-Martin Periodinane (DMP) gave ketone **37** (87%) which was reduced with $NaBH_4$ to the *β*-alcohol **38** in excellent yields (89%).[20] Attempted Mitsunobu reaction of alcohol **34** using triphenylphosphine, di-*iso*-propyl azodicarboxylate and acetic acid failed to give the *β*-alcohol acetate in significant conversion.[21] While this sequence is not redox economic,[22] we anticipated the ketone functionality may have different bioactivities compared to the alcohol since it can only serve as a H-bond acceptor. Saponification of dioxinone **34** with potassium hydroxide in THF gave the desired resorcylic acid **35** in 45% yield and the corresponding decarboxylated resorcylate **36** in 24% yield. It was anticipated that *β*-alcohol **38** might react similarly, thus, to suppress this undesired reaction the saponification was carried out using potassium *tert*-butoxide in water,[23] which gave the *β*-alcohol resorcylic acid **39** in 52% as the sole product. Saponification of the ketone analog **37** was more complicated due to anticipated self-aldol reactions with common saponification methods. Thus, reaction of **37** with lithium diisopropylamide, in an attempt to protect the ketone as its enolate, followed by addition of potassium trimethylsilanoate gave lactone **40** in 24%, presumably *via* an anionically accelerated retro-Diels Alder reaction, followed by rapid quenching of the quino-methide ketene intermediate with acetone.



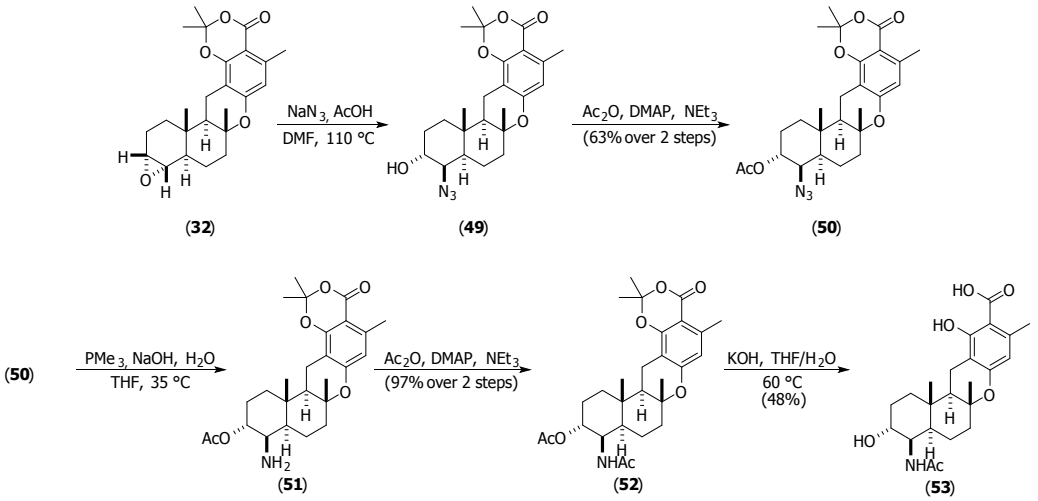
Scheme 8: Synthesis of unsubstituted analogs of hongoquercin B.

The syntheses of methyl branched hongoquercins are described in Scheme 9. Reaction of the α-epoxide **32** with the methylcopper magnesium bromide and boron trifluoride etherate complex gave alcohol **43** in good yield (80%).[24, 25] The course of this reaction is dependent on the order of addition. Whilst initial preparation of the $Me_2CuMgBr$ and boron trifluoride etherate complex and reaction gave alcohol **43** in good yield, the addition of boron trifluoride etherate to a mixture of the epoxide and $Me_2CuMgBr$ gave both alcohol **43** and bromohydrin **42**, the structure of which was determined by X-Ray crystallography. Alternative methylation protocols including methyl Grignard, trimethyl aluminium or the methyl cuprate derived from the reaction of MeMgBr and CuBr · SMe_2 failed to give alcohol **43** or showed incompatibility with the dioxinone group. Bromohydrin **42** was also obtained when a mixture of methylmagnesium bromide and magnesium chloride was allowed to react with epoxide **32**. Bromohydrin **42** was reconverted into alcohol **34** *via* Raney-Nickel mediated dehalogenation in 90% yield. Oxidation of *α*-alcohol **43** with Dess Martin periodinane gave ketone **45** (89%) and subsequent stereoselective reduction with sodium borohydride gave the *β*-alcohol **46** (85%).[20] Saponification of dioxinones **43** and **46** with potassium *tert*-butoxide in water respectively gave the resorcylic acids **44** (70%) and **47** (37%), while reaction of **45** with lithium diisopropylamide followed by potassium trimethylsilanoate gave lactone **48** (33%).



Scheme 9: Synthesis of methyl substituted analogs of hongoquercin B.

The syntheses of azido- and amino-hongoquercins are described in Scheme 10. Ring opening of the α-epoxide **32** with sodium azide in acetic acid and DMF gave the *trans*-diaxial azido-alcohol **49**. The reduction of this compound to the corresponding amino-alcohol proved problematical and the use of hydrogenolysis over palladium on carbon or palladium hydroxide, with thioacetic acid, or with Raney nickel and thioacetic acid[26, 27] failed to provide the corresponding amine or acetamide. An attempted Staudinger reaction was also unproductive and led to the recovery of the epoxide **32** (48%)[28] However, protection of azido-alcohol **49** with acetic anhydride gave acetoxy azide **50** (63%),[29] which on reaction with trimethylphosphine in THF and aqueous sodium hydroxide gave amine **51**, which was directly allowed to react with acetic anhydride, DMAP and triethylamine to produce the acetamido-ester **52** in 97% over 2 steps.[30] Chemoselective saponification of the acetate and dioxinone groups gave the resorcylic acid **53** in moderate yields (48%).



Scheme 10: Synthesis of azido- and amino-analogs of hongoquercin B.

CONCLUSION

In conclusion, several analogs of hongoquercin A and B were synthesized employing a late stage derivatization strategy from the hongoquercin alkene **8**. A dual bioinspired synthesis involving polyketide aromatization and a dual gold(I)-indium(III) catalyzed polyenye cyclization gave alkene **8** with full control of relative stereochemistry. This common precursor **8** was converted into the analogs **29** to **53** through late-stage functional group manipulation thereby enhancing the structural diversity of analogs of hongoquercin antibiotics. Further studies on the lithium diisopropylamide mediated formation of lactones **40** and **48** are ongoing.

Experimental Section

General Methods. CH_2Cl_2, $ClCH_2CH_2Cl$, $CH_3OCH_2CH_2OCH_3$, DMF, THF, Et_2O, MeOH, EtOH and PhMe were purified by filtration through activated alumina columns or purchased as extra dry solvents and stored over 4Å molecular sieves. NEt_3, $HNiPr_2$, pyridine and $NiPr_2Et$ were purchased as extra dry reagents and stored over 4Å molecular sieves. Pentane refers to the petroleum alkane fraction boiling between 40 °C and 60 °C. The concentration of *n*–BuLi was determined by titration against diphenylacetic acid according to the procedure by Kofron and Baclawski.[31] 2-Phenyl-1,3-dioxane-4,6-dione and 2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid were prepared according to literature procedures.[7b]

Reactions were carried out in cooled oven-dried (180 °C) glassware under a nitrogen or argon atmosphere using standard Schlenk techniques and with transfers by cannulas and syringes. Unless stated to the contrary, reactions were carried out at room temperature, when reaction temperatures refer to the external bath temperature. In all cases DrySyn heating mantels were used for reactions at elevated temperatures. Unless stated to the contrary, chromatography was carried out using the flash techniques of Still.[32] The progress of reactions was monitored by analytical thin-layer chromatography (TLC) on silica gel coated aluminum oxide F_{254} plates. Components on TLC plates were visualized under UV light or by spraying with $KMnO_4$ or acidic vanillin and warming. Flash column chromatography was performed by employing silica gel 60 Å, particle size 40−63μm.

^{1}H-NMR and proton decoupled ^{13}C-NMR spectra were respectively recorded at 400 MHz and 101 MHz in deuterated solvents at ambient temperature with chemical shifts are reported in ppm (δ) relative to Me_4Si and referenced to the residual solvent peak ($CDCl_3$: ^{1}H at 7.26 ppm, ^{13}C at 77.16 ppm; CD_3OD: ^{1}H at 3.31 and 4.87 ppm, ^{13}C at 49.0 ppm). Assignments of the ^{1}H-NMR and ^{13}C-NMR spectra were made by the analysis of chemical shift and coupling constant values, and as appropriate using COSY, DEPT-135, HSQC and HMBC. MS spectra were recorded by the Imperial College Mass Spectrometry Service under conditions of electrospray ionization (ESI), chemical ionization (CI) or electron ionization (EI). Infra-red spectra of solids and liquids were recorded as thin films. Melting points were recorded on a melting point apparatus and are uncorrected. X-Ray diffraction data were recorded at the Imperial College X-ray Crystallography Facility. Elemental microanalyses were recorded at the University of Cambridge Microanalysis Facility.

(*E*)-3,7-Dimethylocta-2,6-dien-1-yl benzoate (15)
A mixture of pyridine (6.33 g, 6.48 mL, 80.0 mmol, 2.00 equiv) and DMAP (978 mg, 8.00 mmol, 0.20 equiv) was added in one portion with stirring to geraniol (**14**) (6.16 g, 7.00 mL, 40.0 mmol, 1.00 equiv) in Et_2O (120 mL). Subsequently, PhCOCl (6.19 g, 5.11 mL, 44.0 mmol, 1.10 equiv) was added dropwise with stirring. After 20 h, reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL), the layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 40 mL), aqueous HCl (1 M; 3 x 30 mL) and brine (2 x 40 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (2 : 1 pentane : Et_2O) gave benzoate **15** (9.23 g, 35.7 mmol, 90%) as a colorless oil: R_f 0.65 (pentane : EtOAc 4 : 1); IR ν_{max} 1716, 1267, 1107, 710 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 2H), 7.58 – 7.53 (m, 1H), 7.43 (dd, *J* = 8.4, 7.0 Hz, 2H), 5.47 (tp, *J* = 7.0, 1.3 Hz, 1H), 5.09 (ddq, *J* = 8.3, 5.6, 1.5 Hz, 1H), 4.84 (dq, *J* = 7.1, 0.7 Hz, 2H), 2.19 – 2.10 (m, 2H), 2.10 – 2.04 (m, 2H), 1.77 (d, *J* = 1.7 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.61 (d, *J* = 1.3 Hz, 3H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$) δ 166.8, 142.5, 132.9, 132.0, 130.7, 129.7, 128.4, 123.9, 118.5, 62.0, 39.7, 26.5, 25.8, 17.9, 16.7; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{17}H_{23}O_2)^+$: 259.1693, found: 259.1705. When the reaction was carried out on a 70 mmol scale, the yield was 96%. On a 100 mmol scale the yield was ~99%. The experimental procedure followed the one above with pyridine (15.8 g, 16.2 mL, 200 mmol, 2.00 equiv) and DMAP (2.44 g, 20.0 mmol, 0.20 equiv) added in two portions with stirring to geraniol (**14**) (15.5 g, 17.6 mL, 100 mmol, 1.00 equiv) in Et_2O (500 mL). Subsequently, PhCOCl (15.5 g, 12.8 mL, 110 mmol, 1.10 equiv) was added dropwise with stirring. Work-up as above and chromatography (2 : 1 pentane : Et_2O) gave benzoate **15** (25.6 g, 99.1 mmol, 99%) as colorless oil. Analytical data were in good agreement with reported values.[10]

(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl benzoate (16)
SeO_2 (429 mg, 3.87 mmol, 0.10 equiv) and *t*-BuOOH (70 wt.-% in H_2O, 15.7 mL, 77.4 mmol, 2.00 equiv) were added sequentially in one portion with stirring to benzoate **15** (10.0 g, 38.7 mmol, 1.00 equiv) in CH_2Cl_2 (150 mL). After 30 h, reaction was quenched with a saturated aqueous $NaHCO_3$ (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with distilled water (50 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure (excess of *t*-BuOOH was removed by the addition and co-evaporation of PhMe). The resultant crude oil was used without further purification.

