Synthesis of Arieianal, a Prenylated Benzoic Acid from *Piper arieianum*

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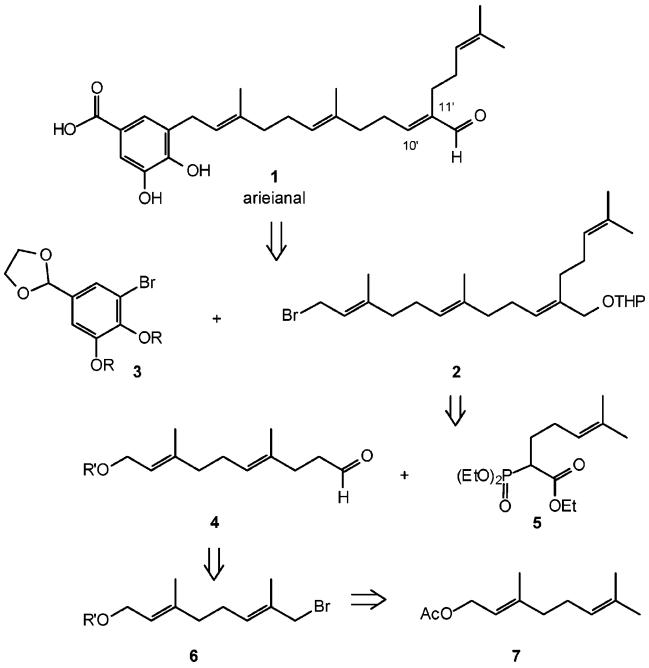
Arieianal (**1**) is a complex prenylated benzoic acid that was isolated from *Piper arieianum*. It has been synthesized through a convergent sequence that joins a functionalized diterpenoid chain to a protected aromatic core. Key steps include use of a copper enolate for selective displacement of an allylic bromide in the presence of an allylic acetate and a stereoselective Horner−Wadsworth−Emmons condensation to afford the desired *E* olefin of the isoprenoid side chain. After the diterpenoid chain was joined to the aromatic ring, use of sodium metal in hot *s*BuOH allowed selective cleavage of two benzyl ether protecting groups, and a sequence of oxidations gave the target compound. This synthesis confirms the structure assigned to the natural product and establishes a route that may be used to prepare more active analogues.

Leafcutter ants display fascinating behaviors that attract interest simply from the standpoint of scientific curiosity. At the same time, they inflict enormous damage on agricultural endeavors from the southern United States to northern Argentina, so they also attract attention on economic grounds. For a number of years, we investigated native plants that coexist with leafcutters, looking for natural chemical defenses against this pest.[1] Our studies uncovered a variety of natural products, including sesquiterpenoids (e.g., lasidiol angelate[2a] and caryophyllene epoxide[2b]), diterpenoids (including kolovanes[3a,b] and clerodanes[3c]), triterpenoids,[4] flavanones,[5] and alkaloids.[6] Investigations of several plant species have yielded compounds that can be grouped as prenylated derivatives of benzoic acids.[7] One of the more interesting compounds in this last class is arieianal (**1**), which was isolated from an antrepellent extract of *Piper arieianum* that showed significant activity.[8] A total synthesis of arieianal was undertaken because it was isolated in amounts too small for a full set of bioassays with leafcutter ants and their mutualistic fungus, because it has an interesting structure, and because we have developed an interest in the synthesis of prenylated aromatic compounds.[9]

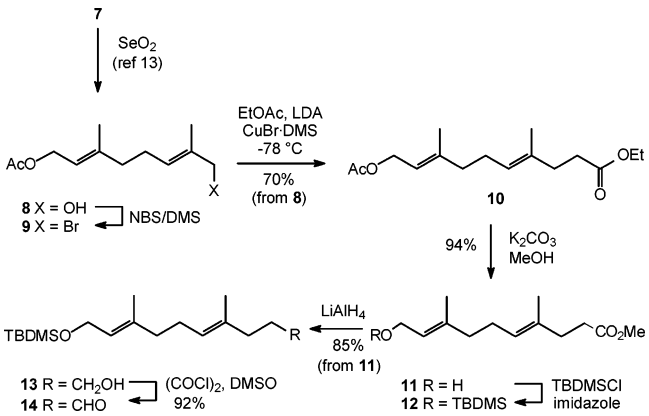
Results and Discussion

Arieianal (**1**) is characterized by the presence of an oxidized diterpenoid side chain attached to a 3,4-dihydroxybenzoic acid. One of the common ways of preparing prenylated aromatics is through halogen−metal exchange on a suitably protected aromatic halide followed by coupling of the resulting anion with the desired isoprenoid electrophile.[10] In this particular case, choice of protecting groups is particularly important given the array of functionality present and the risk of cyclization under common deprotection conditions.[11] With this caveat, we envisioned preparation of compound **1** through a convergent coupling of bromide **2** with the anion derived from a protected aryl unit (**3**, Scheme 1). To prepare the desired bromide **2**, we planned to use a Horner−Wadsworth−Emmons (HWE) condensation to install the C10′−C11′ double bond stereoselectively from aldehyde **4** and the known phosphonoester **5**.[12] Aldehyde **4** in turn could be traced to the geraniol derivative **6** and ultimately to geranyl acetate (**7**).

