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Microwave-Mediated Claisen Rearrangement Followed by Phenol Oxidation: A Simple Route to Naturally Occurring 1,4-Benzoquinones. The First Syntheses of Verapliquinones A and B and Panicein A

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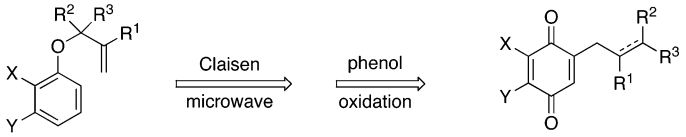

naturally occurring benzoquinone

The naturally occurring 1,4-benzoquinones 2-methoxy-6-propyl-1,4-benzoquinone (**1**), 2-methoxy-6-pentyl-1,4-benzoquinone (primin **2**), 2-methoxy-6-pentadecyl-1,4-benzoquinone (**3**), 2-methoxy-6-heptadecyl-1,4-benzoquinone (dihydroirisquinone, pallasone B; **4**) were synthesized by a simple protocol involving microwave accelerated Claisen rearrangement of allyl ethers **10**, followed by hydrogenation of the side chain alkene, and oxidation to the quinone. The Claisen-based methodology was extended to the first synthesis of the marine benzoquinones verapliquinones A and B (**5** and **6**), and panicein A (**7**). Isoarnebifuranone (**9**) was also synthesized by a similar strategy.

Introduction

Quinones, particularly the terpenoid benzoquinones, are widespread in Nature,[1] and are essential for many life processes. Although quinones, the largest group of natural pigments, do contribute to natural color, their major role is in redox processes. For example, the ubiquinones act as essential electron-transfer agents in the respiratory chain, and pyrroloquinolinequinone (PQQ) is a redox cofactor. Other quinone natural products also possess potent biological activity: for example, adriamycin (doxorubicin) is a front-line cancer chemotherapy treatment. Although quinones such as these are structurally quite complex, even the relatively simple terpenoid benzoquinones possess significant biological activity, primin **2**, for example, being a potent skin sensitizer (see below). Although naturally occurring benzoquinones have been synthesized by a variety of routes, there is no general route to these natural products. We now report a simple and versatile route to benzoquinones based on the Claisen rearrangement,[2] and illustrate it by the synthesis of the naturally occurring benzoquinones 2-methoxy-6-propyl-1,4-benzoquinone (**1**), 2-methoxy-6-pentyl-1,4-benzoquinone (primin **2**), 2-methoxy-6-pentadecyl-1,4-benzoquinone (**3**), 2-methoxy-6-heptadecyl-1,4-benzoquinone (dihydroirisquinone, pallasone B) (**4**), verapliquinones A and B (**5** and **6**), panicein A (**7**), and isoarnebifuranone (**9**) (Figure 1).[3] Of these, the verapliquinones and panicein A have not previously been synthesized.

Results and Discussion

The 6-alkyl-2-methoxy-1,4-benzoquinones **1**−**4** are isolated from a variety of natural sources. 2-Methoxy-6-propyl-1,4-benzoquinone (**1**) is found in the fungus *Camarops microspora*;[4] the compound was originally synthesized by Dean et al. in 1955,[5] and more recently by König et al.[6] Primin (2-methoxy-6-pentyl-1,4-benzoquinone) **2**, originally isolated from the primose *Primula obconica*,[7]

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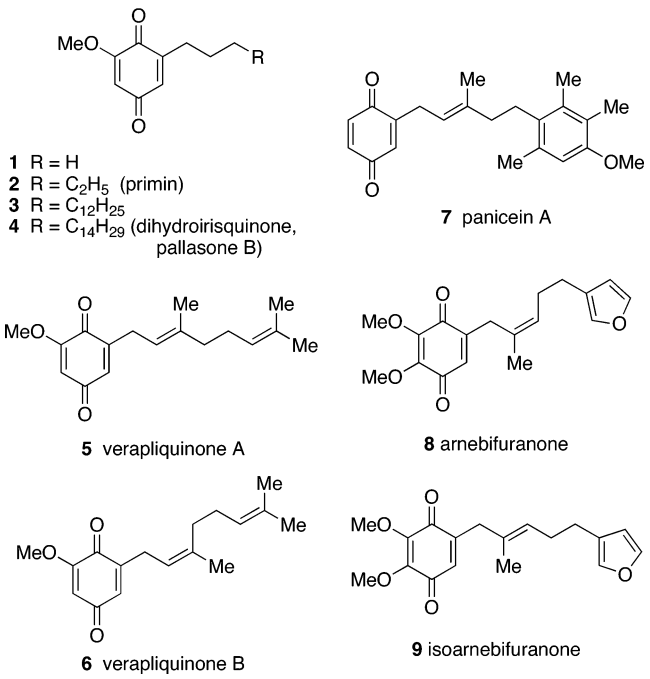
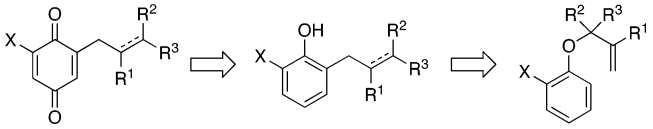


FIGURE 1. Structures of some naturally occurring benzoquinones.

and more recently from wood of *Miconia* species,[8] is the most studied of the alkylbenzoquinones because of its allergenic properties.[9] It is a potent sensitizer and induces contact dermitis. It was first prepared in 1967 by Schildknecht,[10] and has been the subject of further synthetic studies, including those of König et al. as part of a study of the allergenic properties of 6-alkyl-2-methoxy-1,4-benzoquinones,[6] and more recently Mabic et al.[9] 2-Methoxy-6-pentadecyl-1,4-benzoquinone (**3**) is isolated from seed oils of various iris species (*Iris pseudacorus*, *I. sibirica*, *I. missourensis*),[11] and has been synthesized by König as part of the aforementioned study.[6] The seed oil of *I. pseudacorus* also contains irisquinone, hydrogenation of which gives dihydroirisquinone.[12] This dihydro derivative, also known as pallasone B, is isolated from *I. pallash fisch* (var. *chinensis fisch*),[13] and in trace amounts from other iris species.[11] Pallasone B has been previously synthesized.[14]

Simple retrosynthetic analysis of the quinones **1**−**4** suggests that they could be obtained by oxidation of the corresponding 2-methoxy-6-substituted phenols, themselves obtained by Claisen rearrangement of the appropriately substituted allyl aryl ethers (Scheme 1). Since its discovery almost a century ago, the aromatic Claisen rearrangement has found a myriad of uses in organic synthesis,[2] and not surprisingly there are examples of its use in the synthesis of benzoquinones, albeit few.[5,15−17]

SCHEME 1. Retrosynthetic Analysis of 2,6-Disubstuted-1,4-benzoquinones



The requisite allyl aryl ethers **10** were prepared by Mitsunobu reaction (Ph_3P, DIAD) of 2-methoxyphenol with the appropriate allylic alcohol, which was prepared by addition of vinylmagnesium bromide to the corresponding aldehyde, although 2-methoxyphenyl allyl ether (**10a**) is commercially available (or readily prepared by reaction of 2-methoxyphenol with allyl bromide). Although the Claisen rearrangement of the allyl ether **10a** has been carried out by prolonged heating at 180 °C,[18] we investigated a range of conditions using the allyl ether **10b** as substrate, including microwave heating, conditions that are reported to accelerate Claisen rearrangements.[19−25] Heating under reflux for 3 h in 1,2-dichlorobenzene resulted in isolation of the required rearrangement product in 50% yield as a single (presumably *E*) isomer. However, under controlled microwave irradiation (focused reactor, 300 W, 180 °C), the allyl ether **10b** underwent rapid Claisen rearrangement in DMF as solvent in excellent yield in 25 min. Application of these conditions to the other allyl aryl ethers **10** resulted in equally rapid reactions, and gave the rearrangement products **11** in good yield (Table 1) as single geometric isomers. In the case of **11c**, the (*E*)-geometry of the double bond was proved by ^{1}H NMR spectroscopy; in the rearrangement products **11b** and **11d**, overlap of NMR signals prevented unambiguous assignment of the alkene geometry, but they are assumed to be (*E*). The next step was to hydrogenate the double bond to give the 2-methoxy-6-alkylphenols **12** in good yield. Finally, phenolic oxidation gave the corresponding 2-methoxy-6-alkyl-1,4-benzoquinones **1**−**4** (Scheme 2), whose properties matched those described for the natural products. All oxidations were initially carried out with Fremy's salt (potassium nitrosodisulfonate),[26] but in cases where this proved unsatisfactory, oxygen in the presence of salcomine was used.[27,28]

