Meroterpenoid Synthesis via Sequential Polyketide Aromatization and Radical Anion Cascade Triene Cyclization: Biomimetic Total Syntheses of Austalide Natural Products

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Ⓢ *Supporting Information*

(±)-17S-Dihydroaustalide K (R = CHOH)
(±)-Austalide K (R = CO)
(±)-13-Deacetoxyaustalide I (R = COO)
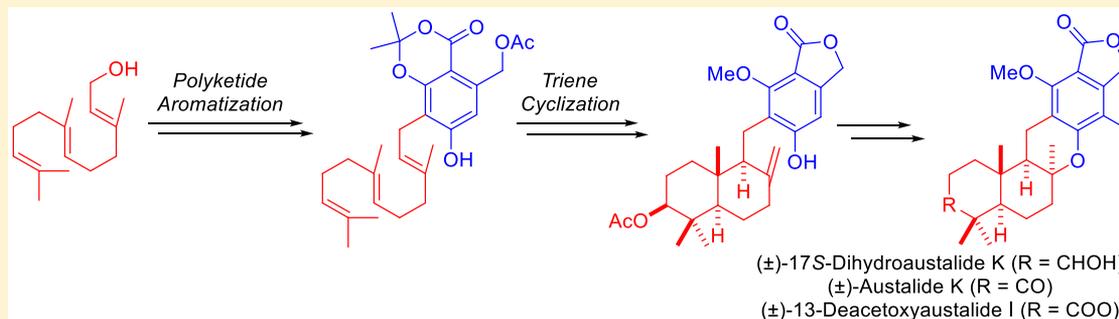
ABSTRACT: The first total synthesis of five austalide natural products, (±)-17S-dihydroaustalide K, (±)-austalide K, (±)-13-deacetoxyaustalide I, (±)-austalide P, and (±)-13-deoxyaustalide Q acid, was accomplished via a series of biomimetic transformations. Key steps involved polyketide aromatization of a *trans,trans*-farnesol-derived β,δ-diketodioxinone into the corresponding β-resorcylate, followed by titanium(III)-mediated reductive radical cyclization of an epoxide to furnish the drimene core. Subsequent phenylselenonium ion induced diastereoselective cyclization of the drimene completed the essential carbon framework of the austalides to access (±)-17S-dihydroaustalide K, (±)-austalide K, and (±)-13-deacetoxyaustalide I via sequential oxidations. Furthermore, (±)-13-deacetoxyaustalide I could serve as a common intermediate to be derivatized into other related natural products, (±)-austalide P and (±)-13-deoxyaustalide Q acid, by functionalizing the cyclic lactone moiety.

■ INTRODUCTION

The austalides (Figure 1) are a diverse group of meroterpenoid natural products featuring a *trans,transoid,cis*-fused ring system. The first 12 members were isolated from the whole maize cultures of *Aspergillus ustus*, strain MRC 1163 in the 1980s.[1] Additional new members were isolated recently from the metabolites of the fungi *Aspergillus aureolatus*, *Penicillium thomii*, and *Penicillium lividum*.[2] Initial profiling of the isolated natural products showed them to possess a broad spectrum of bioactivity such as cytotoxic and antibacterial properties as well as inhibiting *endo*-1,3-β-D-glucanase.[2]

The biosynthesis of austalide K (**2**) was first proposed in 1987 (Scheme 1).[3a] It was postulated that 6-[(2E,6E)farnesyl]-5,7-dihydroxy-4-methylphthalide (**6**), a key intermediate in the biogenesis of mycophenolic acid, first undergoes cyclization via a stereospecific attack of the phenol on the 11*si*,21*si*-face of the alkene to provide chromene **7**. Subsequent epoxidation of the terminal alkene gives epoxide **8**, which could undergo cationic polyene cyclization to furnish the *trans,transoid,cis*-fused ring motif. However, further investigations on the fate of the hydrogen atom incorporation using $^{13}C,^{2}H$- and ^{2}H-labeled mevalonolactones provided evidence to exclude the intermediacy of chromene **7**.[3b] This has led to an alternative

proposal on the biosynthesis of the austalides involving polyene cyclization of epoxide **9** to generate carbocation intermediate **10**, followed by enzyme-controlled stereospecific cyclization of the phenolic oxygen to furnish the chromane structure with the *cis*-fused ring. It is important to note that concerted polyene cyclization of epoxide **9** would lead to the formation of a stereoisomer of austalide K (**2**), featuring an all-*trans*-fused ring system.

Inspired by the pioneering work of Hyatt and co-workers and Harris and co-workers on dioxinone thermolysis and biomimetic polyketide aromatization,[4] our group focused on the biomimetic synthesis of β-resorcylate-derived natural products utilizing β,δ-diketodioxinones.[5] Recently, we disclosed a scalable and efficient synthesis of dioxinone β-ketoesters **13** with the use of regioselective thermolysis of dioxane-4,6-dione ketodioxanones **11** (Scheme 2).[6] Utilization of our recent findings with sequential polyketide aromatization and polyene cyclization greatly facilitated concise syntheses of hongoquercin A and B.[7] Herein, we report further studies on
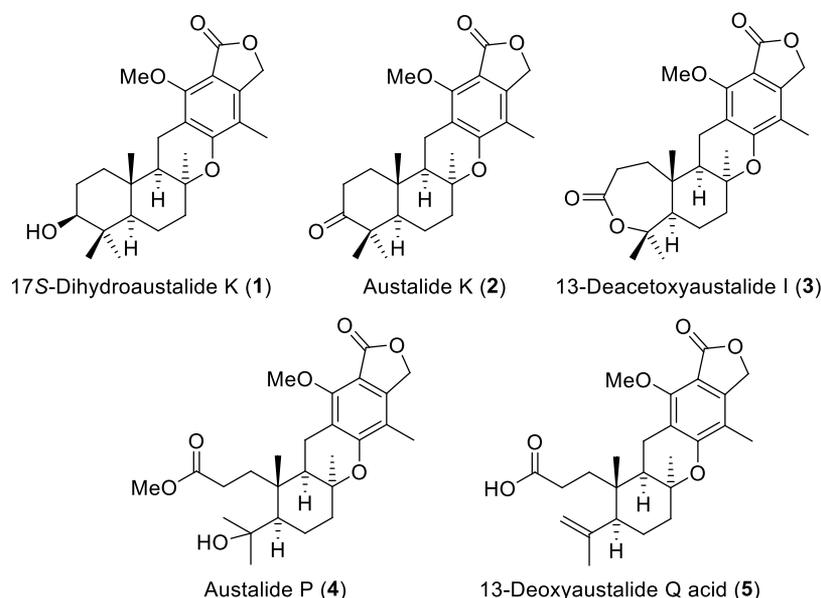
Figure 1. Representative austalide natural products.

Scheme 1. Proposed Biosynthesis of Austalides K (2)
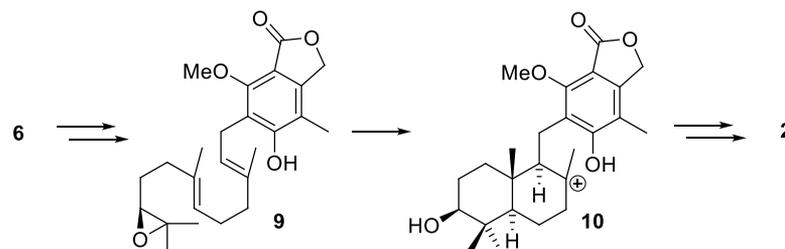
Scheme 2. Thermolysis of Dioxane-4,6-dione Ketodioxanones 11
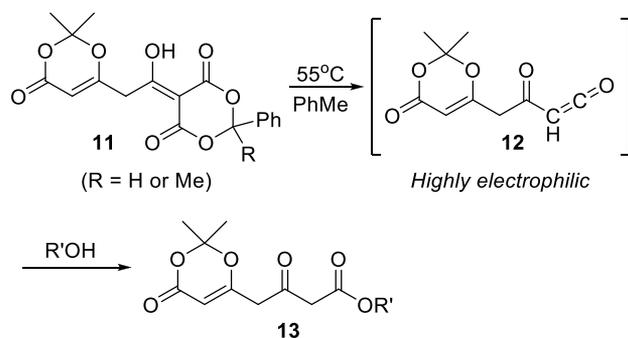
the biomimetic total syntheses of the austalide natural products via a series of biomimetic transformations.

■ RESULTS AND DISCUSSION

We considered that austalide P (**4**) and 13-deoxyaustalide Q acid (**5**) could be derived from 13-deacetoxyaustalide I (**3**) by functionalizing the cyclic lactone moiety (Scheme 3). Late-stage arene methylation and deacetylation of acetate **14** would allow access to 17S-dihydroaustalide K (**1**), followed by sequential oxidations of the alcohol functionality to give austalide K (**2**) and 13-deacetoxyaustalide I (**3**). In order to construct the *trans,transoid,cis*-fused ring motif, we envisioned the use of two sequential diastereoselective cyclizations. First, a titanium(III)-mediated radical triene cyclization of epoxide **16** would give drimene **15** to furnish the first *trans*-fused ring with an exocyclic alkene, acting as an equivalent of carbocation **10**.

