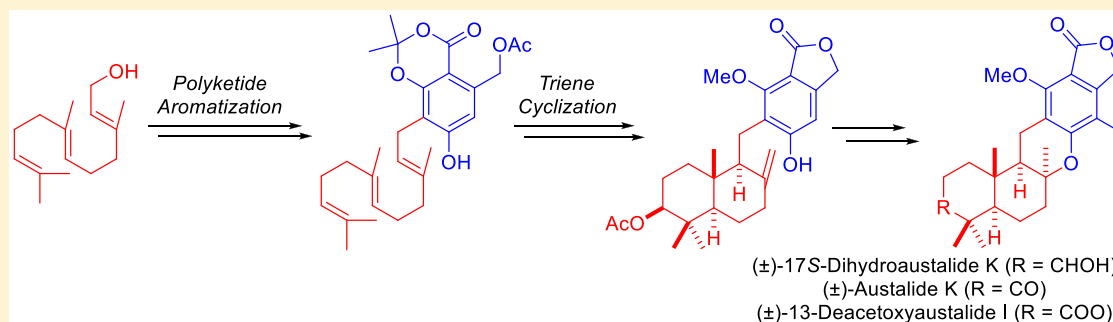


Meroterpenoid Synthesis via Sequential Polyketide Aromatization and Radical Anion Cascade Triene Cyclization: Biomimetic Total Syntheses of Austalide Natural Products

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^S Supporting Information



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 -resorcyate, 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-[(2*E*,6*E*)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 ¹³C, ²H- and ²H-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 -resorcyate-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

Received: January 15, 2019

Published: April 2, 2019

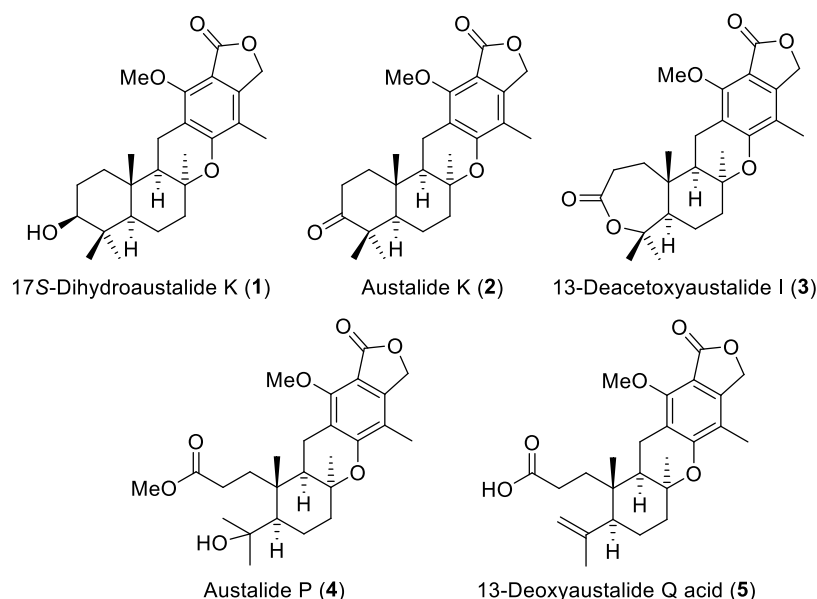
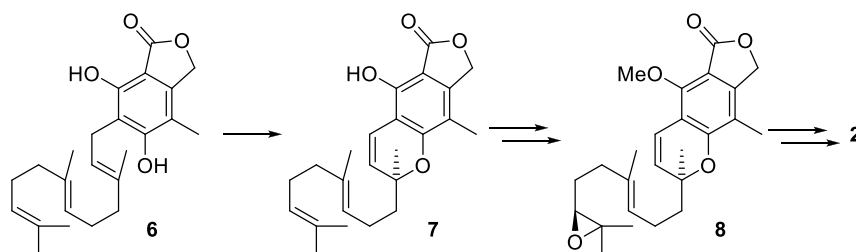


