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Chemical Synthesis Study Establishes the Correct Structure of the Potent Anti-Inflammatory Agent Myrsinoic Acid F

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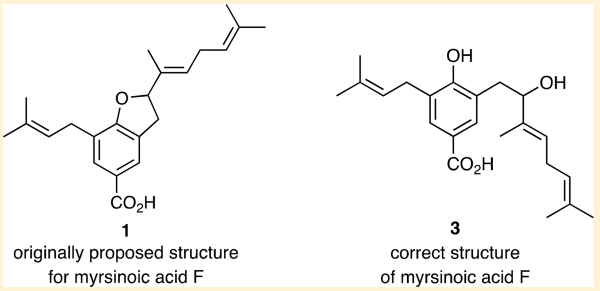
Supporting Information

ABSTRACT: A total synthesis of compound **3** from *p*-bromophenol is reported and thereby establishing that this, rather than its cyclodehydrated counterpart **1** (as postulated originally), is the correct structure of the natural product myrsinoic acid F. The biological evaluation of compound **3** in a mouse-ear edema assay established that it is a significantly more potent anti-inflammatory agent than the NSAID indometacin.



In 2002, Hirota and co-workers reported[1] the isolation and structural elucidation of a series of anti-inflammatory agents, named myrsinoic acids, from the fresh leaves and twigs of *Myrsine seguinii*, a hardwood of the *Myrsinaceae* family found in various parts of Asia from Myanmar to Japan. The most active of these compounds was myrsinoic acid F (MA-F) and to which structure **1** (Figure 1) was assigned[1] on the basis of a

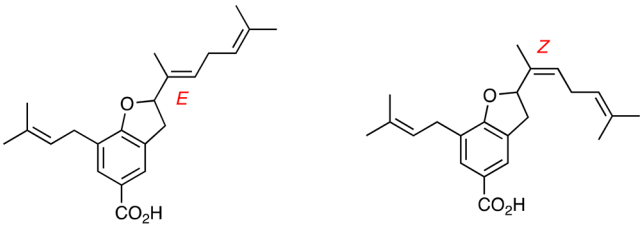


Figure 1. Originally proposed structure of myrsinoic acid (**1**) and its *Z*-isomer (**2**).

range of NMR spectroscopic and mass spectrometric studies. This compound and various structurally related co-metabolites have since been encountered in certain other plants (e.g., *Rapanea ferruginea* and *Myrsine coriacea*) found in several parts of the globe, and a number of these have been shown to exhibit potentially useful biological properties including selective cytotoxic, anti-microbial, and anti-leishmanial effects.[2] The anti-inflammatory properties of these compounds may arise through their inhibition of DNA polymerase λ.[3]

Recently, we reported[4] total syntheses of compound **1** and its *Z*-isomer **2**. Each of these compounds proved to be a potent anti-inflammatory agent, as determined in a mouse-ear edema assay. However, neither of them corresponds to the structure of MA-F. Clearly, then, the question arises as to the correct structure of MA-F. In considering this matter and the similarities of the physical data for certain acyclic precursors (i.e., ones lacking the dihydrobenzofuran ring) to compound **1** with those reported for the natural product, the possibility arose that the *p*-hydroxybenzoic acid **3** (Figure 2) represents

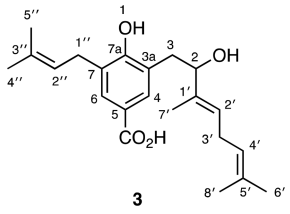


Figure 2. Revised structure **3** proposed for myrsinoic acid F.

the correct structure. It is conceivable that the molecular ion for such a species would not be observed in the electron-impact mass spectrum (because of its facile dehydration under the conditions involved) and so leading to an erroneous structural assignment.[5] Interestingly, compound **3** has been reported in the patent literature[6] as a natural product isolated from the aerial parts of the Southern African tree *Rapanaea melanophloeos*, but we have been unable to secure copies of the spectral data for this material. Accordingly, we sought to adapt our syntheses of compounds **1** and **2** to the preparation of