To extend the microwave-mediated Claisen rearrangement based methodology to more complex benzoquinones, we considered the marine natural products verapliquino-

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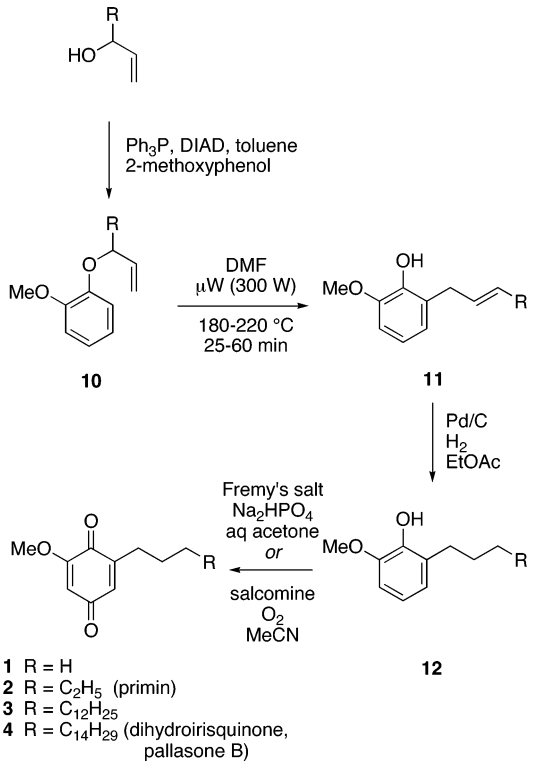
SCHEME 2. Synthesis of 2-Methoxy-6-propyl-1,4-benzoquinone (1), 2-Methoxy-6-pentyl-1,4-benzoquinone (primin 2), 2-Methoxy-6-pentadecyl-1,4-benzoquinone (3), and 2-Methoxy-6-heptadecylyl-1,4-benzoquinone (dihydroirisquinone, pallasone B; 4)[a]



[a] For compounds **10**−**12**: **a**, R = H; **b**, R = C_2H_5; **c**, R = $C_{12}H_{25}$; **d**, R = $C_{14}H_{29}$.

TABLE 1. Synthesis of 2-Methoxy-6-propyl-1,4-benzoquinone (1), 2-Methoxy-6-pentyl-1,4-benzoquinone (primin 2), 2-Methoxy-6-pentadecyl-1,4-benzoquinone (3), and 2-Methoxy-6-heptadecylyl-1,4-benzoquinone (dihydroirisquinone, pallasone B; 4; a, R = H; b, R = C_2H_5; c, R = $C_{12}H_{25}$; d, R = $C_{14}H_{29}$)

		yield/%			
	R	**10**	**11**	**12**	**1**−**4**
a	H		70	83	72[a]
b	C_2H_5	49	96	80	79[a]
c	$C_{12}H_{25}$	44	75	88	56[b]
d	$C_{14}H_{29}$	74	92	85	48[b]

[a] Oxidation with Fremy's salt. [b] Oxidation with salcomine/O_2.

nes A and B (**5** and **6**) and panicein A (**7**) as suitable targets, particularly since they have not been synthesized to date. The verapliquinones A and B were isolated from an *Aplidium* sp. (Ascidiacea) collected off the Breton coast, and characterized as a mixture of *E*,*Z*-isomers by NMR spectroscopy.[29] Separation of the isomers was reported to be extremely difficult even by HPLC, and only enough pure verapliquinone A and verapliquinone B for a UV spectrum was obtained. Panicein A was isolated from the breadcrumb sponge *Halichondria panicea* isolated in the Bay of Naples in 1973, and its structure assigned by NMR spectroscopy,[30] although the geometry of the double bond was not reported. Panicein A, along with the corresponding hydroquinone, has also been isolated from the sponge *Reniera mucosa* by Salva and co-workers,[31] and the hydroquinone is also found in *R. fulva*.[32] Again, no conclusive proof of the alkene geometry was offered, although nOe studies confirm the (*E*)-geometry of the double bond in the hydroquinone.[33] Therefore, we assume that panicein A has the structure **7**.

Since the verapliquinones and panicein A contain a trisubstituted alkene side chain, the Claisen rearrangement precursor of necessity contains a quaternary center. Therefore a slightly different strategy was required for the preparation of the required allyl aryl ether. The synthesis of the verapliquinones is shown in Scheme 3, and starts from the known propargylic alcohol 3,7-dimethyloct-6-en-1-yn-3-ol (**13**),[34] prepared by the addition of ethynylmagnesium bromide to 6-methyl-5-hepten-2-one in 69% yield. The propargyl alcohol **13** was then coupled to commercially available 2-methoxyphenol by using a method developed for tertiary propargyl ethers that involves the copper(II)-catalyzed reaction of the corresponding trifluoroacetate in the presence of DBU.[35] This gave the aryl alkynyl ether **14** in 56% yield, hydrogenation of which over Lindlar's catalyst gave the required allyl aryl ether **15**. Microwave-mediated Claisen rearrangement of ether **15** gave the required 2-(3,7-dimethyl-octa-2,6-dienyl)-6-methoxyphenol (**16**) as a mixture of *E*,*Z*-isomers in 83% yield. The two isomers of **16** were not separable by flash chromatography, so they were taken as a mixture and oxidized to the 1,4-benzoquinones with use of Fremy's salt to give a 2:1 mixture of verapliquinone A (**5**) and verapliquinone B (**6**) (Scheme 3). The major isomer of the synthetic material was assigned as the *E*-alkene (verapliquinone A) by comparison with the published ^{1}H NMR spectroscopic data of the natural product,[29] although in common with the original authors, we could not separate the *E*,*Z*-isomers.

The route to panicein A is similar in its requirement for a tertiary allyl ether substrate for the Claisen rearrangement. The starting material is the propargylic alcohol, 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methylpentyn-3-ol (**17**), prepared by addition of ethynylmagnesium bromide to the known ketone 4-(4-methoxy-2,3,6-trimethylphenyl)butan-2-one, obtained in four steps from

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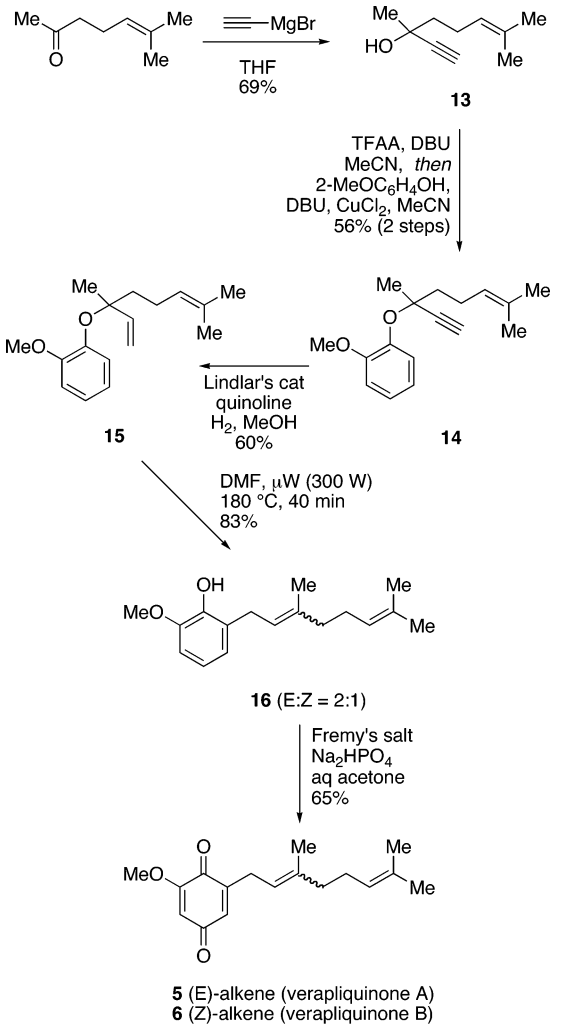
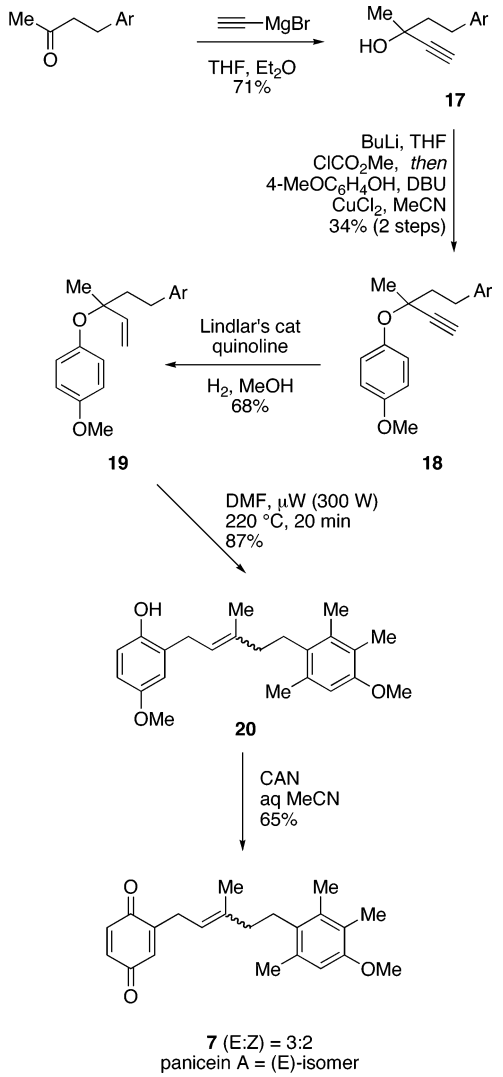
SCHEME 3. Synthesis of Verapliquinones A and B (5 and 6)