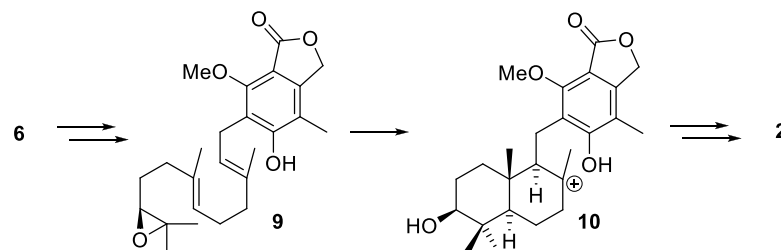
Figure 1. Representative austalide natural products.

Scheme 1. Proposed Biosynthesis of Austalides K (2)

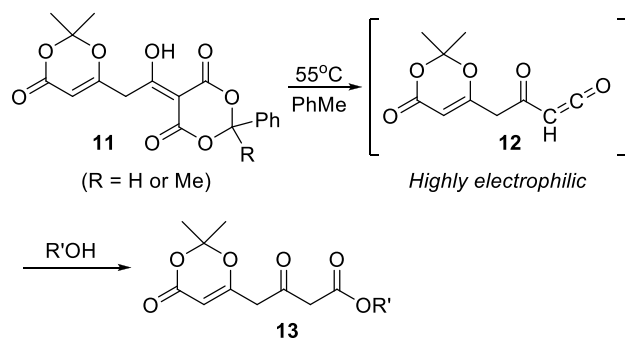
First Proposed Biosynthesis of Austalides