Scheme 3. Retrosynthetic Analysis of the Austalides
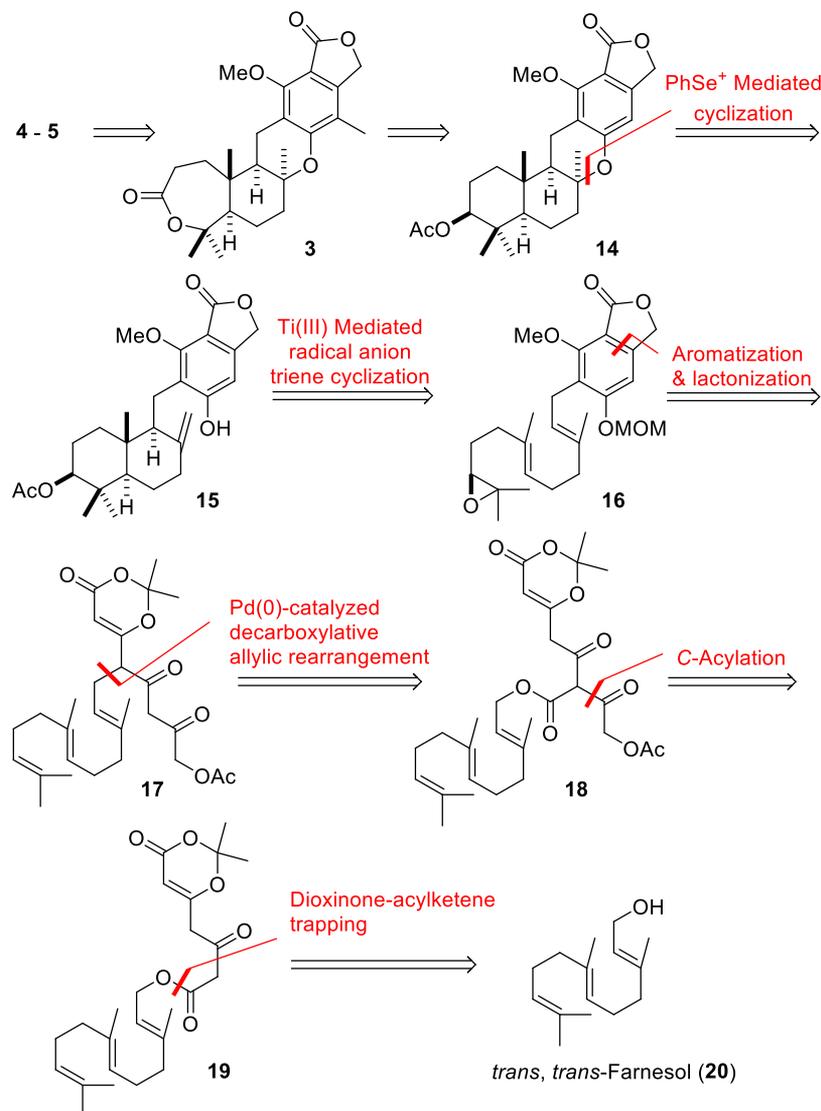
Subsequent phenylselenonium ion induced diastereoselective cyclization of the drimene **15** should provide the desired *cis*-fused ring to complete the essential carbon framework. Epoxide **16** should be available from a farnesol-derived β-resorcylate, which was accessible via sequential cycloaromatization and lactonization of β,δ-diketodioxinones **17**. Dioxinone β,δ-diketoester **18**, synthesized via C-acylation of dioxinone β-ketoester **19**, should undergo palladium(0)-catalyzed decarboxylative allylic rearrangement to provide β,δ-diketodioxinone **17**. Finally, dioxinone β-ketoester **19** is available by trapping a dioxinone acylketene **12** with *trans,trans*-farnesol (**20**) following our recently published protocols.[6]

The synthesis of β-resorcylate **22** (Scheme 4) was undertaken by trapping dioxinone acylketene **12**, generated in situ from 4,6-dione ketodioxanone **21**, with *trans,trans*-farnesol (**20**) to provide dioxinone β-ketoester **19** (87%).[6] Subsequent MgCl-mediated regioselective C-acylation of the dioxinone β-ketoester **19** with acetoxyacetyl chloride gave dioxinone β,δ-diketoester **18**, which was allowed to react with a catalytic amount of Pd₂(dba)₃ in the presence of tri(2-furyl)phosphine to induce a decarboxylative allylic rearrangement to provide β,δ-diketodioxinone **17**, which was directly

aromatized by treatment with triethyl amine to provide β-resorcylate **22** (39% over two steps from dioxinone β-ketoester **19**).

With the β-resorcylate **22** in hand, attention was focused on the functionalization of the aromatic core as well as installing the terminal epoxide for the triene cyclization reaction (Scheme 5). The phenol group of β-resorcylate **22** was first protected as the MOM ether **23** (75%), followed by lactonization under basic conditions to give phthalide **24** (93%). Methylation of the resulting phenol of phthalide **24** gave methyl ether **25** (98%), which was allowed to react with *N*-bromosuccinimide with regioselective electrophilic addition at the terminal alkene of the terpene chain to form bromohydrin **26** (77%). Subsequent potassium carbonate (K₂CO₃)-mediated cyclization of bromohydrin **26** gave the desired racemic epoxide **16** (97%).

Next, the terpene side chain of epoxide **16** was functionalized (Scheme 6). Treatment of the epoxide **16** with a titanocene(III) catalyst, generated from titanocene(IV) dichloride, manganese, trimethylsilyl chloride, and 2,4,6-collidine,[8] initiated a radical anion cascade cyclization, producing alcohol **27** (40% over two steps) after desilylation

Scheme 4. Synthesis of Terpene Resorcylate 22

Scheme 5. Synthesis of Epoxide 16

by reaction with tri-*n*-butylstannane in the presence of 2,2-azobis(isobutyronitrile), meroterpenoid **14** (94%) was isolated as a single diastereoisomer with the desired *trans,transoid,cis*-fused ring system, the relative stereochemistry of which was confirmed by additional NOESY experiments.

With the key meroterpenoid **14** in hand after establishing the correct relative stereochemistry, we directed our attention to the arene methylation and sequential oxidation reactions to complete the synthesis of (±)-17S-dihydroaustalide K (**1**), (±)-austalide K (**2**), and (±)-13-deacetoxyaustalide I (**3**) (Scheme 7). Electrophilic aromatic substitution reaction of meroterpenoid **14** with *N*-bromosuccinimide gave bromide **30** (93%), which was subjected to the palladium-catalyzed Suzuki−Miyaura cross-coupling reaction with potassium methyltrifluoroborate to furnish the hexa-substituted arene **31** (88%).[10] Finally, selective acetate deprotection with magnesium methoxide completed the synthesis of (±)-17S-dihydroaustalide K (**1**) (88%).[11] Furthermore, Dess−Martin periodinane-mediated oxidation of (±)-17S-dihydroaustalide K (**1**) gave (±)-austalide K (**2**) (83%), and subsequent Baeyer−Villiger oxidation with *m*CPBA gave (±)-13-deacetoxyaustalide I (**3**) (96%). The analytical data for these synthetic materials were in substantial agreement with those reported for the isolated natural product.[1b,2c]

(±)-13-Deacetoxyaustalide I (**3**) was also used in alternative derivatization reactions for the synthesis of additional austalide natural products (Scheme 8). Reaction of (±)-13-deacetoxyaustalide I (**3**) with sodium methoxide resulted in trans-esterification to provide (±)-austalide P (**4**) (80%).[12] Under acidic conditions at elevated temperature, the cyclic lactone moiety of (±)-13-deacetoxyaustalide I (**3**) was hydrolyzed accompanied by elimination of the resulting tertiary alcohol to give (±)-13-deoxyaustalide Q acid (**5**) (71%).[13] The analytical data of the synthetic products were compared with data reported for the isolated natural products and were found to be in substantial agreement.[2a,c]

with tetrabutylammonium fluoride. Acetylation of the alcohol **27** yielded acetate **28** (98%), followed by MOM deprotection with pyridinium *p*-toluenesulfonate (PPTS) and *t*BuOH to furnish phenol **15** (86%). The relative stereochemistry of phenol **15** was unambiguously determined by X-ray crystallography, confirming the formation of the *trans*-fused ring system. Reaction of *N*-(phenylseleno)phthalimide and stannic chloride with phenol **15** resulted in the formation of a selenonium ion intermediate, which was intramolecularly trapped by the phenolic group to provide the 6-*exo-trig* cyclized phenyl-selenide **29** (58%).[9] After removal of the phenylselenyl group