SCHEME 4. Synthesis of Panicein A (7; Ar = 4-methoxy-2,3,6-trimethylphenyl)



2,3,5-trimethylphenol.[36] In this instance, copper(II)-catalyzed coupling of the tertiary trifluoroacetate to a phenol gave poor yields, so a modification using a propargylic carbonate was used.[17] This gave the required 4-methoxyphenyl propargyl ether (**18**) in modest yield (Scheme 4). Lindlar reduction of **18** was followed by a high-yielding microwave-mediated Claisen rearrangement to give the phenol **20** as a 3:2 mixture of alkene isomers. These *E*,*Z*-isomers proved inseparable so were oxidized as a mixture with cerium(IV) ammonium nitrate to give an inseparable 3:2 mixture of quinones **7**. nOe spectroscopic studies were conducted on the mixture of quinones: preirradiation of the major $ArCH_2$ signal at δ 3.17 resulted in 5.2% enhancement of the major alkene methyl signal at δ 1.75, whereas preirradiation of the minor alkene methyl signal at δ 1.90 resulted in 4.1% enhancement of the minor alkene signal at δ 5.21. Hence this confirmed that the major isomer had the natural *E* geometry.

Finally the synthesis of the furan-containing quinone arnebifuranone was addressed. This natural product was originally isolated in 1984 from the roots of *Arnebia euchroma*, and assigned as the *E*-alkene.[37] Subsequent synthetic studies by Moore and co-workers established that the natural product had the *Z*-alkene geometry, although the compound was unstable and readily isomerized to the *E* isomer.[38] Further studies confirmed the facile double bond isomerization.[39] Our Claisen rearrangement-based synthesis starts with the aldehyde **21**, prepared in three steps from furan-3-carboxaldehyde.[40] Reaction with isopropenylmagnesium bromide gives the known allylic alcohol **22**,[38] Mitsunobu reaction of which with 2,3-dimethoxyphenol gave the Claisen precursor **23**. Microwave Claisen rearrangement results in formation of the phenol as a 9:1 mixture of alkene isomers with the more stable *E* isomer predominating. Oxidation of this mixture of alkenes with oxygen in the presence of

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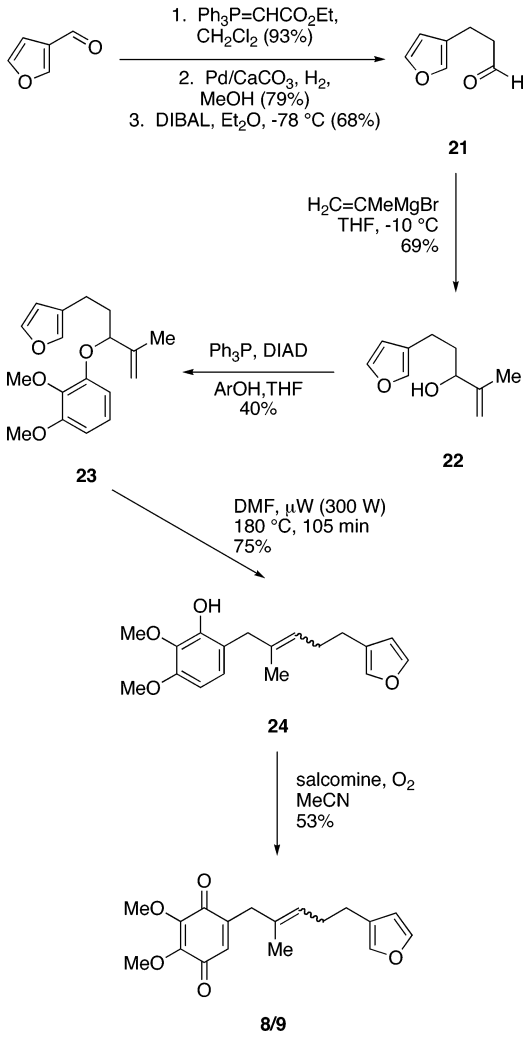
SCHEME 5. Synthesis of Isoarnebifuranone 9



salcomine gave isoarnebifuranone (**9**) as the major product (Scheme 5).

The Claisen rearrangements described in Schemes 3−5 all result in mixtures of alkene isomers, and this is clearly a limitation of the methodology. Despite its widespread use in organic synthesis, this aspect of the aromatic Claisen rearrangement, i.e., the question of alkene geometry arising from rearrangement of substituted aryl allyl ethers (Scheme 1, $R^2 \neq R^3$), surprisingly remains almost unexplored, with only a handful of examples in the literature.[2] Studies are underway in our laboratory to address this issue. Nevertheless, the present protocol involving the formation and microwave-mediated Claisen rearrangement of allyl aryl ethers, followed by phenol oxidation results in the synthesis of a range of naturally occurring benzoquinones. The method has been used to effect the first synthesis of the verapliquinones A and B, and panicein A.

Experimental Section

Commercially available reagents were used throughout without further purification unless otherwise stated; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40−60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen atmosphere. Fully characterized compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000−600 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded at 300 or 400 MHz (^1H frequencies, corresponding ^{13}C frequencies are 75 and 100 MHz); J values were recorded in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups, as assigned from DEPT, are noted; all others are C. Microwave reactions were carried out in a CEM Discover 300W focused microwave reactor.

2-Allyl-6-methoxyphenol (11a). 1-Allyloxy-2-methoxybenzene (**10a**) (0.300 g, 6.1 mmol) in anhydrous DMF (4 mL) was heated to 180 °C in a sealed tube in a microwave reactor (300 W) for 30 min. The mixture was then diluted with ether (20 mL), washed with water (6 × 10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **11a** as a colorless oil (0.210 g, 70%) (lit.[18] clear oil); IR (film)/cm^{-1} 3529 (O−H); ^1H NMR (300 MHz; $CDCl_3$) δ 6.84−6.74 (3H, m), 6.07−5.98 (1H, m), 5.71 (1H, s), 5.12−5.05 (2H, m), 3.90 (3H, s), 3.44−3.42 (2H, d, J = 6.5).

6-Methoxy-2-propylphenol (12a). 2-Allyl-6-methoxyphenol (**11a**) (0.227 g, 1.38 mmol) in ethyl acetate (3 mL) was added to 10% Pd/C in ethyl acetate (2 mL). The mixture was stirred under a hydrogen atmosphere overnight (17 h). The mixture was filtered through Celite, washed through with ethyl acetate (20 mL), and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **12a** as a colorless oil (0.109 g, 83%) (lit.[6] bp 71−72 °C at 0.5 mmHg); IR (film)/cm^{-1} 3549 (O−H); ^1H NMR (300 MHz; $CDCl_3$) δ 6.82−6.74 (3H, m), 5.72 (1H, s), 3.91 (3H, s), 2.69−2.63 (2H, m), 1.72−1.62 (2H, m), 1.00 (3H, t, J = 7.1).

2-Methoxy-6-propyl-1,4-benzoquinone (1). To 6-methoxy-2-propylphenol (**12a**) (0.178 g, 1.07 mmol) in acetone (60 mL) was added Fremy's salt (1.15 g, 4.28 mmol) in sodium hydrogen phosphate buffer (40 mL). The mixture was stirred for 1.5 h at room temperature, then extracted with ethyl acetate (3 × 60 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude compound was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:4) to give the title compound **1** as a yellow solid (0.139 g, 72%); mp 75−77 °C (from ethyl acetate/light petroleum) (lit.[5] mp 78−79 °C; lit.[4] mp 77−78 °C); IR (KBr)/cm^{-1} 1690 (C=O), 1650 (C=O); ^1H NMR (400 MHz; $CDCl_3$) δ 6.43−6.42 (1H, m), 5.84 (1H, d, J = 2.5), 3.77 (3H, s), 2.35 (2H, td, J = 7.6, 1.4), 1.54−1.44 (2H, m), 0.93−0.89 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 194.8 (C), 188.0 (C), 159.2 (C), 147.6 (C), 133.3 (CH), 107.5 (CH), 56.7 (Me), 31.0 (CH_2), 21.3 (CH_2), 14.1 (Me).