Revised Proposed Biosynthesis of Austalides



Scheme 2. Thermolysis of Dioxane-4,6-dione Ketodioxanones 11

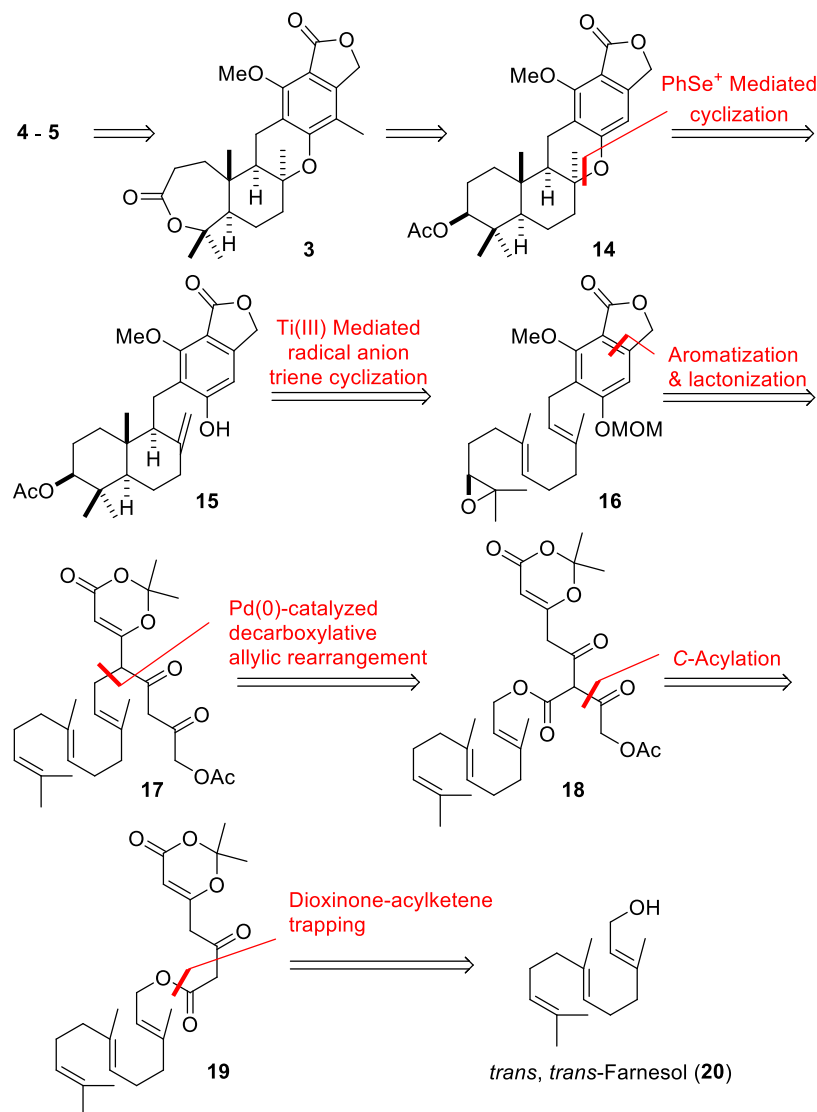


the biomimetic total syntheses of the austalide natural products via a series of biomimetic transformations.

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 Australides



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 -resorcyate, 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

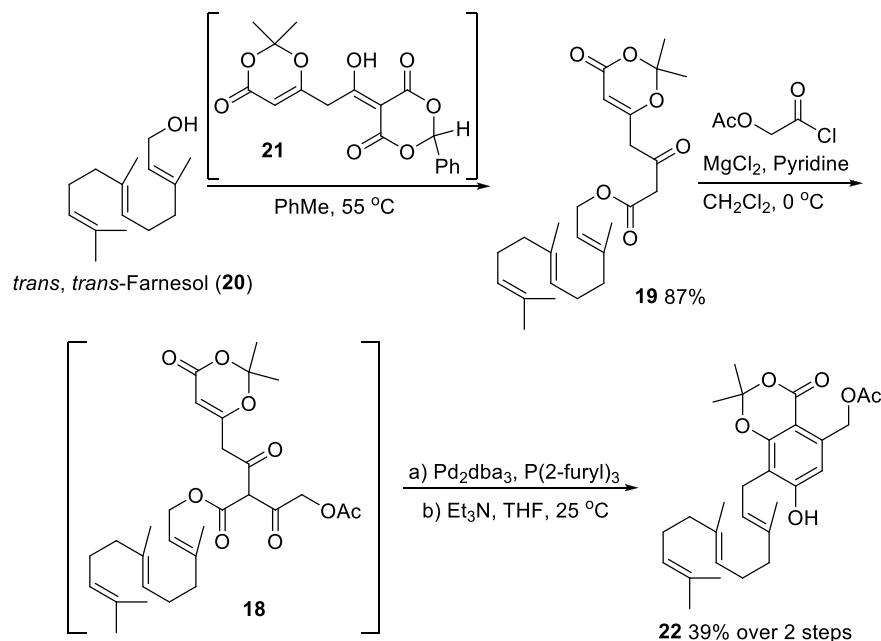
The synthesis of β -resorcyate **22** (Scheme 4) was undertaken by trapping dioxinone acylketene **12**, generated in situ from 4,6-dione ketodioxanone **21**, with *trans,trans*-farnesol (**20**) to provide dioxinone β -ketoester **19** (87%).⁶ Subsequent MgCl-mediated regioselective C-acylation of 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 -resorcyate **22** (39% over two steps from dioxinone β -ketoester **19**).

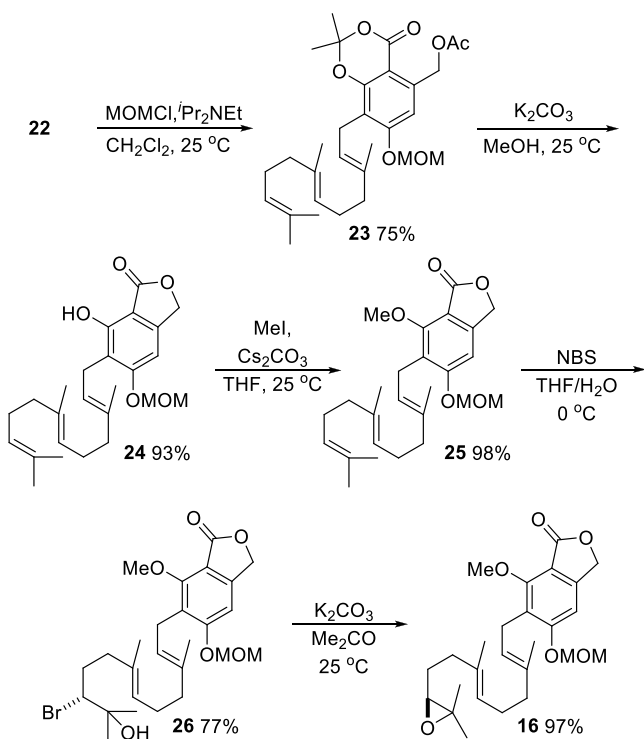
With the β -resorcyate **22** in hand, attention was focused on the functionalization of the aromatic core as well as installing the terminal epoxide for the triene cyclization reaction (Scheme 5). The phenol group of β -resorcyate **22** was first protected as the MOM ether **23** (75%), followed by 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 Resorcyate 22