Scheme 6. Synthesis of Meroterpenoid 14
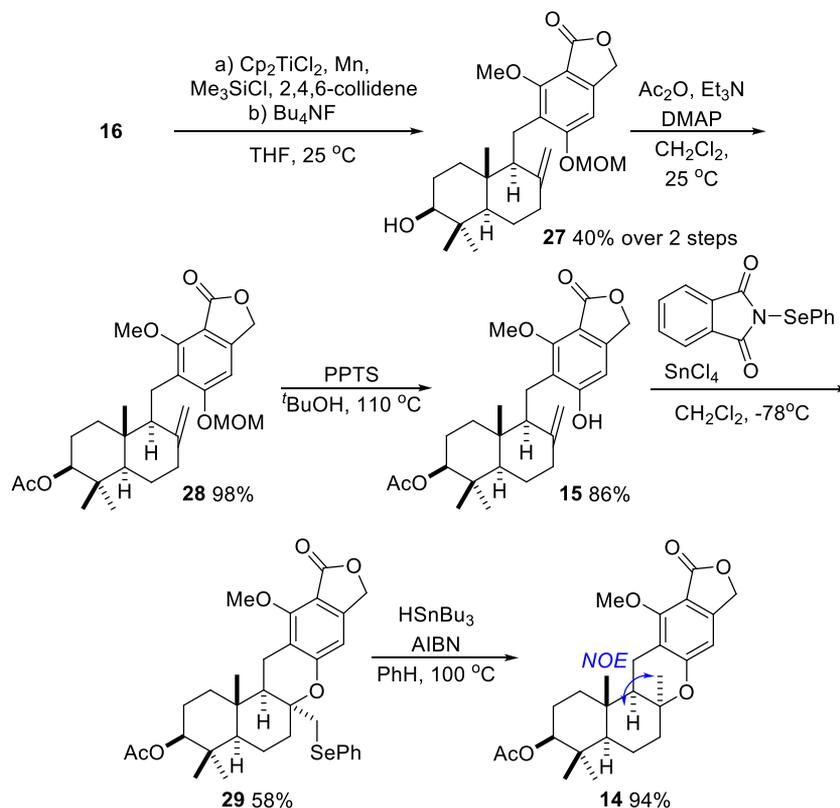
Scheme 7. Synthesis of (±)-17S-Dihydroaustalide K (1), (±)-Austalide K (2), and (±)-13-Deacetoxyaustalide I (3)
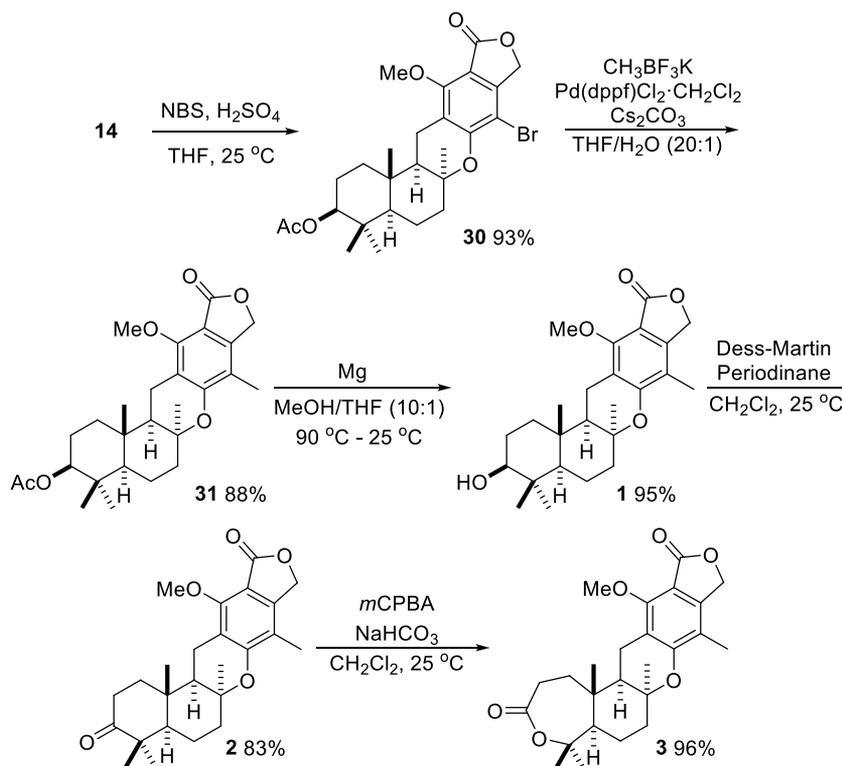
■ CONCLUSION

In conclusion, the first total synthesis of five austalide natural products, (±)-17S-dihydroaustalide K (1), (±)-austalide K (2), (±)-13-deacetoxyaustalide I (3), (±)-austalide P (4), and

(±)-13-deoxyaustalide Q acid (5), was completed in 17−20 steps. A series of biomimetic transformations were employed to construct the carbon skeleton of these natural products. The aromatic core was synthesized by biomimetic polyketide

Scheme 8. Synthesis of (±)-Austalide P (4) and (±)-13-Deoxyaustalide Q Acid (5)
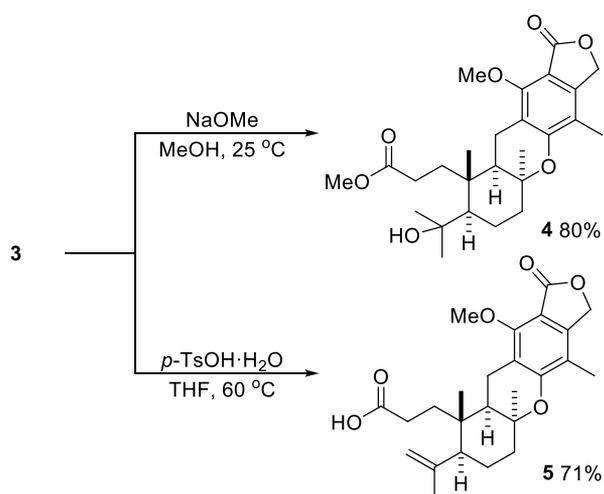
aromatization, whereas the fused ring motif was constructed by sequential reductive radical anion triene cyclization of an epoxide, followed by phenylselenium-mediated diastereoselective cyclization reaction. Further studies on the synthesis of novel meroterpenoids using such biomimetic approaches are ongoing in our laboratory.

■ EXPERIMENTAL SECTION

General Methods. All reagents and solvents were used directly without further purification unless otherwise specified. The syntheses of malonate, dioxinone acid, and dioxinone β-ketoesters **19** were carried out according to Barrett et al.[6,7] All solvents were purified and dried by distillation under an atmosphere of N_2 before use. THF was redistilled from Na-Ph_2CO. CH_2Cl_2, Et_3N, MeOH, and pyridine were redistilled from CaH_2. PhH and PhMe were redistilled from Na. Me_2CO and ^tBuOH were dried over 4 Å activated molecular sieves under N_2 for 24 h. All air- and moisture-sensitive reactions were carried out under an atmosphere of N_2 using standard Schlenk techniques in oven-dried glassware equipped with a magnetic stirring bar. The progress of reactions was monitored by analytical thin layer chromatography (TLC) on silica-gel-coated aluminum oxide F_{254} plates. Developed TLC were visualized under UV light and stained with an acidic vanillin solution. Flash column chromatography was performed employing silica gel 60 Å, with a particle size of 40–63 μm. All ^1H and proton-decoupled ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, at ambient temperature in deuterated solvents as noted. NMR spectra are referenced to residual solvent peaks ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.0 for ^{13}C NMR; CD_3OD δ = 3.31 and 4.87 for ^1H NMR and δ = 49.0 for ^{13}C NMR), and chemical shifts are reported in parts per million. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Imperial College Mass Spectrometry Service with the use of TOF and magnetic analyzers for ESI and EI techniques, respectively. Melting points were uncorrected. X-ray diffraction data were recorded by the Imperial College X-ray Crystallography Facility.