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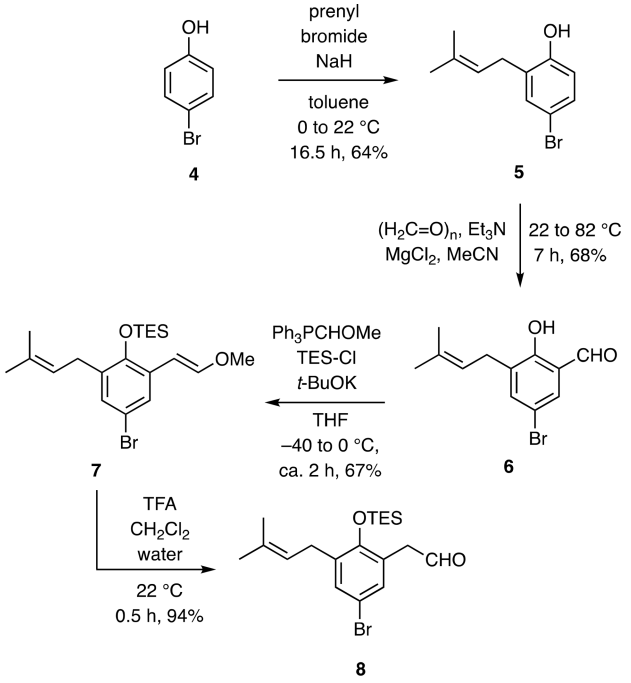
target **3** in order to compare its spectral data with those reported for MA-F. The outcomes of such studies are reported here together with the results of evaluating the anti-inflammatory properties of compound **3** and certain synthetic analogues in a mouse-ear edema assay.

RESULTS AND DISCUSSION

Synthetic Studies. The successful synthesis of compound **3** from *p*-bromophenol used the first two steps involved in the preparation of dihydrobenzofuran **1** as well as minor variations on the third and fourth ones.[4] Thus, as shown in Scheme 1,

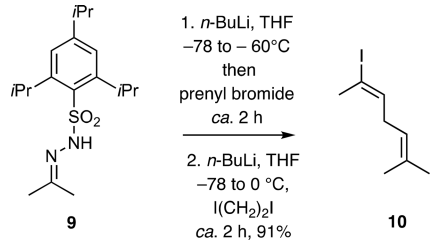
Scheme 1. Conversion of *p*-Bromophenol (4) into Aryl Acetaldehyde 8



reaction of *p*-bromophenol (**4**) with prenyl bromide in the presence of sodium hydride afforded the known,[7] *C*-alkylated product **5** (64%). Formylation of product **5** using paraformaldehyde in the presence of Et_3N and $MgCl_2$ gave compound **6** (68%) that was subjected to Wittig olefination using the ylide $Ph_3P{=}CH(OMe)$ in the presence of triethylsilyl chloride (TES-Cl) and potassium *tert*-butoxide. As a result, the previously unreported enol ether **7** (67%) was obtained, and its hydrolysis with trifluoroacetic acid (TFA) as catalyst gave the arylated acetaldehyde **8** in 94% yield.

The known alkenyl iodide required for completion of the assembly of the geranyl-type side-chain associated with target **3** was synthesized by the more concise and higher yielding route shown in Scheme 2. This employed the Bond modification[8] of the Shapiro reaction as the key step and allowed for the direct introduction of the halogen. Thus, acetone 2,4,6-triisopropylbenzenesulfonylhydrazone (**9**)[4] was treated with *n*-BuLi, and then prenyl bromide was added at −78 to −60 °C. The intermediate was treated in situ, again at −78 °C, with a second aliquot of *n*-BuLi, and the ensuing anion was allowed to warm to 0 °C at which point gas evolution was observed. Once this had ceased (after *ca.* 0.5 h), the reaction mixture was recooled to −78 °C before being treated with 1,2-diiodoethane. Quenching the reaction with sodium thiosulfate