Scheme 1. Retrosythetic Analysis of Arieianal (**1**)



Scheme 2. Selective Extension of the Geranyl Chain



Synthesis of arieianal began with a SeO_2 oxidation of geranyl acetate (**7**) to afford the known hydroxy ester **8**[13] (Scheme 2). Conversion of alcohol **8** to the bromide **9** occurred smoothly upon standard treatment with NBS and DMS.[14] A two-carbon chain extension was necessary to

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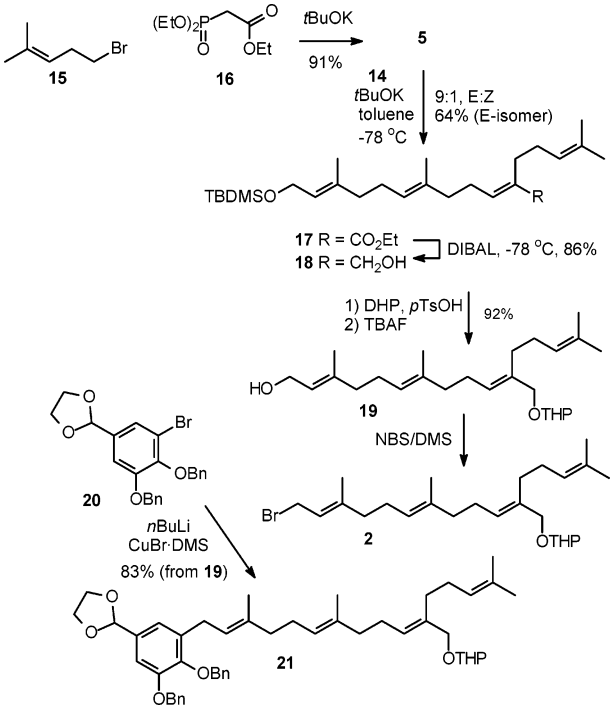
convert compound **9** to ester **10**. Kuwajima and Doi[15] have reported preparation of γ,δ-unsaturated esters by reaction of monofunctional allylic halides, including geranyl bromide, with a copper reagent prepared from ethyl acetate, LDA, and CuI at −30 °C. Application of this procedure to compound **9** could give the desired product **10** if selective displacement of the bromide could be accomplished in the presence of the acetate moiety. However, treatment of compound **9** with the lithium enolate of ethyl acetate under these conditions did not give the desired product, and use of LDA with CuBr·DMS at that temperature gave a complex mixture based on TLC analysis. Fortunately, when the reaction was conducted at −78 °C, ester **10** was obtained in good yield through selective displacement of the allylic bromide in the presence of the allylic acetate.

Ester **10** was transformed to the intermediate aldehyde **14** through a short sequence of functional group manipulations. Treatment of ester **10** with K_2CO_3 furnished alcohol **11**,[16] through transesterification of the acetate and ethyl ester groups, which was protected as the silyl ether **12**. Compound **12** was reduced immediately with $LiAlH_4$ to furnish alcohol **13** in 85% yield from compound **11**. A Swern protocol[17] then was used to oxidize the resulting alcohol **13** to the desired aldehyde **14**.

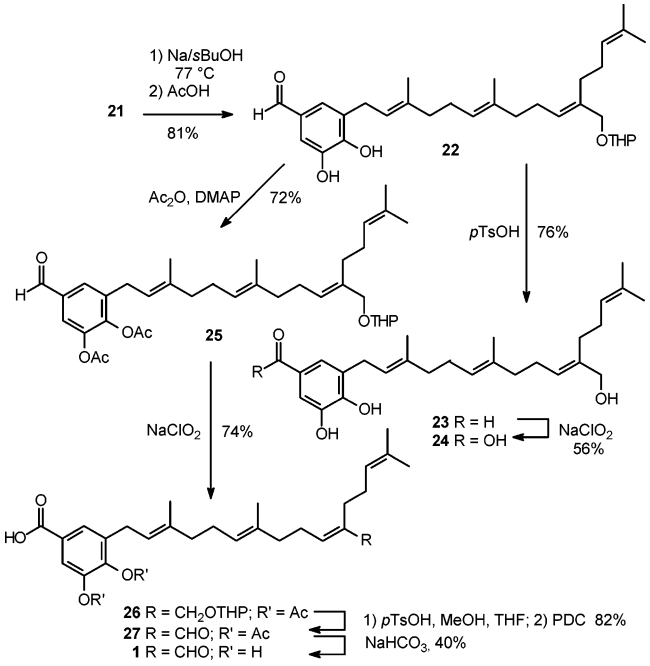
Elaboration of aldehyde **14** to the complete diterpenoid chain was anticipated through an HWE condensation with phosphonate **5**, and this intermediate was prepared by a variation on the procedure of Kodama et al.[12] After some experimentation, it was found that use of a limited amount of homoprenyl bromide (**15**) relative to the triethyl phosphonoacetate (**16**) made it possible to obtain the monoalkylated product **5** in 91% yield instead of the 42% previously reported. The coupling of aldehyde **14** and phosphonoester **5** was accomplished through an HWE[18] reaction under thermodynamic control in a 9:1 *E*/*Z* ratio. While the isomers could be isolated at this point, the separation is more facile at the stage of the alcohol **19**. To obtain this alcohol, ester **17** was treated with DIBAL at −78 °C.[17] The resulting alcohol **18** was protected as a THP ether and then treated with TBAF to afford the key intermediate **19** in excellent yield. Because this compound was readily purified and reasonably stable, the olefin isomers could be separated and material could be stored at this stage and then converted to the allylic bromide **2** through a standard NBS/DMS protocol[14] just prior to the coupling reaction. A halogen−metal exchange strategy was explored to couple the protected aryl unit **20**[19a] and bromide **2**. Unfortunately, attempts to couple the lithium anion derived from compound **20** by a halogen−metal exchange with *n*BuLi and bromide **2** went unrewarded. In sharp contrast, upon addition of CuBr·DMS to the reaction mixture, the desired reaction proceeded smoothly to afford the desired product **21** in high yield (Scheme 3).