(7-Hydroxy-2,2-dimethyl-4-oxo-8-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-4H-benzo[d][1,3]dioxin-5-yl)methyl Acetate (22). $MgCl_2$ (7.12 g, 74.8 mmol) and pyridine (23 mL, 288 mmol) were added with stirring to β-ketoester **19** (24.9 g, 57.6 mmol) in CH_2Cl_2 (200 mL) at 0 °C. After 15 min, $AcCH_2COCl$ (7.40 mL, 69.1 mmol) was added dropwise, and the reaction mixture was further stirred for 2 h at 0 °C. Saturated aqueous NH_4Cl (100 mL) was added, and the pH was adjusted to ~2 with aqueous HCl (1 M). The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give

the crude dioxinone β,δ-diketoester **18**. P(2-furyl)$_3$ (2.67 g, 11.5 mmol) and Pd_2dba_3 (2.64 g, 2.88 mmol) were added sequentially with stirring to this crude dioxinone β,δ-diketoester **18** in THF (300 mL) at 25 °C. After 3 h, Et_3N (24.0 mL, 173 mmol) was added, and the resulting mixture was stirred for an additional 18 h. Reaction was quenched with aqueous HCl (1 M; 200 mL); the two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (pentane/EtOAc 19:1 to 10:1) to give β-resorcylate **22** (10.7 g, 22.7 mmol, 39% over two steps) as a yellow oil: R_f 0.26 (pentane/Et_2O 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 1H), 5.53 (s, 2H), 5.23–5.12 (m, 1H), 5.11–5.00 (m, 2H), 3.33 (d, J = 7.2 Hz, 2H), 2.15 (s, 3H), 2.16–1.90 (m, 8H), 1.79 (s, 3H), 1.69 (s, 6H), 1.66 (s, 3H), 1.58 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 160.8, 160.5, 156.1, 139.8, 138.7, 135.5, 131.3, 124.3, 123.5, 120.3, 114.5, 109.8, 105.3, 103.6, 64.1, 39.7, 39.6, 26.7, 26.3, 25.7 (2C), 21.9, 21.0, 17.7, 16.2, 16.0; IR ν_{max} (neat) 3290, 1724, 1699, 1597, 1422, 1377, 1274, 1207, 1029 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{28}H_{39}O_6$ 471.2747; found 471.2731.

(7-(Methoxymethoxy)-2,2-dimethyl-4-oxo-8-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-4H-benzo[d][1,3]dioxin-5-yl)methyl Acetate (23). MOMCl (1.03 mL; 13.6 mmol) was added with stirring to $^iPr_2EtN$ (5.92 mL; 34.0 mmol) and β-resorcylate **22** (3.19 g, 6.79 mmol) in CH_2Cl_2 (60 mL). After 3 h, saturated aqueous NH_4Cl (30 mL) was added, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and chromatographed (pentane/EtOAc 9:1) to give MOM ether **23** (2.61 g, 5.07 mmol, 75%) as a colorless oil: R_f 0.17 (pentane/EtOAc 9:1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 5.54 (s, 2H), 5.26 (s, 2H), 5.15–5.03 (m, 3H), 3.48 (s, 3H), 3.30 (d, J = 7.5 Hz, 2H), 2.16 (s, 3H), 2.08–1.89 (m, 8H), 1.76 (s, 3H), 1.69 (s, 6H), 1.66 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 160.24, 160.17, 155.8, 139.7, 135.7, 135.1, 131.3, 124.3, 124.0, 121.0, 118.2, 107.2, 105.3, 105.0, 94.1, 64.2, 56.4, 39.74, 39.66, 26.7, 26.6, 25.70 (2C), 25.66, 21.9, 20.9, 17.6, 16.1, 16.0; IR ν_{max} (neat) 2968, 2918, 2856, 1728, 1609, 1582, 1376, 1293, 1222, 1151, 1044, 964 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{30}H_{43}O_7$ 515.3009; found 515.2994. Anal. Calcd for $C_{30}H_{42}O_7$: C, 70.01; H, 8.23. Found: C, 69.75; H, 8.37.

7-Hydroxy-5-(methoxymethoxy)-6-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)isobenzofuran-1(3H)-one (24). K_2CO_3 (3.51 g, 25.4 mmol) was added with stirring to ether **23** (2.61 g, 5.07 mmol) in MeOH (70 mL) at 25 °C. After 18 h, aqueous citric acid (1 M) was added to pH ~3, and the mixture was diluted with CH_2Cl_2 (100 mL). The two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed (pentane/Et_2O 2:1) to provide lactone **24** (1.96 g, 4.73 mmol, 93%) a colorless oil, which solidified upon standing: R_f 0.44 (pentane/Et_2O 2:1); mp 61–62 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.21 (s, 1H), 4.75 (s, 2H), 4.71 (s, 2H), 4.71–4.66 (m, 1H), 4.58–4.53 (m, 2H), 2.97 (s, 3H), 2.88 (d, J = 7.2 Hz, 2H), 1.61–1.37 (m, 8H), 1.28 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.7, 162.1, 154.7, 145.5, 135.8, 135.0, 131.3, 124.3, 124.1, 121.2, 117.7, 104.8, 99.1, 94.2, 70.4, 56.3, 39.8, 39.7, 26.7, 26.5, 25.7, 21.8, 17.6, 16.1, 16.0; IR ν_{max} (neat) 3414, 1730, 1627, 1610, 1151, 1064, 1036, 959 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{35}O_5$ 415.2484; found 415.2482. Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.44; H, 8.27. Found: C, 72.31; H, 8.35.

7-Methoxy-5-(methoxymethoxy)-6-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)isobenzofuran-1(3H)-one (25). MeI (0.86 mL, 13.8 mmol) was added dropwise with stirring to a suspension of Cs_2CO_3 (4.50 g, 13.8 mmol) and lactone **24** (1.91 g, 4.60 mmol) in THF (46 mL) at 25 °C. After 16 h, saturated aqueous NH_4Cl (30 mL) was added, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated,

and chromatographed (pentane/Et$_2$O 2:1) to provide methyl ether **25** (1.94 g, 4.53 mmol, 98%) as a colorless oil: R_f 0.34 (pentane/Et$_2$O 2:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88 (s, 1H), 5.27 (s, 2H), 5.17 (s, 2H), 5.16−5.10 (m, 1H), 5.09−5.02 (m, 2H), 4.06 (s, 3H), 3.48 (s, 3H), 3.42 (d, J = 7.1 Hz, 2H), 2.09−1.88 (m, 8H), 1.79 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 168.8, 161.3, 158.0, 148.2, 135.5, 135.0, 131.3, 124.8, 124.3, 124.0, 122.0, 110.5, 101.9, 94.2, 68.8, 62.6, 56.3, 39.8, 39.7, 26.7, 26.5, 25.7, 22.7, 17.6, 16.1, 16.0; IR ν_{max} (neat) 1752, 1604, 1232, 1151, 1078, 1041, 926 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{37}$O$_5$ 429.2641; found 429.2650. Anal. Calcd for C$_{26}$H$_{36}$O$_5$: C, 72.87; H, 8.47. Found: C, 72.79; H, 8.55.

6-((2E,6E)-10-Bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl)-7-methoxy-5-(methoxymethoxy)-isobenzofuran-1(3H)-one (26). *N*-Bromosuccinimide (959 mg, 5.39 mmol) was added with stirring to methyl ether **25** (2.10 g, 4.90 mmol) in THF (46 mL) and H$_2$O (23 mL) at 0 °C. After 2 h, Na$_2$S$_2$O$_5$ (0.5 M; 30 mL) and EtOAc (30 mL) were added, and the two phases were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/EtOAc 2:1) to provide bromohydrin **26** (1.99 g, 3.79 mmol, 77%) as a colorless oil: R_f 0.14 (pentane/Et$_2$O 1:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88 (s, 1H), 5.28 (s, 2H), 5.17 (s, 2H), 5.17−5.11 (m, 2H), 4.07 (s, 3H), 3.95 (dd, J = 11.4, 1.9 Hz, 1H), 3.48 (s, 3H), 3.42 (d, J = 7.1 Hz, 2H), 2.33−2.22 (m, 1H), 2.19−1.88 (m, 6H), 1.79 (s, 3H), 1.78−1.68 (m, 1H), 1.55 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 168.8, 161.4, 158.0, 148.2, 135.3, 133.1, 125.8, 124.8, 122.1, 110.5, 102.0, 94.3, 72.4, 70.8, 68.8, 62.6, 56.3, 39.7, 38.1, 32.1, 26.6, 26.5, 25.8, 22.7, 16.1, 15.8; IR ν_{max} (neat) 3484, 1752, 1605, 1233, 1151, 1118, 1077. 1042, 978, 943 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{37}$BrO$_6$ 525.1852; found 525.1865.

6-((2E,6E)-9-((S)-3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)-7-methoxy-5-(methoxymethoxy)-isobenzofuran-1(3H)-one (16). K$_2$CO$_3$ (1.56 g, 2.96 mmol) was added with stirring to bromohydrin **26** in Me$_2$CO (60 mL) at 25 °C. After 18 h, H$_2$O (50 mL) and CH$_2$Cl$_2$ (100 mL) were added, and the two phases were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL), and the combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/Et$_2$O 1:1) to provide epoxide **16** (1.28 g, 2.88 mmol, 97%) as a colorless oil: R_f 0.38 (pentane/Et$_2$O 1:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88 (s, 1H), 5.27 (s, 2H), 5.17 (s, 2H), 5.16−5.02 (m, 2H), 4.06 (s, 3H), 3.47 (s, 3H), 3.41 (d, J = 7.1 Hz, 2H), 2.66 (t, J = 6.3 Hz, 1H), 2.29−1.89 (m, 6H), 1.78 (s, 3H), 1.63−1.58 (m, 1H), 1.57 (s, 3H), 1.56−1.50 (m, 1H), 1.28 (s, 3H), 1.23 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 168.7, 161.3, 158.0, 148.2, 135.4, 134.1, 124.8, 124.7, 122.1, 110.5, 102.0, 94.2, 68.8, 64.1, 62.6, 58.2, 56.3, 39.7, 36.2, 27.4, 26.5, 24.9, 22.7, 18.7, 16.1, 16.0; IR ν_{max} (neat) 1752, 1604, 1232, 1117, 1077, 1041, 978 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{37}$O$_7$ 445.2590; found 445.2598.

