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

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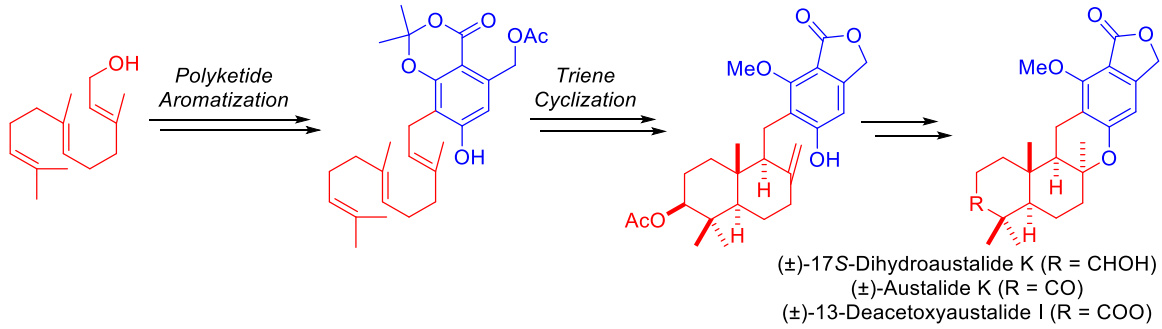
ABSTRACT GRAPHIC



ABSTRACT

The first total synthesis of five austalide natural products (±)-17*S*-dihydroaustalide K, (±)-austalide K, (±)-13-deacetoxyaustalide I, (±)-austalide P and (±)-13-deoxyaustalide Q acid were accomplished *via* a series of biomimetic transformations. Key steps involved polyketide aromatization of a *trans*, *trans*-farnesol derived *β,δ*-diketo-dioxinone into the corresponding *β*-resorcylate, followed by titanium(III)-mediated reductive radical cyclization of an epoxide to furnish the drimene core. Subsequent phenyl-selenonium ion induced diastereoselective cyclization of the drimene completed the essential carbon framework of the austalides to access (±)-17*S*-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 twelve 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 fungus *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]

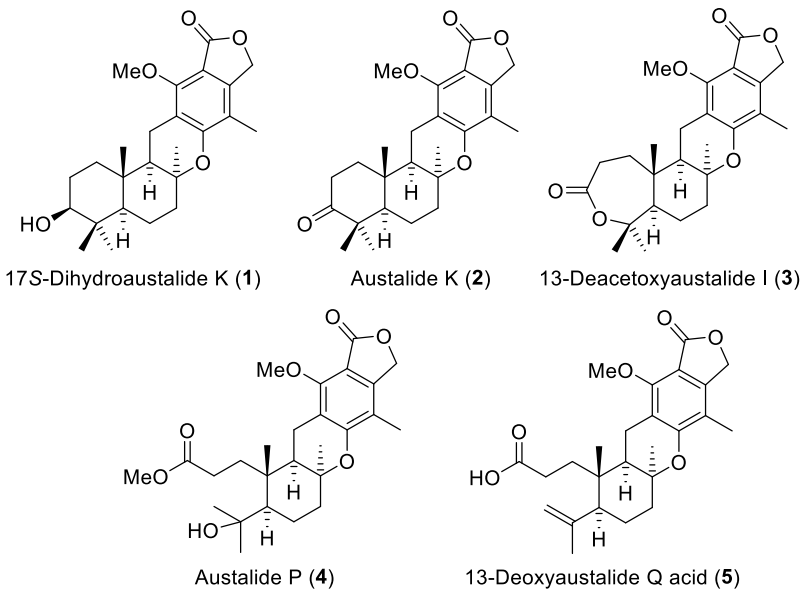
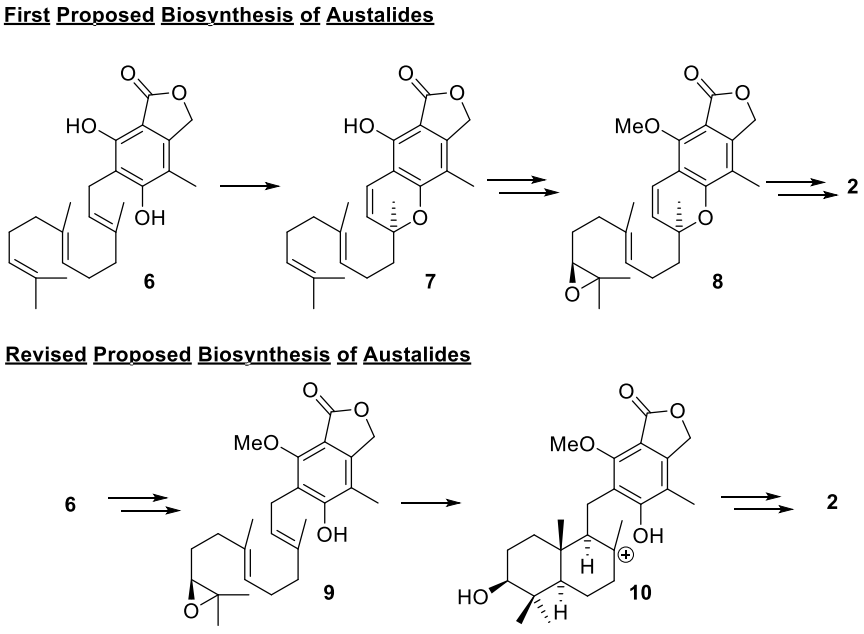