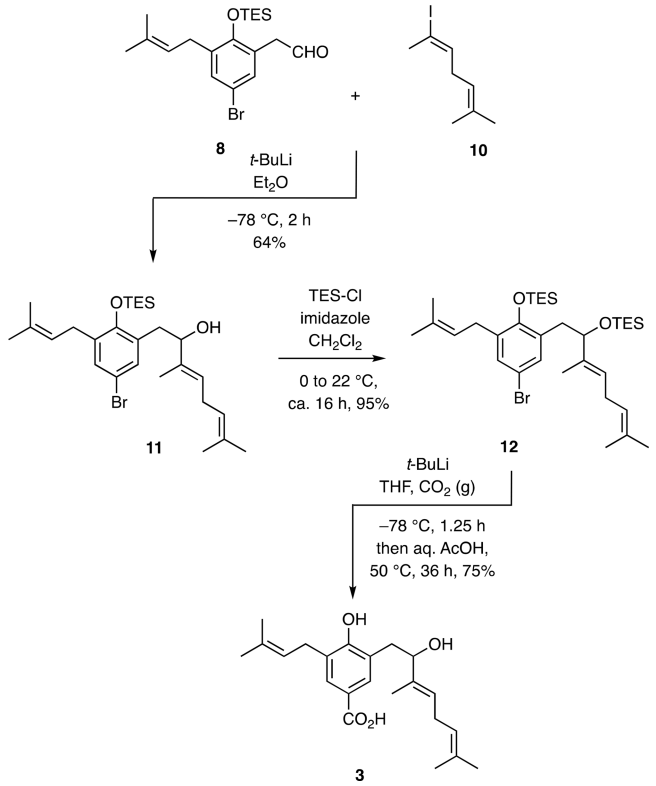
Scheme 2. Direct Synthesis of Alkenyl Iodide 10



followed by conventional workup gave the light-sensitive iodide **10** in 91% yield. This material was identical in all respects with a sample prepared by the earlier route.[4]

As shown in Scheme 3, the conversion of compound **8** into target **3** proved to be a relatively straightforward process. Thus,

Scheme 3. Conversion of Compound 8 into the Correct Structure (3) of Myrsinoic Acid F



the alkenyllithium obtained by treating an ethereal solution of iodide **10**[4] with *t*-BuLi was treated, in situ, with aldehyde **8** and thus affording, after aqueous workup, the allylic alcohol **11** in 64% yield. Reaction of the latter compound with TES-Cl in the presence of imidazole afforded the bis-ether **12** (95%), and this served as the immediate precursor to target **3**. Treatment of a THF solution of compound **12** maintained at −78 °C with *t*-BuLi led to the anticipated metal-for-bromine exchange, and the ensuing aryllithium was trapped with dry, gaseous carbon dioxide. The resulting mixture was treated with aqueous AcOH and heated at 50 °C for 36 h. After cooling, extractive workup, and flash column chromatography, carboxylic acid **3** was obtained in 75% yield as a clear, light-yellow oil.

The NMR and MS data derived from acid **3** were in complete accord with the assigned structure. Of particular note, the 70 eV electron-impact mass spectrum of this

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compound did not display a molecular ion at m/z 358. In contrast, in the ESI mass spectrum (run in negative mode) a molecular-associated ion was observed at m/z 357. Furthermore, comparisons of the ^{1}H and ^{13}C NMR spectroscopic data sets derived from the synthetic material proved to be identical with those reported[1] for MA-F (see Tables 1 and 2). The only notable difference between the two data sets centered on the chemical shifts of the resonances due to the hydroxycarbonyl group carbons (δ_C 172.5 for **3** vs 170.9 reported for MA-F), a feature that can be attributed to minor variations in the pH of the media in which the two data sets were acquired.