Scheme 5. Synthesis of Epoxide 16



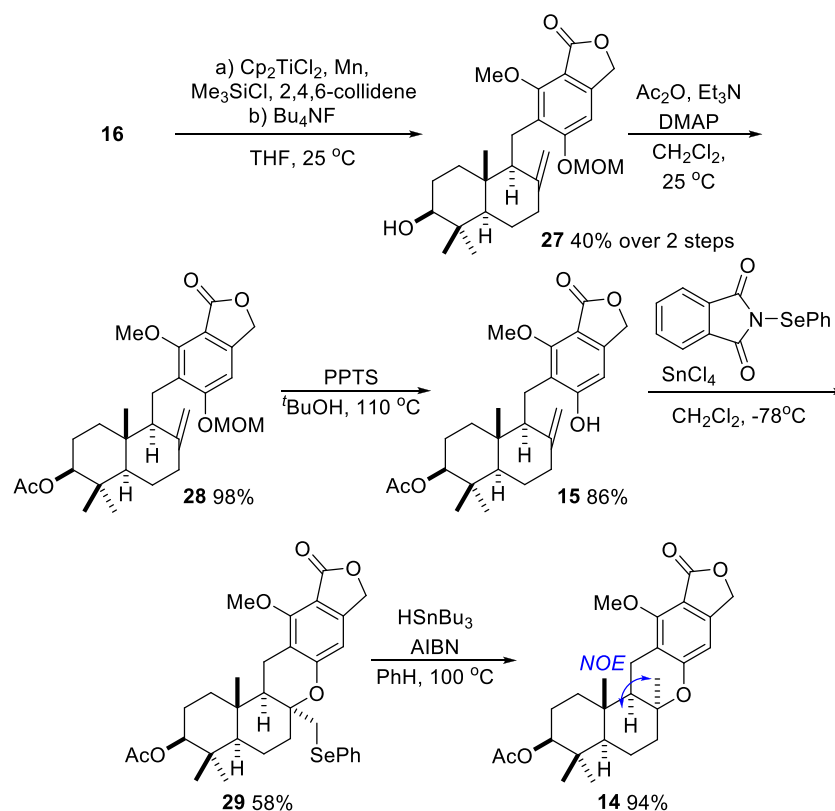
with tetrabutylammonium fluoride. Acetylation of the alcohol **27** yielded acetate **28** (98%), followed by MOM deprotection with pyridinium *p*-toluenesulfonate (PPTS) and ^tBuOH to furnish phenol **15** (86%). The relative stereochemistry of phenol **15** was unambiguously determined by X-ray crystallography, 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 phenylselenide **29** (58%).⁹ After removal of the phenylselenyl group

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.