Figure 1. Representative austalide natural products.

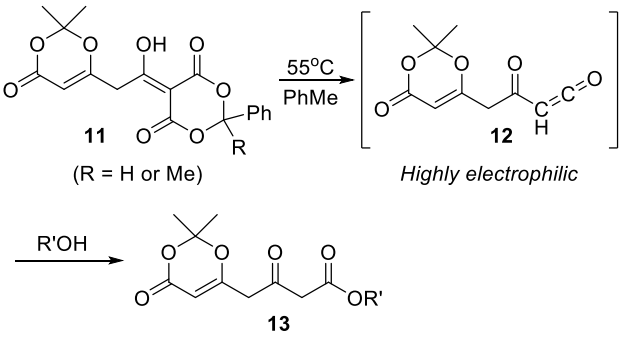
The biosynthesis of austalide K (**2**) was first proposed in 1987 (Scheme 1).[3a] It was postulated that 6-[(2*E*,6*E*)farnesyl]-5,7-dihydroxy-4-methylphthalide (**6**), a key intermediate in the biogenesis of mycophenolic acid, first undergoes cyclization *via* a stereospecific attack of the phenol 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 rings motif. However, further investigations on the fate of the hydrogen atom incorporation using of (^{13}C, ^{2}H)- and ^{2}H-labelled 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 systems.



Scheme 1. Proposed biosynthesis of austalides K (**2**).

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*-resorcylates derived natural products utilizing *β*,*δ*-diketo dioxinones.[5] Recently, we have disclosed a scalable and efficient synthesis of dioxinone *β*-keto esters **13** with the use of regioselective thermolysis of dioxane-