6-(((1S,4aR,6S,8aR)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)methyl)-7-methoxy-5-(methoxymethoxy)isobenzofuran-1(3H)-one (27). Cp$_2$TiCl$_2$ (197 mg, 0.792 mmol) and Mn powder (1.74 g, 31.7 mmol) were added with stirring to THF (50 mL) at 25 °C. After 30 min, when the solution changed from red to green, 2,4,6-collidine (3.67 mL, 27.7 mmol) and Me$_3$SiCl (2.01 mL, 15.8 mmol) were added sequentially with stirring. After 5 min, epoxide **16** (1.76 g, 3.96 mmol) in THF (50 mL) was added dropwise with stirring. After 16 h, aqueous citric acid (1 M; 100 mL) was added with stirring, and when effervescence ceased, Et$_2$O (100 mL) was added, and the two phases were separated. The aqueous layer was extracted with Et$_2$O (3 × 50 mL), and the combined organic layers were dried (MgSO$_4$), filtered, concentrated, and dissolved in THF (50 mL). Bu$_4$NF (1 M in THF; 16.0 mL, 16.0 mmol) was added, and the resulting mixture was stirred for 2 h at 25 °C. The reaction mixture was concentrated and chromatographed (pentane/Et$_2$O 1:4) to provide alcohol **27** (697 mg, 1.57 mmol, 40%) as a white foam: R_f 0.17 (pentane/Et$_2$O 1:4);

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.87 (s, 1H), 5.31−5.23 (m, 2H), 5.15 (s, 2H), 4.96 (s, 1H), 4.70 (s, 1H), 4.06 (s, 3H), 3.51 (s, 3H), 3.27 (dd, J = 11.5, 4.6 Hz, 1H), 2.92 (dd, J = 13.8, 9.7 Hz, 1H), 2.73 (dd, J = 13.8, 3.7 Hz, 1H), 2.50 (dd, J = 10.0, 3.4 Hz, 1H), 2.39−2.22 (m, 1H), 1.94−1.87 (m, 2H), 1.79−1.59 (m, 3H), 1.46−1.39 (m, 1H), 1.40−1.32 (m, 1H), 1.15 (dd, J = 12.5, 2.8 Hz, 1H), 1.00 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 168.9, 161.6, 158.5, 148.7, 148.1, 125.2, 110.6, 106.9, 102.1, 94.6, 78.9, 68.7, 62.4, 56.6, 55.3, 54.8, 40.1, 39.2, 38.4, 36.5, 28.3, 28.0, 24.1, 19.6, 15.4, 14.2; IR ν_{max} (neat) 3489, 1748, 1606, 1463, 1323, 1077, 1042, 732 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{26}$H$_{37}$O$_6$ 445.2590; found 445.2592.

(2S,4aR,5S,8aR)-5-((4-Methoxy-6-(methoxymethoxy)-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1,1,4a-trimethyl-6-methylenedecahydronaphthalen-2-yl Acetate (28). DMAP (9 mg, 0.0704 mmol), Et$_3$N (108 µL, 0.774 mmol) and Ac$_2$O (74 µL, 0.774 mmol) were added sequentially with stirring to alcohol **27** (313 mg, 0.704 mmol) in CH$_2$Cl$_2$ (3 mL) at 25 °C. After 2 h, saturated aqueous NaHCO$_3$ (2 mL) was added, and the two phases were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 3 mL), and the combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/Et$_2$O 1:1) to provide acetate **28** (337 mg, 0.693 mmol, 98%) as a white solid: R_f 0.33 (pentane/Et$_2$O 1:1); mp 155−158 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88 (s, 1H), 5.29−5.25 (m, 2H), 5.16 (s, 2H), 4.95 (s, 1H), 4.70 (s, 1H), 4.52 (dd, J = 11.6, 4.6 Hz, 1H), 4.06 (s, 3H), 3.51 (s, 3H), 2.92 (dd, J = 13.8, 9.6 Hz, 1H), 2.73 (dd, J = 13.8, 3.9 Hz, 1H), 2.57−2.48 (m, 1H), 2.36−2.27 (m, 1H), 2.06 (s, 3H), 1.93−1.83 (m, 2H), 1.81−1.59 (m, 3H), 1.49−1.32 (m, 2H), 1.22 (dd, J = 12.5, 2.7 Hz, 1H), 0.87 (s, 6H), 0.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 171.1, 168.9, 161.6, 158.4, 148.5, 148.2, 125.0, 110.5, 107.1, 102.1, 94.5, 80.8, 68.7, 62.6, 56.6, 55.0, 54.8, 39.9, 38.3, 38.1, 36.2, 28.3, 24.4, 24.0, 21.3, 19.8, 16.6, 14.2; IR ν_{max} (neat) 1753, 1729, 1606, 1463, 1234, 1078, 1043, 978, 920, 732 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{28}$H$_{39}$O$_7$ 487.2696; found 487.2674.

(2S,4aR,5S,8aR)-5-((6-Hydroxy-4-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1,1,4a-trimethyl-6-methylenedecahydronaphthalen-2-yl Acetate (15). Pyridinium *p*-toluenesulfonate (842 mg, 3.35 mmol) was added with stirring to acetate **28** (326 mg, 0.670 mmol) in ^{t}BuOH (25 mL), and the mixture was heated to 100 °C for 36 h. After being cooled, brine (30 mL) and CH$_2$Cl$_2$ (40 mL) were added, and the two phases were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 30 mL), and the combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/EtOAc 3:2) to provide phenol **15** (225 mg, 0.580 mmol, 86%) as a white solid: R_f 0.12 (pentane/Et$_2$O 1:1); mp 222−223 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.55 (s, 1H), 6.15 (s, 1H), 5.13 (s, 2H), 5.03 (s, 1H), 4.81 (s, 1H), 4.51 (dd, J = 11.6, 4.6 Hz, 1H), 4.08 (s, 3H), 2.90−2.75 (m, 2H), 2.42−2.32 (m, 2H), 2.06 (s, 3H), 2.02−1.87 (m, 2H), 1.78−1.62 (m, 3H), 1.48−1.36 (m, 2H), 1.23 (dd, J = 12.5, 2.8 Hz, 1H), 0.87 (s, 6H), 0.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 171.1, 168.9, 160.9, 158.8, 149.4, 148.1, 122.8, 109.6, 107.3, 103.8, 80.8, 68.4, 62.7, 55.2, 54.8, 40.2, 38.2, 38.1, 36.2, 28.2, 24.3, 24.0, 21.3, 19.2, 16.5, 14.2; IR ν_{max} (neat) 3295, 1730, 1605, 1429, 1235, 1077, 1027 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{35}$O$_6$ 443.2434; found 443.2434.

((3S,4aR,6aS,13aR,13bS)-12-Methoxy-4,4,13b-trimethyl-11-oxo-6a-((phenylselanyl)methyl)-1,3,4,4a,5,6,6a,9,11,-13,13a,13b-dodecahydro-2H-benzo[a]furo[3,4-i]xanthen-3-yl Acetate (29). Phenol **15** (100 mg, 0.226 mmol) in CH$_2$Cl$_2$ (10 mL) was added dropwise with stirring to *N*-(phenylseleno)phthalimide (410 mg, 1.36 mmol) and SnCl$_4$ (1 M in CH$_2$Cl$_2$; 1.13 mL, 1.13 mmol) in CH$_2$Cl$_2$ (20 mL) at −78 °C. After 7 h, NaOH (2 M; 1 mL) was added and the reaction mixture was filtered through Celite. NaOH (2 M; 10 mL) was added; the two phases were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/Et$_2$O 1:1) to provide phenylselenide **29** (79 mg, 0.132 mmol, 58%) as a colorless oil: R_f 0.26 (pentane/

Et$_2$O 1:1); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45−7.40 (m, 2H), 7.23−7.16 (m, 3H), 6.39 (s, 1H), 5.09 (s, 2H), 4.53 (dd, J = 11.8, 4.6 Hz, 1H), 4.08 (s, 3H), 3.12 (d, J = 12.6 Hz, 1H), 2.95 (d, J = 12.6 Hz, 1H), 2.77 (d, J = 18.9 Hz, 1H), 2.44 (dd, J = 18.9, 8.4 Hz, 1H), 2.30 (dt, J = 14.0, 3.0 Hz, 1H), 2.05 (s, 3H), 1.94−1.57 (m, 7H), 1.19 (td, J = 13.2, 3.9 Hz, 1H), 1.03 (dd, J = 11.3, 2.7 Hz, 1H), 0.92 (s, 3H), 0.85 (s, 3H), 0.66 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 171.0, 168.8, 160.7, 157.3, 147.4, 133.3 (2C), 130.2, 129.1 (2C), 127.3, 116.0, 108.2, 105.3, 80.4, 79.1, 68.6, 62.1, 53.9, 45.5, 38.03, 37.97, 37.8, 37.7, 37.3, 28.4, 23.4, 21.3, 17.5, 17.4, 16.8, 14.4; IR ν$_{max}$ (neat) 1751, 1734, 1613, 1592, 1429, 1366, 1238, 1131, 1027, 1078, 733 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{32}$H$_{38}$O$_6$Se 599.1912; found 599.1913.