Because compound **21** represents the carbon skeleton of arieianal, a series of functional group manipulations was required to complete the synthesis. Hydrogenolysis of the benzyl ethers may be problematic in the presence of the isoprenoid olefins, but cleavage with sodium in hot *s*BuOH proved straightforward,[19] as it was during the synthesis of montadial A and isopiperoic acid.[19a] During the acidic workup the dioxolane was cleaved to afford aldehyde **22** (Scheme 4). This was followed by removal of the THP ether with *p*TsOH in MeOH to provide the corresponding alcohol **23**. Treatment of the aromatic aldehyde **23** with $NaClO_2$ resulted in smooth oxidation to the carboxylic acid **24** in the presence of the phenolic groups and the isoprenoid allylic alcohol with no obvious overoxidation or cyclization

Scheme 3. Assembly of the Arieianal Skeleton



Scheme 4. Total Synthesis of Arieianal



of the isoprenoid chain. Unfortunately, the final oxidation of the isoprenoid allylic alcohol **24** to the aldehyde arieianal proved more problematic. Treatment with MnO_2, a mild reagent for oxidation of allylic alcohols, did not give the desired aldehyde, and attempted oxidation with PDC, the Dess−Martin periodinane, and Swern conditions went unrewarded. Because the catechol functionality may be sensitive to these oxidants, or cyclization with the prenyl chain may occur under the reaction conditions, it appeared necessary to protect the phenols of catechol **22** prior to oxidation of the allylic alcohol.

Treatment of catechol **22** with acetic anhydride and DMAP afforded diacetate **25** in 72% yield. Oxidation of this aromatic aldehyde with $NaClO_2/NaH_2PO_4$ furnished the carboxylic acid-THP ether **26**. An attempt to cleave the

THP ether in the presence of catalytic *p*TsOH in MeOH gave a mixture of mono- and diacetates that was difficult to separate by flash chromatography. However treatment of compound **26** with a solution of *p*TsOH in a 4:1 mixture of THF and MeOH selectively removed the THP ether in the presence of the acetate groups, and oxidation of the allylic alcohol could be conducted with PDC under standard conditions to afford aldehyde **27** in good yield. Finally, treatment of aldehyde **27** with a solution of $NaHCO_3$[20] furnished arieianal (**1**) as a brown oil, with ^1H and ^{13}C NMR spectra identical to those of the natural product, in ~3% overall yield from compound **8**.

In conclusion, the total synthesis of arieianal (**1**) has been completed by a highly convergent strategy. The key reactions used to assemble the terpenoid side chain were a selective alkylation of a copper enolate with an allylic bromide in the presence of an allylic acetate, and an HWE condensation that favored the desired *E* olefin. Once this chain was joined to a protected aromatic core through halogen−metal exchange, use of Na in hot *s*BuOH allowed selective cleavage of the benzyl protecting groups without side reactions. After the resulting catechol proved sensitive to even mild oxidation conditions, incorporation of acetate protecting groups on the catechol allowed oxidation to the desired aldehyde in high yield. This synthesis confirms the structure originally assigned to arieianal and provides a route that can be modified to prepare analogues of the natural product for further biological studies.

Experimental Section

General Experimental Procedures. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone and used immediately. Dichloromethane, EtOAc, *s*BuOH, diisopropylamine, benzene, and toluene were distilled freshly from CaH_2. DMF was used directly without further purification. All nonaqueous reactions were done under an argon atmosphere, in oven-dried or flame-dried glassware and with magnetic stirring. Flash chromatography was done on silica gel with an average 40−63 μm particle size. The ^1H and ^{13}C NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ as solvent and $(CH_3)_4Si$ as internal standard. High-resolution and electrospray (ES) mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. The elemental analyses were executed by Atlantic Microlab, Inc. (Norcross, GA).

(4*E*,8*E*)-Ethyl 10-Acetoxy-4,8-dimethyldeca-4,8-dienoate (10). A solution of LDA [prepared from *n*BuLi (60.2 mL, 139 mmol) and diisopropylamine (20.3 mL, 145 mmol) at −78 °C] in THF (120 mL) was transferred by cannula to a solution of CuBr·DMS (13.1 g, 63.7 mmol) and anhydrous EtOAc (14.7 mL, 150 mmol) in THF (100 mL) at −78 °C. The reaction mixture was allowed to stir for 30 min, and then bromide **9**[14] in THF (50 mL) at −78 °C was added via cannula. The reaction was allowed to stir for another 80 min and then quenched by addition of saturated NH_4Cl (50 mL). The aqueous layer was extracted with ether, and the combined organic layer was washed with 10% NH_4OH solution. The aqueous layer was extracted with ether, and the total organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. After final purification by flash chromatography (4:1 hexane/EtOAc), the desired product **10** was obtained as a clear oil (11.4 g, 70% from alcohol **8**) with ^1H and ^{13}C NMR spectra identical to that reported for material prepared by a different route.[21]