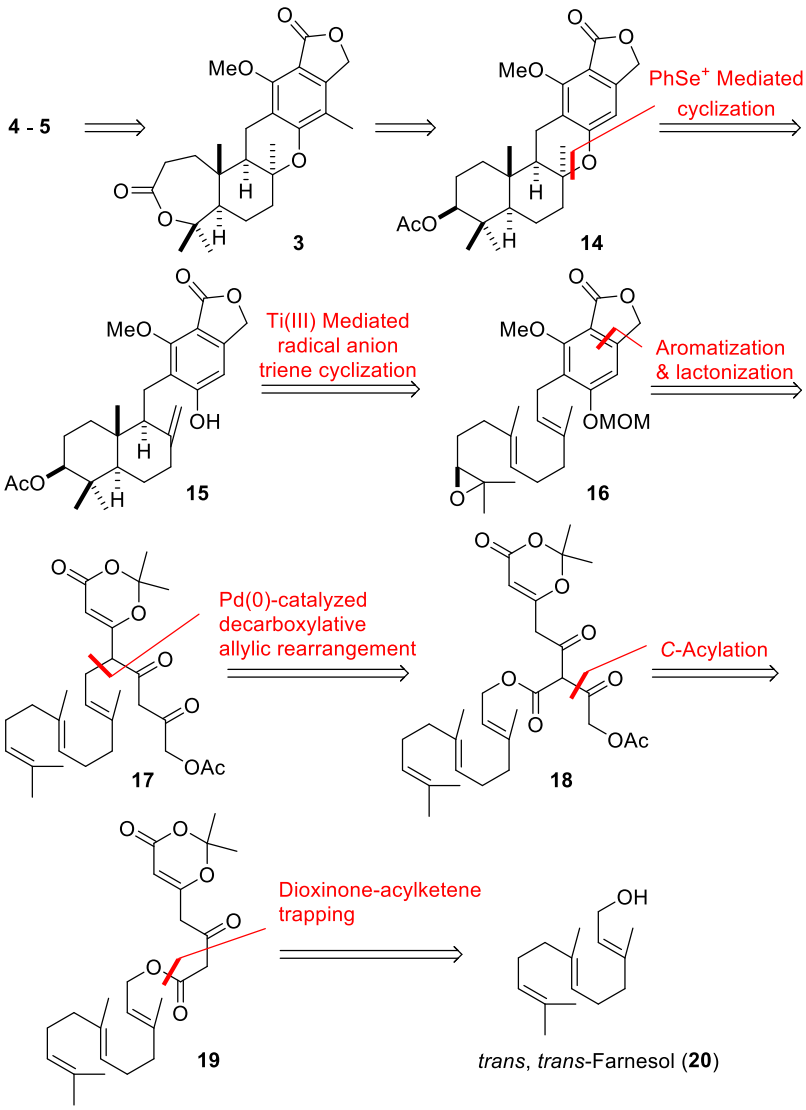
4,6-dione-keto-dioxanones **11** (**Scheme 2**).[6] Utilization of our recent findings with sequential polyketide aromatization and polyene cyclization greatly facilitated concise syntheses of hongoquercin A and B.[7] Herein, we report further studies on the biomimetic total syntheses of the austalide natural products *via* a series of biomimetic transformations.



Scheme 2. Thermolysis of dioxane-4,6-dione-keto-dioxanones **11**.

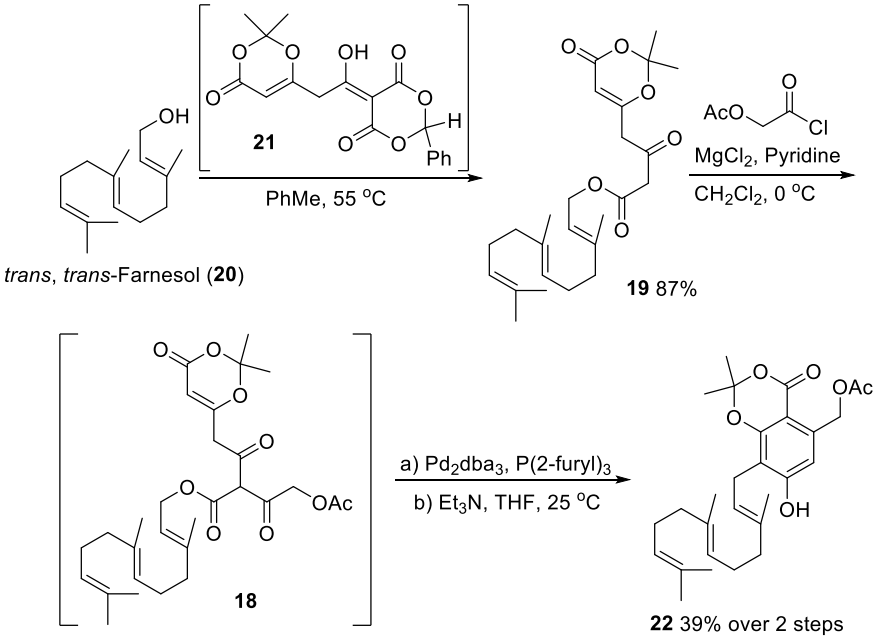
RESULTS AND DISCUSSION

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 17*S*-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 rings motif, we envisioned the use of two sequential diastereoselective cyclizations. Firstly, 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**. Subsequent phenyl-selenonium 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*-diketo dioxinones **17**. Dioxinone *β*, *δ*-diketo-ester **18**, synthesized *via C*-acylation of dioxinone *β*-keto-ester **19**, should undergo palladium(0)-catalyzed decarboxylative allylic rearrangement to provide *β*, *δ*-diketo-dioxinone **17**. Finally, dioxinone *β*-keto-ester **19** is available from trapping a dioxinone-acylketene **12** with *trans*,*trans*-farnesol (**20**) following our recently published protocols.[6]