1-Methoxy-2-(pent-1-en-3-yloxy)benzene (10b). To a solution of 2-methoxyphenol (3.00 g, 2.66 mL, 24.2 mmol), pent-1-en-3-ol (2.48 mL, 2.08 g, 24.2 mmol), and triphenylphosphine (8.26 g, 31.5 mmol) in anhydrous toluene (70 mL) at 0 °C was slowly added diisopropyl azodicarboxylate (DIAD) (6.20 mL, 6.37 g, 31.5 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for 24 h under a nitrogen atmosphere. The mixture was concentrated to a third of its original volume in vacuo and light petroleum was added to precipitate triphenylphosphine oxide. The precipitate was removed by filtration, washed with light petroleum (30 mL), and evaporated in vacuo. The mixture was then dissolved in ethyl acetate (50 mL), washed with NaOH (2 M; 2 × 40 mL), water (2 × 40 mL), and brine (40 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **10b** (2.25 g, 49%) as a colorless oil; IR (film)/cm^{-1} 1588 (C=C); ^1H NMR (300 MHz; $CDCl_3$) δ 6.94−6.84 (4H, m), 5.89−5.85 (1H, m), 5.28−5.18 (2H, m), 4.55−4.48 (1H, m), 3.87 (3H, s), 1.92−1.72 (2H, m), 1.03 (3H, t, J = 7.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 150.7 (C), 148.2 (C), 138.4 (CH), 121.8 (CH), 121.1 (CH), 117.2 (CH_2), 116.9 (CH), 112.5 (CH), 82.5 (CH), 56.4 (Me), 28.8 (CH_2), 10.2 (Me); MS (EI) 192 (M^+, 19%), 153 (19),

137 (13), 125 (100). Found: C, 75.4; H, 8.7. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4. Found: M^+, 192.1151. $C_{12}H_{16}O_2$ requires 192.1150.

2-Methoxy-6-(pent-2-enyl)phenol (11b). (a) Microwave Heating in DMF. 1-Methoxy-2-(pent-1-en-3-yloxy)benzene (**10b**) (0.200 g, 1.05 mmol) was dissolved in DMF (3 mL) in a sealed tube. The mixture was heated in a microwave reactor (300 W) at 180 °C for 25 min. The mixture was diluted in ethyl acetate (15 mL), washed with water (5 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was then purified by flash chromatography on silica, eluting with dichloromethane and light petroleum (1:3) to give the title compound **11b** (0.191 g, 96%) as a colorless oil; IR (film)/cm^{-1} 3539 (O−H); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.83−6.72 (3H, m), 5.70 (1H, s), 5.61−5.53 (2H, m), 3.89 (3H, s), 3.36 (2H, d, J = 5.0), 2.09−2.00 (2H, m), 0.99 (3H, t, J = 7.4); ^{13}C NMR (75 MHz; $CDCl_3$) δ 146.7 (C), 143.7 (C), 133.7 (CH), 127.3 (C), 127.2 (CH), 122.5 (CH), 119.7 (CH), 108.8 (CH), 56.4 (Me), 33.0 (CH_2), 25.9 (CH_2), 14.2 (Me); MS (CI) 193 (MH^+, 19%), 137 (100). Found: MH^+, 193.1225. $C_{12}H_{16}O_2$ + H requires 193.1229.

(b) Microwave Heating in Toluene. 1-Methoxy-2-(pent-1-en-3-yloxy)benzene (**10b**) (0.200 g, 1.05 mmol) was dissolved in toluene (3 mL) in a sealed tube. The mixture was heated in a microwave reactor (300 W) at 180 °C for 2.5 h. The solvent was evaporated in vacuo and the crude product was then purified by flash chromatography on silica, eluting with dichloromethane and light petroleum (1:3) to give the title compound **11b** (0.105 g, 53%) as a colorless oil; data as above.

(c) Microwave Heating in 1,2-Dichlorobenzene. 1-Methoxy-2-(pent-1-en-3-yloxy)benzene (**10b**) (0.208 g, 1.09 mmol) was dissolved in 1,2-dichlorobenzene (3 mL) in a sealed tube. The mixture was heated in a microwave reactor (300 W) at 190 °C for 10 min. The crude product was then purified by flash chromatography on silica, eluting with dichloromethane and light petroleum (1:3) to give the title compound **11b** (0.150 g, 72%) as a colorless oil; data as above.

(d) Heating under Reflux in 1,2-Dichlorobenzene. 1-Methoxy-2-(pent-1-en-3-yloxy)benzene (**10b**) (0.250 g, 1.31 mmol) was dissolved in 1,2-dichlorobenzene (3 mL). The reaction mixture was heated under reflux for 3 h. The crude product was then purified by flash chromatography on silica, eluting with dichloromethane and light petroleum (1:3) to give the title compound **11b** (0.124 g, 50%) as a colorless oil; data as above.

2-Methoxy-6-pentylphenol (12b). A solution of 2-methoxy-6-pent-2-enylphenol (**11b**) (0.102 g, 0.53 mmol) in ethyl acetate (1.5 mL) was added to Pd/C (10%; 0.010 g) in ethyl acetate (0.5 mL). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen for 17 h. The product was filtered through a short pad of Celite and washed through with ethyl acetate (5 mL). The solvent was evaporated in vacuo and the crude product purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:9) to give the title compound **12b** (0.082 g, 80%) as a colorless oil (lit.[9] colorless liquid); IR (film)/cm^{-1} 3539 (O−H), 2960, 2935, 2848, 1614, 1593, 1475; ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.83−6.72 (3H, m), 5.73 (1H, s), 3.89 (3H, s), 2.66 (2H, t, J = 7.5), 1.77−1.60 (2H, m), 1.40−1.35 (4H, m), 0.93 (3H, t, J = 6.0).

2-Methoxy-6-pentyl-1,4-benzoquinone (primin 2). To a solution of 2-methoxy-6-pentylphenol (**12b**) (0.038 g, 0.20 mmol) in acetone (12 mL) was added Fremy's salt (0.215 g, 0.8 mmol) in sodium hydrogen phosphate buffer (10 mL). The reaction mixture was stirred for 3 h, then extracted with ethyl acetate (2 × 20 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give the title compound **2** (0.033 g, 79%) as a golden crystalline solid, mp 64.5−65.5 °C (from methanol) (lit.[8] mp 64−65 °C); IR (KBr)/cm^{-1} 1680 (C=O), 1655 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.48 (1H, s), 5.87 (1H, s), 3.81 (3H, s), 2.42 (2H, td, J = 7.6, 1.4), 1.44−1.43 (2H, m), 1.28−1.23 (4H, m), 0.89 (3H, t, J = 7.0).

1-Methoxy-2-(pentadec-1-en-3-yloxy)benzene (10c). To a solution of 2-methoxyphenol (0.274 g, 2.21 mmol), pentadec-1-en-3-ol (see the Supporting Information) (0.500 g, 2.21 mmol), and triphenylphosphine (4.430 g, 3.82 mmol) in anhydrous toluene (5 mL) at −10 °C was added DIAD (0.87 mL, 0.894 g, 4.42 mmol). The solution was then allowed to warm to room temperature and stirred under a nitrogen atmosphere for 24 h. The solution was diluted with ethyl acetate (10 mL) and washed with NaOH (2 M; 2 × 5 mL), water (5 mL), and brine (5 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:99) to give the title compound **10c** (0.323 g, 44%) as a colorless oil; IR (film)/cm^{-1} 1594 (C=C); ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.70−7.10 (4H, m), 5.71−5.83 (1H, ddd, J = 17.2, J = 10.5, J = 6.6), 5.24 (1H, d, J = 17.2), 5.19 (1H, d, J = 10.5), 4.58 (1H, q, J = 6.6), 3.87 (3H, s), 1.10−2.00 (22H, m), 0.91 (3H, t, J = 6.8); ^{13}C NMR (100 MHz; $CDCl_3$) δ 150.3 (C), 147.8 (C), 138.3 (CH), 121.4 (CH), 120.6 (CH), 116.5 (CH_2), 116.4 (CH), 112.1 (CH), 80.8 (CH), 55.9 (Me), 35.5 (CH_2), 31.9 (CH_2), 29.8−29.4 (7 × CH_2), 25.4 (CH_2), 22.7 (CH_2), 14.2 (Me); MS (CI) 332 (M^+, 16%), 286 (83), 153 (17), 125 (45), 124 (100). Found: MH^+, 333.2791. $C_{22}H_{36}O_2$ + H requires 333.2794.