In order to assist with the development of a structure–activity relationship (SAR) profile for MA-F related compounds, the monoether **11** was subjected to desilylation by treating a THF solution with aqueous AcOH at 50 °C for 18 h (Scheme 4) and thereby forming the known[4] bromo-analogue, **13** (80%), of compound **3**. All the spectroscopic data derived from this product were in complete accord with the illustrated structure and matched those recorded earlier.[4]

Table 1. Comparison of the ^{1}H NMR Spectroscopic Data Recorded for Compound 3 with Those Reported[1] for Myrsinoic Acid F (MA-F)

compound **3** δ_H[a,b]	MA-F δ_H[b,c]	assignment[d,e]
7.80 (d, J = 2.1 Hz, 1H)	7.77 (s, 1H)	H-6
7.68 (d, J = 2.1 Hz, 1H)	7.67 (s, 1H)	H-4
5.42 (m, 1H)	5.42 (t, J = 6.2 Hz, 1H)	H-2′
5.33 (m, 1H)	5.34 (broad s, 1H)	H-2″
5.03 (m, 1H)	5.04 (t, J = 6.8 Hz, 1H)	H-4′
4.35 (d, J = 8.8 Hz, 1H)	4.35 (d, J = 8.5 Hz, 1H)	H-2
3.38 (d, J = 7.3 Hz, 2H)	3.37 (d, J = 6.5 Hz, 2H)	H-1″
3.04 (dd, J = 14.7, 9.1 Hz, 1H)	3.03 (dd, J = 14.2, 9.3 Hz, 1H)	H-3
2.76 (d, J = 14.7 Hz, 1H)	2.76 (d, J = 14.2 Hz, 1H)	H-3
2.71 (t, J = 7.3 Hz, 2H)	2.71 (t, J = 6.8 Hz, 2H)	H-3′
1.76 (s, 3H)	1.75 (s, 3H)	H-4″
1.74 (s, 3H)	1.73 (s, 6H)	H-7′ or H-5″
1.73 (s, 3H)		H-5″ or H-7′
1.69 (s, 3H)	1.69 (s, 3H)	H-6′
1.62 (s, 3H)	1.62 (s, 3H)	H-8′

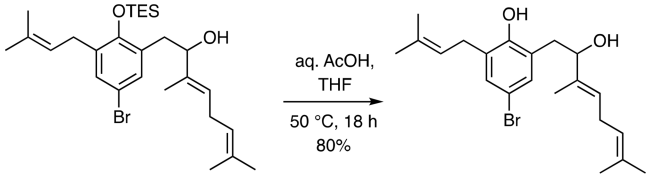
[a]Spectrum recorded in $CDCl_3$ at 400 MHz. [b]Signals due to the carboxylic acid and hydroxy group protons not observed. [c]Spectrum recorded in $CDCl_3$ at 500 MHz. [d]These assignments derived from ref 1. [e]See Figure 2 for atom numbering.

Table 2. Comparison of the ^{13}C NMR Chemical Shifts of Compound 3 with Those Reported[1] for Myrsinoic Acid F (MA-F)

compound **3** δ_C[a]	MA-F δ_C[b]	$\Delta\delta$	assignment[c,d]
172.5	170.9	+1.6	C=O
159.2	159.0	+0.2	C-7a
136.1	136.0	+0.1	C-1′
133.4	133.2	+0.2	C-5′
132.5	132.4	+0.1	C-3″
131.9	131.8	+0.1	C-4
131.0	130.9	+0.1	C-6
129.9	129.8	+0.1	C-7
125.9	125.8	+0.1	C-2′
125.8	125.6	+0.2	C-3a
122.1(0)	122.0	+0.1	C-2″
122.0(6)	121.9	+0.1	C-4′
120.7	120.4	+0.3	C-5
80.2	80.2	0	C-2
38.5	38.4	+0.1	C-3
28.9	28.8	+0.1	C-1″
26.7	26.6	+0.1	C-3′
26.0	25.8	+0.2	C-4″
25.8	25.7	+0.1	C-6′
18.0	17.9	+0.1	C-5″
17.9	17.7	+0.2	C-8′
12.2	12.1	+0.1	C-7′

[a]Spectrum recorded in $CDCl_3$ at 100 MHz. [b]Spectrum recorded in $CDCl_3$ at 125 MHz. [c]Assignments derived from ref 1. [d]See Figure 2 for atom numbering.