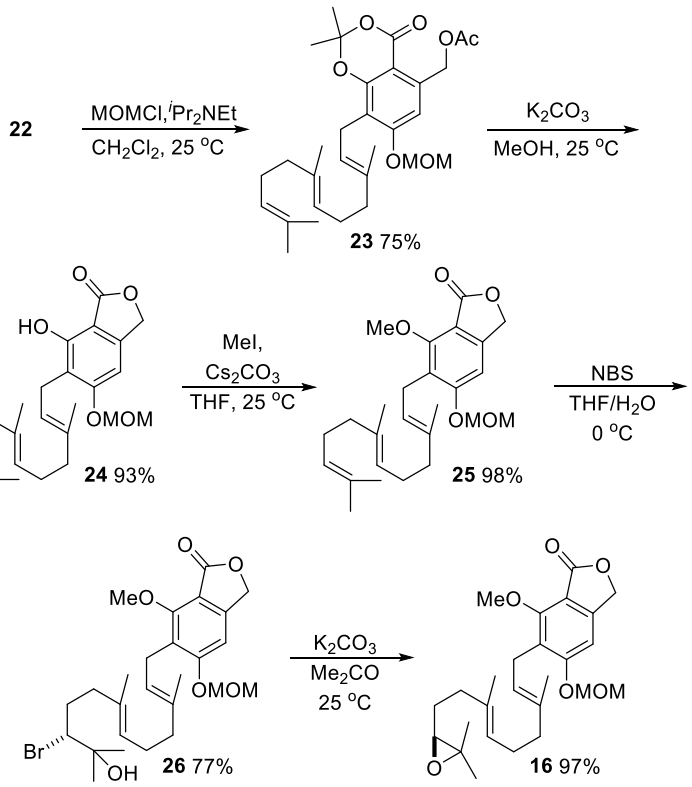
Scheme 3. Retrosynthetic analysis of the austalides.

The synthesis of *β*-resorcylate **22** (**Scheme 4**) was undertaken by trapping dioxinone-acylketene **12**, generated *in situ* from 4,6-dione-keto-dioxanone **21**, with *trans*, *trans*-farnesol (**20**) to provide dioxinone *β*-keto-ester **19** (87%).[6] Subsequent magnesium chloride mediated regioselective *C*-acylation of the dioxinone *β*-keto-ester **19** with acetoxyacetyl chloride gave dioxinone *β*, *δ*-diketo-ester **18**, which was allowed to react with a catalytic amount of $Pd_2(dba)_3$ in the presence of tri-(2-furyl)phosphine to induce a decarboxylative allylic rearrangement to provide *β*, *δ*-diketo-dioxinone **17**, which was directly aromatized by treatment with triethyl amine to provide *β*-resorcylate **22** (39% over 2 steps from dioxinone *β*-keto-ester **19**).



Scheme 4. Synthesis of terpene resorcylate **22**.