$NaBH_4$ (350 mg, 9.28 mmol, 0.24 equiv) was added with stirring to the ice-cold crude oil in MeOH (110 mL) in several portions over 30 min. After 2 h at 0 °C, the mixture was concentrated under reduced pressure, the residue was dissolved in Et_2O (100 mL) and quenched with distilled water (50 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were washed with distilled water (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (2 : 1 to 1 : 1 pentane : Et_2O) gave allylic alcohol **16** (6.07 g, 22.1 mmol, 57%) as a colorless oil: R_f 0.19 (pentane : EtOAc 4 : 1); IR ν_{max} 3417, 1715, 1269, 711 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.00 (m, 2H), 7.60 – 7.50 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 5.47 (tq, *J* = 7.0, 1.4 Hz, 1H, H2), 5.37 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 2H), 3.97 (s, 2H), 2.26 – 2.14 (m, 2H), 2.16 – 2.06 (m, 2H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.43 (s, 1H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$) δ 166.8, 141.9, 135.4, 133.0, 130.6, 129.7, 128.5, 125.4, 119.0, 69.0, 62.0, 39.2, 25.8, 16.7, 13.8; HRMS (ESI-ToF) m/z: $[M + Na]^+$ calcd. for $(C_{17}H_{22}O_3 + Na)^+$: 297.1461, found: 297.1471. Analytical data were in good agreement with literature values.[10,11] Upon repeating this experiment on a 100 mmol scale the yield dropped to 28% with methyl benzoate (4.70 g, 54%)

obtained after the reduction. Glyme was shown to be an appropriate substitute for methanol in the reduction step giving an overall yield of 56% on a 100 mmol scale. The experimental procedure followed the one above with SeO_2 (1.10 g, 9.91 mmol, 0.10 equiv) and *t*-BuOOH (70 wt.-% in H_2O, 40.2 mL, 198 mmol, 2.00 equiv) added sequentially in one portion with stirring to benzoate **15** (25.6 g, 99.1 mmol, 1.00 equiv) in CH_2Cl_2 (300 mL). Work-up as above and removal of volatiles *via* co-evaporation with PhMe gave a crude oil, which was dissolved in 1,2-dimethoxyethane (100 mL). To the ice-cold crude oil was added $NaBH_4$ (900 mg, 23.8 mmol, 0.24 equiv) in several portions with stirring over 30 mins. Work-up as above and chromatography (2 : 1 to 1 : 1 pentane : Et_2O) gave allylic alcohol **16** (15.0 g, 54.7 mmol, 56%) as a colorless oil.

(2*E*,6*E*)-8-Bromo-3,7-dimethylocta-2,6-dien-1-yl benzoate (17)

CBr_4 (3.14 g, 9.46 mmol, 2.00 equiv) was added in one portion with stirring to the ice-cold allylic alcohol **16** (1.30 g, 4.73 mmol, 1.00 equiv) in Et_2O (50.0 mL). PPh_3 (2.48 g, 9.46 mmol, 2.00 equiv) was added in several portions over 15 min. After stirring for 18 h, the mixture was diluted with CH_2Cl_2 (20 mL) and quenched with saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic layers were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL), filtered through Celite and chromatographed (100 % pentane to 4 : 1 pentane : Et_2O) to give bromide **17** (1.44 g, 4.28 mmol, 91%) as a colorless oil: R_f 0.61 (pentane : EtOAc 3 : 1); IR ν_{max} 1715, 1268, 1107, 1097, 711 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.11 – 7.98 (m, 2H), 7.61 – 7.50 (m, 1H), 7.49 – 7.39 (m, 2H), 5.63 – 5.53 (m, 1H), 5.47 (ddq, *J* = 7.1, 5.6, 1.3 Hz, 1H), 4.91 – 4.79 (m, 2H), 3.95 (d, *J* = 0.7 Hz, 2H), 2.23 – 2.15 (m, 2H), 2.15 – 2.08 (m, 2H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.76 (q, *J* = 0.9 Hz, 3H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$) δ 166.8, 141.6, 133.0, 132.6, 130.6, 130.6, 129.7, 128.5, 119.1, 61.9, 41.8, 38.7, 26.5, 16.7, 14.8; HRMS (ESI-ToF) m/z: $[M - OBz]^{\bullet}$ calcd. for $(C_{10}H_{16}Br)^{\bullet}$: 215.0435, found: 215.0441. Analytical data were in good agreement with literature values.[10]

(2*E*,6*E*)-3,7-Dimethyl-11-(trimethylsilyl)undeca-2,6-dien-10-yn-1-ol (18)

n–BuLi (2.36 M, 8.75 mL, 20.7 mmol, 4.50 equiv) was added dropwise with stirring to the dry-ice cold 1-(trimethylsilyl)propyne (2.33 g, 3.07 mL, 20.7 mmol, 4.50 equiv) in THF (95.0 mL). The resulting solution was stirred at -78 °C for 2 h, when bromide **17** (1.55 g, 4.61 mmol, 1.00 equiv) in THF (38.0 mL) was added dropwise with stirring and allowed to warm up to 23 °C. After 16 h, reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with distilled water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (5 : 1 to 3 : 1 pentane : Et_2O) gave a crude mixture containing silyl enynol **18** as yellow oil, which was used for the next step without further purification: R_f 0.30 (pentane : EtOAc 3 : 1); IR ν_{max} 3330, 1248, 837, 759 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.41 (tq, *J* = 6.9, 1.3 Hz, 1H), 5.16 (dddd, *J* = 6.9, 5.6, 2.6, 1.3 Hz, 1H), 4.19 – 4.12 (m, 2H), 2.30 (ddd, *J* = 7.7, 6.9, 1.1 Hz,2H), 2.21 – 2.16 (m, 2H), 2.16 – 2.08 (m, 2H), 2.07 – 2.00 (m, 2H), 1.68 (dd, *J* = 1.3, 0.7 Hz, 3H), 1.60 (q, *J* = 0.9 Hz, 3H), 1.17 (s), 0.14 (s, 9H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$) δ 139.8, 134.0, 125.2, 123.6, 107.5, 84.8, 59.6, 39.6, 38.7, 26.4, 19.4, 16.4, 16.0, 0.3; HRMS (ESI-ToF) m/z: $[M - OH]^+$ calcd. for $(C_{16}H_{27}Si)^+$: 247.1877, found: 247.1890.

(2*E*,6*E*)-3,7-Dimethylundeca-2,6-dien-10-yn-1-ol (13)

Bu_4NF (1 M in THF; 13.0 mL, 13.0 mmol, 2.82 equiv) was added dropwise with stirring to the ice-cold crude silyl enynol **18**. After 19 h, reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (3 : 1 pentane : Et_2O) gave dienynol **13** (838 mg, 4.36 mmol, 95%) as a yellow oil: R_f 0.26 (pentane: EtOAc 3 : 1); IR ν_{max} 3341, 1249, 1019, 839, 759 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.42 (tq, *J* = 6.9, 1.3 Hz, 1H), 5.18 (ddq, *J* = 8.3, 5.5, 1.3 Hz, 1H), 4.15 (dd, *J* = 7.2, 3.5 Hz, 2H), 2.31 – 2.25 (m, 2H), 2.23 – 2.17 (m, 2H), 2.17 – 2.10 (m, 2H), 2.05 (dd, *J* = 9.2, 6.1 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.61 (t, *J* = 1.1 Hz, 3H), 1.13 (s, 1H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$) δ 139.7, 133.7, 125.3, 123.6, 84.5, 68.5, 59.6, 39.5, 38.5, 26.3, 17.7, 16.4, 16.0; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{13}H_{21}O)^+$: 193.1587, found: 193.1587. Major peak m/z: $[M - OH]^+$ calcd. for $(C_{13}H_{19})^+$: 175.1481, found. 175.1481. Analytical data were in good agreement with literature values.[13] For larger scale reactions (>8 mmol) the yield was 67 – 72%. The experimental procedure followed the one above with n–BuLi (2.36 M, 38.1 mL, 90 mmol, 4.50 equiv) added dropwise with stirring to the dry-ice cold 1-(trimethylsilyl)propyne (10.1 g, 13.3 mL, 90 mmol, 4.50 equiv) in THF (250 mL). After 2 h at -78 °C, bromide **17** (6.74 g, 20.0 mmol, 1.00 equiv) in THF (80 mL) was added dropwise with stirring. Work-up as above and chromatography (5 : 1 to 3 : 1 pentane : Et_2O) afforded a crude oil. Bu_4NF (1 M in THF; 56.4 mL, 56.4 mmol, 2.82 equiv) was added dropwise with stirring at 0 °C. Work-up as above and chromatography (3 : 1 pentane : Et_2O) gave dienynol **13** (2.76 g, 14.4 mmol, 72%) as a yellow oil.

(2*E*,6*E*)-3,7-Dimethylundeca-2,6-dien-10-yn-1-yl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-oxobutanoate (12)

DCC (781 mg, 3.79 mmol, 1.82 equiv) and DMAP (463 mg, 3.79 mmol, 1.82 equiv) were sequentially added in one portion with stirring to 2-phenyl-1,3-dioxane-4,6-dione (728 mg, 3.79 mmol, 1.82 equiv) in CH_2Cl_2 (32.0 mL). After 15 min, 2-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)acetic acid (705 mg, 3.79 mmol, 1.82 equiv) was added in one portion. After 18 h, the mixture was cooled to 0 °C, the precipitate was filtered off and the solid was washed with small portions of CH_2Cl_2 until the precipitate appeared colorless. The filtrate was washed with aqueous HCl (1 M, 2 x 20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in PhMe (8.00 mL) and dienynol **13** (400 mg, 2.08 mmol, 1.00 equiv) in PhMe (8.00 mL) was added in one portion with stirring. The resulting pale-yellow solution was heated to 55 °C for 4 h after which the solution was concentrated. Chromatography (9 : 1 to 7 : 1 to 4 : 1 pentane : EtOAc) gave *β*-keto ester **12** (730 mg, 1.81 mmol, 87%) as orange oil: R_f 0.09 (pentane : EtOAc 4 : 1); IR ν_{max} 1724, 1638, 1389, 1375, 1272, 1202, 1016 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.36 (d, *J* = 0.6 Hz, 1H), 5.33 (tq, *J* = 7.2, 1.3 Hz, 1H), 5.15 (ddd, *J* = 5.4, 4.1, 2.8 Hz, 1H), 4.66 (d, *J* = 7.3 Hz, 2H), 3.51 (s, 2H), 3.50 (s, 2H), 2.31 – 2.24 (m, 2H), 2.23 – 2.16 (m, 2H), 2.15 – 2.10 (m, 2H), 2.10 – 2.04 (m, 2H), 1.94 (t, *J* = 2.5 Hz, 1H), 1.71 (s, 9H), 1.61 (d, *J* = 1.3 Hz, 3H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$) δ 195.8, 166.5, 163.7, 160.6, 143.5, 133.9,

124.9, 117.6, 107.5, 97.3, 84.5, 68.6, 62.8, 49.3, 47.1, 39.5, 38.5, 26.2, 25.2, 17.7, 16.6, 16.0; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{23}H_{31}O_6)^+$: 403.2115, found: 403.2106. Major peak m/z: $[M + Na]^+$ calcd. for $(C_{22}H_{30}O_6Na)^+$: 425.1935, found: 425.1947.