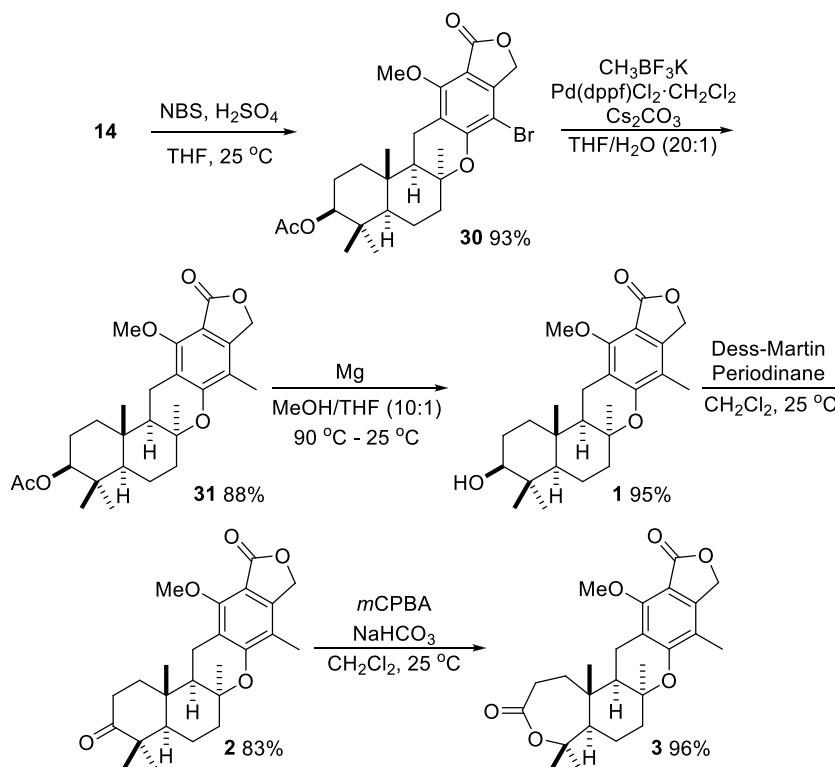
With the key meroterpenoid **14** in hand after establishing the correct relative stereochemistry, we directed our attention to the arene methylation and sequential oxidation reactions to complete the synthesis of (±)-17*S*-dihydroaustalide **K** (**1**), (±)-austalide **K** (**2**), and (±)-13-deacetoxyaustalide **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 (±)-17*S*-dihydroaustalide **K** (**1**) (88%).¹¹ Furthermore, Dess–Martin periodinane-mediated oxidation of (±)-17*S*-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 transesterification 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}

Scheme 6. Synthesis of Meroterpenoid 14



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

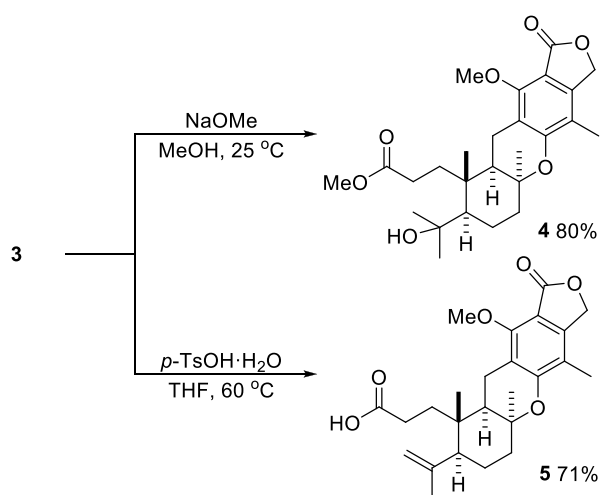


CONCLUSION

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-Ph₂CO. CH_2Cl_2 , Et_3N , MeOH, and pyridine were redistilled from CaH₂. PhH and PhMe were redistilled from Na. Me₂CO 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 F₂₅₄ 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 μ m. All ¹H and proton-decoupled ¹³C 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 ¹³C NMR; CD_3OD δ = 3.31 and 4.87 for ¹H NMR and δ = 49.0 for ¹³C 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 $\times$ 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**. $P(2\text{-furyl})_3$ (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 $\times$ 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 -resorcyate **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); ¹³C{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 ^tPr₂EtN (5.92 mL; 34.0 mmol) and β -resorcyate **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 $\times$ 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); ¹³C{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 $\times$ 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); ¹³C{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 $\times$ 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered, concentrated,

and chromatographed (pentane/Et₂O 2:1) to provide methyl ether **25** (1.94 g, 4.53 mmol, 98%) as a colorless oil: *R*_f 0.34 (pentane/Et₂O 2:1); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₆H₃₇O₅ 429.2641; found 429.2650. Anal. Calcd for C₂₆H₃₆O₅: 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 H₂O (23 mL) at 0 °C. After 2 h, Na₂S₂O₅ (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 (MgSO₄), 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/Et₂O 1:1); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₆H₃₇BrO₆ 525.1852; found 525.1865.