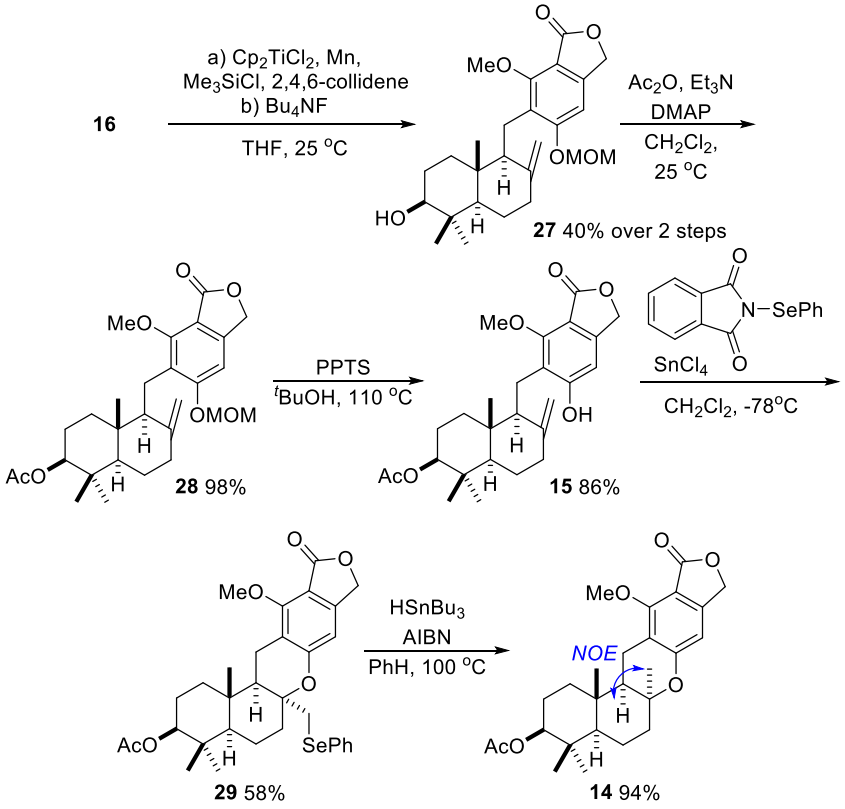
With the *β*-resorcylate **22** in hand, attention was focused on the functionalization of the aromatic core as well as installing the terminal epoxide for the triene cyclization reaction (**Scheme 5**). The phenol group of *β*-resorcylate **22** was first protected as the MOM ether **23** (75%), followed by lactonization under basic condition 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 mediated cyclization of bromohydrin **26** gave the desired racemic epoxide **16** (97%).



Scheme 5. Synthesis of epoxide **16**.

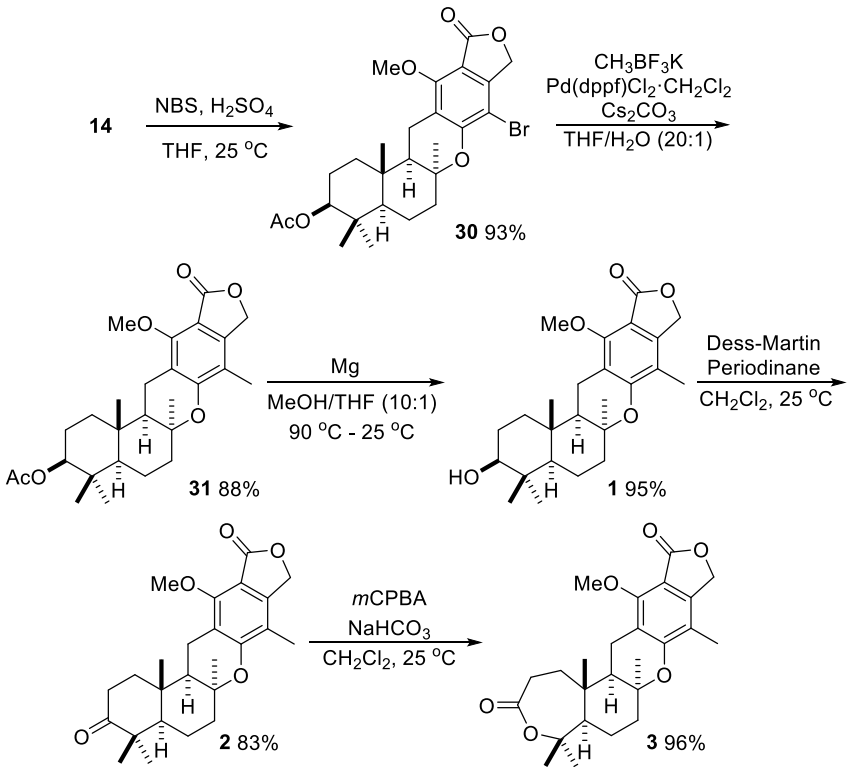
Next, the terpene side chain of epoxide **16** was functionalized (**Scheme 6**). Treatment of the epoxide **16** with a titanocene(III) catalyst, generated from titanocene(IV) dichloride, manganese, trimethylsilyl chloride and 2,4,6-collidine,[8] initiated a radical anion cascade cyclization, thereby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