Scheme 4. Synthesis of the Bromo-Analogue 13 of Myrsinoic Acid F



11 13

Biological Studies. With significant quantities of the synthetically derived compounds **3**, **7**, **8**, **12**, and **13** to hand, and in order to begin developing an SAR profile for the class, each of these was assayed in the same mouse-ear edema assay used to evaluate the anti-inflammatory properties of compounds **1** and **2**.[4] These tests revealed, as shown in the Supporting Information, that MA-F (**3**) is a significantly more potent anti-inflammatory agent than the widely prescribed NSAID indometacin and even more active than its cyclic congener **1** (that showed[4] activities similar to indometacin in the same assay). Similarly, the bromo-analogue **13** displayed significant anti-inflammatory effects, while the structurally simpler congeners also possessed some activity. The perhaps counterintuitive observation that the less concentrated samples of certain of the test compounds showed greater inhibition rates is not uncommon in animal tests. This could be attributed, in relevant cases, to partial cleavage of the associated TES-ether moiety under the assay conditions.

In conclusion, the studies reported herein serve to establish the correct structure, **3**, of the potent anti-inflammatory natural product myrsinoic acid F and provide a rational basis for the original misassignment as the dihydrobenzofuran **1**. The synthetic sequences established in the course of both the present and earlier[4] studies are likely to provide effective means for accessing other members of the myrsinoic acid class of natural product as well as various analogues. They should also enable syntheses of related and biologically active natural products such as the amorfrutins.[9]

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, ^{1}H and ^{13}C NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a Bruker spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ triplet appearing at δ_C 77.1(6) were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t =

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triplet; q = quartet; m = multiplet or combinations of the above. IR spectra were recorded, using neat samples, on an attenuated total reflectance (ATR) infrared spectrometer. Samples were analyzed as either thin films or finely divided solids. Low-resolution ESI mass spectra were recorded on a single quadrupole mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Analytical TLC was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid:$Ce(SO_4)_2$:H_2SO_4 (conc.):H_2O (37.5 g:7.5 g:37.5 g:720 mL) or $KMnO_4$:K_2CO_3:5% NaOH aqueous solution:H_2O (3 g:20 g:5 mL:300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[10] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from Sigma−Aldrich (Sydney, Australia) and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX Finechem (Melbourne, Australia). THF, MeOH, and CH_2Cl_2 were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Pangborn et al.[11] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. *(E)-[4-Bromo-2-(2-methoxyvinyl)-6-(3-methylbut-2-en-1-yl)phenoxy]triethylsilane (**7**).* A magnetically stirred suspension of methoxymethyltriphenylphosphonium chloride (7.64 g, 22.3 mmol) in dry THF (150 mL) was cooled to −40 °C and treated with a solution of *t*-BuOK (3.76 g, 33.5 mmol) in dry THF (30 mL). The ensuing mixture was maintained at this temperature for 0.3 h, and the resulting dark-red reaction mixture was treated with a solution of benzaldehyde **6**[4] (2.79 g, 10.4 mmol) in dry THF (30 mL) before being warmed to 0 °C, stirred at this temperature for 1 h, treated with TES-Cl (4.45 mL, 26.5 mmol), stirred at 0 °C for 1 h, then treated with NH_4Cl (100 mL of a saturated aqueous solution), and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 95:5 v/v hexanes/toluene elution). Concentration of the appropriate fractions (R_f = 0.9 in 9:1 v/v hexanes/EtOAc) afforded enol ether **7** (2.86 g, 67%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 2.6 Hz, 1H), 7.01 (d, J = 2.6 Hz, 1H), 6.17 (d, J = 7.2 Hz, 1H), 5.39 (d, J = 7.2 Hz, 1H), 5.25 (m, 1H), 3.77 (s, 3H), 3.24 (d, J = 7.2 Hz, 2H), 1.77 (s, 3H), 1.67 (s, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.75 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 148.4, 134.0, 133.7, 129.9, 129.6, 129.2, 121.9, 114.2, 99.9, 60.9, 28.8, 25.9, 18.0, 6.9, 5.8; IR (ATR) ν_{max} 2957, 2913, 1648, 1433, 1262, 1096, 1004, 907, 822, 740 cm^{-1}; MS (ESI, + ve) m/z (%) 435 and 433 $[M + Na]^+$ (100 and 92), 413 (18), 332 (20), 147 (19); HRMS (TOF ESI, + ve) m/z 433.1171 $[M + Na]^+$ (calcd for $C_{20}H_{31}{}^{79}BrO_2SiNa$, 433.1174).