8-((2*E*,6*E*)-3,7-Dimethylundeca-2,6-dien-10-yn-1-yl)-7-hydroxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (9)

$MgCl_2$ (68.0 mg, 0.718 mmol, 1.00 equiv) and pyridine (114 mg, 120 µL, 1.44 mmol, 2.00 equiv) were added sequentially in one portion with stirring to ice-cold *β*-keto ester **12** (289 mg, 0.718 mmol, 1.00 equiv) in CH_2Cl_2 (3.60 mL). After 15 min, AcCl (85.0 mg, 76.6 µL, 1.08 mmol, 1.50 equiv) was added dropwise, and, after 1 h at 0 °C, reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the pH was adjusted to 1–2 with aqueous HCl (1 M). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in THF (4.30 mL) and tri(2-furyl)phosphine (53.0 mg, 0.228 mmol, 0.32 equiv) and tris(dibenzylideneacetone)dipalladium(0) (35.0 mg, 0.0382 mmol, 0.05 equiv) were added sequentially in one portion with stirring. After 1.5 h, cesium acetate (413 mg, 2.15 mmol, 3.00 equiv) in 2-propanol (4.30 mL) was added in one portion. After 1.5 h, reaction was quenched with aqueous HCl (1 M, 15 mL), the organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (19 : 1 to 15 : 1 pentane : EtOAc) gave resorcylate **9** (129 mg, 0.337 mmol, 47%) as yellow-white oil which solidified on standing.

Alternatively, $MgCl_2$ (95.0 mg, 0.996 mmol, 1.00 equiv) and pyridine (158 mg, 161 µL, 1.99 mmol, 2.00 equiv) were added sequentially each in one portion with stirring to ice-cold *β*-keto ester **12** (401 mg, 0.996 mmol, 1.00 equiv) in CH_2Cl_2 (5.00 mL). After 15 min, AcCl (117 mg, 106 µL, 1.49 mmol, 1.50 equiv) was added dropwise, and after 1 h at 0 °C, reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the pH was adjusted to 1-2 with aqueous HCl (1 M). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in THF (4.30 mL) and tri(2-furyl)phosphine (69.0 mg, 0.299 mmol, 0.30 equiv) and tris(dibenzylideneacetone)dipalladium(0) (46.0 mg, 0.0498 mmol, 0.05 equiv) were added sequentially in one portion with stirring. After 1.5 h, Et_3N (302 mg, 417 µL, 2.99 mmol, 3.00 equiv) was added in one portion, and, after 20 h, reaction was quenched with an aqueous HCl (1 M; 15 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (19 : 1 to 16 : 1 to 12 : 1 pentane : EtOAc) gave resorcylate **9** (176 mg, 0.460 mmol, 46%) as yellow-white oil, which solidified upon standing: R_f 0.33 (pentane : EtOAc 7 : 3); IR ν_{max} 3294, 1726, 1692, 1607, 1590, 1451, 1409, 1388, 1376, 1295, 1275, 1209, 1166, 1107 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.40 (d, *J* = 0.9 Hz, 1H), 5.91 (s, 1H, OH), 5.22 – 5.15 (m, 1H), 5.12 (tt, *J* = 5.6, 1.4 Hz, 1H), 3.32 (d, *J* = 7.3 Hz, 2H), 2.59 (d, *J* = 0.8 Hz, 3H), 2.29 – 2.21 (m, 2H), 2.21 – 2.15 (m, 2H), 2.15 – 2.09 (m, 2H), 2.06 (dt, *J* = 7.3, 3.1 Hz, 2H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.69 (s, 6H), 1.59 (d, *J* = 1.3 Hz, 3H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ 161.0, 160.1, 156.1, 143.1, 138.6, 134.0, 125.0, 121.1, 113.8, 112.7, 105.6, 105.0, 84.5, 68.5, 39.7, 38.5, 26.3, 25.9, 22.2, 22.0, 17.7, 16.4, 16.0; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{31}O_4)^+$: 383.2217, found. 383.2234; Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.29; H, 7.80.

(±)-2,2,5,7a,13a-Pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (8)

2-Dicyclohexylphosphino-2',4',6'-tri-*iso*-propylbiphenylgold(I) bis(trifluoromethanesulfonyl)imide (28 mg, 0.029 mmol, 0.025 equiv) was added in one portion with stirring to resorcylate **9** (444 mg, 1.16 mmol, 1.00 equiv) in CH_2Cl_2 (25 mL). After 30 min, $In(OTf)_3$ (16 mg, 0.029 mmol, 0.025 equiv) was added in one portion. After 17 h, reaction was quenched with water (20 mL), the organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$) and filtered. Concentration under reduced pressure and chromatography (15 : 1 pentane : EtOAc) gave pentacyclic resorcylate **8** (325 mg, 0.85 mmol, 73%) as a white solid: m.p. 198 °C – 200 °C (CH_2Cl_2/pentane); R_f 0.61 (pentane : EtOAc 4 : 1); IR ν_{max} 1727, 1616, 1573, 1305, 1289, 1279,1208, 1167, 1129 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.34 (d, *J* = 0.9 Hz, 1H), 5.58 (dq, *J* = 10.0, 3.2 Hz, 1H), 5.38 (dq, *J* = 9.9, 2.1 Hz, 1H), 2.66 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.57 (s, 3H), 2.33 – 2.23 (m, 1H), 2.13 (ddq, *J* = 5.2, 3.9, 2.7, 1.9 Hz, 2H), 2.07 (dt, *J* = 12.9, 3.4 Hz, 1H), 2.03 (dt, *J* = 3.2, 1.6 Hz, 1H), 1.87 (dt, *J* = 12.8, 4.0 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.66 – 1.62 (m, 1H), 1.59 (td, *J* = 6.5, 5.9, 3.7 Hz, 1H), 1.50 – 1.42 (m, 1H), 1.27 (d, *J* = 1.0 Hz, 3H), 1.22 (dd, *J* = 5.0, 4.1 Hz, 1H), 0.82 (d, *J* = 0.8 Hz, 3H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$) δ 161.0, 159.1, 156.2, 142.3, 129.9, 126.1, 114.6, 108.6, 104.9, 104.2, 78.9, 48.8, 46.0, 40.2, 35.2, 35.0, 26.3, 25.6, 25.2, 23.2, 22.1, 21.5, 17.0, 11.5; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{31}O_4)^+$: 383.2217, found. 383.2223.

(*E*)-7-Hydroxy-2,2,5-trimethyl-8-(3-methyl-5-(2-methylcyclohexa-2,5-dien-1-yl)pent-2-en-1-yl)-4*H*-benzo[*d*][1,3]dioxin-4-one, (*E*)-7-hydroxy-2,2,5-trimethyl-8-(3-methyl-5-(6-methylenecyclohex-2-en-1-yl)pent-2-en-1-yl)-4*H*-benzo[*d*][1,3]dioxin-4-one, and (*E*)-7-hydroxy-2,2,5-trimethyl-8-(3-methyl-5-(2-methylcyclohexa-1,5-dien-1-yl)pent-2-en-1-yl)-4*H*-benzo[*d*][1,3]dioxin-4-one (21)

Resorcylate **9** (30.0 mg, 78.4 µmol, 1.00 equiv) in PhMe (1.00 mL) was added dropwise with stirring to 2-(dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl)gold(I) bis(trifluoromethanesulfonyl)imide (53.0 mg, 3.92 µmol, 0.05 equiv). After 17 h, the mixture was filtered through a silica plug with CH_2Cl_2 (2 x 5.00 mL) and EtOAc (1 x 5.00 mL) and the combined filtrates were concentrated under reduced pressure. Chromatography (17 : 1 to 9 : 1 pentane : EtOAc) gave a mixture of the three alkenes **21** (13.0 mg, 34.0 µmol, 42%) as a yellow oil: R_f 0.23 (pentane : EtOAc 4 : 1); IR ν_{max} 3337, 2924, 1728, 1696, 1607, 1592, 1452, 1295, 1277, 1209 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 0.9 Hz, 1H), 6.37 (dd, *J* = 1.7, 0.9 Hz, 1H), 5.87 – 5.75 (m, 1H), 5.66 – 5.60 (m, 1H), 5.59 – 5.51 (m, 1H), 5.45 – 5.40 (m, 1H), 5.35 – 5.27 (m, 1H), 5.23 – 5.16 (m, 1H), 3.32 (d, *J* = 7.2 Hz, 2H), 2.77 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.66 (t, *J* = 5.3 Hz, 1H), 2.59 (t, *J* = 0.9 Hz, 5H), 2.56 (d, *J* = 0.7 Hz, 1H), 2.39 – 2.26 (m, 1H), 2.22 – 2.07 (m, 3H), 2.07 – 1.82 (m, 2H), 1.82 – 1.80 (m, 2H), 1.79 (q, *J* = 1.5 Hz, 1H), 1.70 (d, *J* = 4.3 Hz, 3H), 1.68 (s, 3H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ 161.5, 161.3, 160.1, 159.4, 144.3, 143.0, 142.4, 138.1, 137.0, 130.6, 126.0, 125.9, 124.9, 124.2, 124.1, 122.9, 122.2, 121.3, 117.9, 116.0, 113.7, 113.5, 105.0, 104.9, 49.1, 41.8, 38.6, 35.6, 33.9, 33.6, 32.1, 31.8, 31.0, 30.5, 29.8, 28.8, 26.0,

25.9, 23.4, 22.4, 22.2, 22.0, 21.4, 17.1, 16.4, 11.5; HRMS (ESI-ToF) m/z: $[M - H]^-$ calcd. for $(C_{24}H_{29}O_4)^-$: 381.2071, found. 381.2057.

(±)-2,2,5,8-Tetramethyl-8-(4-methyloct-3-en-7-yn-1-yl)-9,10-dihydro-4*H*,8*H*-[1,3]dioxino[4,5-*f*]chromen-4-one (27)

The experimental procedure followed that for compound **21** with 0.30 equiv of $Bi(OTf)_3$. Chromatography (pentane : EtOAc 15 : 1) gave chromane **27** (8.0 mg, 0.0209 mmol, 26%) as yellow oil: R_f 0.47 (pentane : EtOAc 3 : 1); IR ν_{max} 1728, 1574, 1282 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.2 Hz, 1H), 5.26 – 5.14 (m, 1H), 2.89 (d, *J* = 6.5 Hz, 1H), 2.58 (s, 4H), 2.29 – 2.25 (m, 2H), 2.20 (d, *J* = 6.9 Hz, 1H,), 2.12 (q, *J* = 7.5 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.94 (dq, *J* = 3.9, 2.4, 1.7 Hz, 1H), 1.79 (dq, *J* = 23.1, 6.8 Hz, 2H), 1.70 (s, 9H), 1.61 (d, *J* = 1.3 Hz, 3H), 1.30 (s, 3H); HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{31}O_4)^+$: 383.2217, found: 383.2208.

(±)-2,2,5,7a,13a-Pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (29)

Pd/C (5%, 10 mg) was added in one portion with stirring to resorcylate **8** (25 mg, 0.063 mmol, 1.00 equiv) in MeOH (3.0 mL) and EtOAc (1.0 mL). The black suspension was purged with H_2 three times. After 17 h stirring under H_2, the mixture was filtered through Celite® and the solids rinsed with EtOAc (3 x 20 mL). The combined organic layers were concentrated under reduced pressure. Chromatography (9 : 1 pentane : Et_2O) gave resorcylate **29** (20 mg, 0.052 mmol, 80%) as white solid: m.p. 162 °C – 164 °C (CH_2Cl_2/pentane); R_f 0.58 (pentane : EtOAc 7 : 3); IR ν_{max} 1724, 1615, 1572, 1450, 1375, 1299, 1282, 1207, 1171, 1129, 901, 730 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 1.0 Hz, 1H), 2.61 (dd, *J* = 17.0, 5.1 Hz, 1H), 2.57 (s, 3H), 2.28 – 2.18 (m, 1H), 2.00 (dt, *J* = 12.5, 3.2 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.72 (s, 3H), 1.70 (d, *J* = 2.1 Hz), 1.69 (s, 3H), 1.57 (d, *J* = 5.0 Hz, 1H), 1.53 (t, *J* = 4.9 Hz, 2H), 1.41 (d, *J* = 9.6 Hz, 1H), 1.39 – 1.33 (m, 2H), 1.32 – 1.28 (m, 2H) 1.28 (dd, *J* = 4.3, 3.3 Hz), 1.24 (d, *J* = 8.1 Hz), 1.21 (d, *J* = 0.9 Hz, 3H), 1.02 – 0.91 (m, 1H), 0.83 (s, 3H); ^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$) δ 161.0, 159.0, 156.2, 142.2, 114.6, 108.6, 104.9, 104.1, 78.9, 49.9, 47.7, 40.2, 38.8, 36.5, 28.1, 26.8, 26.6, 26.3, 25.6, 22.1, 21.3, 21.1, 16.7, 12.2; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{33}O_4)^+$: 385.2373, found: 385.2370. Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.29; H, 8.59.