6-((2E,6E)-9-((5S)-3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)-7-methoxy-5-(methoxymethoxy)-isobenzofuran-1(3H)-one (16). K₂CO₃ (1.56 g, 2.96 mmol) was added with stirring to bromohydrin **26** in Me₂CO (60 mL) at 25 °C. After 18 h, H₂O (50 mL) and CH₂Cl₂ (100 mL) were added, and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL), and the combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (pentane/Et₂O 1:1) to provide epoxide **16** (1.28 g, 2.88 mmol, 97%) as a colorless oil: *R*_f 0.38 (pentane/Et₂O 1:1); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₆H₃₇O₆ 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). Cp₂TiCl₂ (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 Me₃SiCl (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, Et₂O (100 mL) was added, and the two phases were separated. The aqueous layer was extracted with Et₂O (3 × 50 mL), and the combined organic layers were dried (MgSO₄), filtered, concentrated, and dissolved in THF (50 mL). Bu₄NF (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/Et₂O 1:4) to provide alcohol **27** (697 mg, 1.57 mmol, 40%) as a white foam: *R*_f 0.17 (pentane/Et₂O 1:4);

¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₆H₃₇O₆ 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), Et₃N (108 μL, 0.774 mmol) and Ac₂O (74 μL, 0.774 mmol) were added sequentially with stirring to alcohol **27** (313 mg, 0.704 mmol) in CH₂Cl₂ (3 mL) at 25 °C. After 2 h, saturated aqueous NaHCO₃ (2 mL) was added, and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 3 mL), and the combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (pentane/Et₂O 1:1) to provide acetate **28** (337 mg, 0.693 mmol, 98%) as a white solid: *R*_f 0.33 (pentane/Et₂O 1:1); mp 155–158 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 (ESI) *m/z* [M + H]⁺ calcd for C₂₈H₃₉O₇ 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 ^tBuOH (25 mL), and the mixture was heated to 100 °C for 36 h. After being cooled, brine (30 mL) and CH₂Cl₂ (40 mL) were added, and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL), and the combined organic layers were dried (MgSO₄), 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/Et₂O 1:1); mp 222–223 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₆H₃₅O₆ 443.2434; found 443.2434.

((3S,4aR,6aS,13aR,13bS)-12-Methoxy-4,4,13b-trimethyl-11-oxo-6a-((phenylselenanyl)methyl)-1,3,4,4a,5,6,6a,9,11,13,13a,13b-dodecahydro-2H-benzo[*a*]furo[3,4-*i*]xanthene-3-yl Acetate (29). Phenol **15** (100 mg, 0.226 mmol) in CH₂Cl₂ (10 mL) was added dropwise with stirring to *N*-(phenylseleno)phthalimide (410 mg, 1.36 mmol) and SnCl₄ (1 M in CH₂Cl₂; 1.13 mL, 1.13 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (pentane/Et₂O 1:1) to provide phenylselenide **29** (79 mg, 0.132 mmol, 58%) as a colorless oil: *R*_f 0.26 (pentane/

Et₂O 1:1); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₃₂H₃₈O₆Se 599.1912; found 599.1913.

(3S,4aR,6aS,13aR,13bS)-12-Methoxy-4,4,6a,8,13b-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 HSnBu₃ (62 μ L, 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/Et₂O 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/Et₂O 1:1); mp 212–213 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₆H₃₄O₆ 443.2434; found 443.2419.

