Synthesis of Prenylated Quinones by the Oxydative Degradation Approach. Birch vs Vinylogous Birch Hydrogenolysis (BIHY vs VIBIHY) in Controlling $^2\Delta$ Stereochemistry of the Prenyl Chain

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Two novel approaches toward prenylated quinones are described. The first (route A) involves the following three basic operations: (a) construction of a 4-hydroxybenzylamine carrying a tertiary allyl alcohol (cinnamyl alcohol) side chain of appropriate length (C_5, C_{10}, etc), followed by (b) vinylogous Birch reductive cleavage with concomitant isomerization of the double bond (vinylogous Birch hydrogenolysis, VIBIHY) and (c) Fremy's salt oxidative degradation of the resulting prenylated phenolic benzylamines to the corresponding quinones. The required phenolic cinnamyl alcohols were successfully synthesized by means of two alternative routes, namely: (1) cyclopalladation of phenolic benzylamines followed by ketovinylation and treatment of the resulting β-aryl substituted α,β unsaturated ketone with methyllithium and (2) reaction of the dilithio derivatives of the appropriate phenolic benzylamine with the desired α,β unsaturated aldehyde, followed by acid rearrangement. The key feature of this approach, namely, the so-called vinylogous Birch hydrogenolysis (VIBIHY) takes place very efficiently on the phenolic tertiary cinnamyl alcohol stage, provided that the reaction (Li/NH_3) is carried out on its bissilylated derivative. Unfortunately, its stereochemistry cannot be properly controlled, as it leads to the formation of ca. 2.5:1 (E/Z) mixture of (Δ^2) alkenes. The second generation approach (route B), which solves this problem, requires the following: (a) preparation of a 4-hydroxybenzylamine carrying a 3-methyl-2-buten-1-ol (dimethylallyl alcohol) side chain, or higher homologue, followed by (b) Birch hydrogenolysis (BIHY) and step c above. The key Birch hydrogenolysis takes place with almost complete control of the stereochemically labile Δ^2 double bond, thereby making this approach the one of choice for the synthesis of isoprenyl benzoquinones.

Having versatile and flexible routes toward prenylated quinones and related substances is still a matter of current interest for synthetic chemists, due to the key roles some of them play in living organisms[1] and also because of their often interesting pharmacological properties.[2]

As Rapoport has pointed out, control of the stereochemical integrity of the isoprenyl chain should be of uppermost concern for a synthetic chemist working in this area.[3] Accordingly, acid-catalyzed coupling of phenols and polyphenols with the appropriate polyprenyl chain precursor[4] are nowadays mostly ignored because of the problems (E,Z isomerization and side chain and/or intramolecular cyclization) that arise under these conditions. Nevertheless, for some particular cases, conditions have been found to avoid (or minimize) these undesired side reactions.[5]

Modern synthetic methodology relies, instead, on stereocontrolled cross-coupling reactions involving organometallics. Notable among the most recent developments are the following two strategies: (1) catalyzed or uncatalyzed prenylation of quinones or masked quinones[6] with allylmagnesium,[6] allylsilanes,[7] allyltin,[8] or allylnickel[9] reagents and (2) prenylation of organometallics derived from quinone synthons, which has been particularly successful for lithium,[10] tin,[11] and copper[12] reagents.

These and other methods[13] allow for attaching simple (C_5, C_{10}, C_{15}, etc.) prenyl groups ortho to an existing phenol.[14] However, an effective regioselective and stereoselective prenylation of quinones and aromatic compounds remains problematic.

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(5) Polyprenyl aryl ethers undergo BF_3-catalyzed rearrangement with high regio- and stereocontrol. Schmid, R.; Antoulas, S.; Rüttimann, A.; Schmid, M.; Vecchi, M.; Weiser, H. *Helv. Chim. Acta* **1990**, *73*, 1276. Yoshizawa, T.; Toyofuku, H.; Tachibana, K.; Kuroda, T. *Chem. Lett.* **1982**, 1131.