2-Methoxy-6-(pentadec-2-enyl)phenol (11c). 1-Methoxy-2-(pentadec-1-en-3-yloxy)benzene (**10c**) (0.150 g, 0.45 mmol) in anhydrous DMF (3 mL) in a sealed tube was heated to 220 °C for 1 h in a microwave reactor (300 W). The solution was then diluted with ethyl acetate (15 mL), washed with water (3 × 10 mL) and brine (10 mL), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:99) to give the title compound **11c** (0.112 g, 75%) as a colorless oil; IR (film)/cm^{-1} 3554 (O−H); ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.65−6.85 (3H, m), 5.73 (1H, s), 5.50−5.66 (2H, m), 3.89 (3H, s), 3.38 (2H, d, J = 6.3), 2.01−2.07 (2H, m), 1.24−1.41 (20H, m), 0.91 (3H, t, J = 6.7); ^{13}C NMR (100 MHz; $CDCl_3$) δ 146.3 (C), 143.3 (C), 131.9 (CH), 127.7 (CH), 126.9 (C), 122.1 (CH), 119.3 (CH), 108.4 (CH), 55.9 (Me), 32.60 (CH_2), 31.57 (CH_2), 31.9 (CH_2), 29.8−29.2 (8 × CH_2), 22.7 (CH_2), 14.2 (Me); MS (CI) 333 (MH^+, 56%), 332 (M^+, 100%), 331 (39), 163 (12), 137 (74). Found: MH^+, 333.2780. $C_{22}H_{36}O_2$ + H requires 333.2794.

2-Methoxy-6-pentadecylphenol (12c). A solution of 2-methoxy-6-(pentadec-2-enyl)phenol (**11c**) (0.088 g, 0.26 mmol) in ethyl acetate (2 mL) was added to Pd/C (10%; 0.009 g) in ethyl acetate (1 mL). The solution was stirred under a hydrogen atmosphere for 48 h at room temperature, then filtered through Celite and washed through with ethyl acetate (3 × 5 mL). The solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:99) to give the title compound **12c** (0.076 g, 88%) as a colorless oil; IR (film)/cm^{-1} 3544 (O−H); ^{1}H NMR (300 MHz; $CDCl_3$) 6.72−6.58 (3H, m), 5.61 (1H, s), 3.77 (3H, s), 2.55 (2H, t, J = 7.5), 1.60−1.20 (26H, m), 0.81 (3H, t, J = 5.9); ^{13}C NMR (75 MHz; $CDCl_3$) δ 146.6 (C), 143.8 (C), 129.1 (C), 122.7 (CH), 119.5 (CH), 108.5 (CH), 56.3 (Me), 32.3 (CH_2), 30.3−29.8 (12 × CH_2), 23.1 (CH_2), 14.5 (Me); MS (CI) 335 (MH^+, 81%), 334 (M^+, 100), 333 (67). Found: MH^+, 335.2964. $C_{22}H_{38}O_2$ + H requires 335.2950.

2-Methoxy-6-pentadecyl-1,4-benzoquinone (3). 2-Methoxy-6-pentadecylphenol (**12c**) (0.076 g, 0.23 mmol) was dissolved in anhydrous acetonitrile (2 mL) and salcomine catalyst (0.014 g, 0.05 mmol) was added. Oxygen was bubbled through the solution for 15 min and the reaction mixture was then stirred in air at room temperature for 24 h. The reaction mixture was then filtered through Celite and washed through with ethyl acetate (3 × 10 mL) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:9) to give the title compound **3** (0.045 g, 56%)

as a yellow solid; mp 64−66 °C (from methanol) (lit.[6]mp 80−82 °C); IR (KBr)/cm^{-1} 1685 (C=O), 1653 (C=O); ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.47 (1H, s), 5.87 (1H, s), 3.81 (3H, s), 2.42 (2H, t, J = 7.6), 1.5−1.20 (26H, m), 0.87 (3H, t, J = 6.8); ^{13}C NMR (75 MHz; $CDCl_3$) δ 187.7 (C), 182.1 (C), 158.8 (C), 147.6 (C), 132.9 (CH), 107.1 (CH), 56.2 (Me), 31.9 (CH_2), 29.7−29.0 (10 × CH_2), 28.7 (CH_2), 27.7 (CH_2), 22.7 (CH_2), 14.1 (Me); MS (CI) 349 (MH^+, 67%), 347 (27), 227 (26), 187 (18), 167 (25), 154 (27), 153 (100), 149 (37), 115 (40), 113 (14). Found: MH^+, 349.2748. $C_{22}H_{36}O_3$ + H requires 349.2743.

1-Methoxy-2-(heptadec-1-en-3-yloxy)benzene (10d). To a solution of 2-methoxyphenol (0.43 mL, 0.49 g, 3.93 mmol), heptadec-1-en-3-ol (see the Supporting Information) (1.66 g, 3.93 mmol), and triphenylphosphine (1.55 g, 5.90 mmol) in anhydrous toluene (15 mL) was added DIAD (1.16 mL, 1.19 g, 5.90 mmol). The solution was then stirred at room temperature for 24 h. The solution was diluted with ethyl acetate (30 mL) and washed with NaOH (2 M; 20 mL), water (3 × 20 mL), and brine (20 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **10d** (1.05 g, 74%) as a colorless solid; mp 42.5−43.5 °C (from ethyl acetate−light petroleum); IR (film)/cm^{-1} 1589 (C=C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.93−6.86 (4H, m), 5.89 (1H, ddd, J = 17.3, 10.4, 6.8), 5.27−5.16 (2H, m), 4.57 (1H, q, J = 6.8), 3.87 (3H, s), 1.95−1.85 (1H, m), 1.76−1.62 (1H, m), 1.55−1.41 (2H, m), 1.27 (22H, br), 0.92−0.87 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ 150.1 (C), 147.7 (C), 138.2 (CH), 121.2 (CH), 120.5 (CH), 116.5 (CH_2), 116.3 (CH), 112.0 (CH), 80.8 (CH), 55.9 (Me), 35.4 (CH_2), 31.8 (CH_2), 29.6−29.3 (9 × CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.1 (Me); MS (EI) 360 (M^+, 50%), 137 (48), 124 (100), 109 (37). Found: M^+, 360.3018. $C_{24}H_{40}O_2$ requires 360.3028.

2-Heptadec-2-enyl-6-methoxyphenol (11d). 1-Methoxy-2-(heptadec-1-en-3-yloxy)benzene (**10d**) (0.300 g, 2.78 mmol) in anhydrous DMF (4 mL) in a sealed tube was heated to 180 °C for 30 min in a microwave reactor (300 W). The solution was diluted with ether (20 mL), washed with water (6 × 10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **11d** (0.275 g, 92%) as a colorless solid; mp 42.5−43.5 °C (from ethyl acetate−light petroleum); IR (KBr)/cm^{-1} 3549 (O−H); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.81−6.73 (3H, m), 5.69 (1H, s), 5.58 (2H, m), 3.39 (3H, s), 3.36 (2H, d, J = 5.9), 2.03−1.98 (2H, m), 1.34−1.27 (24H, br), 0.89 (3H, t, J = 6.5); ^{13}C NMR (75 MHz; $CDCl_3$) δ 146.7 (C), 143.7 (C), 132.4 (CH), 128.0 (CH), 127.3 (C), 122.5 (CH), 119.7 (CH), 108.8 (CH), 56.4 (Me), 33.0 (CH_2), 32.3 (CH_2), 30.1−29.6 (11 × CH_2), 23.1 (CH_2), 14.5 (Me); MS (CI) 361 (MH^+, 100%), 285 (38), 137 (47). Found: MH^+, 361.3098. $C_{24}H_{40}O_2$ + H requires 361.3107.

2-Heptadecyl-6-methoxyphenol (12d). 2-Heptadec-2-enyl-6-methoxyphenol (**11d**) (0.270 g, 0.75 mmol) in ethyl acetate (4 mL) was added to Pd/C (10%; 0.027 g) in ethyl acetate (1 mL). The solution was stirred under a hydrogen atmosphere for 4 h, then filtered through Celite and washed through with ethyl acetate (10 mL). The solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **12d** (0.230 g, 85%) as a colorless solid; mp 44.5−45.5 °C (from ethyl acetate-light petroleum) (lit.[41] mp 52.1−52.7 °C); IR (KBr)/cm^{-1} 3442 (O−H); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.79−6.71 (3H, m), 5.68 (1H, s), 3.89 (3H, s), 2.64 (2H, t, J, 7.7), 1.62−1.58 (2H, m), 1.27 (28H, br), 0.89 (3H, t, J = 6.4); ^{13}C NMR (75 MHz; $CDCl_3$) δ 146.6 (C), 143.8 (C), 129.1 (C), 122.7 (CH), 119.5 (CH), 108.5 (CH), 56.3 (Me), 32.3 (CH_2), 30.2−29.8 (14 × CH_2), 23.1 (CH_2), 14.5 (Me).