*2-{5-Bromo-3-(3-methylbut-2-en-1-yl)-2-[(triethylsilyl)oxy]-phenyl}acetaldehyde (**8**).* A magnetically stirred solution of enol ether **7** (370 mg, 0.90 mmol) in CH_2Cl_2 (10 mL) containing water (50 μL) was treated with TFA (250 μL, 3.26 mmol) and maintained at 22 °C for 0.5 h. The resulting mixture was quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution) before being extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 99:1 → 95:5 v/v hexanes/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.8 in 9:1 v/v hexanes/EtOAc), aldehyde **8** (337 mg, 94%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (t, J = 2.1 Hz, 1H), 7.17 (d, J = 2.6 Hz, 1H), 7.10 (d, J = 2.6 Hz, 1H), 5.26 (m, 1H), 3.59 (d, J = 2.1 Hz, 2H), 3.27 (d, J = 7.3 Hz, 2H), 1.79 (s, 3H), 1.68 (s, 3H), 0.96 (t, J = 7.8 Hz, 9H), 0.75 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 151.9, 135.0, 134.5, 131.8, 131.4, 125.4, 121.3, 114.4, 45.6, 28.8, 25.9, 18.0, 6.9, 5.8; IR (ATR) ν_{max} 2958, 1728, 1455, 1271, 1200, 1006, 911, 817, 742 cm^{-1}; MS (ESI, + ve) m/z (%) 453 and 451 $[M + Na + MeOH]^+$ (100 and 95), 399 and 397 $[M + H]^+$ (both <1), 373 (18), 301 (10), 147 (7); HRMS (TOF ESI, + ve) m/z 397.1194 $[M + H]^+$ (calcd for $C_{19}H_{30}{}^{79}BrO_2Si$, 397.1193).

*(E)-2-Iodo-6-methylhepta-2,5-diene (**10**).* A magnetically stirred solution of hydrazone **9**[4] (2.00 g, 5.91 mmol) in THF (30 mL) was cooled to −78 °C and treated with *n*-BuLi (5.33 mL of 2.38 M solution in hexanes, 12.7 mmol). The resulting orange solution was stirred at −78 °C for 1 h and treated dropwise with prenyl bromide (820 μL, 7.11 mmol). The yellow solution was allowed to warm to −60 °C over 1 h, recooled to −78 °C, and treated with *n*-BuLi (2.70 mL of 2.38 M solution in hexanes, 6.43 mmol). The solution turned orange and was stirred at −78 °C for 0.25 h, warmed to 0 °C, and maintained at this temperature for 0.5 h during which time gas evolution was observed. The reaction was then recooled to −78 °C and treated with 1,2-diiodoethane (2.08 g, 7.40 mmol). After 0.3 h at −78 °C the reaction mixture was warmed to 22 °C, stirred at this temperature for 0.5 h, and treated with $Na_2S_2O_3$ (50 mL of a saturated aqueous solution) before being extracted with EtOAc (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, cyclohexane elution) to afford, after concentration of the appropriate fractions (R_f = 0.9 in hexanes), iodide **10**[4] (1.27 g, 91%) as a clear, pink-orange and light-sensitive oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (m, 1H), 5.07 (m, 1H), 2.70 (t, J = 7.5 Hz, 2H), 2.39 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 133.2, 120.1, 93.6, 29.8, 27.6, 25.8, 17.9. This material was identical, in all respects, with a sample prepared as described[4] earlier.