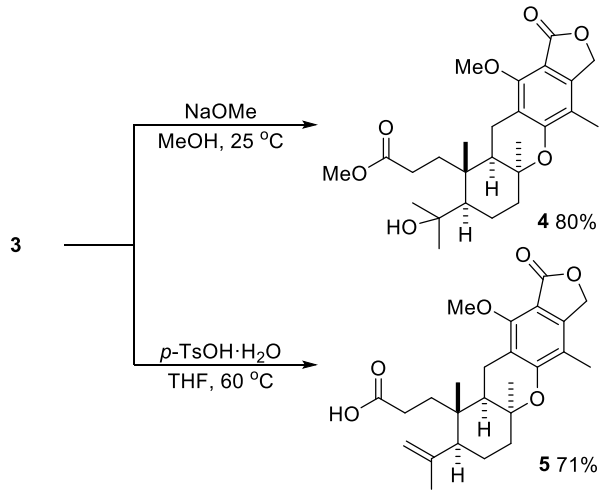
Scheme 6. Synthesis of meroterpenoid **14**.

With the key meroterpenoid **14** in hand after establishing the correct relative stereochemistry, attention was directed 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 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 (±)-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]



Scheme 7. Synthesis of (±)-17*S*-dihydroaustalide K (**1**), (±)-austalide K (**2**) and (±)-13-deacetoxyaustalide I (**3**).

(±)-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 with 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,2c]



Scheme 8. Synthesis of (±)-austalide P (**4**) and (±)-13-deoxyaustalide Q acid (**5**).

CONCLUSION

In conclusion, the first total synthesis of five austalide natural products (±)-17*S*-dihydroaustalide K (**1**), (±)-austalide K (**2**), (±)-13-deacetoxyaustalide I (**3**), (±)-austalide P (**4**) and (±)-13-deoxyaustalide Q acid (**5**) were completed in seventeen to twenty 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 aromatization while the fused rings 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 approach 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*-keto esters **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 ^{t}BuOH 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, particle size 40 - 63 μm. All ^{1}H and proton-decoupled ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz respectively at ambient temperature in deuterated solvents as noted. NMR spectra were referenced to residual solvent peaks ($CDCl_3$: δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR; CD_3OD δ = 3.31 & 4.87 for ^{1}H NMR and δ = 49.0 for ^{13}C NMR) and chemical shifts were reported in ppm. 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-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-4*H*-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*-keto-ester **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*-diketo-ester **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*-diketo-ester **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 additional 18 h. Reaction was quenched with aqueous HCl (1 M; 200 mL) and 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 2 steps) as a yellow oil: R_f 0.26 pentane : Et_2O 2 : 1); ^{1}H 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{^{1}H} 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-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-4*H*-benzo[*d*][1,3]dioxin-5-yl)methyl acetate (23). MOMCl (1.03 mL; 13.6 mmol) was added with stirring to ^{i}Pr$_2$EtN (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); ^{1}H 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{^{1}H} 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-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)isobenzofuran-1(3*H*)-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); m.p. 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-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)isobenzofuran-1(3*H*)-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_2O 2 : 1) to provide methyl ether **25** (1.94 g, 4.53 mmol, 98%) as a colorless oil: R_f 0.34 (pentane : Et_2O 2 : 1); ^1H 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); $^{13}C\{^1H\}$ 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-((2*E*,6*E*)-10-Bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl)-7-methoxy-5-(methoxymethoxy)isobenzofuran-1(3*H*)-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_2O (23 mL) at 0 °C. After 2 h, $Na_2S_2O_5$ (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_2O 1 : 1); ^1H 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); $^{13}C\{^1H\}$ 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-((2*E*,6*E*)-9-((*S*)-3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl)-7-methoxy-5-(methoxymethoxy)isobenzofuran-1(3*H*)-one (16). K_2CO_3 (1.56 g, 2.96 mmol) was added with stirring to bromohydrin **26** in Me_2CO (60 mL) at 25 °C. After 18 h, H_2O (50 mL) and CH_2Cl_2 (100 mL) were 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_2O 1 : 1) to

provide epoxide **16** (1.28 g, 2.88 mmol, 97%) as a colorless oil: R_f 0.38 (pentane : Et_2O 1 : 1); ^1H 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); $^{13}C\{^1H\}$ 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 $C_{26}H_{37}O_6$ 445.2590; Found 445.2598.