2-Heptadecyl-6-methoxy-1,4-benzoquinone (dihydroirisquinone, pallasone B; 4). 2-Heptadecyl-6-methoxyphenol (**12d**) (0.200 g, 0.56 mmol) was dissolved in anhydrous acetonitrile (4 mL) and salcomine catalyst (0.036 g, 0.11 mmol) was added. Oxygen was bubbled through the solution for 15 min, and the mixture was stirred in air at room temperature for 24 h. The solution was filtered through Celite, washed through with dichloromethane (20 mL), and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:4) to give the title compound **4** (0.102 g, 48%) as a yellow solid; mp 97.5−98.5 °C (from ethyl acetate−light petroleum) (lit.[12] mp 90.5−91.0 °C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.48 (1H, d, J = 2.1), 5.88 (1H, d, J = 2.1), 3.82 (3H, s), 2.43 (2H, t, J = 7.0), 1.50−1.47 (2H, m), 1.30−1.25 (28H, m), 0.88 (3H, t, J = 6.2); ^{13}C NMR (75 MHz; $CDCl_3$) δ 190.4 (C), 184.8 (C), 161.5 (C), 150.2 (C), 135.5 (CH), 109.7 (CH), 58.9 (Me), 34.6 (CH_2), 32.4−31.9 (12 × CH_2), 31.4 (CH_2), 30.3 (CH_2), 25.4 (CH_2), 16.8 (Me).

1-(3,7-Dimethyloct-6-en-1-yn-3-yloxy)-2-methoxybenzene (14). To a solution of 3,7-dimethyloct-6-en-1-yn-3-ol (**13**) (see the Supporting Information) (3.06 g, 20.1 mmol) in anhydrous acetonitrile (11 mL) under nitrogen and cooled to below −5 °C was added DBU (3.92 mL, 3.99 g, 26.2 mmol). Trifluoroacetic anhydride (2.81 mL, 4.22 g, 20.1 mmol) was added over a 25 min period while maintaining the temperature below 2 °C. The resulting solution was allowed to stir at 0 °C for 30 min before the addition to the 2-methoxyphenol solution (described below).

To a solution of 2-methoxyphenol (1.92 mL, 2.17 g, 17.5 mmol) in anhydrous acetonitrile (11 mL) under nitrogen and cooled to below −4 °C was added DBU (3.39 mL, 3.46 g, 22.7 mmol) and $CuCl_2 \cdot 2H_2O$ (0.003 g). The solution of the trifluoroacetate (above), maintained at 0 °C, was added to the 2-methoxyphenol solution over a 40 min period while maintaining the temperature below 0 °C. After being stirred for 5 h below 0 °C, the mixture was concentrated in vacuo and the residue partitioned between water (50 mL) and ethyl acetate (150 mL). The organic fraction was washed with HCl (2 M; 50 mL), NaOH (2 M; 50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL) and dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **14** as a colorless oil (2.55 g, 56%); IR (film)/cm^{-1} 3298 (C≡C−H); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.42 (1H, dd, J = 7.8, 1.4), 7.08−7.02 (1H, m), 6.92−6.86 (2H, m), 5.20−5.14 (1H, m), 3.82 (3H, s), 2.55 (1H, s), 2.43−2.22 (2H, m), 2.06−1.82 (2H, m), 1.70 (3H, d, J = 1.1), 1.65 (3H, s), 1.58 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 153.0 (C), 144.7 (C), 132.0 (C), 123.9 (CH), 123.7 (CH), 123.4 (CH), 120.3 (CH), 112.2 (CH), 85.3 (C), 77.0 (C), 74.6 (CH), 55.7 (Me), 42.3 (CH_2), 26.7 (Me), 25.7 (Me), 23.3 (CH_2), 17.7 (Me); MS (EI) 258 (M^+, 2%), 215 (12), 124 (100), 69 (68). Found: M^+, 258.1630. $C_{17}H_{22}O_2$ requires 258.1620.

1-(3,7-Dimethylocta-1,6-dien-3-yloxy)-2-methoxybenzene (15). 1-(3,7-Dimethyloct-6-en-1-yn-3-yloxy)-2-methoxybenzene (**14**) (1.26 g, 4.92 mmol) was dissolved in anhydrous methanol (15 mL), and Lindlar catalyst (0.047 g) and quinoline (1 mL) were added. The mixture was evacuated and then stirred under hydrogen for 4 h. The mixture was filtered through Celite, washed through with methanol (30 mL), and concentrated in vacuo. The residue was dissolved in dichloromethane (30 mL), washed with HCl (2 M; 2 × 30 mL), water (30 mL), and brine (30 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **15** as a colorless oil (0.77 g, 60%); IR (film)/cm^{-1} 1588 (C=C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.05 (1H, dd, J = 7.9, 1.5), 7.01−6.95 (1H, m), 6.88 (1H, m), 6.84−6.78 (1H, m), 6.12 (1H, dd, J = 17.9, 10.7), 5.19−5.12 (3H, m), 3.82 (3H, s), 2.16 (2H, q, J = 7.9), 1.86−1.77 (2H, m), 1.70 (3H, s), 1.62 (3H, s), 1.40 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 153.0 (C), 145.1 (C), 143.4 (CH), 131.5 (C), 124.4 (CH), 123.00 (CH), 122.99 (CH), 120.2 (CH), 114.1 (CH_2),

(41) Jinno, S.; Okita, T. *Chem. Pharm. Bull.* **1998**, *46*, 1688−1694.

112.3 (CH), 82.8 (C), 55.8 (Me), 41.4 (CH_2), 25.7 (Me), 22.7 (CH_2), 22.1 (Me), 17.6 (Me).

2-(3,7-Dimethylocta-2,6-dienyl)-6-methoxyphenol (16). 1-(3,7-Dimethylocta-1,6-dien-3-yloxy)-2-methoxybenzene (**15**) (0.400 g, 1.54 mmol) in anhydrous DMF (5 mL) was heated at 180 °C in a sealed tube in a microwave reactor (300 W) for 40 min. The mixture was diluted with ether (30 mL) and washed with water (3 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **16** as a colorless oil (0.330 g, 83%) as a mixture of *E*,*Z* isomers; IR (film)/cm^{-1} 3544 (O−H); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.80−6.72 (3H, m), 5.71 (1H, s), 5.36 (1H, td, J = 7.3, 1.3), 5.19−5.10 (1H, m), 3.89 (3H, s), 3.38 (2H, d, J = 6.8), 2.19−2.06 (4H, m), 1.76−1.59 (9H).

2-(3,7-Dimethylocta-2,6-dienyl)-6-methoxy-1,4-benzoquinone (Verapliquinones A and B; 5/6). To a solution of 2-(3,7-dimethylocta-2,6-dienyl)-6-methoxyphenol (**16**) (mixture of *E*,*Z* isomers) (0.247 g, 0.95 mmol) in acetone (60 mL) was added Fremy's salt (1.02 g, 3.8 mmol) in sodium hydrogen phosphate buffer (40 mL). The reaction mixture was stirred at room temperature for 1.5 h then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:9) to give the title compounds **5/6** as an orange oil (0.156 g, 60%) (lit.[29] yellow oil) (2:1 mixture of geometric isomers; this ratio was determined by ^{1}H NMR integrations of methyl peaks at δ 1.76 and 1.69; the major isomer was assigned as verapliquinone A (**5**) by comparison with published NMR data;[29] IR (film)/cm^{-1} 1685 (C=O), 1655 (C=O); ^{1}H NMR (400 MHz; $CDCl_3$) major isomer (*verapliquinone A*) δ 6.47−6.44 (1H, m), 5.87−5.86 (1H, d, J = 2.1), 5.15 (1H, t, J = 7.3), 5.08−5.06 (1H, m), 3.28 (3H, s), 3.14 (2H, d, J = 7.3), 2.11−2.05 (4H, m), 1.69 (3H, s), 1.63 (3H, s), 1.60 (3H, s); ^{1}H NMR (400 MHz; $CDCl_3$) minor isomer (*verapliquinone B*) δ 6.47−6.44 (1H, m), 5.87−5.86 (1H, d, J = 2.1), 5.15 (1H, t, J = 7.3), 5.08−5.06 (1H, m), 3.28 (3H, s), 3.14 (2H, d, J = 7.3), 2.11−2.05 (4H, m), 1.76 (3H, s), 1.65 (3H, s), 1.59 (3H, s).