(4*E*,8*E*)-Methyl 10-Hydroxy-4,8-dimethyldeca-4,8-dienoate (11).[16,22] Solid K_2CO_3 (3.0 g, 21.8 mmol) was added to a solution of acetate **10** (4.8 g, 16.8 mmol) in MeOH (30 mL), and the reaction mixture was stirred for 85 min. After the reaction was quenched by addition of HCl (3.0 M, 9.0 mL), the aqueous layer was extracted with EtOAc, the solvent volume was reduced, and the aqueous layer was extracted with ether. The combined organic extract was rinsed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo to give alcohol **11** as a clear oil (3.57 g, 94%) with spectral data identical to that previously reported for material prepared by a different route.[16] This compound was used directly in the next step without further purification.

(4*E*,8*E*)-10-(*tert*-Butyldimethylsilyloxy)-4,8-dimethyldeca-4,8-dien-1-ol (13). TBDMSCl (6.7 g, 44.3 mmol) was added to a solution of ester **11** (6.7 g, 29.5 mmol) in CH_2Cl_2 (200 mL) followed by imidazole (6.03 g, 88.6 mmol). The reaction mixture was stirred overnight and then quenched by addition of H_2O (10 mL). The aqueous layer was extracted with ether, and the combined organic layer was washed with brine and dried ($MgSO_4$). After filtration and concentration in vacuo, the oily product **12** was used in the next step without further purification. Flash chromatography (4:1 hexane/EtOAc) was used to purify a small sample for elemental analysis: ^1H NMR δ 5.30 (m, 1H), 5.14 (m, 1H), 4.19 (d, J = 5.7 Hz, 2H), 3.66 (s, 3H), 2.43−2.38 (m, 2H), 2.32−2.27 (m, 2H), 2.14−1.97 (m, 4H), 1.62 (s, 3H), 1.61 (s, 3H); ^{13}C NMR δ 174.1, 136.9, 133.7, 125.1, 124.8, 60.6, 51.7, 39.6, 34.9, 33.3, 26.5, 26.3 (3C) 18.7, 16.6, 16.1, −4.8 (2C); *anal*. C 67.05%, H 10.78%, calcd for $C_{19}H_{36}O_3Si$, C 67.01%, H 10.65%.

Solid $LiAlH_4$ (1.42 g, 37.3 mmol) was added to a solution of ester **12** in THF (150 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature over a period of 3 h. This reaction was quenched by the addition of saturated Na_2SO_4 (50 mL) and left overnight. The aqueous layer was extracted with ether, the combined organic layer was rinsed with brine and dried ($MgSO_4$), and the filtrate was concentrated in vacuo. The initial product was purified by flash chromatography (4:1 hexane/EtOAc) to give alcohol **13** as a clear oil (7.84 g, 85% yield for the two steps): ^1H NMR δ 5.30 (t, J = 5.2 Hz, 1H), 5.15 (t, J = 6.6 Hz, 1H), 4.19 (d, J = 6.2 Hz, 2H), 3.62 (t, J = 6.4 Hz, 2H), 2.13−2.00 (m, 6H), 1.71−1.62 (m, 8H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 136.9, 135.0, 124.8 (2C), 62.8, 60.6, 39.7, 36.2, 30.8, 26.4, 26.3 (3C), 18.7, 16.5, 16.1, −4.8 (2C); *anal*. C 69.12%, H 11.58%, calcd for $C_{18}H_{36}O_2Si$, C 69.17%, H 11.61%.

(4*E*,8*E*)-10-(*tert*-Butyldimethylsilyloxy)-4,8-dimethyldeca-4,8-dienal (14). Oxallyl chloride (3.1 mL, 35.1 mmol) was added to CH_2Cl_2 (70 mL) at −78 °C, and after 10 min DMSO (4.98 mL, 70.2 mmol) was added dropwise and the solution was stirred for ~15 min. A solution of alcohol **13** in CH_2Cl_2 (30 mL) was transferred via cannula to the reaction mixture at −78 °C, and this reaction mixture was stirred for an additional 15 min. After Et_3N (17.5 mL, 125.4 mmol) was added, the temperature was brought to 0 °C. This solution was diluted with CH_2Cl_2 (100 mL) and quenched by the addition of H_2O (20 mL). After extraction of the aqueous layer with ether, the combined organic layer was rinsed with brine, dried ($MgSO_4$), and concentrated in vacuo. The initial product was purified by flash chromatography (5:1 hexane/EtOAc) to afford aldehyde **14** (7.1 g, 92%) as a clear oil: ^1H NMR δ 9.75 (t, J = 1.9 Hz, 1H), 5.32−5.26 (m, 1H), 5.17−5.12 (m, 1H), 4.19 (dq, J = 6.4 Hz, 0.7 Hz, 2H), 2.54−2.48 (m, 2H), 2.31 (t, J = 7.6 Hz, 2H), 2.15−1.98 (m, 4H), 1.62 (s, 6H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 202.9, 136.8, 133.4, 125.4, 124.9, 60.6, 42.4, 39.6, 32.1, 26.4, 26.3 (3C), 18.7, 16.6, 16.4, −4.8 (2C); *anal.* C 69.68%, H 11.18%, calcd for $C_{18}H_{34}O_2Si$, C 69.62%, H 11.04%.