(±)-11-Hydroxy-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (30)

Aqueous KOH (5 M; 1.0 mL, 5 mmol, 100 equiv) was added with vigorous stirring to resorcylate **29** (20 mg, 0.052 mmol, 1.00 equiv) in THF (1.0 mL). After 6 days at 60 °C, the mixture was diluted with H_2O (10 mL) and EtOAc (10 mL) and acidified with aqueous HCl (1 M; 10 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (1 : 4 : 5 EtOAc : CH_2Cl_2 : pentane) gave resorcylic acid **30** (16 mg, 0.046 mmol, 89%) as an off-white solid: m.p, 183 – 185 °C (CH_2Cl_2); R_f 0.15 (pentane : EtOAc 7 : 3), IR ν_{max} 2927, 1616, 1595, 1576, 1454, 1269, 1263, 1183, 1109, 800 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 6.13 – 6.09 (m, 1H), 2.70 (dd, *J* = 16.9, 5.0 Hz, 1H), 2.46 (d, *J* = 2.9 Hz, 3H), 2.26 (ddd, *J* = 15.9, 13.6, 6.7 Hz, 1H), 1.97 (dt, *J* = 12.5, 3.2 Hz, 1H), 1.84 – 1.77 (m, 1H), 1.77 – 1.70 (m, 1H), 1.68 (d, *J* = 11.7 Hz, 1H), 1.60 – 1.56 (m, 1H), 1.55 – 1.50 (m, 1H), 1.47 – 1.41 (m, 2H), 1.40 (d, *J* = 2.8 Hz), 1.34 – 1.30 (m, 4H), 1.27 – 1.24 (m, 1H), 1.21 (d, *J* = 0.9 Hz, 3H), 1.02 (s, 1H), 0.88 (d, *J* = 0.8 Hz, 3H); ^{13}C-NMR (101 MHz, CD_3OD) δ 175.6, 164.5, 159.0, 141.8, 112.9, 109.0, 104.9, 79.2, 51.6, 47.8, 41.3, 40.0, 37.5, 30.8, 29.2, 27.7, 24.2, 22.4, 21.2, 17.8, 12.4; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{21}H_{29}O_4)^+$: 345.2060, found: 345.2068.

(±)-11-Hydroxy-6a,9,12b-trimethyl-1,4a,5,6,6a,12,12a,12b-octahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (31)

Aqueous KOH (5 M; 1.5 mL, 7.5 mmol, 129 equiv) was added in one portion with stirring to resorcylate **8** (22 mg, 0.058 mmol, 1.00 equiv) in THF (1.5 mL). After vigorously stirring for 6 days at 60 °C, the mixture was diluted with water (5 mL) and EtOAc (5 mL) and acidified with aqueous HCl (1 M; 10 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (1 : 2 : 7 EtOAc : CH_2Cl_2 : pentane) gave resorcylic acid **31** (16 mg, 0.047 mmol, 81%) as an off-white solid: m.p. 158 °C – 162 °C (CH_2Cl_2); R_f 0.12 (pentane : EtOAc 7 : 3); IR ν_{max} 2927, 1621, 1454, 1264 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 6.12 (dd, *J* = 2.2, 0.9 Hz, 1H), 5.66 – 5.53 (m, 1H), 5.39 (dq, *J* = 9.8, 2.1 Hz, 1H), 2.80 – 2.67 (m, 1H), 2.46 (s, 3H), 2.39 – 2.26 (m, 1H), 2.14 (dq, *J* = 5.8, 3.2 Hz, 2H), 2.06 – 2.01 (m, 1H), 2.00 – 1.94 (m, 1H), 1.94 – 1.84 (m, 1H), 1.73 (ddd, *J* = 16.3, 8.9, 4.1 Hz, 1H), 1.68 – 1.59 (m, 1H), 1.59 – 1.54 (m, 1H), 1.54 – 1.44 (m, 1H), 1.35 – 1.31 (m, 1H), 1.26 (d, *J* = 0.9 Hz, 3H), 0.85 (d, *J* = 0.9 Hz, 3H); ^{13}C{^{1}H}-NMR (101 MHz, CD_3OD) δ 164.1, 159.0, 154.3, 141.8, 131.0, 126.9, 112.9, 109.0, 105.2, 79.3, 50.4, 47.2, 41.4, 36.1, 36.0, 26.2, 24.2, 24.1, 21.7, 18.1, 11.8; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{21}H_{27}O_4)^+$: 343.1904, found: 343.1905; also found m/z: $[M + D]^+$ calcd. for $(C_{21}H_{26}DO_4)^+$: 344.1965; found: 344.1967; Anal. Calcd for $C_{21}H_{26}O_4.0.5H_2O$ C, 71.77; H, 7.74. Found: C, 71.89; H, 7.49.

(±)-3a,6,9,9,11b-Pentamethyl-1a,1b,3,3a,11,11a,11b,12,13,13a-decahydro-2*H*,7*H*-[1,3]dioxino[4,5-*a*]oxireno[2',3':5,6]benzo[1,2-*j*]xanthen-7-one (32)

m-CPBA (65.0 mg, 0.291 mmol, 1.05 equiv) was added in two portions with stirring to resorcylate **8** (106 mg, 0.277 mmol, 1.00 equiv) in CH_2Cl_2 (3.00 mL) and saturated aqueous $NaHCO_3$ (0.5 M, 0.84 mL). After 3 h, further *m*-CPBA (18.0 mg, 83.1 µmol, 0.3 equiv) was added, and, after 1.5 h, reaction was quenched with water. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (1 x 10 mL). The combined organic layers were washed with aqueous NaOH (1 M; 15 mL), distilled water (10 mL) and brine (15 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (6 : 1 to 4 : 1 pentane : EtOAc) gave epoxide **32** (95.0 mg, 0.238 mmol, 86%) as white foam: R_f 0.18 (pentane : EtOAc 4 : 1); IR ν_{max} 1718, 1615, 1571, 1289, 1279, 1206, 1128, 1036, 919, 900, 727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 0.2 Hz, 1H), 3.19 (t, *J* = 3.4 Hz, 1H), 2.79 (dt, *J* = 4.0, 0.9 Hz, 1H), 2.59 (dd, *J* = 17.0, 4.8 Hz, 1H), 2.56 (s, 3H), 2.27 – 2.10 (m, 1H), 2.16 – 2.09 (m, 1H), 2.06 (ddd, *J* = 12.8, 6.6, 2.5 Hz, 1H), 1.94 – 1.88 (m, 1H) 1.87 (td, *J* = 5.0, 4.0, 2.3 Hz, 1H), 1.71 (d, *J* =

5.6 Hz, 1H), 1.71 (d, *J* = 0.7 Hz, 3H), 1.67 (d, *J* = 0.7 Hz, 3H), 1.67 – 1.60 (m, 1H), 1.57 (dd, *J* = 13.2, 3.3 Hz, 1H), 1.53 – 1.50 (m, 1H) 1.50 (m, 1H), 1.26 (d, *J* = 1.0 Hz, 3H), 1.03 – 0.95 (m, 1H,), 0.83 (d, *J* = 0.6 Hz, 3H); $^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$) δ 160.8, 158.8, 156.1, 142.2, 114.5, 108.2, 104.9, 104.2, 78.2, 54.8, 51.8, 47.9, 47.5, 40.0, 34.3, 31.7, 26.3, 25.5, 24.5, 22.0, 21.4, 20.8, 17.2, 12.6; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{31}O_5)^+$: 399.2166, found. 399.2176.

(±)-11-Hydroxy-10-iodo-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (33)

Et_3SiH (48 mg, 0.066 mL, 0.42 mmol, 2.4 equiv) and SmI_2 (0.1 M in THF; 3.2 mL, 0.32 mmol, 1.88 equiv) were sequentially added dropwise with stirring to strictly deoxygenated epoxide **32** (69 mg, 0.17 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL). After 20 min, the mixture was diluted with Et_2O (5 mL) and quenched with H_2O (5 mL). Saturated aqueous $NaHCO_3$ (5 mL) was added and the organic layer was separated. The aqueous layer was further extracted with Et_2O (2 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (3 : 1 pentane : Et_2O to 3:1 pentane : EtOAc) gave iodohydrin **33** (75 mg, 0.14 mmol, 82%) as a white solid.

Alternatively: SmI_2 in THF (0.1 M; 2.3 mL, 0.23 mmol, 1.8 equiv) was added dropwise with stirring to a strictly deoxygenated epoxide **32** (50 mg, 0.13 mmol, 1.00 equiv) in CH_2Cl_2 (8.0 mL). After 1 h, the mixture was diluted with Et_2O (10 mL) and quenched with H_2O (10 mL). Saturated aqueous $NaHCO_3$ (10 mL) was added, the organic layer was separated, and the aqueous layer was further extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (1 : 1 : 8 pentane : EtOAc : CH_2Cl_2) gave iodohydrin **33** (65 mg, 0.12 mmol, 98%) as a white solid: m.p.: 117 – 120 °C (dec.) (CH_2Cl_2/pentane); R_f 0.21 (pentane : EtOAc 7 : 3); IR ν_{max} 3425, 1727, 1701, 1619, 1573, 1307, 1293, 1284, 1171, 1130, 1047 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.31 (s, 1H), 4.39 (q, *J* = 2.7 Hz, 1H), 4.26 (dt, *J* = 3.9, 2.1 Hz, 1H), 2.99 (s, 1H, -OH), 2.56 (d, *J* = 6.9 Hz, 1H), 2.54 (s, 3H), 2.34 – 2.28 (m, 1H), 2.28 – 2.23 (m, 1H), 2.07 (d, *J* = 10.3 Hz, 1H), 1.90 – 1.79 (m, 1H), 1.71 (s, 3H), 1.69 (s, 1H), 1.67 (s, 3H), 1.62 (dd, *J* = 5.5, 4.2 Hz, 1H), 1.61 – 1.59 (m, 1H), 1.58 (d, *J* = 3.3 Hz, 1H), 1.55 (d, *J* = 4.5 Hz, 1H), 1.51 (d, *J* = 3.7 Hz, 1H), 1.39 – 1.37 (m, 1H), 1.22 (s, 3H), 1.12 (s, 3H); $^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$) δ 161.2, 158.8, 156.2, 142.2, 114.5, 108.0, 105.0, 104.1, 78.3, 73.1, 51.0, 42.3, 39.5, 37.3, 36.7, 31.5, 28.5, 26.3, 25.6, 23.2, 22.1, 21.0, 15.9, 14.2; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{32}IO_5)^+$: 527.1289, found: 527.1284; Anal. Calcd for $C_{24}H_{31}IO_5$: C, 54.76; H, 5.94. Found: C, 54.66; H, 5.88.