5-(4-Methoxy-2,3,6-trimethylphenyl)-3-(4-methoxyphenoxy)-3-methylpentyne (18). (a) To a solution of 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methylpentyn-3-ol (**17**) (see the Supporting Information) (0.520 g, 2.11 mmol) in THF at 0 °C was added dropwise *n*-butyllithium (2.5 M in hexanes; 1.27 mL, 3.17 mmol). The mixture was stirred at this temperature for 30 min and methyl chloroformate (0.25 mL, 3.17 mmol) was then added dropwise. The reaction mixture was allowed to warm to room temperature, then stirred for a further 1.5 h. The reaction mixture was then partitioned between dichloromethane (10 mL) and water (10 mL) and the organic layer separated. The aqueous layer was further extracted with ether (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:9) to afford 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methoxycarbonyloxy-3-methylpentyne as a pale oil (0.444 g, 69%), used without further purification; IR ($CHCl_3$)/cm^{-1} 3305 (C≡C−H), 2112 (C≡C),1750 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.56 (1H, s), 3.79 (6H, s), 2.87−2.80 (2H, m), 2.68 (1H, s), 2.33 (3H, s), 2.24 (3H, s), 2.14 (3H, s), 2.10−1.84 (2H, m), 1.80 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 153.4 (C), 151.6 (C), 134.0 (C), 131.8 (C), 127.5 (C), 120.9 (C), 108.3 (CH), 80.9 (C), 74.6 (C), 72.1 (CH), 53.5 (Me), 52.4 (Me), 38.8 (Me), 24.2 (Me), 22.2 (CH_2), 18.2 (Me), 13.6 (Me), 9.9 (Me); MS (CI) 322 (MNH_4^+, 12%), 261 (12), 229 (94), 163 (100). Found: M + NH_4^+, 322.2012. $C_{18}H_{24}O_4$ + NH_4 requires 322.2013.

(b) To a solution of 4-methoxyphenol (0.150 g, 1.22 mmol) in acetonitrile (1 mL) at −20 °C was added anhydrous copper(II) chloride (0.160 mg, 0.1 mol %) and DBU (0.24 mL, 1.59 mmol). The mixture was stirred for 15 min and a solution of the above carbonate in acetonitrile (4 mL) was then added dropwise. The reaction mixture was stirred overnight at 0 °C, then quenched with water (10 mL) and extracted into ether (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to afford the title compound **18** as a pale oil (0.212 g, 49%); IR ($CHCl_3$)/cm^{-1} 3305 (C≡C−H), 2121 (C≡C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.18−7.13 (2H, m), 6.84−6.79 (2H, m), 6.57 (1H, s), 3.79 (3H, s), 3.78 (3H, s), 2.98−2.87 (2H, m), 2.62 (1H, s), 2.33 (3H, s), 2.25 (3H, s), 2.14 (3H, s), 2.04−1.87 (2H, m), 1.59 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$) 156.0 (C), 155.8 (C), 149.4 (C), 136.6 (C), 134.3 (C), 130.7 (C), 123.8 (CH), 123.2 (C), 114.3 (CH), 110.7 (CH), 85.6 (C), 76.3 (C), 75.5 (CH), 56.0 (2 × Me), 42.4 (CH_2), 27.3 (Me), 25.0 (CH_2), 20.7 (Me), 16.1 (Me), 12.4 (Me); MS (CI) 370 (MNH_4^+, 5%), 353 (5), 231 (15), 163 (100). Found: M + NH_4^+, 370.2376. $C_{23}H_{28}O_3$ + NH_4 requires 370.2377.

5-(4-Methoxy-2,3,6-trimethylphenyl)-3-(4-methoxyphenoxy)-3-methylpentene (19). 5-(4-Methoxy-2,3,6-trimethylphenyl)-3-(4-methoxyphenoxy)-3-methylpentyne (**18**) (0.180 g, 0.511 mmol) was dissolved in anhydrous methanol (5 mL) and Lindlar catalyst (0.020 g) and quinoline (0.25 mL) were added. The mixture was then evacuated and stirred under a hydrogen atmosphere overnight. The mixture was then filtered through Celite, washed with methanol (20 mL), and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:9) to afford the title compound **19** as a pale oil (0.123 g, 68%); IR ($CHCl_3$)/cm^{-1} 1595 (C=C); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.97−6.93 (2H, m), 6.79−6.75 (2H, m), 6.55 (1H, s), 6.21−6.12 (1 H, m), 5.24−5.16 (2 H, m), 3.78 (3H, s), 3.77 (3H, s), 2.75−2.69 (2H, m), 2.28 (3H, s), 2.19 (3H, s), 2.13 (3H, s), 1.85−1.73 (2H, m), 1.43 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 155.7 (C), 155.3 (C), 150.0 (C), 143.9 (CH), 136.4 (C), 134.1 (C), 131.2 (C), 123.2 (CH), 115.0 (C), 114.3 (CH), 110.7 (CH), 81.8 (CH_2), 56.0 (Me), 55.9 (Me), 41.6 (CH_2), 24.4 (CH_2), 22.8 (Me), 20.7 (Me), 16.1 (Me), 12.4 (Me); MS (CI) 372 (MNH_4^+, 30%), 355 (33), 248 (100). Found: M + NH_4^+, 372.2536. $C_{23}H_{30}O_3$ + NH_4 requires 372.2533.

4-Methoxy-2-[5-(4-methoxy-2,3,6-trimethylphenyl)-3-methylpent-2-enyl]phenol (20). A solution of 5-(4-methoxy-2,3,6-trimethylphenyl)-3-(4-methoxyphenoxy)-3-methylpentene (**19**) (0.100 g, 0.282 mmol) in DMF (1 mL) in a sealed tube was heated at 220 °C for 20 min in a microwave reactor (300 W). The reaction mixture was then diluted with ethyl acetate (8 mL), the organics separated, and the aqueous layer further extracted with ethyl acetate (10 mL). The combined organics were then dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:4) to afford the title compound **20** as a pale oil (0.087 mg, 87%), in a 3:2 (*E*:*Z*) mixture of geometric isomers; IR ($CHCl_3$)/cm^{-1} 3605 (O−H); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.77−6.62 (3H, m), 6.57 (1H, s), 6.56 (1H, m), 5.41 (0.6H, m), 5.37 (0.4H, m), 4.77 (0.6H, s), 4.71 (0.4H, s), 3.79 (3H, s), 3.74 (1.8H, s), 3.72 (1.2H, s), 3.37 (1.2H, d, J = 7.0 Hz), 3.31 (0.8H, d, J = 7.0 Hz), 2.75−2.68 (2H, m), 2.34 (1.2H, s), 2.31 (1.8H, s), 2.28−2.10 (2H, m), 2.26 (1.2H, s), 2.22 (1.8H, s), 2.11 (3H, s), 1.89 (1.2H, s), 1.87 (1.8H, s); ^{13}C NMR (75 MHz; $CDCl_3$) δ 155.8 (C), 155.7 (C), 154.1 (C), 148.6 (C), 148.5 (C), 139.2 (C), 138.8 (C), 136.4 (C), 136.3 (C), 134.1 (C), 134.0 (C), 131.2 (C), 128.5 (C), 128.4 (C), 123.3 (C), 123.2 (C), 122.8 (CH), 121.8 (CH), 116.7 (CH), 116.6 (CH), 116.1 (CH), 112.5 (CH), 112.4 (CH), 110.8 (CH), 110.7 (CH), 56.1 (Me), 56.0 (Me), 40.0 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 24.0 (Me), 20.9 (Me), 20.8 (Me), 16.9 (Me), 16.2 (Me), 16.1 (Me),12.4 (Me); MS (CI) 372 (MNH_4^+, 10%), 355 (10), 219 (13), 163 (100), 151 (72). Found: M + NH_4^+, 372.2535. $C_{23}H_{30}O_3$ + NH_4 requires 372.2533.