6-(((1*S*,4a*R*,6*S*,8a*R*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)methyl)-7-methoxy-5-(methoxymethoxy)isobenzofuran-1(3*H*)-one (27). Cp_2TiCl_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_3SiCl (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 has ceased, Et_2O (100 mL) was added and the two phases were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and dissolved in THF (50 mL). Bu_4NF (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_2O 1 : 4) to provide alcohol **27** (697 mg, 1.57 mmol, 40%) as a white foam: R_f 0.17 (pentane : Et_2O 1 : 4); ^1H 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); $^{13}C\{^1H\}$ 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.

(2*S*,4a*R*,5S,8a*R*)-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_3N (108 μL, 0.774 mmol) and Ac_2O (74 μL, 0.774 mmol) were added sequentially with stirring to alcohol **27** (313 mg, 0.704 mmol) in CH_2Cl_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_2Cl_2 (3 × 3 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (pentane : Et_2O 1 : 1) to provide acetate **28** (337 mg, 0.693 mmol, 98%) as a white solid: R_f 0.33 (pentane : Et_2O 1 : 1); m.p. 155 – 158 °C; ^1H 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); $^{13}C\{^1H\}$ 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 (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{39}O_7$ 487.2696; Found 487.2674.

(2*S*,4a*R*,5*S*,8a*R*)-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 cooling, brine (30 mL) and CH_2Cl_2 (40 mL) were added and the two phases were separated. The aqueous layer was extracted with CH_2Cl_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_2O 1 : 1); m.p. 222 – 223 °C; ^1H 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.

((3*S*,4a*R*,6a*S*,13a*R*,13b*S*)-12-Methoxy-4,4,13b-trimethyl-11-oxo-6a-((phenylselanyl)methyl)-1,3,4,4a,5,6,6a,9,11,13,13a,13b-dodecahydro-2*H*-benzo[*a*]furo[3,4-*i*]xanthen-3-yl acetate (29). Phenol **15** (100 mg, 0.226 mmol) in CH_2Cl_2 (10 mL) was added dropwise with stirring to *N*-(phenylseleno)phthalimide (410 mg, 1.36 mmol) and $SnCl_4$ (1 M in CH_2Cl_2; 1.13 mL, 1.13 mmol) in CH_2Cl_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 and the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (pentane : Et_2O 1 : 1) to provide phenylselenide **29** (79 mg, 0.132 mmol, 58%) as a colorless oil: R_f 0.26 (pentane : Et_2O 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 $C_{32}H_{38}O_6Se$ 599.1912; Found 599.1913.

(3*S*,4a*R*,6a*S*,13a*R*,13b*S*)-12-Methoxy-4,4,6a,13b-tetramethyl-11-oxo-1,3,4,4a,5,6,6a,9,11,13,13a,13b-dodecahydro-2*H*-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_2O 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_2O 1 : 1); m.p. 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.

(3*S*,4a*R*,6a*S*,13a*R*,13b*S*)-8-Bromo-12-methoxy-4,4,6a,13b-tetramethyl-11-oxo-1,3,4,4a,5,6,6a,9,11,13,13a,13b-dodecahydro-2*H*-benzo[*a*]furo[3,4-*i*]xanthen-3-yl acetate (30). *N*-Bromosuccinimide (19 mg, 0.105 mmol) and H_2SO_4 (13μL,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 $Na_2S_2O_3$ (50 mg, 0.316 mmol) were added and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 0.5 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (pentane : Et_2O 7 : 3) to provide bromide **30** (34 mg, 0.0652 mmol, 93%) as a white foam: R_f 0.19 (pentane : Et_2O 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 $C_{26}H_{34}O_6Br$ 521.1539; Found 521.1549.