(±)-11-Hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (34)

Raney-Ni (50% aqueous suspension; 1.4 mL) was added portionwise with stirring to iodohydrin **33** (75 mg, 0.14 mmol, 1.00 equiv) in EtOH (7.0 mL). After heating at reflux for 3 h, the mixture was filtered through Celite® and the solids rinsed with EtOH (20 mL). The filtrate was concentrated under reduced pressure, and the residue dissolved in EtOAc (20 mL) and washed with water (10 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (3 : 1 to 1 : 1 pentane : Et_2O) gave *α*-alcohol **34** (50 mg, 0.12 mmol, 88%) as a white solid: m.p. 97 – 100 °C (CH_2Cl_2/pentane); R_f 0.12 (pentane : EtOAc 7 : 3); IR ν_{max} 3430, 1707, 1614, 1570, 1282, 1207, 1170, 1127, 1097, 907, 727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 4.07 (q, *J* = 2.9 Hz, 1H), 2.61 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.55 (s, 3H), 2.29 – 2.18 (m, 1H), 2.00 (dt, *J* = 12.6, 3.2 Hz, 1H), 1.81 – 1.78 (m, 1H), 1.77 – 173 (m, 1H), 1.71 (s, 3H), 1.73 (s, 1H), 1.67 (s, 3H), 1.64 (d, *J* = 5.0 Hz, 1H), 1.61 (d, *J* = 4.7 Hz, 1H), 1.56 (dt, *J* = 7.9, 2.5 Hz, 1H), 1.53 – 1.46 (m, 2H), 1.47 – 1.40 (m, 1H), 1.40 – 1.30 (m, 2H), 1.21 (s, 3H), 0.82 (s, 3H); $^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$) δ 161.0, 159.0, 156.2, 142.1, 114.6, 108.5, 104.9, 104.1, 78.7, 66.1, 49.4, 40.0, 39.4, 36.3, 35.1, 32.7, 28.4, 26.3 (2 x C), 25.5, 22.1, 21.0, 16.7, 11.1; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{33}O_5)^+$: 401.2323, found: 401.2330. Similar yields (90%) were obtained when the bromohydrin **40** was allowed to react in this fashion.

(±)-3,11-Dihydroxy-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (35)

Aqueous KOH (5 M, 1.0 mL) was added dropwise with stirring to *α*-alcohol **34** (37 mg, 0.092 mmol, 1.00 equiv) in THF (1.0 mL). After vigorous stirring for 6 days at 60 °C, the mixture was diluted with H_2O (10 mL) and EtOAc (10 mL) and acidified with aqueous HCl (1 M, 10 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 to 2 : 8 to 3 : 7 EtOAc : CH_2Cl_2) gave resorcylic acid **35** (15 mg, 0.042 mmol, 45%) as a yellow-transparent film: R_f 0.09 (pentane : EtOAc 1 : 1); IR ν_{max} 3478, 2928, 2862, 1621, 1578, 1452, 1262, 1175 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.92 (s, 1H, OH), 6.22 (d, *J* = 0.8 Hz, 1H), 4.11 (d, *J* = 3.3 Hz, 1H), 2.76 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.51 (s, 3H), 2.30 (dd, *J* = 16.8, 13.3 Hz, 1H), 2.05 – 2.00 (m, 1H), 1.80 (dd, *J* = 13.2, 3.1 Hz, 1H), 1.77 – 1.74 (m, 1H), 1.72 (d, *J* = 6.0 Hz, 1H), 1.67 (d, *J* = 4.5 Hz, 1H), 1.64 (d, *J* = 5.7 Hz, 1H), 1.63 (d, *J* = 4.3 Hz, 1H), 1.60 – 1.46 (m, 2H), 1.41 (s, 1H), 1.38 (dd, *J* = 9.7, 2.7 Hz, 2H), 1.23 (d, *J* = 0.9 Hz, 3H), 0.84 (s, 3H); $^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$): δ 175.6, 163.9, 159.0, 141.6, 112.8, 108.2, 102.7, 78.7, 66.4, 49.7, 40.1, 39.6, 36.4, 35.1, 32.8, 28.5, 26.4, 24.3, 21.1, 17.0, 11.1; HRMS (ESI-ToF) m/z: $[M - H]^-$ calcd. for $(C_{21}H_{27}O_5)^-$: 359.1864, found: 359.1867.

(±)-6a,9,12b-Trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2H-benzo[a]xanthene-3,11-diol (36)

Aqueous KOH (5 M, 1.0 mL) was added dropwise with stirring to *α*-alcohol **34** (37 mg, 0.092 mmol, 1.00 equiv) in THF (1.0 mL). After vigorous stirring for 6 days at 60 °C, the mixture was diluted with H_2O (10 mL) and EtOAc (10 mL) and acidified with aqueous HCl (1 M, 10 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 to 2 : 8 to 3 : 7 EtOAc : CH_2Cl_2) gave phenol **36** (7.0 mg, 0.022 mmol, 24%) as a yellow-white film: R_f 0.29 (pentane : EtOAc 1 : 1); IR ν_{max} 3381, 1587, 1445, 1333, 1260, 1172, 1059, 1035, 1018, 988, 822 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.24 (s, 1H), 6.17 (d, *J* = 1.6 Hz, 1H), 4.68 (s, 1H), 4.13 – 4.06 (m, 1H), 2.67 (dd, *J* = 16.2, 5.1 Hz, 1H), 2.37 – 2.29 (m, 1H), 2.20 (s, 3H), 2.00 (dt, *J* = 12.6, 3.3 Hz, 1H), 1.81 – 1.78 (m, 1H), 1.77 (dd, *J* = 4.4, 2.3 Hz, 1H), 1.74

(dd, *J* = 4.7, 3.4 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.66 – 1.62 (m, 1H), 1.61 – 1.58 (m, 1H), 1.53 – 1.44 (m, 2H), 1.41 (t, *J* = 4.3 Hz, 1H), 1.39 – 1.34 (m, 2H), 1.22 (d, *J* = 1.0 Hz, 3H), 0.85 – 0.81 (m, 3H); $^{13}C\{^{1}H\}$-NMR (126 MHz, $CDCl_3$): δ, 154.2, 153.9, 137.4, 110.4, 107.2, 106.8, 77.0, 66.4, 50.0, 40.3, 39.6, 36.3, 35.2, 32.9, 28.5, 26.4, 21.3, 21.0, 16.9, 11.1; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{20}H_{29}O_3)^+$: 317.2111, found: 317.2102. Phenol **36** has a similar R_f value to the starting material. Reactions might therefore be considered incomplete due to the similarity of the R_f value. Noteworthy, while the starting *α*-alcohol **34** is UV-active and stains with acidic vanillin, phenol **36** is not strongly UV-active and only appears upon staining with acidic vanillin.

(±)-2,2,5,7a,13a-Pentamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4,11(10*H*)-dione (37)

Dess-Martin periodinane (201 mg, 0.474 mmol, 2.00 equiv) was added with stirring in two portions over the course of 5 mins to ice-cold *α*-alcohol **34** (95.0 mg, 0.237 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL). After 1.5 h, the mixture was concentrated and loaded onto a column with a Celite® pad. Chromatography (1 : 1 to 1 : 2 pentane : CH_2Cl_2) gave ketone **37** (82.0 mg, 0.206 mmol, 87%) as a white solid: m.p. 223 – 226 °C (dec.) (CH_2Cl_2/pentane); R_f 0.22 (pentane : EtOAc 7 : 3); IR ν_{max} 1709, 1615, 1572, 1451, 1299, 1279, 1206, 1170, 1128, 1038, 912, 899, 725 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 2.63 (dd, *J* = 16.7, 5.0 Hz, 1H), 2.54 (s, 3H), 2.49 – 2.35 (m, 2H), 2.35 – 2.29 (m, 1H), 2.28 – 2.18 (m, 2H), 2.17 – 2.09 (m, 1H), 2.04 (dt, *J* = 12.9, 3.2 Hz, 1H), 1.74 (d, *J* = 5.1 Hz, 1H), 1.71 (s, 3H, H1), 1.68 (s, 1H), 1.67 (s, 3H), 1.65 – 1.57 (m, 1H), 1.55 – 1.45 (m, 2H), 1.45 – 1.38 (m, 1H), 1.25 (s, 3H), 1.05 (s, 3H); $^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$) δ 210.5, 160.8, 158.6, 156.1, 142.4, 114.5, 107.9, 104.9, 104.2, 78.2, 49.0, 46.3, 43.9, 39.5, 38.3, 37.2, 35.8, 26.3, 26.3, 25.5, 22.0, 20.8, 17.3, 11.5; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{31}O_5)^+$: 399.2166, found: 399.2174; Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.19; H, 7.52.

(±)-11-Hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (38)

$NaBH_4$ (2.3 mg, 0.062 mmol, 1.30 equiv) was added in one portion with stirring to ice-cold ketone **37** (19 mg, 0.048 mmol, 1.00 equiv) in EtOH (1.0 mL). After 1 h at 0 °C, the mixture was diluted with Et_2O (5.0 mL) and reaction was quenched with saturated aqueous NH_4Cl (3.0 mL). The organic layer was separated, and the aqueous layer was further extracted with Et_2O (3 x 5.0 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (1 : 1 : 8 EtOAc : pentane : CH_2Cl_2) gave *β*-alcohol **38** (17 mg, 0.042 mmol, 89%) as a white foam: R_f 0.08 (pentane : EtOAc 7 : 3); IR ν_{max} 3440, 2930, 1718, 1615, 1572, 1452, 1388, 1376, 1287, 1209, 1129, 1042, 902, 731 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 1.0 Hz, 1H), 3.65 (tt, *J* = 10.6, 4.8 Hz, 1H), 2.63 – 2.58 (m, 1H), 2.56 (s, 3H), 2.28 (dd, *J* = 16.8, 13.3 Hz, 1H), 2.02 (dt, *J* = 12.6, 3.0 Hz, 1H), 1.90 – 1.85 (m, 1H), 1.85 – 1.81 (m, 1H), 1.72 (s, 3H), 1.70 (d, *J* = 1.0 Hz, 1H), 1.68 (s, 3H), 1.65 (dd, *J* = 4.8, 2.2 Hz, 1H), 1.59 – 1.51 (m, 1H), 1.51 – 1.46 (m, 1H), 1.48 – 1.34 (m, 2H), 1.30 (dd, *J* = 11.3, 1.5 Hz, 1H), 1.27 – 1.23 (m, 1H), 1.22 (d, *J* = 0.9 Hz, 3H), 1.13 – 1.03 (m, 1H), 0.87 (s, 3H); $^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$) δ 161.0, 158.9, 156.2, 142.3, 114.6, 108.3, 104.9, 104.2, 78.7, 71.1, 49.5, 45.3, 40.1, 37.2, 37.2, 35.8, 30.7, 26.4, 26.3, 25.6, 22.1, 21.0, 17.1, 12.3; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{33}O_5)^+$: 401.2323, found: 401.2318.

(±)-3,11-Dihydroxy-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (39)

H_2O (0.300 mL, 16.6 mmol, 391 eq) was added dropwise to an ice-cold suspension of KO-*t*Bu (162 mg, 1.44 mmol, 34.0 eq) in Et_2O (0.50 mL). After 5 min, *β*-alcohol **38** (17.0 mg, 0.0424 mmol, 1.00 eq) in THF (0.4 mL) and Et_2O (0.4 mL) was added dropwise with stirring. The flask was rinsed with THF (0.4 mL) and Et_2O (0.4 mL), which was added dropwise with stirring. After 48 h, the mixture was diluted with H_2O (10 mL) and EtOAc (10 mL) and acidified with aqueous HCl (1 M, 10 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (2 : 8 EtOAc : CH_2Cl_2) gave resorcylic acid **39** (8.00 mg, 0.0222 mmol, 52%) as a transparent-white film: R_f 0.06 (pentane : EtOAc 1 : 1); IR ν_{max} 3437, 2925, 2853, 1618, 1577, 1453, 1262,1034 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 6.11 (d, *J* = 0.8 Hz, 1H), 3.63 – 3.50 (m, 1H), 2.70 (dd, *J* = 16.9, 5.0 Hz, 1H), 2.46 (s, 3H), 2.37 – 2.23 (m, 1H), 1.98 (dt, *J* = 11.8, 3.1 Hz, 1H), 1.84 (q, *J* = 5.2, 4.3 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.78 – 1.64 (m, 1H), 1.61 (dtd, *J* = 7.4, 4.7, 2.1 Hz, 1H), 1.53 – 1.48 (m, 1H), 1.48 – 1.40 (m, 1H), 1.31 – 1.29 (m, 1H), 1.28 – 1.28 (m, 3H), 1.21 (d, *J* = 0.9 Hz, 3H), 1.18 – 1.04 (m, 1H), 0.90 (d, *J* = 0.7 Hz, 3H); $^{13}C\{^{1}H\}$-NMR (101 MHz, CD_3OD) δ 175.6, 164.5, 159.0, 141.8, 112.9, 108.9, 104.9, 79.2, 71.6, 51.1, 46.5, 41.3, 38.3, 37.9, 36.8, 31.4, 27.5, 24.2, 21.2, 18.2, 12.5; HRMS (ESI-ToF) m/z: $[M – H]^-$ calcd. for $(C_{21}H_{27}O_5)^-$: 359.1864, found: 359.1863.