(3S,4aR,6aS,13aR,13bS)-8-Bromo-12-methoxy-4,4,6a,8,13b-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 H₂SO₄ (13 μ L, 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 NaHCO₃ (0.4 mL) and Na₂S₂O₃ (50 mg, 0.316 mmol) were added, and the two phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 0.5 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (pentane/Et₂O 7:3) to provide bromide **30** (34 mg, 0.0652 mmol, 93%) as a white foam: *R*_f 0.19 (pentane/Et₂O 7:3); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₆H₃₄O₆Br 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)Cl₂·CH₂Cl₂ (21 mg, 0.0257 mmol), CH₃BF₃K (23 mg, 0.187 mmol), and Cs₂CO₃ (122 mg, 0.375 mmol) in THF (1.5 mL) and H₂O (75 μ L) was heated to 80 °C for 18 h. After being cooled to 25 °C, H₂O (1 mL) and Et₂O (1 mL) were added, and the two phases were separated. The aqueous layer was extracted with Et₂O (3 $\times$ 1 mL), and the combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (pentane/Et₂O 7:3) to provide arene **31** (50 mg, 0.110 mmol, 88%) as a white foam: *R*_f 0.26 (pentane/Et₂O 7:3); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₇H₃₇O₆ 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 CH₂Cl₂ (3 $\times$ 1 mL), and the combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (pentane/Et₂O 1:1) to provide (±)-17S-dihydroaustalide K (**1**) (13 mg, 0.0314 mmol, 95%) as a white solid: *R*_f 0.12 (pentane/Et₂O 1:1); mp 198–200 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₅H₃₅O₅ 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-decahydro-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 CH₂Cl₂ (2 mL) at 25 °C. After 1 h, the mixture was concentrated and chromatographed (pentane/Et₂O 1:1) to give (±)-austalide K (**2**) (28 mg, 0.0679 mmol, 83%) as a white solid: *R*_f 0.34 (pentane/Et₂O 1:1); mp 160–164 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₅H₃₃O₅ 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)]. NaHCO₃ (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 CH₂Cl₂ (1 mL) at 25 °C. After 19 h, saturated aqueous NaHCO₃ (1 mL) was added, and phases were separated. The aqueous layer was extracted with CH₂Cl₂ (3 $\times$ 1 mL), and the combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (Et₂O) to provide (±)-13-deacetoxyaustalide I (**3**) (22 mg, 0.0513 mmol, 96%) as a white solid: *R*_f 0.37 (Et₂O); mp 93–95 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100

MHz, CDCl₃) 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 C₂₅H₃₃O₆ 429.2277; found 429.2291.

(±)-Austalide P [Methyl 3-((5aS,8R,9S,9aR)-8-(2-hydroxypropan-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 NH₄Cl (1 mL) and Et₂O (2 mL) were added; the phases were separated, and the aqueous layer was extracted with Et₂O (3 × 1 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (pentane/Et₂O 1:1) to provide (±)-austalide P (4) (9.3 mg, 0.0202 mmol, 80%) as a white foam: R_f 0.21 (pentane/Et₂O 1:1); ¹H NMR (400 MHz, CD₃OD) 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); ¹³C{¹H} NMR (100 MHz, CD₃OD) 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 C₂₆H₃₇O₇ 461.2539; found 461.2531.

(±)-13-Deoxyaustalide Q Acid [3-((5aS,8S,9S,9aR)-11-methoxy-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·H₂O (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, H₂O (1 mL) and Et₂O (1 mL) were added and the two phases separated, and the aqueous layer was extracted with Et₂O (3 × 1 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated, and chromatographed (Et₂O) to provide (±)-13-deoxyaustalide Q acid (5) (10 mg, 0.0233 mmol, 71%) as a white foam: R_f 0.42 (Et₂O); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C{¹H} NMR (100 MHz, CDCl₃) 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 C₂₅H₃₃O₆ 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.

¹H and ¹³C 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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank GlaxoSmithKline for the endowment (to A.G.M.B.) as well as Drs. Alfred and Isabel Bader for their additional support. We additionally thank the EPSRC for support with Grant No. EP/N022815/1.

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■ NOTE ADDED AFTER ASAP PUBLICATION

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