(3*S*,4a*R*,6a*S*,13a*R*,13b*S*)-12-Methoxy-4,4,6a,8,13b-pentamethyl-11-oxo-1,3,4,4a,5,6,6a,9,11,13,13a,13b-dodecahydro-2*H*-benzo[*a*]furo[3,4-*i*]xanthen-3-yl acetate (31). A degassed solution of bromide **30** (65 mg,

0.125 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (21 mg, 0.0257 mmol), CH_3BF_3K (23 mg, 0.187 mmol) and Cs_2CO_3 (122 mg, 0.375 mmol) in THF (1.5 mL) and H_2O (75 μL) was heated to 80 °C for 18 h. After cooling to 25 °C, H_2O (1 mL) and Et_2O (1 mL) were added and the two phases were separated. The aqueous layer was extracted with Et_2O (3 × 1 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (pentane : Et_2O 7 : 3) to provide arene **31** (50 mg, 0.110 mmol, 88%) as a white foam: R_f 0.26 (pentane : Et_2O 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.

(±)-17*S*-Dihydroaustalide K [(3*S*,4a*R*,6a*S*,13a*R*,13b*S*)-3-Hydroxy-12-methoxy-4,4,6a,8,13b-pentamethyl-1,2,3,4,4a,5,6,6a,9,13,13a,13b-dodecahydro-11*H*-benzo[*a*]furo[3,4-*i*]xanthen-11-one (1)]. Magnesium turnings (4 mg, 0.164 mmol) was 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 hr. When the reaction mixture had turned into a milky solution and effervescence has ceased, it was cooled to 25 °C and stirred for 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_2Cl_2 (3 × 1 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (pentane : Et_2O 1 : 1) to provide (±)-17*S*-dihydroaustalide K (**1**) (13 mg, 0.0314 mmol, 95%) as a white solid: R_f 0.12 (pentane : Et_2O 1 : 1) ; m.p. 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 [(5a*R*,7aS,14aR,14bS)-13-Methoxy-5,5,7a,9,14b-pentamethyl-1,2,5a,6,7,7a,10,14,14a,14b-decahydro-5*H*-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 (±)-17*S*-dihydroaustalide K (**1**) (34 mg, 0.0820 mmol) in CH_2Cl_2 (2 mL) at 25 °C. After 1 h, the mixture was concentrated and chromatographed (pentane : Et_2O 1 : 1) to give (±)-austalide K (**2**) (28 mg, 0.0679 mmol, 83%) as a white solid: R_f 0.34 (pentane : Et_2O 1 : 1); m.p. 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 [(5a*R*,7a*S*,14a*R*,14b*S*)-13-Methoxy-5,5,7a,9,14b-pentamethyl-1,2,5a,6,7,7a,10,14,14a,14b-decahydro-5*H*-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_2Cl_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_2Cl_2 (3 × 1 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (Et_2O) to provide (±)-13-deacetoxyaustalide I (**3**) (22 mg, 0.0513 mmol, 96%) as a white solid: R_f 0.37 (Et_2O); m.p. 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-((5a*S*,8*R*,9*S*,9a*R*)-8-(2-hydroxypropan-2-yl)-11-methoxy-4,5a,9-trimethyl-1-oxo-3,5a,6,7,8,9,9a,10-octahydro-1*H*-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_4Cl (1 mL) and Et_2O (2 mL) were added and the phases were separated, and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (pentane : Et_2O 1 : 1) to provide (±)-austalide P (**4**) (9.3 mg, 0.0202 mmol, 80%) as a white foam: R_f 0.21 (pentane : Et_2O 1 : 1); ^1H NMR (400 MHz, CD_3OD) 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_3OD) 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-((5a*S*,8*S*,9*S*,9a*R*)-11-Methoxy-4,5a,9-trimethyl-1-oxo-8-(prop-1-en-2-yl)-3,5a,6,7,8,9,9a,10-octahydro-1*H*-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_2O (56 mg, 0.327 mmol) was added. The resulting mixture was heated to 70 °C for 1 h. After cooling back to 25 °C, H_2O (1 mL) and Et_2O (1 mL) were added and the two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated and chromatographed (Et_2O) to provide (±)-13-deoxyaustalide Q acid (**5**) (10 mg, 0.0233 mmol, 71%) as a white foam: R_f 0.42 (Et_2O); ^1H 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

^1H 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**, **22 - 31** and X-ray structural data for **15**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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