*(E)-1-{5-Bromo-3-(3-methylbut-2-en-1-yl)-2-[(triethylsilyl)oxy]-phenyl}-3,7-dimethylocta-3,6-dien-2-ol (**11**).* A magnetically stirred solution of iodide **10** (1.00 g, 4.24 mmol) in dry Et_2O (20 mL) was cooled to −78 °C, treated dropwise with *t*-BuLi (3.67 mL of a 1.5 M solution in hexanes, 5.51 mmol), maintained at this temperature for 1 h, and treated with a solution of aldehyde **8** (1.12 g, 2.82 mmol) in dry Et_2O (5 mL). The ensuing mixture was maintained at −78 °C for 1 h before being diluted with brine (20 mL), warmed, and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 98:2 → 95:5 v/v hexanes/EtOAc elution). Concentration of the appropriate fractions (R_f = 0.4 in 9:1 v/v hexanes/EtOAc) gave compound **11** (1.11 g, 64%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 2.6 Hz, 1H), 7.07 (d, J = 2.6 Hz, 1H), 5.36 (t, J = 7.3 Hz, 1H), 5.24 (m, 1H), 5.05 (m, 1H), 4.21 (m, 1H), 3.25 (d, J = 7.3 Hz, 2H), 2.82 (dd, J = 13.8 and 8.7 Hz, 1H), 2.75−2.67 (complex m, 3H), 1.79 (m, 1H), 1.78 (s, 3H), 1.70 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.62 (s, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.76 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 136.4, 134.5, 134.1, 132.0, 131.7, 131.2, 130.5, 126.1, 122.6, 121.7, 114.2, 77.6, 37.3, 28.9, 26.8, 25.9, 25.8, 18.0, 17.9, 11.7, 6.9, 5.8; IR (ATR) ν_{max} 3391, 2958, 2913, 2877, 1452, 1267, 1198, 910, 816, 739 cm^{-1}; MS (ESI, + ve) m/z (%) 531 and 529 $[M + Na]^+$ (73 and 70), 130 (100), 88 (14); HRMS (TOF ESI, + ve) m/z 529.2113 $[M + Na]^+$ (calcd for $C_{27}H_{43}{}^{79}BrO_2SiNa$ 529.2113).

*(E)-{4-Bromo-2-[3,7-dimethyl-2-((triethylsilyl)oxy)octa-3,6-dien-1-yl]-6-(3-methylbut-2-en-1-yl)phenoxy}triethylsilane (**12**).* A magnetically stirred solution of compound **11** (430 mg, 0.85 mmol) and imidazole (157 mg, 2.30 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C and treated with TES-Cl (0.31 mL, 1.82 mL). The resulting solution was allowed to warm to 22 °C, stirred at this temperature for 16 h, treated with $NaHCO_3$ (10 mL of a saturated aqueous solution), and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, hexanes →95:5 v/v hexanes/EtOAc elution). Concentration of the appropriate fractions (R_f = 0.9 in 9:1 v/v hexanes/EtOAc) afforded compound **12** (499 mg, 95%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 2.6 Hz, 1H), 7.02 (d, J = 2.6 Hz, 1H), 5.24 (m, 2H), 5.05 (m, 1H), 4.14 (m, 1H), 3.23 (m, 2H), 2.73−2.55 (complex m, 4H), 1.77 (s, 3H), 1.69