(3S,4aR,6aS,13R,13bS)-12-Methoxy-4,4,6a,13b-tetramethyl-11-oxo-1,3,4,4a,5,6,6a,9,11,13,13a,13b-dodecahydro-2H-benzo[a]furo[3,4-i]xanthen-3-yl Acetate (14). Phenylselenide **29** (46 mg, 0.0770 mmol), AIBN (13 mg, 0.0770 mmol), and HSnBu$_3$ (62 μL, 0.231 mmol) in PhH (2 mL) were purged with Ar for 5 min and heated to 100 °C for 5 h. The reaction mixture was directly purified by chromatography (pentane/Et$_2$O 1:1) through a pad of KF to give meroterpenoid **14** (31 mg, 0.0700 mmol, 91%) as a white solid: R$_f$ 0.29 (pentane/Et$_2$O 1:1); mp 212−213 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.50 (s, 1H), 5.13 (s, 2H), 4.49 (dd, J = 11.7, 4.7 Hz, 1H), 4.13 (s, 3H), 2.88 (d, J = 18.7 Hz, 1H), 2.71 (dd, J = 18.6, 8.0 Hz, 1H), 2.23−2.14 (m, 1H), 2.04 (s, 3H), 1.87 (dt, J = 13.3, 3.7 Hz, 1H), 1.74−1.50 (m, 5H), 1.40 (d, J = 8.1 Hz, 1H), 1.17 (s, 3H), 1.13 (dd, J = 13.4, 4.0 Hz, 1H), 1.00 (dd, J = 11.3, 2.1 Hz, 1H), 0.89 (s, 3H), 0.84 (s, 3H), 0.66 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 170.9, 168.9, 161.6, 157.4, 147.4, 116.0, 107.9, 105.2, 80.5, 76.6, 68.6, 62.0, 54.2, 48.1, 40.1, 37.9, 37.8, 37.6, 28.4, 27.0, 23.4, 21.2, 17.7 (2C), 16.8, 14.3; IR ν$_{max}$ (neat) 1730, 1752, 1612, 1592, 1366, 1238, 1130, 1081, 1025, 901, 731 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{26}$H$_{34}$O$_6$ 443.2434; found 443.2419.

(3S,4aR,6aS,13aR,13bS)-8-Bromo-12-methoxy-4,4,6a,13b-tetramethyl-11-oxo-1,3,4,4a,5,6,6a,9,11,13,13a,13b-dodecahydro-2H-benzo[a]furo[3,4-i]xanthen-3-yl Acetate (30). N-Bromosuccinimide (19 mg, 0.105 mmol) and H$_2$SO$_4$ (13 μL,0.244 mmol) were added sequentially with stirring to meroterpenoid **14** (31 mg, 0.0700 mmol) in THF (0.4 mL). After 17 h, saturated aqueous NaHCO$_3$ (0.4 mL) and Na$_2$S$_2$O$_3$ (50 mg, 0.316 mmol) were added, and the two phases were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 0.5 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/Et$_2$O 7:3) to provide bromide **30** (34 mg, 0.0652 mmol, 93%) as a white foam: R$_f$ 0.19 (pentane/Et$_2$O 7:3); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.07 (s, 2H), 4.50 (dd, J = 11.8, 4.5 Hz, 1H), 4.15 (s, 3H), 2.90 (d, J = 18.8 Hz, 1H), 2.75 (dd, J = 18.8, 8.1 Hz, 1H), 2.38−2.29 (m, 1H), 2.04 (s, 3H), 1.86 (dd, J = 13.5, 3.7 Hz, 1H), 1.79−1.51 (m, 5H), 1.44 (d, J = 8.2 Hz, 1H), 1.19 (s, 3H), 1.17−1.08 (m, 1H), 1.01 (d, J = 11.0 Hz, 1H), 0.90 (s, 3H), 0.85 (s, 3H), 0.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 170.9, 168.4, 157.4, 156.4, 146.9, 117.5, 109.2, 98.3, 80.4, 78.1, 69.3, 62.2, 54.1, 48.0, 39.9, 37.9, 37.8, 37.7, 28.4, 27.1, 23.3, 21.3, 18.3, 17.8, 16.8, 14.2; IR ν$_{max}$ (neat) 1759, 1733, 1603, 1465, 1436, 1366, 1246, 1135, 1029, 904, 732 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{26}$H$_{34}$O$_6$Br 521.1539; found 521.1549.

(3S,4aR,6aS,13aR,13bS)-12-Methoxy-4,4,6a,8,13b-pentamethyl-11-oxo-1,3,4,4a,5,6,6a,9,11,13,13a,13b-dodecahydro-2H-benzo[a]furo[3,4-i]xanthen-3-yl Acetate (31). A degassed solution of bromide **30** (65 mg, 0.125 mmol), Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (21 mg, 0.0257 mmol), CH$_3$BF$_3$K (23 mg, 0.187 mmol), and Cs$_2$CO$_3$ (122 mg, 0.375 mmol) in THF (1.5 mL) and H$_2$O (75 μL) was heated at 80 °C for 18 h. After being cooled to 25 °C, H$_2$O (1 mL) and Et$_2$O (1 mL) were added, and the two phases were separated. The aqueous layer was extracted with Et$_2$O (3 × 1 mL), and the combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/Et$_2$O 7:3) to provide arene **31** (50 mg, 0.110 mmol, 88%) as a white foam: R$_f$ 0.26 (pentane/Et$_2$O 7:3); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.11 (s, 2H), 4.50 (dd, J = 11.7, 4.6 Hz, 1H), 4.09 (s, 3H), 2.90 (d, J = 18.6 Hz, 1H), 2.74 (dd, J = 18.6,

8.1 Hz, 1H), 2.33−2.16 (m, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 1.95−1.81 (m, 1H), 1.72−1.54 (m, 5H), 1.40 (d, J = 7.8 Hz, 1H), 1.21−1.16 (m, 1H), 1.16 (s, 3H), 1.01 (d, J = 9.9 Hz, 1H), 0.90 (s, 3H), 0.85 (s, 3H), 0.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 170.9, 169.5, 158.8, 155.3, 145.3, 115.7, 114.3, 107.2, 80.5, 76.4, 68.2, 61.9, 54.2, 47.9, 40.2, 37.9, 37.8, 37.7, 28.5, 27.3, 23.4, 21.3, 17.9, 17.8, 16.8, 14.3, 10.7; IR ν$_{max}$ (neat) 1754, 1609, 1368, 1245, 1146, 1135, 1041, 1029, 904, 732 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{27}$H$_{37}$O$_6$ 457.2590; found 457.2594.

(±)-17S-Dihydroaustalide K [(3S,4aR,6aS,13aR,13bS)-3-Hydroxy-12-methoxy-4,4,6a,8,13b-pentamethyl-1,2,3,4,4a,-5,6,6a,9,13,13a,13b-dodecahydro-11H-benzo[a]furo[3,4-i]-xanthen-11-one (1)]. Magnesium turnings (4 mg, 0.164 mmol) were added with stirring to a solution of arene **31** (15 mg, 0.0329 mmol) in MeOH (1 mL) and THF (0.1 mL), and the resulting suspension was heated at reflux for 1 h. When the reaction mixture had turned into a milky solution and effervescence has ceased, it was cooled to 25 °C and stirred for an additional 20 h. Aqueous HCl (1 M) was added until pH ~1, and the two phases were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 1 mL), and the combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/Et$_2$O 1:1) to provide (±)-17S-dihydroaustalide K (**1**) (13 mg, 0.0314 mmol, 95%) as a white solid: R$_f$ 0.12 (pentane/Et$_2$O 1:1); mp 198−200 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.11 (s, 2H), 4.09 (s, 3H), 3.24 (dd, J = 11.7, 4.5 Hz, 1H), 2.91 (d, J = 18.6 Hz, 1H), 2.73 (dd, J = 18.7, 8.2 Hz, 1H), 2.29−2.22 (m, 1H), 2.03 (s, 3H), 1.89 (dt, J = 13.1, 3.5 Hz, 1H), 1.62−1.52 (m, 5H), 1.39 (d, J = 8.2 Hz, 1H), 1.18 (d, J = 6.2 Hz, 1H), 1.15 (s, 3H), 1.09 (td, J = 13.2, 3.8 Hz, 1H), 1.03 (s, 3H), 0.93 (d, J = 11.5 Hz, 1H), 0.78 (s, 3H), 0.61 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 169.5, 158.9, 155.3, 145.3, 115.7, 114.3, 107.2, 78.8, 76.4, 68.2, 61.9, 54.1, 48.0, 40.3, 38.8, 38.1, 38.0, 28.5, 27.3, 27.1, 18.0, 17.9, 15.7, 14.2, 10.7; IR ν$_{max}$ (neat) 3494, 1752, 1610, 1477, 1368, 1148, 1135, 1040, 904, 732 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{25}$H$_{35}$O$_5$ 415.2484; found 415.2486.