(±)-13-Hydroxy-6a,10,10,14b-tetramethyl-1,4,4a,5,6,6a,9,14,14a,14b-decahydro-2*H*,10*H*-benzo[*a*]pyrano[4,3-*i*]xanthene-3,12-dione (40)

n–BuLi (2.30 M, 0.140 mL, 0.326 mmol, 1.30 equiv) was added dropwise with stirring to dry-ice cold HN*i*Pr_2 (45.7 *μ*L, 33.0 mg, 0.326 mmol, 1.30 eq) in THF (1.5 mL). The resulting solution was stirred at -78 °C for 30 min, then warmed up to 0 °C for 30 min and cooled back down to -78 °C, when ketone **37** (100 mg, 0.251 mmol, 1.00 equiv) in THF (2.5 mL) was added dropwise with stirring. After 1 h, KOTMS (322 mg, 2.51 mmol, 10.0 eq) was added with stirring and the mixture was allowed to warm up to 23 °C. After 13 h, reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (9 : 1 CH_2Cl_2 : EtOAc) gave lactone **40** (20.0 mg, 0.0603 mmol, 24%) as a white film: R_f 0.43 (pentane : EtOAc 1 : 1); IR ν_{max} 1652, 1631, 1584, 1388, 1357, 1297, 1267, 1222, 1168, 1100, 731 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.63 (s, 1H), 6.16 – 6.09 (m, 1H), 2.86 (d, *J* = 2.4 Hz, 2H), 2.81 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.49 (dt, *J* = 8.6, 2.8 Hz, 1H), 2.46 – 2.41 (m, 1H), 2.41 – 2.35 (m, 1H), 2.32 (dd, *J* = 15.5, 1.6 Hz, 1H), 2.27 – 2.21 (m, 1H), 2.21 – 2.14 (m, 1H), 2.10 – 2.03 (m, 1H), 1.83 – 1.70 (m, 1H), 1.71 – 1.65 (m, 1H), 1.65 – 1.57 (m, 1H), 1.51 (ddt, *J* = 7.3, 4.0, 2.4 Hz, 1H), 1.46 (s, 3H), 1.45 (d, *J* = 4.1 Hz, 5H), 1.30 (d, *J* = 0.9 Hz, 3H), 1.08 (s, 3H); $^{13}C\{^{1}H\}$-NMR (101 MHz, $CDCl_3$) δ 210.8, 169.8, 161.8,

159.5, 137.3, 108.5, 108.1, 100.1, 81.7, 78.4, 49.2, 46.5, 44.0, 39.7, 39.4, 38.5, 37.3, 36.0, 27.5, 27.3, 26.5, 21.0, 17.3, 11.6; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{31}O_5)^+$: 399.2166, found: 399.2162.

(±)-7-(Hydroxymethyl)-3a,6,9b-trimethyl-1a,1b,3,3a,9,9a,9b,10,11,11a-decahydro-2H-oxireno[2',3':3,4]benzo[1,2-a]xanthen-8-ol (41)

$LiBHEt_3$ in THF (1 M; 0.110 mL, 0.105 mmol, 1.05 eq.) was added dropwise with stirring to ice-cold epoxide **32** (40.0 mg, 0.100 mmol, 1.00 eq) in THF (1.00 mL). After 2 h, reaction was quenched with saturated aqueous NH_4Cl (15 mL) and the organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (4 : 1 pentane : Et_2O) gave benzylic alcohol **41** (33.0 mg, 0.0958 mmol, 95%) as a transparent film: R_f 0.43 (pentane : EtOAc 1 : 1); IR ν_{max} 1627, 1585, 1457, 1421, 1350, 1227, 1217, 1191, 1107 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.31 (s, 1H), 4.94 (s, 2H), 3.20 (t, *J* = 3.5 Hz, 1H), 2.80 (d, *J* = 3.8 Hz, 1H), 2.75 (d, *J* = 5.0 Hz, 1H), 2.25 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.13 – 2.09 (m, 1H), 2.09 – 2.04 (m, 1H), 2.03 (s, 3H), 1.97 – 1.90 (m, 1H), 1.89 – 1.84 (m, 1H), 1.81 – 1.68 (m, 1H), 1.68 – 1.60 (m, 1H), 1.57 (d, *J* = 3.5 Hz, 1H), 1.53 (t, *J* = 3.4 Hz, 1H), 1.50 (d, *J* = 2.8 Hz, 1H), 1.25 (s, 3H), 0.99 (s, 1H), 0.84 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$) δ 152.9, 146.9, 132.3, 112.6, 111.7, 109.3, 77.4, 61.5, 55.1, 52.0, 48.4, 47.7, 40.3, 34.4, 31.8, 24.7, 21.4, 20.9, 17.7, 17.4, 12.7; HRMS (EI) m/z: $[M - OH]^{\bullet}$ calcd. for $(C_{21}H_{27}O_3)^{\bullet}$: 327.1960, found. 327.1955.

(±)-10-Bromo-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (42)

$MgCl_2$ (7.5 mg, 0.079 mg, 0.40 equiv) was added in one portion with stirring to epoxide **32** (77 mg, 0.19 mmol, 1.00 equiv) in THF (2.0 mL) at -78 °C, followed by the dropwise addition of MeMgBr in Et_2O (3 M; 0.070 mL, 0.20 mmol, 1.05 equiv). After gradually warming up over 24 h, the mixture was diluted with Et_2O (5 mL) and reaction was quenched with saturated aqueous NH_4Cl (5 mL). The organic layer was separated, and the aqueous layer was further extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with distilled water (10 mL) and brine (15 mL) and the organic layer was dried ($MgSO_4$), filtered concentrated under reduced pressure. Chromatography (6 : 1 to 3 : 1 pentane : EtOAc) gave bromohydrin **42** (46 mg, 0.096 mmol, 50%) as pale-yellow oil which solidified to a white solid: m.p. 120 °C (dec.) (CH_2Cl_2/pentane); R_f 0.23 (pentane : EtOAc 7 : 3); IR ν_{max} 3439, 1701, 1616, 1571, 1296, 1284, 1205, 1195, 1168, 1129, 1047, 910, 898, 731 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 1.0 Hz, 1H), 4.25 (q, *J* = 2.7 Hz, 1H), 4.14 – 4.09 (m, 1H), 2.58 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.55 (s, 3H), 2.34 – 2.26 (m, 1H), 2.26 – 2.18 (m, 1H), 2.12 – 2.09 (m, 1H), 2.08 – 2.05 (m, 1H), 1.80 (d, *J* = 9.4 Hz, 1H), 1.75 (d, *J* = 12.9 Hz, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.63 (d, *J* = 4.4 Hz, 1H), 1.61 (d, *J* = 3.2 Hz, 1H), 1.59 (dd, *J* = 4.8, 2.2 Hz, 1H), 1.56 – 1.49 (m, 1H), 1.49 – 1.44 (m, 1H), 1.23 (s, 3H), 1.10 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ 161.1, 158.8, 156.2, 142.3, 114.6, 108.1, 105.0, 104.2, 78.4, 71.3, 57.2, 50.7, 43.3, 39.9, 36.7, 31.7, 26.3, 25.9, 25.6, 23.2, 22.1, 21.0, 16.1, 14.5; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{32}BrO_5)^+$: 479.1428, found. 479.1423; Anal. Calcd for $C_{24}H_{31}BrO_5$: C, 60.13; H, 6.52. Found: C, 59.98; H, 6.48.

(±)-11-Hydroxy-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (43)

MeMgBr in Et_2O (3 M; 0.13 mL, 0.40 mmol, 2.4 equiv) was added dropwise with stirring to $CuBr.SMe_2$ (16 mg, 0.079 mmol, 0.46 equiv) in THF (1.0 mL) -78 °C. After 1 h at -78 °C, $BF_3.OEt_2$ in Et_2O (46.5%; 0.20 mL) was added dropwise with stirring. After 5 min, epoxide **32** (67 mg, 0.17 mmol, 1.00 equiv) in THF and Et_2O (1 : 2, 6.0 mL) were added dropwise. After 40 min at -78 °C, the mixture was diluted with Et_2O (10 mL) and poured onto an ice-water mixture (30 mL) which was acidified with aqueous HCl (1 M; 5 mL). The organic layer was separated, and the aqueous layer was further extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (3 : 1 to 1 : 1 pentane : Et_2O) gave *α*-alcohol **43** (56 mg, 0.14 mmol, 80%) as a white solid: m.p. 97 – 100 °C (CH_2Cl_2/pentane); R_f 0.17 (pentane : EtOAc 7 : 3); IR 3456, 1707, 1614, 1570, 1283, 1206, 1197, 1128, 1042, 908, 727 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 1.0 Hz, 1H), 3.82 (q, *J* = 2.6 Hz, 1H), 2.56 (s, 3H), 2.52 (d, *J* = 5.0 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.07 (dt, *J* = 12.3, 3.1 Hz, 1H), 1.95 – 1.87 (m, 1H), 1.85 (ddd, *J* = 10.2, 4.9, 2.4 Hz, 1H), 1.82 – 1.76 (m, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.67 – 1.63 (m, 1H), 1.63 – 1.59 (m, 1H), 1.58 – 1.56 (m, 1H), 1.59 – 1.52 (m, 1H), 1.46 (dd, *J* = 13.8, 4.2 Hz, 1H), 1.39 – 1.30 (m, 1H), 1.20 (d, *J* = 0.9 Hz, 3H), 0.93 (d, *J* = 7.6 Hz, 3H), 0.89 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$) δ 161.0, 158.9, 156.2, 142.1, 114.5, 108.3, 104.9, 104.0, 78.7, 71.7, 50.6, 42.6, 41.2, 40.5, 36.5, 32.3, 26.3, 25.5, 24.6, 24.3, 22.1, 20.8, 16.2, 14.8, 14.4; HRMS (ESI-ToF) m/z: $[M - H]^-$ calcd. for $(C_{25}H_{33}O_5)^-$: 413.2333, found: 413.2334; Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.44; H, 8.27. Found: C, 72.03; H, 8.07.