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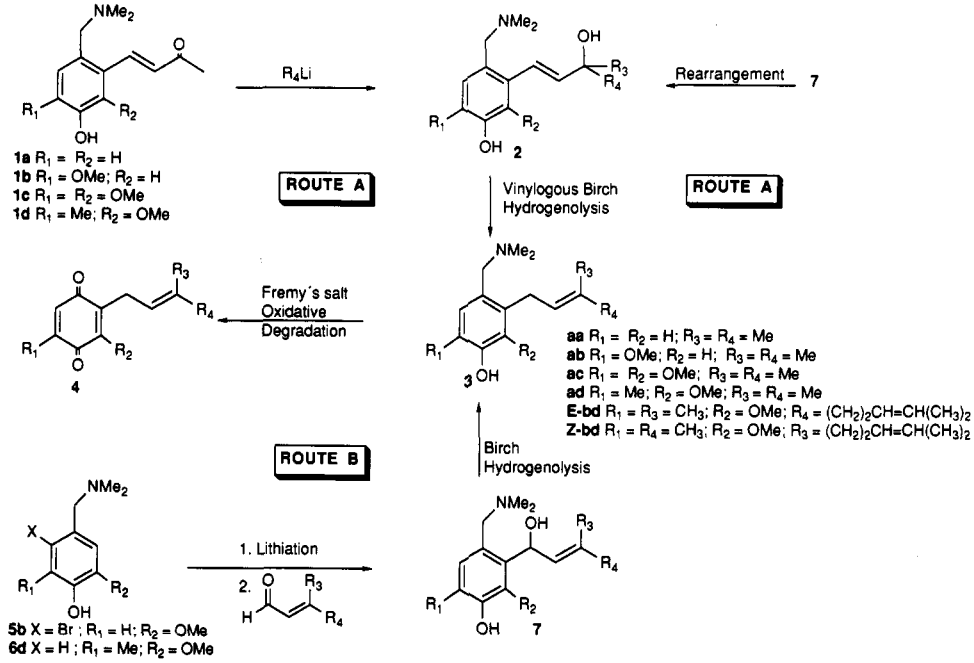
Scheme I



Our previous work on the synthesis of simple benzoquinones by the so-called oxidative degradation approach (ODA) illustrated the successful use of 4-[(dimethylamino)methyl]phenols as valuable precursors of benzoquinones.[15] The regioselective functionalization of these phenolic precursors was accomplished by the directed lithiation of the unprotected phenols,[16] but its scope was somewhat limited.[15] Accordingly, we decided to search for novel routes which would allow for the regioselective introduction of straight or modified isoprenyl chains of variable length onto the appropriate 4-hydroxybenzylamines which should provide the desired prenylated quinones by the action of Fremy's salt.

Although the aforementioned methods are acceptable for the preparation of polyprenyl quinones we have developed an efficient and flexible synthesis of polyprenylated aromatic compounds including both phenolic and nonphenolic derivatives.[17] Described herein is an account of our research on the polyprenylation of a variety of aromatic nuclei.[18]

As illustrated in Scheme I, central to our initial plan (route A) for the synthesis of prenylated quinones and aromatics were the following two objectives: (1) the regioselective introduction of the four-carbon atom chain of a methyl vinyl ketone onto our quinone synthon, namely, a 4-[(dimethylamino)methyl]phenol, followed by conversion of the resulting phenolic α,β unsaturated ketone **1** to a phenolic tertiary cinnamyl alcohol (**1** → **2**) having the desired number of side-chain carbon atoms (5, 10, 15, etc.) and (2) the reductive removal of the alcohol unit of the tertiary cinnamyl alcohols **2**, together with concomitant isomerization of the double bond, thereby furnishing the isoprenylated phenols **3**. Eventually, **3** should undergo Fremy's salt promoted oxidative degradation to provide the target isoprenylated quinones **4**.[15]

Of major concern for the overall success of the plan was the regio- and stereochemical outcome of the so-called vinylogous Birch hydrogenolysis (VIBIHY) of cinnamyl alcohols. Herein we describe that whereas regiochemistry works properly, stereochemistry at Δ^2, as expected, cannot be properly controlled by this route. Fortunately, Birch hydrogenolysis (BIHY) of the easily available, isomeric benzylallyl alcohols (α-vinyl benzyl alcohols) **7** takes place with almost complete retention of configuration at the key Δ^2 double bond, thereby providing a very simple solution to the key problem of our planned synthesis. To the best of our knowledge this strikingly different behavior of cinnamyl and benzylallyl alcohol derivatives toward Birch hydrogenolysis conditions has not hitherto been reported.