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(s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.62 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.82−0.68 (complex m, 15H), 0.46−0.27 (complex m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 137.4, 134.1, 133.6, 132.4, 132.1, 131.8, 129.8, 125.0, 122.7, 122.1, 113.6, 78.2, 38.1, 28.9, 26.7, 25.9, 25.8, 18.0, 17.8, 11.1, 7.0, 6.9, 5.8, 4.8; IR (ATR) ν_{max} 2956, 2912, 2877, 1455, 1270, 1200, 1065, 1004, 812, 740 cm^{-1}; MS (ESI, + ve) m/z (%) 645 and 643 $[M + Na]^+$ (100 and 90), 121 (10); HRMS (TOF ESI, + ve) m/z 643.2974 $[M + Na]^+$ (calcd for $C_{33}H_{57}{}^{79}BrO_2Si_2Na$, 643.2978).

*(E)-4-Hydroxy-3-(2-hydroxy-3,7-dimethylocta-3,6-dien-1-yl)-5-(3-methylbut-2-en-1-yl)benzoic Acid (**3**).* A magnetically stirred solution of compound **12** (200 mg, 0.32 mmol) in THF (5 mL) was cooled to −78 °C and treated with *t*-BuLi (0.53 mL of 1.5 M solution in hexanes, 0.80 mmol). The resulting yellow solution was stirred at −78 °C for 0.75 h, and then dry $CO_2(g)$ was bubbled into the reaction mixture for 0.5 h. The resulting clear, colorless solution was treated with AcOH (2 mL of a 50% v/v aqueous solution), heated at 50 °C for 36 h before being cooled to 22 °C, treated with TLC-grade silica gel (500 mg), and concentrated under reduced pressure. The resulting free-flowing powder was subjected to flash chromatography (silica, 8:2 → 1:1 v/v hexanes/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.5 in 3:2 v/v hexanes/EtOAc), carboxylic acid **3** (86 mg, 75%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table 2; IR (ATR) ν_{max} 2965, 2915, 1679, 1600, 1408, 1263, 1214, 776 cm^{-1}; MS (ESI, −ve) m/z (%) 357 $[M - H]^-$ (100), 101 (71), 62 (21); HRMS (TOF ESI, −ve) m/z 357.2051 $[M - H]^-$ (calcd for $C_{22}H_{29}O_4$, 357.2060).

*(E)-4-Bromo-2-(2-hydroxy-3,7-dimethylocta-3,6-dien-1-yl)-6-(3-methylbut-2-en-1-yl)phenol (**13**).* A magnetically stirred solution of allylic alcohol **11** (100 mg, 0.20 mmol) in THF (2 mL) was treated with AcOH/H_2O (2 mL of a 1:1 v/v aqueous solution), and the resulting mixture was heated at 50 °C for 18 h, cooled, and treated with $NaHCO_3$ (5 mL of a saturated aqueous solution) before being extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (silica, 95:5 v/v hexanes/EtOAc elution) to afford, after concentration of the appropriate fractions (R_f = 0.8 in 9:1 v/v hexanes/EtOAc), diol **13** (63 mg, 80%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.11 (d, J = 2.5 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 5.41 (m, 1H), 5.29 (m, 1H), 5.05 (m, 1H), 4.30 (d, J = 9.3 Hz, 1H), 3.32 (d, J = 7.3 Hz, 2H), 2.98 (m, 1H), 2.71 (t, J = 7.3 Hz, 2H), 2.61 (d, J = 14.5 Hz, 1H), 2.30 (s, 1H), 1.76 (s, 3H), 1.71 (m, 9H), 1.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 136.1, 133.3, 132.4, 131.9, 131.2, 130.8, 127.9, 125.8, 121.9(2), 121.8(6), 111.8, 80.3, 38.0, 28.7, 26.6, 25.8, 25.7, 17.8, 17.7, 12.0. These data matched those recorded on an authentic sample.[4]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00778.

Biological evaluations of **3**, **7**, **8**, and **10**, and **12**; references; and ^{1}H and ^{13}C NMR spectra of **3**, **7**, **8**, and **10**−**13** (PDF)

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Notes

The authors declare no competing financial interest.

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