(±)-3,11-Dihydroxy-4,6a,9,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (44)

H_2O (100 µL, 9.97 mg, 0.554 mmol, 6.95 eq) was added dropwise to an ice-cold suspension of KO-*t*Bu (129 mg, 1.15 mmol, 14.4 eq) in Et_2O (0.50 mL). After 5 min, *α*-alcohol **43** (33.0 mg, 0.0796 mmol, 1.00 eq) in THF/Et_2O (2:1, 1.0 mL) was added dropwise with stirring. The flask was rinsed with THF (0.2 mL) and Et_2O (0.2 mL), which was also added dropwise with stirring. After 2 weeks, the mixture was diluted with H_2O (10 mL) and EtOAc (10 mL) and acidified with aqueous HCl (1 M, 5 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (2 : 8 EtOAc : CH_2Cl_2) gave resorcylic acid **44** (21.0 mg, 0.0561 mmol, 70%) as a white foam: R_f 0.05 (pentane : EtOAc 1 : 1); IR ν_{max} 3420, 2927, 2864, 1621, 1578,1453, 1264, 1170 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 6.11 (s, 1H), 3.73 (q, *J* = 2.7 Hz, 1H), 2.64 (dd, *J* = 16.9, 5.0 Hz, 1H), 2.46 (s, 3H), 2.35 – 2.21 (m, 1H), 2.14 – 1.97 (m, 1H), 1.97 – 1.89 (m, 1H), 1.86 (ddd, *J* = 9.6, 4.6, 2.7 Hz, 1H), 1.81 – 1.76 (m, 1H), 1.76 – 1.73 (m, 1H), 1.72 (d, *J* = 9.2 Hz, 1H), 1.59 (t, *J* = 4.5 Hz, 1H), 1.57 – 1.53 (m, 1H), 1.53 – 1.41 (m, 2H, 1.35 – 1.32 (m, 1H), 1.19 (s, 3H), 0.95 (d, *J* = 7.9 Hz, 3H), 0.93 (s, 3H); $^{13}C\{^1H\}$-NMR (101

MHz, CD_3OD) δ 174.9, 163.9, 158.3, 141.1, 112.2, 108.1, 10.49, 78.6, 71.9, 51.9, 43.3, 41.6, 41.2, 36.9, 33.0, 25.1, 24.1, 23.6, 20.4, 16.7, 14.5, 14.1; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{22}H_{31}O_5)^+$: 375.2166, found: 375.2176.

(±)-2,2,5,7a,10,13a-Hexamethyl-7a,8,9a,12,13,13a,13b,14-octahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthene-4,11(10*H*)-dione (45)

Dess-Martin periodinane (139 mg, 0.328 mmol, 2.00 equiv) was added in two portions with stirring over 5 mins to ice-cold *α*-alcohol **43** (68.0 mg, 0.164 mmol, 1.00 equiv) in CH_2Cl_2 (4.00 mL). After 1.5 h, the mixture was concentrated and loaded onto a column with a Celite® pad. Chromatography (1 : 1 to 1 : 2 pentane: CH_2Cl_2) gave ketone **45** (60.0 mg, 0.145 mmol, 89%) as a white solid: m.p. 170 – 171 °C (CH_2Cl_2/pentane); R_f 0.26 (pentane : EtOAc 7 : 3); IR ν_{max} 1726, 1616, 1575, 1288, 1170, 1130 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.39 – 6.31 (m, 1H), 2.70 – 2.63 (m, 1H) 263 – 2.58 (m, 1H), 2.57 (s, 3H), 2.52 – 2.43 (m, 1H), 2.39 – 2.35 (m, 1H), 2.35 – 2.30 (m, 1H), 2.15 (dd, *J* = 6.6, 3.2 Hz, 1H), 2.1 (dd, *J* = 7.0, 3.7 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.77 – 1.75 (m, 1H), 1.74 (s, 3H), 1.73 (d, *J* = 1.9 Hz, 1H), 1.69 (s, 3H), 1.67 – 1.58 (m, 1H), 1.52 (dd, *J* = 13.3, 6.0 Hz, 1H), 1.49 – 1.41 (m, 1H), 1.26 (d, *J* = 1.4 Hz, 3H), 1.15 (d, *J* = 7.8 Hz, 3H), 1.11 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$) δ 215.0, 160.8, 158.5, 156.0, 142.3, 114.4, 107.7, 104.9, 104.1, 78.1, 50.1, 48.4, 48.4, 39.9, 38.3, 36.1, 34.3, 26.2, 25.5, 23.6, 22.0, 20.6, 16.6, 14.6, 13.6; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{25}H_{33}O_5)^+$: 413.2323, found: 413.2321; Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.75; H, 7.81.

(±)-11-Hydroxy-2,2,5,7a,10,13a-hexamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (46)

$NaBH_4$ (2.3 mg, 0.066 mmol, 1.3 equiv) was added in one portion with stirring to ice-cold ketone **45** (21 mg, 0.051 mmol, 1.00 equiv) in EtOH (1.0 mL). After 1 h at 0 °C, the mixture was diluted with Et_2O (5.0 mL) and reaction quenched with saturated aqueous NH_4Cl (3.0 mL). The organic layer was separated, and the aqueous layer was further extracted with Et_2O (3 x 5.0 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (1 : 2 pentane : Et_2O) gave *β*-alcohol **46** (18 mg, 0.043 mmol, 85%) as a white foam: R_f 0.09 (pentane : EtOAc 7 : 3); IR ν_{max} 3438, 1711, 1615, 1572, 1450, 1388, 1284, 1205, 1129, 1046, 914, 731 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 3.76 (ddd, *J* = 9.5, 7.3, 5.6 Hz, 1H), 2.56 (s, 3H), 2.52 (dd, *J* = 17.5, 5.8 Hz, 1H), 2.26 – 2.20 (m, 1H), 2.08 (dd, *J* = 9.2, 2.9 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.82 (dt, *J* = 13.1, 3.5 Hz, 1H), 1.75 (s, 1H), 1.73 (s, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.65 (dd, *J* = 9.3, 3.5 Hz, 2H), 1.51 (dd, *J* = 13.2, 5.0 Hz, 1H), 1.38 (q, *J* = 2.7, 1.9 Hz, 1H), 1.36 (d, *J* = 3.2 Hz, 1H), 1.20 (d, *J* = 1.1 Hz, 3H), 1.09 (dtd, *J* = 13.3, 8.8, 8.2, 3.4 Hz, 1H), 0.92 (s, 3H), 0.90 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$) δ 161.0, 158.8, 156.2, 142.3, 114.5, 108.1, 104.9, 104.1, 78.7, 73.7, 50.8, 48.9, 40.6, 40.0, 37.9, 36.1, 26.3, 25.8, 25.6, 25.1, 22.1, 20.8, 16.6, 15.5, 9.0; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{25}H_{35}O_5)^+$: 415.2479, found: 415.2474.

(±)-3,11-Dihydroxy-4,6a,9,12b-tetramethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (47)

H_2O (0.300 mL, 16.6 mmol, 382 eq) was added dropwise to an ice-cold suspension of KO-*t*Bu (160 mg, 1.44 mmol, 34.0 eq) in Et_2O (0.50 mL). After 5 min, *β*-alcohol **46** (18.0 mg, 0.0434 mmol, 1.00 eq) in THF (0.4 mL) and Et_2O (0.4 mL) was added dropwise with stirring. The flask was rinsed with THF (0.3 mL) and Et_2O (0.3 mL), which was also added dropwise with stirring. After 48 h, the mixture was diluted with H_2O (5 mL) and EtOAc (5 mL) and acidified with aqueous HCl (1 M, 10 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (1 : 9 to 3 : 7 EtOAc : CH_2Cl_2) gave resorcylic acid **47** (6.00 mg, 0.0160 mmol, 37%) as a white film: R_f 0.07 (pentane : EtOAc 1 : 1); IR ν_{max} 3421 (br, s), 2922, 2852, 1651, 1622, 1456, 1264, 1045 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 6.11 (d, *J* = 0.9 Hz, 1H), 3.72 (dt, *J* = 11.6, 5.0 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.46 (s, 3H), 2.35 – 2.24 (m, 1H), 2.08 – 2.02 (m, 1H), 2.01 – 1.98 (m, 1H), 1.81 (dd, *J* = 8.6, 4.9 Hz, 1H), 1.77 (d, *J* = 6.0 Hz, 1H,), 1.75 – 1.66 (m, 1H), 1.62 (tt, *J* = 9.2, 4.2 Hz, 1H), 1.49 (dd, *J* = 13.1, 5.0 Hz, 1H), 1.46 – 1.38 (m, 3H), 1.19 (d, *J* = 0.8 Hz, 3H), 1.18 – 1.07 (m, 1H), 0.94 (d, *J* = 0.7 Hz, 3H), 0.91 (d, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, CD_3OD) δ 175.6, 164.5, 158.9, 141.8, 112.8, 108.7, 105.4, 79.2, 74.5, 52.5, 50.1, 41.8, 41.5, 39.0, 37.2, 33.1, 26.2, 24.2, 21.0, 17.7, 15.9, 9.5; HRMS (ESI-ToF) m/z: $[M - H]^-$ calcd. for $(C_{22}H_{29}O_5)^-$: 373.2020, found: 373.2010.

(±)-13-Hydroxy-4,6a,10,10,14b-pentamethyl-1,4,4a,5,6,6a,9,14,14a,14b-decahydro-2*H*,10*H*-benzo[*a*]pyrano[4,3-*i*]xanthene-3,12-dione (48)

n–BuLi (2.30 M, 0.0800 mL, 0.189 mmol, 1.30 equiv) was added dropwise with stirring to dry-ice cold $HNiPr_2$ (26.5 *μ*L, 19.0 mg, 0.189 mmol, 1.30 eq) in THF (0.5 mL). The resulting solution was stirred at -78 °C for 30 min, then warmed up to 0 °C for 30 min and cooled back down to -78 °C, when ketone **45** (60.0 mg, 0.145 mmol, 1.00 equiv) in THF (1.0 mL) was added dropwise with stirring. After 1 h, KOTMS (187 mg, 1.45 mmol, 10.0 eq) was added with stirring and the mixture was allowed to warm up to 23 °C. After 12 h, reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (9 : 1 CH_2Cl_2 : EtOAc) gave lactone **48** (20.0 mg, 0.0485 mmol, 33%) as a white film: R_f 0.55 (pentane : EtOAc 1 : 1); IR ν_{max} 1707, 1653, 1631, 1585, 1388, 1357, 1297, 1285, 1169, 1100, 732 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.62 (s, 1H), 6.12 (d, *J* = 1.0 Hz, 1H), 2.86 (d, *J* = 2.5 Hz, 2H), 2.80 (dd, *J* = 16.8, 5.0 Hz, 1H), 2.56 – 2.45 (m, 1H), 2.44 – 2.40 (m, 1H), 2.40 – 2.35 (m, 1H), 2.37 – 2.27 (m, 1H), 2.23 – 2.14 (m, 1H), 2.09 (dq, *J* = 13.1, 3.0 Hz, 1H), 1.84 (dq, *J* = 11.0, 3.5, 2.6 Hz, 1H), 1.73 – 1.62 (m, 1H), 1.62 – 1.55 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.40 (dt, *J* = 7.2, 3.6 Hz, 1H), 1.36 (dq, *J* = 5.3, 2.4 Hz, 1H), 1.33 (d, *J* = 2.1 Hz, 1H), 1.29 (d, *J* = 0.9 Hz, 3H), 1.14 (s, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$) δ 212.3, 169.8, 161.8, 159.5, 137.3, 108.5, 108.1, 100.1, 81.7, 78.0, 53.1, 49.5, 44.7, 39.9, 39.4, 39.0, 37.2, 36.8, 27.5, 27.3, 23.3, 20.9, 17.3, 12.8, 11.8; HRMS (ESI-ToF) m/z: $[M + H]^+$ calcd. for $(C_{25}H_{33}O_5)^+$: 413.2323, found: 413.2325.