(±)-Austalide K [(5aR,7aS,14aR,14bS)-13-Methoxy-5,5,7a,9,14b-pentamethyl-1,2,5a,6,7,7a,10,14,14a,14b-deca-hydro-5H-furo[3,4-i]oxepino[4,3-a]xanthene-3,12-dione (2)]. Dess−Martin periodinane (52 mg, 0.123 mmol) was added with stirring to (±)-17S-dihydroaustalide K (**1**) (34 mg, 0.0820 mmol) in CH$_2$Cl$_2$ (2 mL) at 25 °C. After 1 h, the mixture was concentrated and chromatographed (pentane/Et$_2$O 1:1) to give (±)-austalide K (**2**) (28 mg, 0.0679 mmol, 83%) as a white solid: R$_f$ 0.34 (pentane/Et$_2$O 1:1); mp 160−164 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.12 (s, 2H), 4.11 (s, 3H), 2.93 (d, J = 18.5 Hz, 1H), 2.81 (dd, J = 18.6, 8.2 Hz, 1H), 2.54 (ddd, J = 16.1, 11.7, 7.0 Hz, 1H), 2.47−2.36 (m, 1H), 2.31−2.25 (m, 1H), 2.11 (ddd, J = 13.4, 6.9, 3.8 Hz, 1H), 2.05 (s, 3H), 1.88−1.74 (m, 1H), 1.72−1.60 (m, 1H), 1.57−1.47 (m, 4H), 1.19 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 0.73 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 216.6, 169.4, 158.6, 155.4, 145.52, 115.3, 114.4, 107.3, 76.2, 68.2, 62.0, 54.2, 47.3, 47.1, 39.7, 38.4, 37.6, 34.1, 27.1, 26.7, 21.7, 19.1, 18.3, 14.2, 10.7; IR ν$_{max}$ (neat) 1754, 1702, 1610, 1477, 1367, 1141, 904 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{25}$H$_{33}$O$_5$ 413.2328; found 413.2327.

(±)-13-Deacetoxyaustalide I [(5aR,7aS,14aR,14bS)-13-Methoxy-5,5,7a,9,14b-pentamethyl-1,2,5a,6,7,7a,10,14,14a,14b-decahydro-5H-furo[3,4-i]oxepino[4,3-a]xanthene-3,12-dione (3)]. NaHCO$_3$ (9 mg, 0.107 mmol) and m-CPBA (18.4 mg, 0.107 mmol) were added with stirring to (±)-austalide K (**2**) (22 mg, 0.0533 mmol) in CH$_2$Cl$_2$ (1 mL) at 25 °C. After 19 h, saturated aqueous NaHCO$_3$ (1 mL) was added, and phases were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 1 mL), and the combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (Et$_2$O) to provide (±)-13-deacetoxyaustalide I (**3**) (22 mg, 0.0513 mmol, 96%) as a white solid: R$_f$ 0.37 (Et$_2$O); mp 93−95 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.14 (s, 2H), 4.13 (s, 3H), 2.96 (d, J = 18.6 Hz, 1H), 2.84 (dd, J = 18.7, 8.1 Hz, 1H), 2.69 (ddd, J = 15.6, 11.2, 3.1 Hz, 1H), 2.60 (ddd, J = 15.6, 8.3, 2.7 Hz, 1H), 2.25 (dt, J = 14.2, 3.1 Hz, 1H), 2.06 (s, 3H), 2.02−1.84 (m, 3H), 1.75−1.62 (m, 2H), 1.56 (d, J = 7.8 Hz, 1H), 1.54−1.53 (m, 1H), 1.52 (s, 3H), 1.42 (s, 3H), 1.21 (s, 3H), 0.83 (s, 3H); ^{13}C{^{1}H} NMR (100

MHz, CDCl$_3$) δ 175.1, 169.3, 158.3, 155.3, 145.6, 115.1, 114.3, 107.4, 85.8, 76.0, 68.2, 62.0, 53.6, 47.3, 40.4, 39.3, 37.3, 32.5, 31.8, 27.1, 25.8, 22.1, 18.7, 16.7, 10.6; IR ν_{max} (neat) 1749, 1609, 1477, 1372, 1282, 1142, 1112, 905, 731 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{25}$H$_{33}$O$_6$ 429.2277; found 429.2291.

(±)-Austalide P [Methyl 3-((5aS,8R,9S,9aR)-8-(2-hydroxy-propan-2-yl)-11-methoxy-4,5a,9-trimethyl-1-oxo-3,5a,6,7,8,9,9a,10-octahydro-1H-furo[3,4-b]xanthen-9-yl)-propanoate (4)]. NaOMe (0.5 M; 0.50 mL; 0.250 mmol) was added with stirring to (±)-13-deacetoxyaustalide I (3) (10.8 mg, 0.0252 mmol) in MeOH (0.50 mL) at 25 °C. After 1 h, saturated aqueous NH$_4$Cl (1 mL) and Et$_2$O (2 mL) were added; the phases were separated, and the aqueous layer was extracted with Et$_2$O (3 × 1 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (pentane/Et$_2$O 1:1) to provide (±)-austalide P (4) (9.3 mg, 0.0202 mmol, 80%) as a white foam: R_f 0.21 (pentane/Et$_2$O 1:1); ^{1}H NMR (400 MHz, CD$_3$OD) δ 5.20 (s, 2H), 4.04 (s, 3H), 3.67 (s, 3H), 3.01 (d, J = 18.6 Hz, 1H), 2.76 (dd, J = 18.6, 7.9 Hz, 1H), 2.65–2.55 (m, 1H), 2.42 (tdd, J = 11.5, 4.8, 2.5 Hz, 1H), 2.37–2.27 (m, 1H), 2.15–2.10 (m, 1H), 2.05 (s, 3H), 1.88–1.75 (m, 2H), 1.68 (d, J = 8.0 Hz, 1H), 1.66–1.57 (m, 1H), 1.57–1.48 (m, 2H), 1.27 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 0.70 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD$_3$OD) δ 176.9, 171.8, 160.4, 156.6, 147.5, 117.3, 115.8, 108.2, 78.3, 75.7, 69.8, 62.2, 52.1, 52.0, 42.8, 41.4, 40.5, 34.9, 33.2, 30.1, 28.1, 27.7, 22.6, 19.5, 18.8, 10.6; IR ν_{max} (neat) 3514, 2971, 1740, 1610, 1436, 1368, 1141, 1045, 898, 732 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{26}$H$_{37}$O$_7$ 461.2539; found 461.2531.

(±)-13-Deoxyaustalide Q Acid [3-((5aS,8S,9S,9aR)-11-Me-thoxy-4,5a,9-trimethyl-1-oxo-8-(prop-1-en-2-yl)-3,5a,6,7,-8,9,9a,10-octahydro-1H-furo[3,4-b]xanthen-9-yl)propanoic Acid (5)]. (±)-13-Deacetoxyaustalide I (3) (14 mg, 0.0327 mmol) was dissolved in THF (1 mL), and p-TsOH·H$_2$O (56 mg, 0.327 mmol) was added. The resulting mixture was heated to 70 °C for 1 h. After being cooled back to 25 °C, H$_2$O (1 mL) and Et$_2$O (1 mL) were added and the two phases separated, and the aqueous layer was extracted with Et$_2$O (3 × 1 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated, and chromatographed (Et$_2$O) to provide (±)-13-deoxyaustalide Q acid (5) (10 mg, 0.0233 mmol, 71%) as a white foam: R_f 0.42 (Et$_2$O); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.12 (s, 2H), 4.90 (s, 1H), 4.69 (s, 1H), 4.11 (s, 3H), 2.89 (d, J = 18.5 Hz, 1H), 2.77 (dd, J = 18.4, 7.8 Hz, 1H), 2.52–2.26 (m, 2H), 2.23–2.06 (m, 3H), 2.04 (s, 3H), 1.74 (s, 3H), 1.74–1.70 (m, 2H), 1.68–1.61 (m, 1H), 1.57 (d, J = 7.8 Hz, 1H), 1.49–1.44 (m, 1H), 1.20 (s, 3H), 0.60 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 179.1, 169.5, 158.6, 155.5, 146.7, 145.5, 115.2, 114.4, 114.2, 107.3, 76.5, 68.3, 62.0, 50.1, 40.0, 39.6, 39.0, 32.9, 28.5, 27.4, 23.8, 23.6, 18.1 (2C), 10.7; IR ν_{max} (neat) 3261, 2933, 1749, 1705, 1610, 1369, 1148, 1131, 910, 732 cm^{-1}; HRMS (ES) m/z [M + H]$^+$ calcd for C$_{25}$H$_{33}$O$_6$ 429.2277; found 429.2285.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00142.