Ethyl 2-(Diethoxyphosphoryl)-6-methylhept-5-enoate (5). Solid *t*BuOK (6.0 g, 50.6 mmol) was added to a solution of phosphonoacetate **16** (9.1 mL, 44.6 mmol) in DMF (20.0 mL) at 0 °C, and the resulting mixture was stirred for 10 min. The homoallylic bromide **15** (5.0 g, 29.7 mmol) was added to the reaction mixture, and it was allowed to warm to room temperature. The reaction mixture was left to stir for 18 h and then quenched by addition of HCl (3.0 M, 12.0 mL). The aqueous layer was extracted with ether, and the combined organic layer was rinsed with brine, dried ($MgSO_4$), and concentrated in vacuo. The initial product was purified by flash chromatography (2:1 to 1:1 hexane/EtOAc) to furnish the desired product **5** (8.29 g, 91%) as a clear oil. The ^1H NMR spectrum was identical to the partial data previously reported[12] with additional resonances at 2.13−1.96 (m, 3), 1.93−1.80 (m, 1H); ^{31}P NMR 23.0.

(2*E*,6*E*,10*E*)-Ethyl 12-(*tert*-Butyldimethylsilyloxy)-6,10-dimethyl-2-(4-methylpent-3-enyl)dodeca-2,6,10-trienoate (17). Solid *t*BuOK (1.36 g, 12.02 mmol) was added to a solution of phosphono ester **5** (3.17 g, 10.35 mmol) in toluene (50 mL), and the mixture was stirred at room temperature until most of the *t*BuOK was dissolved. The reaction mixture was brought to −78 °C, and a solution of aldehyde **14** (2.72 g, 8.77 mmol) in toluene (60 mL) was transferred via cannula within 40 min. After 3 h, the reaction mixture was quenched by addition of saturated NH_4Cl (20 mL). The aqueous layer was extracted with ether, and the combined organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give the initial product **17** as a 9:1 *E*/*Z* mixture. This oil was purified by flash chromatography (95:5 hexane/EtOAc) to afford the *E*-isomer (2.6 g, 64%). For the *E*-isomer: ^{1}H NMR δ 6.73 (t, *J* = 7.2 Hz, 1H), 5.33−5.29 (m, 1H), 5.17−5.12 (m, 2H), 4.22−4.15 (m, 4H), 2.34−2.23 (m, 4H), 2.15−1.99 (m, 8H), 1.68 (s, 3 H), 1.63 (s, 3 H), 1.62 (s, 3 H), 1.60 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 168.0, 142.3, 136.8, 134.1, 132.2, 132.1, 124.9, 124.5, 123.8, 60.3, 60.3, 39.5, 38.6, 27.8, 27.3, 27.0, 26.4, 26.0 (3C), 25.7, 18.4, 17.6, 16.4, 16.0, 14.3, −5.0 (2C); *anal.* C 72.46%, H 11.11%, calcd for $C_{28}H_{50}O_3Si$, C 72.67%, H 10.89%.

For the *Z*-isomer: ^{1}H NMR δ 5.83 (t, *J* = 7.3 Hz, 1H), 5.33−5.29 (m, 1H), 5.16−5.08 (m, 2H), 4.24−4.17 (m, 4H), 2.52 (m, 2H), 2.25 (t, *J* = 7.14 Hz, 2H), 2.16−1.98 (m, 8H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 168.1, 141.6, 136.9, 134.4, 132.0, 131.7, 124.6, 124.3, 123.6, 60.3, 59.9, 39.5, 39.2, 34.7, 28.0, 27.9, 26.3, 26.0 (3C), 25.7, 18.4, 17.6, 16.3, 15.8, 14.3, −5.1(2C).

(2*E*,6*E*,10*E*)-12-(*tert*-Butyldimethylsilyloxy)-6,10-dimethyl-2-(4-methylpent-3-enyl)dodeca-2,6,10-trien-1-ol (18). A solution of DIBAL in toluene (19.0 mL, 12.7 mmol) was added dropwise to a solution of ester **17** (2.5 g, 5.5 mmol) in toluene (80 mL) at −78 °C over 45 min. The reaction mixture was stirred for 15 min at −78 °C, diluted with ether (100 mL), and then quenched with saturated Na_2SO_4 (30 mL). The organic layer was separated, and the residue was rinsed with ether. After the combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo, the initial oil was purified by flash chromatography (6:1 hexane/EtOAc) to afford allylic alcohol **18** (1.98 g, 86%) as a clear oil: ^{1}H NMR δ 5.40 (t, *J* = 6.7 Hz, 1H), 5.33−3.28 (m, 1H), 5.15−5.10 (m, 2H), 4.19 (dd, *J* = 6.3, 0.6 Hz, 2H), 4.03 (d, *J* = 4.3 Hz, 2H), 2.19−1.99 (m, 12H), 1.69 (s, 3H), 1.63 (s, 3H) 1.61(s, 6H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 138.8, 136.8, 134.8, 132.0, 126.9, 124.5, 124.4, 124.2, 67.0, 60.4, 39.6, 39.5, 28.3, 27.1, 26.3, 26.1, 26.0 (3C), 25.7, 18.5, 17.7, 16.4, 16.0, −5.0 (2C); HREIMS *m*/*z* 420.3431 [M+] (calcd for $C_{26}H_{48}O_2$, 420.3424).