(±)-10-Azido-11-hydroxy-2,2,5,7a,13a-pentamethyl-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-4-one (49)

AcOH (0.5 mL) and NaN_3 (166 mg, 2.56 mmol, 12.0 equiv) were added sequentially each in one portion to epoxide **32** (85.0 mg, 0.213 mmol, 1.00 equiv) in DMF (3.50 mL). After 15 h at 110 °C, the mixture was poured onto an ice water and saturated aqueous $NaHCO_3$ mixture (1 : 1; 100 mL). The mixture was diluted with EtOAc, stirred for 30 min, the organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), distilled water (20 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Filtering through a small silica plug with EtOAc gave the crude azide **49** which was used without further purification in the next step: R_f 0.18 (pentane : EtOAc 4 : 1); IR ν_{max} 3466, 2924, 2099, 1728, 1706, 1616, 1573, 1288 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 4.05 (q, *J* = 2.8 Hz, 1H), 3.58 (td, *J* = 3.0, 1.4 Hz, 1H), 2.57 (s, 4H) 2.36 (s, 1H), 2.25 (dd, *J* = 16.8, 13.1 Hz, 1H), 2.14 – 2.06 (m, 1H), 2.06 – 2.00 (m, 1H), 1.96 (ddd, *J* = 14.9, 4.6, 2.2 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.82 (dd, *J* = 13.0, 10.2 Hz, 1H), 1.78 (d, *J* = 5.3 Hz, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.65 – 1.48 (m, 3H), 1.25 (s, 3H), 1.01 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$) δ 161.1, 158.8, 156.2, 142.2, 114.5, 108.1, 104.9, 104.1, 78.4, 67.9, 66.8, 50.2, 43.4, 40.1, 36.1, 32.0, 26.2, 25.6, 24.3, 24.0, 22.1, 21.0, 16.2, 13.7; HRMS (APCI) m/z: $[M + H]^+$ calcd. for $(C_{24}H_{32}N_3O_5)^+$: 442.2336, found: 442.2336.

(±)-10-Azido-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-11-yl acetate (50)

NEt_3 (432 mg, 0.595 mL, 4.27 mmol, 20.0 equiv) and Ac_2O(218 mg, 0.202 mL, 2.13 mmol, 10.0 equiv) were sequentially added dropwise to crude azide **49** in CH_2Cl_2 (2.50 mL). DMAP (26.1 mg, 0.213 mmol, 1.00 equiv) was added in one portion, and, after 2 h, the mixture was diluted with CH_2Cl_2 (5.0 mL) and reaction quenched with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (1 : 5 : 4 EtOAc : pentane : CH_2Cl_2) gave acetate **50** (65.0 mg, 0.134 mmol, 63% over 2 steps) as a yellow-white solid: m.p. 74 – 79 °C (CH_2Cl_2/pentane); R_f 0.46 (pentane : EtOAc 7 : 3); IR ν_{max} 2100, 1727, 1616, 1574, 1375, 1286, 1232, 1206, 1170, 1129 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 4.98 (q, *J* = 2.9 Hz, 1H), 3.61 (td, *J* = 2.9, 1.3 Hz, 1H), 2.55 (s, 3H), 2.52 (d, *J* = 4.9 Hz, 1H), 2.25 (dd, *J* = 16.8, 13.3 Hz, 1H), 2.10 (ddd, *J* = 14.2, 8.4, 2.7 Hz, 1H), 2.05 (s, 3H), 1.98 – 1.89 (m, 1H), 1.84 – 1.76 (m, 1H), 1.72 (s, 1H), 1.71 (d, *J* = 4.4 Hz, 5H), 1.68 (d, *J* = 2.7 Hz, 1H), 1.66 (s, 3H), 1.61 (dd, *J* = 13.2, 4.8 Hz, 1H), 1.52 (dd, *J* = 9.2, 3.1 Hz, 1H), 1.33 (d, *J* = 10.2 Hz, 1H), 1.24 (s, 3H), 1.01 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$) δ 170.0, 160.9, 158.7, 156.2, 142.3, 114.4, 108.0, 104.9, 104.2, 78.3, 70.2, 63.9, 50.3, 44.7, 40.1, 35.8, 32.6, 26.2, 25.6, 23.9, 22.1, 21.5, 21.4, 21.1, 16.2, 13.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $(C_{26}H_{34}N_3O_5)^+$: 484.2442, found: 484.2444; Anal. Calcd for $C_{26}H_{33}N_3O_5$: C, 64.58; H, 6.88.; N, 8.69. Found: C, 64.16; H, 6.81; N, 8.62.

(±)-10-Amino-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-11-yl acetate (51)

PMe_3 in THF (1 M; 0.10 mL, 0.10 mmol, 2.5 equiv) was added dropwise to acetate **50** (20 mg, 0.041 mmol, 1.00 equiv) in THF (3.0 mL) and distilled water (5.0 µL). The mixture was warmed to 35 °C after which aqueous NaOH (2 M; 0.10 mL) was added dropwise. After 5 h at 35 °C, the mixture was poured onto a mixture of water and EtOAc (1 : 1, 15 mL). The mixture was adjusted to pH 7 with saturated aqueous NH_4Cl, the organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude amine **51** which was used without further purification in the next step: R_f 0.01 (pentane : EtOAc 7 : 3); IR ν_{max} 3430, 1727, 1618, 1573, 1282, 1129 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 0.9 Hz, 1H), 5.08 – 4.90 (m, 5H, NH_2), 4.84 (q, *J* = 2.7 Hz, 1H, H), 3.04 (d, *J* = 3.3 Hz, 1H), 2.56 (s, 5H), 2.53 (d, *J* = 5.1 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.16 – 2.06 (m, 1H), 2.04 (s, 3H), 1.83 – 1.76 (m, 2H), 1.72 (s, 4H), 1.69 (s, 1H), 1.67 (s, 4H), 1.48 (ddd, *J* = 9.3, 7.1, 4.6 Hz, 1H), 1.37 – 1.33 (m, 1H), 1.23 (s, 3H), 1.07 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$): δ 170.3, 161.0, 158.7, 156.2, 142.3, 114.5, 108.0, 104.9, 104.2, 78.4, 73.2, 54.4, 50.5, 44.2, 40.3, 35.8, 33.0, 26.3, 25.6, 23.6, 22.1, 21.5, 21.0, 20.9, 16.2, 14.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $(C_{26}H_{36}NO_6)^+$: 458.2537, found: 458.2554; Also found m/z: $[M + CH_3CN + H]^+$ calcd. for $(C_{28}H_{39}N_2O_6)^+$: calc. 499.2803, found: 499.2844.

(±)-10-Acetamido-2,2,5,7a,13a-pentamethyl-4-oxo-7a,8,9a,10,11,12,13,13a,13b,14-decahydro-4*H*,9*H*-benzo[*a*][1,3]dioxino[5,4-*j*]xanthen-11-yl acetate (52)

NEt_3 (21 mg, 29 µL, 0.21 mmol, 5.0 equiv) and Ac_2O (8.6 mg, 8.0 µL, 0.083 mmol, 2.0 equiv) were sequentially added dropwise to the crude amine **51** in CH_2Cl_2 (2.0 mL). DMAP (5.0 mg, 0.041 mmol, 1.00 equiv) was added in one portion and after 2 h, the mixture was diluted with CH_2Cl_2 (5.0 mL) and quenched with saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (7 : 3 EtOAc : CH_2Cl_2) gave acetamide **52** (20 mg, 0.040 mmol, 97% over 2 steps) as a white foam: R_f 0.01 (pentane : EtOAc 7 : 3); IR ν_{max} 3331, 1728, 1653, 1616, 1573, 1281, 1238, 1206, 1170, 1129 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.49 (d, *J* = 9.2 Hz, 1H, NH), 4.86 (q, *J* = 2.7 Hz, 1H), 4.15 (dd, *J* = 10.1, 3.9 Hz, 1H), 2.57 (s, 3H), 2.56 (d, *J* = 4.6 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.14 – 2.09 (m, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 1.95 (d, *J* = 11.0 Hz, 1H), 1.87 – 1.84 (m, 1H), 1.83 (d, *J* = 8.3 Hz, 1H), 1.78 (dd, *J* = 11.7, 6.2 Hz, 1H), 1.72 (s, 3H), 1.69 (d, *J* = 8.7 Hz, 1H), 1.67 (s, 3H), 1.66 (s, 1H), 1.58 (d, *J* = 3.8 Hz, 1H), 1.43 – 1.28 (m, 1H), 1.27 (d, *J* = 2.9 Hz, 1H), 1.21 (s, 3H), 1.01 (s, 3H); $^{13}C\{^1H\}$-NMR (101 MHz, $CDCl_3$) δ 169.8, 169.7, 160.9, 158.6, 156.2, 142.5, 114.5, 107.6, 105.0, 104.2, 78.1, 70.6, 51.6, 50.4, 43.3, 39.9, 35.8, 32.2, 26.4, 25.5, 23.8, 23.1, 22.1, 21.5, 21.4, 20.9, 16.2, 14.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd. for $(C_{28}H_{38}NO_7)^+$: 500.2643, found: 500.2635; Also found m/z: $[M + CH_3CN + Na]^+$ calcd. for $(C_{30}H_{40}N_2O_7 + Na)^+$: 563.2733, found: 563.2762.

(±)-4-Acetamido-3,11-dihydroxy-6a,9,12b-trimethyl-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-2*H*-benzo[*a*]xanthene-10-carboxylic acid (53)

Aqueous KOH (2M; 2.0 mL, 4.0 mmol, 67 equiv) was added in one portion to acetamide **52** (30 mg, 0.060 mmol, 1.0 equiv) in THF (2.0 mL). After vigorously stirring at 60 °C for 4 days, the mixture was diluted with EtOAc (5.0 mL) and distilled water (5.0 mL) and acidified to pH 1 with aqueous HCl (1 M). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography (100% EtOAc) gave resorcylic acid **53** (12 mg, 0.028 mmol, 48%) as a white foam: R_f 0.01 (EtOAc 100%); IR ν_{max} 3392, 1651, 1645, 1634, 1622, 1576, 1456, 1418, 1262 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 7.14 (d, *J* = 9.2 Hz, 1H, NH), 6.12 (d, *J* = 0.9 Hz, 1H), 4.09 – 4.01 (m, 1H), 3.75 (q, *J* = 2.8 Hz, 1H), 2.66 (dd, *J* = 16.9, 5.0 Hz, 1H), 2.51 (d, *J* = 2.8 Hz, 1H), 2.46 (s, 3H), 2.29 (dd, *J* = 16.9, 13.2 Hz, 1H), 2.03 (d, *J* = 9.6 Hz, 1H), 2.01 (s, 1H), 2.00 (s, 3H), 1.97 – 1.89 (m, 1H), 1.73 (tt, *J* = 11.8, 6.2 Hz, 1H), 1.63 (d, *J* = 24.2 Hz, 1H), 1.58 (d, *J* = 6.6 Hz, 1H), 1.56 (s, 2H), 1.48 – 1.39 (m, 1H), 1.20 (s, 3H), 1.02 (s, 3H); ^{13}C{^{1}H}-NMR (101 MHz, CD_3OD) δ 173.2, 164.5, 158.8, 155.5, 141.8, 112.8, 109.8, 108.6, 78.8, 69.5, 55.5, 52.1, 44.5, 41.4, 36.9, 33.1, 24.9, 24.5, 24.2, 22.8, 21.0, 17.3, 14.1; HRMS (ESI) m/z: $[M + H]^+$ calcd. for $(C_{23}H_{32}NO_6)^+$: 418.2224, found: 418.2218.

ASSOCIATED CONTENT

^{1}H and ^{13}C NMR spectra for compounds **8**, **9**, **12**, **13**, **15**–**18**, **21**, **27**, **29**–**53** and X-ray structural data for **8**, **33**, **42** and **45**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: agmb@ic.ac.uk

ORCID

Anthony G. M. Barrett: 0000-0002-8485-215X

Philip J. Parsons: 0000-0002-9158-4043

Andrew J. P. White: 0000-0001-6175-1607

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Peter Haycock, Corey Fulop and Dr. Lisa Haigh (Imperial College London) are gratefully acknowledged for their help with NMR and mass spectrometry, respectively. We also extend our thanks to Nigel Howard (University of Cambridge) for elemental microanalyses. We thank GlaxoSmithKline for a generous endowment (to A.G.M.B.).

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