2-[5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpent-2-enyl]-1,4-benzoquinone (Panicein A and isomer; 7). To a solution of 4-methoxy-2-[5-(4-methoxy-2,3,6-trimethylphe-

nyl)-3-methylpent-2-enyl]phenol (**20**) (0.074 g, 0.209 mmol) in MeCN/H_2O (2:1, 1.5 mL) at 0 °C was added cerium ammonium nitrate (0.252 g, 0.460 mmol) in MeCN/H_2O (2:1, 1.5 mL). The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and partitioned between water (10 mL) and ethyl acetate (10 mL). The organic layer was separated and the aqueous layer further extracted with ethyl acetate (2 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:9) to afford the title compound (0.046 g, 65%) as a pale oil (lit.[30] no data) in a 3:2 (*E*:*Z*) mixture of isomers; IR ($CHCl_3$)/cm^{-1} 1660 (C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ 6.76 (0.6H, s), 6.73 (0.6H, d, J = 2.3 Hz), 6.70 (0.4H, s), 6.68 (0.4H, d, J = 2.3 Hz), 6.57 (0.6H, s), 6.56−6.53 (0.6H, m), 6.48 (0.4H, s), 6.42−6.40 (0.4H, m), 5.24 (0.6H, m), 5.18 (0.4H, m), 3.78 (1.8H, s), 3.74 (1.2H, s), 3.17 (1.2H, d, J = 7.2 Hz), 3.04 (0.8H, d, J = 7.2 Hz), 2.73−2.65 (2H, m), 2.31 (1.8H, s), 2.29 (1.2H, s), 2.23 (1.8H, s), 2.21 (1.2H, s), 2.19−2.12 (2H, m), 2.14 (1.8H, s), 2.08 (1.2H, s), 1.90 (1.2H, s), 1.75 (1.8H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 188.0 (C), 187.8 (C), 187.6 (C), 187.4 (C), 155.3 (C), 155.2 (C), 148.4 (C), 148.3 (C), 140.4 (C), 139.8 (C), 136.8 (CH), 136.6 (CH), 136.4 (CH), 136.3 (C), 136.0 (C), 135.9 (C), 133.8 (C), 133.6 (C), 132.3 (CH), 132.1 (CH), 130.6 (C), 130.3 (C), 122.8 (C), 122.8 (C), 118.6 (CH), 117.7 (CH), 110.3 (CH), 110.3 (CH), 55.5 (Me), 55.4 (Me), 39.6 (CH_2), 31.8 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 27.1 (CH_2), 23.7 (Me), 20.6 (Me), 20.4 (Me), 16.4 (Me), 15.8 (Me), 15.8 (Me), 12.0 (Me), 11.9 (Me); MS (CI) 356 (MNH_4^+, 85), 341 (70), 269 (62), 256 (53), 238 (75), 233 (100). Found: M + NH_4^+, 356.2217. $C_{22}H_{26}O_3$ + NH_4 requires 356.2220.

3-[3-(2,3-Dimethoxyphenoxy)-4-methylpent-4-enyl]furan (23). DIAD (1.22 mL, 4.52 mmol) was added to a stirred solution of triphenylphosphine (1.185 g, 4.52 mmol) in THF (15 mL) at −10 °C and the resulting solution was stirred for 10 min. 5-(3-Furyl)-2-methylpenten-3-ol (**22**) (see the Supporting Information) (0.500 g, 3.01 mmol) was added and the stirring continued for 10 min. 2,3-Dimethoxyphenol (0.26 mL, 2.01 mmol) was added and the solution was stirred for a further 2 h at −10 °C then overnight at room temperature. The reaction mixture was then diluted with ethyl acetate (20 mL) and washed with NaOH (2 M; 3 × 10 mL) and water (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:99) to give the title compound **23** (0.244 g, 40%) as a colorless oil; IR (film)/cm^{-1} 1598 (C=C); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.36 (1H, s), 7.21 (1H, s), 6.89 (1H, m), 6.53 (2H, m), 6.28 (1H, s), 4.98 (1H, m), 4.95 (1H, m), 4.56 (1H, m), 3.97 (3H, s), 3.85 (3H, s), 2.69−2.53 (2H, m), 2.22−2.10 (1H, m), 2.01−1.89 (1H, m), 1.75 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ 153.6 (C), 152.1 (C), 144.1 (C), 142.8 (CH), 139.0 (CH), 138.9 (C), 124.30 (C), 123.3 (CH), 113.3 (CH_2), 110.9 (CH), 108.7 (CH), 105.2 (CH), 81.9 (CH), 60.8 (Me), 55.9 (Me), 34.3 (CH_2), 20.9 (CH_2), 17.4 (Me); MS (CI) 303 (MH^+, 50%), 167 (21), 155 (49), 149 (100). Found: MH^+, 303.1589. $C_{18}H_{22}O_4$ + H requires 303.1596.

6-[5-(3-Furyl)-2-methylpent-2-enyl]-2,3-dimethoxyphenol (24). 3-[3-(2,3-Dimethoxyphenoxy)-4-methylpent-4-enyl]-furan (**23**) (0.233 g, 0.77 mmol) in anhydrous DMF (4 mL) in a sealed tube was heated to 180 °C for 1.75 h in a microwave reactor (300 W). The solution was then diluted with ethyl acetate (15 mL), washed with water (2 × 40 mL) and brine (10 mL), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:99) to give the title compound **24** (0.112 g, 75%) as a brown oil (mixture of isomers: cis:trans = 1:9); IR (film)/cm^{-1} 3501 (O−H); ^{1}H NMR (400 MHz; $CDCl_3$) major isomer δ 7.39−7.31 (1H, m), 7.21 (1H, s), 6.72 (1H, d, J = 8.5), 6.42 (1H, d, J = 8.5), 6.28 (1H, s), 5.85 (1H, s), 5.28−5.19 (1H, m), 3.89 (3H, s), 3.85 (3H, s), 3.26 (2H, s), 2.49−2.45 (2H, m), 2.32−2.27 (2H, m), 1.58 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) major isomer δ 150.6 (C), 147.6 (C), 142.6 (CH), 138.9 (CH), 135.4 (C), 134.8 (C), 125.2 (CH), 124.9 (C), 124.5 (CH), 119.2 (C), 111.1 (CH), 103.3 (CH), 60.9 (Me), 55.8 (Me), 38.8 (CH_2), 28.5 (CH_2), 24.9 (CH_2), 16.1 (Me); MS (CI) 303 (MH^+, 17%), 302 (M^+, 30), 167 (100), 149 (22). Found: MH^+, 303.1611. $C_{18}H_{22}O_4$ + H requires 303.1596.

(*E*)-6-[5-(3-Furyl)-2-methylpent-2-enyl]-2,3-dimethoxy-1,4-benzoquinone (isoarnebifuranone; 9). 6-[5-(3-Furyl-2-methylpent-2-enyl]-2,3-dimethoxyphenol (**24**) (0.214 g, 0.71 mmol) was dissolved in anhydrous acetonitrile (5 mL) and salcomine catalyst (0.046 g, 0.14 mmol) was added. Oxygen was bubbled through the solution for 15 min and the reaction mixture was then stirred in air at room temperature for 24 h. The reaction mixture was then filtered through Celite and washed through with ethyl acetate and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica, eluting with ethyl acetate−light petroleum (1:19) to give the title compound **9** (0.118 g, 53%) as an orange oil (lit.[38] red-orange oil) mixture of isomers (cis:trans = 1:9); IR (film)/cm^{-1} 1659 (C=O); ^{1}H NMR (400 MHz; $CDCl_3$) major isomer δ 7.34 (1H, s), 7.19 (1H, s), 6.27 (1H, s), 6.25 (1H, s), 5.31−5.22 (1H, m), 4.02 (3H, s), 3.98 (3H, s), 3.06 (2H, s), 2.49−2.44 (2H, m), 2.31−2.26 (2H, m), 1.55 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) major isomer δ 184.4 (C), 184.1 (C), 145.9 (C), 144.9 (C), 144.6 (C), 142.7 (CH), 138.8 (CH), 130.9 (CH), 130.7 (C), 128.9 (CH), 124.5 (C), 110.9 (CH), 61.3 (Me), 61.2 (Me), 37.9 (CH_2), 28.6 (CH_2), 24.7 (CH_2), 16.2 (Me); MS (CI) 317 (MH^+, 16%), 183 (100). Found: MH^+, 317.1398. $C_{18}H_{20}O_5$ + H requires 317.1389.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **1**−**4**, **5/6** (H only), **7**−**9**, **10a**−**d**, **11a** (H only), **11b**−**d**, **12a**,**b** (H only), **12c**,**d**, **13**−**15**, **16** (H only), **17**−**24**; experimental details for the preparation of pentadec-1-en-3-ol, heptadec-1-en-3-ol, 3,7-dimethyloct-6-en-1-yn-3-ol (**13**), 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methylpentyn-3-ol (**17**), (*E*)-ethyl 3-(3-furyl)propenoate, ethyl 3-(3-furyl)propanoate, 3-(3-furyl)propanal (**21**), and 5-(3-furyl)-2-methylpenten-3-ol (**22**). This material is available free of charge via the Internet at http://pubs.acs.org.

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