(2*E*,6*E*,10*E*)-3,7,15-Trimethyl-11-((tetrahydro-2*H*-pyran-2-yloxy)methyl)hexadeca-2,6,10,14-tetraen-1-ol (19). Neat DHP (1.1 mL, 4.52 mmol) was added to a solution of alcohol **18** (1.9 g, 4.5 mmol) in CH_2Cl_2, followed by addition of *p*TsOH (4.3 mg, 0.02 mmol). The resulting solution was allowed to stir for 3 h and then quenched by addition of saturated $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant oil was dissolved in THF (40 mL) followed by the addition of TBAF (6.3 mL, 6.3 mmol). This solution was stirred for 6 h at room temperature and then quenched by addition of saturated NH_4Cl. The aqueous layer was extracted with ether, and the combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant oil was purified by flash chromatography (4:1 hexane/EtOAc) to give compound **19** (1.62 g, 92%) as a clear oil: ^{1}H NMR δ 5.44−5.39 (m, 2H), 5.14−5.10 (m, 2H), 4.61 (t, *J* = 3.3 Hz, 1H), 4.19−4.15 (m, 3H), 3.92−3.83 (m, 2H), 3.55−3.48 (m, 1H), 2.19−2.00 (m, 12H), 1.89−1.51 (m, 18H); ^{13}C NMR δ 139.5, 135.8, 135.0, 131.6, 128.6, 124.4, 124.1, 123.5, 97.5, 71.2, 62.1, 59.4, 39.6, 39.5, 30.7, 28.5, 27.1, 26.3, 26.2, 25.7, 25.6, 19.5, 17.7, 16.3, 16.0; *anal.* C 76.75%, H 10.88%, calcd for $C_{25}H_{42}O_3$, C 76.87%, H 10.84%.

2-((2*E*,6*E*,10*E*)-12-(2,3-Bis(benzyloxy)-5-(1,3-dioxolan-2-yl)phenyl)-6,10-dimethyl-2-(4-methylpent-3-enyl)dodeca-2,6,10-trienyloxy)tetrahydro-2*H*-pyran (21). Neat DMS (0.29 mL, 3.95 mmol) was added dropwise to a solution of NBS (699 mg, 3.93 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After the resulting yellow mixture was stirred for 10 min, a solution of alcohol **19** (1.0 g, 2.6 mmol) at 0 °C was transferred into the reaction mixture by cannula. The resulting mixture was stirred for 3 h at 0 °C and then quenched by addition of saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting oil, bromide **2**, was used in the next reaction without further purification.

Bromide **20** (3.5 g, 7.9 mmol) was added to a mixture of benzene (10 mL) and ether (5 mL), followed by the dropwise addition of *n*BuLi (3.6 mL, 8.4 mmol). CuBr·DMS (807 mg, 3.9 mmol) was added to the reaction mixture, and it was allowed to stir for 1 h. The solution of bromide **2** in ether (15 mL) was transferred into this reaction mixture, and after 10.5 h, it was quenched by addition of saturated NH_4Cl. The aqueous layer was extracted with ether, and the combined organic extract was washed with 10% NH_4OH followed by brine, dried ($MgSO_4$), and concentrated in vacuo. After final purification by flash chromatography (6:1, 5:1 hexane/EtOAc), the desired product **21** was obtained as a brown oil (1.6 g, 83%): ^{1}H NMR δ 7.48−7.25 (m, 10H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 1.7 Hz, 1H), 5.73 (s, 1H), 5.42 (t, *J* = 6.9 Hz, 1H), 5.26 (m, 1H), 5.13 (br s, 4 H), 4.99 (s, 2H), 4.60 (t, *J* = 3.4 Hz, 1H), 4.18−4.01 (m, 5H), 3.87−3.83 (m, 2H), 3.53−3.47 (m, 1H), 3.34 (d, *J* = 7.1 Hz, 2H), 2.17−1.97 (m, 12H), 1.71−1.47 (m, 18H); *anal.* C 75.81%, H 8.23%, calcd for $C_{48}H_{62}O_6 \cdot 1.5H_2O$, C 75.66%, H 8.60%.

3,4-Dihydroxy-5-((2*E*,6*E*,10*E*)-3,7,15-trimethyl-11-((tetrahydro-2*H*-pyran-2-yloxy)methyl)hexadeca-2,6,10,14-tetraenyl)benzaldehyde (22). Metallic sodium (2.0 g, 85 mmol) was added to a solution of compound **21** (1.4 g, 1.9 mmol) in distilled *s*BuOH (20 mL) at 80 °C. The resulting solution was stirred for 130 min between 75 and 80 °C and then quenched by addition of a mixture of AcOH (6.0 mL), H_2O (10 mL), and $Na_2S_2O_4$ (350 mg). The aqueous layer was extracted with EtOAc, and the combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The initial product was purified by flash chromatography (2:1 hexane/EtOAc) to afford catechol **22** (649 mg, 81%) as a dark brown oil: ^{1}H NMR δ 9.72 (s, 1H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.24 (d, *J* = 1.9 Hz, 1H), 5.40−5.31 (m, 2H), 5.10−5.03 (m, 2H), 4.67 (t, *J* = 3.3 Hz, 1H), 4.19−3.85 (m, 3H), 3.59−3.55 (m, 1H), 3.41 (d, *J* = 7.2 Hz, 2H), 2.13−1.43 (m, 30H); ^{13}C NMR δ 191.9, 149.3, 144.1, 137.3, 135.2, 134.9, 131.7, 129.7, 129.0, 128.1, 126.7, 124.2, 124.0, 121.6, 112.1, 97.5, 71.6, 62.3, 39.6, 39.5, 30.6, 28.5, 28.4, 27.0, 26.2, 26.0, 25.7, 25.4, 19.4, 17.6, 16.0 (2C); HREIMS *m*/*z* 533.3226 [M + Na]$^+$ (calcd for $C_{32}H_{46}O_5Na$, 533.3243).