> ^{1}H and ^{13}C NMR spectra for (±)-17S-dihydroaustalide K (1), (±)-austalide K (2), (±)-13-deacetoxyaustalide I (3), (±)-austalide P (4), (±)-13-deoxyaustalide Q acid (5), and compounds 14−16, 19, and 22−31 (PDF)
>
> X-ray structural data for 15 (PDF, CIF)

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REFERENCES

(1) (a) Horak, R. M.; Steyn, P. S.; Van Rooyen, P. H.; Vleggaar, R.; Rabie, C. J. Structures of the Austalides A−E, Five Noval Toxic Metabolites from Aspergillus Ustus. *J. Chem. Soc., Chem. Commun.* **1981**, 24, 1265−1267. (b) Horak, R. M.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. Metabolites of Aspergillus Ustus. Part 1. Application of the Heteronuclear Selective Population Inversion (SPI) n.m.r. Technique to the Structure Elucidation of the Austalides A−F, Novel Ortho Ester Meroterpenoids. *J. Chem. Soc., Perkin Trans. 1* **1985**, 4, 345−356. (c) Horak, R. M.; Steyn, P. S.; Vleggaar, R. Metabolites of Aspergillus Ustus. Part 2. Stereoelectronic Control in the Acid-Catalysed Hydrolysis of the Ortho Ester Moiety in Austalides A−F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 9 (7), 357−361. (d) Horak, R. M.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. Metabolites of Aspergillus Ustus. Part 3. Structure Elucidation of Austalides G−L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 47, 363−367.

(2) (a) Zhou, Y.; Mándi, A.; Debbab, A.; Wray, V.; Schulz, B.; Müller, W. E. G.; Lin, W.; Proksch, P.; Kurtán, T.; Aly, A. H. New Austalides from the Sponge-Associated Fungus Aspergillus Sp. *Eur. J. Org. Chem.* **2011**, 2011 (30), 6009−6019. (b) Zhou, Y.; Debbab, A.; Wray, V.; Lin, W.; Schulz, B.; Trepos, R.; Pile, C.; Hellio, C.; Proksch, P.; Aly, A. H. Marine Bacterial Inhibitors from the Sponge-Derived Fungus Aspergillus Sp. *Tetrahedron Lett.* **2014**, 55 (17), 2789−2792. (c) Zhuravleva, O. I.; Sobolevskaya, M. P.; Leshchenko, E. V.; Kirichuk, N. N.; Denisenko, V. A.; Dmitrenok, P. S.; Dyshlovoy, S. A.; Zakharenko, A. M.; Kim, N. Y.; Afiyatullov, S. S. Meroterpenoids from the Alga-Derived Fungi Penicillium Thomii Maire and Penicillium Lividum Westling. *J. Nat. Prod.* **2014**, 77 (6), 1390−1395. (d) Peng, J.; Zhang, X.; Wang, W.; Zhu, T.; Gu, Q.; Li, D. Austalides S-U, New Meroterpenoids from the Sponge-Derived Fungus Aspergillus Aureolatus HDN14−107. *Mar. Drugs* **2016**, 14 (7), 131. (e) Sobolevskaya, M. P.; Zhuravleva, O. I.; Leshchenko, E. V.; Zakharenko, A. M.; Denisenko, V. A.; Kirichuk, N. N.; Popov, R. S.; Berdyshev, D. V.; Pislyagin, E. A.; Pivkin, M. V.; et al. New Metabolites from the Alga-Derived Fungi Penicillium Thomii Maire and Penicillium Lividum Westling. *Phytochem. Lett.* **2016**, 15, 7−12.

(3) (a) de Jesus, A. E.; Horak, R. M.; Steyn, P. S.; Vleggaar, R. Metabolites of Aspergillus Ustus. Part 4. Stable-Isotope Labelling Studies on the Biosynthesis of the Austalides. *J. Chem. Soc., Perkin Trans. 1* **1987**, 9, 2253. (b) Dillen, J. L. M.; Horak, R. M.; Maharaj, V. J.; Marais, S. F.; Vleggaar, R. Absolute Configuration and Biosynthesis of the Austalides, Meroterpenoid Metabolites of Aspergillus Ustus: Mode of Cyclisation of the Farnesyl Moiety. *J. Chem. Soc., Chem. Commun.* **1989**, 2 (7), 393.

(4) (a) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. Ketenes. 20. Thermal Decomposition of 2,2,6-Trimethyl-4H-1,3-Dioxin-4-One and 1-Ethoxybutyn-3-One. Acetylketene. *J. Org. Chem.* **1984**, 49 (26), 5105−5108. (b) Harris, T. M.; Harris, C. M. Synthesis of Polyketide-Type Aromatic Natural Products by Biogenetically Modeled Routes. *Tetrahedron* **1977**, 33 (17), 2159−2185.

(5) Cookson, R.; Barrett, T. N.; Barrett, A. G. M. β-Keto-Dioxinones and β,δ-Diketo-Dioxinones in Biomimetic Resorcylate Total Synthesis. *Acc. Chem. Res.* **2015**, 48 (3), 628−642.

(6) (a) Elliott, D. C.; Ma, T.-K.; Selmani, A.; Cookson, R.; Parsons, P. J.; Barrett, A. G. M. Sequential Ketene Generation from Dioxane-4,6-Dione-Keto-Dioxinones for the Synthesis of Terpenoid Resorcylates. *Org. Lett.* **2016**, 18 (8), 1800−1803. (b) Ma, T.-K.; White, A. J. P.; Barrett, A. G. M. Meroterpenoid Total Synthesis: Conversion of Geraniol and Farnesol into Amorphastilbol, Grifolin and Grifolic Acid

by Dioxinone- β -Keto-Acylation, Palladium Catalyzed Decarboxylative Allylic Rearrangement and Aromatization. *Tetrahedron Lett.* **2017**, 58 (28), 2765−2767.

(7) Ma, T.-K.; Elliott, D. C.; Reid, S.; White, A. J. P.; Parsons, P. J.; Barrett, A. G. M. Meroterpenoid Synthesis via Sequential Polyketide Aromatization and Cationic Polyene Cyclization: Total Syntheses of (+)-Hongoquercin A and B and Related Meroterpenoids. *J. Org. Chem.* **2018**, 83 (21), 13276−13286.

(8) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. Titanocene-Catalyzed Cascade Cyclization of Epoxypolyprenes: Straightforward Synthesis of Terpenoids by Free-Radical Chemistry. *Chem. - Eur. J.* **2004**, 10 (7), 1778−1788.

(9) Iwasaki, K.; Nakatani, M.; Inoue, M.; Katoh, T. Studies toward the Total Synthesis of (−)-Kampanol A: An Efficient Construction of the ABCD Ring System. *Tetrahedron Lett.* **2002**, 43 (44), 7937−7940.

(10) Molander, G. A.; Yun, C. S.; Ribagorda, M.; Biolatto, B. B-Alkyl Suzuki-Miyaura Cross-Coupling Reactions with Air-Stable Potassium Alkyltrifluoroborates. *J. Org. Chem.* **2003**, 68 (14), 5534−5539.

(11) Xu, Y.-C.; Lebeau, E.; Walker, C. Selective Deprotection of Esters Using Magnesium and Methanol. *Tetrahedron Lett.* **1994**, 35 (34), 6207−6210.

(12) Okamoto, R.; Takeda, K.; Tokuyama, H.; Ihara, M.; Toyota, M. Toward the Total Synthesis of (±)-Andrastin C. *J. Org. Chem.* **2013**, 78 (1), 93−103.

(13) Mai, D.; Uchenik, D.; Vanderwal, C. Efforts Toward a Synthesis of Crotogoudin and Crotobarin. *Synlett* **2017**, 28 (14), 1758−1762.

■ NOTE ADDED AFTER ASAP PUBLICATION

The table of contents/abstract graphic was corrected April 16, 2019.