3,4-Dihydroxy-5-((2*E*,6*E*,10*E*)-11-(hydroxymethyl)-3,7,-15-trimethylhexadeca-2,6,10,14-tetraenyl)benzaldehyde (23). A solution of compound **22** (203 mg, 0.398 mmol) in MeOH (4 mL) was treated with *p*TsOH (15 mg, 0.089 mmol). After 3.5 h, the reaction was quenched by addition of saturated $NaHCO_3$. The solvent volume was reduced in vacuo, and salt was added. After the aqueous layer was extracted with EtOAc, the combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The initial product was purified by flash chromatography (1:1 hexane/EtOAc) to afford alcohol **23** (129 mg, 76%) as a dark brown oil: ^{1}H NMR δ 9.71 (s, 1H), 7.35 (d, *J* = 1.6 Hz, 1H), 7.22 (d, *J* = 1.5 Hz, 1H), 5.40−5.33 (m, 2H), 5.10−5.08 (m, 2H), 4.06 (s, 2H), 3.42 (d, *J* = 7.2 Hz, 2H), 2.16−1.95 (m, 12H), 1.75 (s, 3H), 1.67 (s, 3H), 1.58 (s, 6H); ^{13}C NMR δ 192.2, 149.4, 144.6, 138.5, 137.8, 135.2, 132.3, 129.3, 128.3, 128.1, 126.9, 124.3, 124.2, 121.9, 112.3, 67.6, 40.0, 39.8, 28.6, 28.4, 27.3, 26.4, 26.0, 25.8, 17.9, 16.3, 16.2.

3,4-Dihydroxy-5-((2*E*,6*E*,10*E*)-11-(hydroxymethyl)-3,7,-15-trimethylhexadeca-2,6,10,14-tetraenyl)benzoic Acid (24). Solid NaH_2PO_4 (90 mg, 0.735 mmol) was added to a solution of aldehyde **23** (129 mg, 0.302 mmol) in a mixture of THF (2.50 mL), H_2O (0.5 mL), and 2-methyl-2-butene (0.10 mL), followed by addition of $NaClO_2$ (85 mg, 0.752 mmol). The

reaction mixture was stirred overnight and then quenched by slow addition of HCl (3.0 M) until the solution became slightly acidic. Salt was added to the aqueous layer, and then it was extracted with EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The initial product was purified by flash chromatography (1:1 hexane/EtOAc) to afford carboxylic acid **24** as a clear oil (75 mg, 56%): ^{1}H NMR δ 7.48 (s, 1H), 7.47 (s, 1H), 5.40, (t, J = 6.6 Hz, 1H), 5.31 (t, J = 6.9 Hz, 1H), 5.09 (m, 2H), 4.06 (s, 2H), 3.37 (d, J = 7.1 Hz, 2H), 2.27−1.96 (m, 12H), 1.73 (s, 3H), 1.66 (s, 3H), 1.57 (s, 6H); ^{13}C NMR δ 172.0, 148.2, 143.4, 138.0, 137.3, 135.1, 132.3, 128.6, 128.0, 124.8, 124.3 (2C), 122.1, 120.8, 115.0, 67.6, 39.7, 30.6, 30.0, 28.6, 28.4, 27.3, 26.4, 25.9, 17.9, 16.3, 16.2; HREIMS *m/z* 441.2626 [M − H]$^-$ (calcd for $C_{27}H_{37}O_5$, 441.2641).

3,4-Diacetoxy-5-((2*E*,6*E*,10*E*)-3,7,15-trimethyl-11-((tetrahydro-2*H*-pyran-2-yloxy)methyl)hexadeca-2,6,10,14-tetraenyl)benzaldehyde (25). Freshly distilled diisopropylamine (0.52 mL, 3.71 mmol) and molecular sieves were added to a solution of compound **22** (378 mg, 0.74 mmol) in CH_2Cl_2 (7 mL), followed by addition of DMAP (0.90 mg, 0.01 mmol) and Ac_2O (0.35 mL, 3.70 mmol). The reaction mixture was allowed to stir overnight at room temperature and then concentrated in vacuo. The resulting oil was purified by flash chromatography (3:1 hexane/EtOAc) to afford aldehyde **25** (315 mg, 72%) as a light brown oil: ^{1}H NMR δ 9.92 (s, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H), 5.42 (t, J = 7.0 Hz, 1H), 5.24 (t, J = 3.3 Hz, 1H), 5.13 (br s, 2H), 4.61 (t, J = 3.3 Hz, 1H), 4.16 (d, J = 11.6 Hz, 1H), 3.91−3.83 (m, 2H), 3.52−3.37 (m, 1H), 3.33 (d, J = 7.1 Hz, 2H), 2.33 (s, 3H), 2.30 (s, 3H), 2.18−1.99 (m, 12H), 1.88−1.47 (m, 18H); ^{13}C NMR δ 190.3, 167.9, 167.4, 145.6, 143.3, 138.4, 137.0, 135.8, 135.0, 134.5, 131.6, 128.5 (2C), 124.3, 124.1, 122.0, 120.0, 97.5, 71.2, 62.0, 39.6 (2C), 30.7, 28.6, 28.5, 27.1, 26.6, 26.3, 25.7, 25.5, 20.6, 20.3, 19.5, 17.6, 16.3, 16.0; HRESIMS *m/z* 617.3459 [M + Na]$^+$ (calcd for $C_{36}H_{50}O_7Na$, 617.3454).

3,4-Diacetoxy-5-((2*E*,6*E*,10*E*)-3,7,15-trimethyl-11-((tetrahydro-2*H*-pyran-2-yloxy)methyl)hexadeca-2,6,10,14-tetraenyl)benzoic Acid (26). 2-Methyl-2-butene (0.20 mL) was added to a solution of compound **25** (314 mg, 0.53 mmol) in THF (4.00 mL), H_2O (1.00 mL), and *s*BuOH (1.00 mL), followed by addition of NaH_2PO_4 (194 mg, 1.59 mmol). After solid $NaClO_2$ (179 mg, 1.58 mmol) was added, the reaction mixture was stirred for 3 h at room temperature. The reaction was then quenched by dropwise addition of saturated NH_4Cl. The aqueous layer was extracted with ether, washed with brine, and dried ($MgSO_4$) and then concentrated in vacuo. The resulting oil was purified by flash chromatography (60:40 hexane/EtOAc) to afford acid **26** (240 mg, 74%): ^{1}H NMR δ 7.87 (s, 1H), 7.79 (d, J = 1.7 Hz, 1H), 5.43 (t, J = 6.9 Hz, 1H), 5.23 (t, J = 6.46, 1H), 5.13 (br s, 2H), 4.66 (t, J = 3.2 Hz, 1H), 4.17 (d, J = 11.6 Hz, 1H), 3.86 (m, 2H), 3.54 (m, 1H), 3.31 (d, J = 6.9 Hz, 2H), 2.32 (s, 3H), 2.29 (s, 3H), 2.13−2.01 (m, 12H), 1.95−1.46 (m, 18H); ^{13}C NMR δ 169.6. 168.1, 167.6, 145.0, 142.5, 138.0, 136.2, 135.5, 135.0, 131.6, 129.4, 129.1, 127.8, 124.3, 124.1, 123.1, 120.3, 97.1, 71.2, 61.9, 39.6, 30.6, 28.7, 28.4, 27.0, 26.4 (2C), 25.7, 25.5, 20.7, 20.6, 20.3, 17.6, 16.2, 16.0; HRESIMS *m/z* 633.3407 [M + Na]$^+$ (calcd for $C_{36}H_{50}O_8$, 633.3403).

3,4-Diacetoxy-5-((2*E*,6*E*,10*E*)-11-formyl-3,7,15-trimethylhexadeca-2,6,10,14-tetraenyl)benzoic Acid (27). Solid *p*TsOH (0.34 mg, 0.0018 mmol) in THF (0.40 mL) was added to acid **26** (22.0 mg, 0.036 mmol), followed by the addition of MeOH (0.10 mL). The reaction mixture was stirred for 2 days and then quenched by dropwise addition of saturated NH_4Cl solution. The aqueous layer was extracted with ether, and the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was dissolved in DMF (0.40 mL) followed by addition of PDC (20 mg, 0.053 mmol). After 75 min, the reaction was quenched by addition of H_2O (4.0 mL), and the aqueous layer was extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford compound **29** as a clear oil (18 mg, 82%). A portion of compound **27** was purified by flash chromatography (9:1:0.01 toluene/hexane/AcOH) for analysis: ^{1}HNMR δ 9.33 (s, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.79 (d, 1.9 Hz, 1H), 6.43 (t, J = 7.2 Hz, 1H), 5.23−5.09 (m, 3H), 3.31 (d, J = 7.0 Hz, 1H), 2.47−2.40 (m, 2H), 2.35−2.23 (m, 8H), 2.17−2.00 (m, 8H), 1.70 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.56 (s, 3H); HRESMS *m/z* 547.2670 [M + Na]$^+$ (calcd for $C_{31}H_{40}O_7Na$, 547.2672).

Arieianal (1). Saturated $NaHCO_3$ (0.50 mL) was added to a solution of carboxylic acid **27** (15 mg, 0.0286 mmol) in MeOH (1.0 mL) and H_2O (0.50 mL), and the solution was stirred for 80 min. The reaction mixture was quenched by dropwise addition of HCl (3.0 M) until the solution was slightly acidic. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford arieianal (**1**) as a brown oil (∼5 mg, 40%), representing an overall yield of ∼3% from compound **8**. Both ^{1}H and ^{13}C NMR spectra were identical to those of the natural product.[8]

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