Several approaches for the preparation of the key phenolic tertiary cinnamyl alcohols **2** were devised at the outset with the purpose of widening the scope of the methodology, but only two of them worked properly, namely the cyclopalladation and the metalation methods. Unfortunately, neither one of the Pd(0)-catalyzed syntheses succeeded.[19-22] The first successful approach (cyclopalladation method) toward **2** relied, instead, on the

(13) The recently developed rearrangement of 4-alkinylcyclobutenones has been successfully applied to a number of naturally occurring quinones. See: Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 989. For the use of chromium carbene complexes for the synthesis of quinones, see: Dötz, K. H.; Kuhn, W. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 732.

(14) See, for example: (a) Murray, R. D. H.; Ballantyne, M. M.; Mathai, K. P. *Tetrahedron Lett.* **1970**, *11*, 243. (b) Mohamed, S. E. N.; Thomas, P.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1983**, 738. Dauben, W. G.; Cogen, J. M.; Behar, V. *Tetrahedron Lett.* **1990**, *23*, 3241. Glüsenkamp, K.-H.; Büchi, G. *J. Org. Chem.* **1986**, *51*, 4481.

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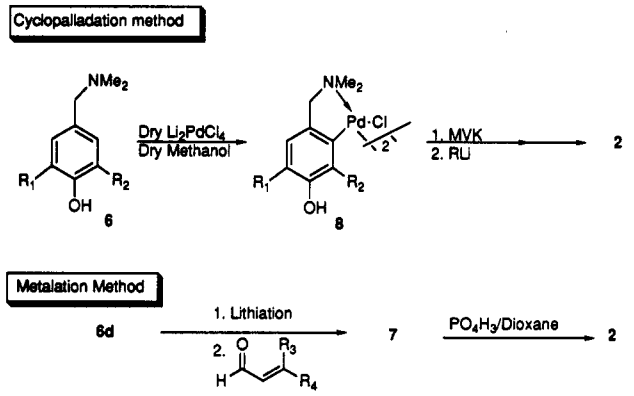
(17) For a recently published organotin-based methodology, see: Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019.

(18) A preliminary account of this work has appeared in print. See: Ballester, P.; Capó, M.; Saá, J. M. *Tetrahedron Lett.* **1990**, *31*, 1339.

(19) Pd(0)-catalyzed reaction between bromophenol **5b** and 2-methyl-3-buten-2-ol failed under either standard or phase-transfer conditions (see refs 20 and 22). The analogous reaction with *o*-iodophenols yielded chromenes. See: Garcías, X.; Ballester, P.; Saá, J. M. *Tetrahedron Lett.* **1991**, *32*, 7739 and references cited therein. On the other hand, Heck reaction (ref 21) between phenolic aryl halides (bromides or iodides) and methyl vinyl ketone also failed under standard or phase-transfer conditions (ref 22).

Scheme II



stoicheiometric use of palladium, i.e., on the cyclopalladation reaction[23] of benzylamines[24] followed by (1) ketovinylation[25] of the resulting cyclopalladated compounds and (2) treatment with methyllithium. From a mechanistic viewpoint, we anticipated that cyclopalladation would take place readily with our electron-rich substrates **6** and, hopefully, with regioselectivity.[26] Since cyclopalladation of 4-hydroxy-substituted benzylamines had not been described,[27] it was unclear where (inter- or intramolecular) palladation of these substrates would occur.

We found that the Mannich bases **6a–6d** reacted smoothly at 0 °C with an equimolar amount of commercial dried lithium tetrachloropalladate in dry methanol, in the presence of 2 equiv of sodium acetate as base. This simple operation provided the highly hindered palladated phenols **8a–8d**,[28] in medium to good isolated yields (63–85%), as shelf-stable yellow solids (if protected from light). It is worth noting in this regard that (1) the use of undried reagent and/or solvent invariably lowered the yields of the desired products and (2) the use of other palladium sources (acetate), solvents (benzene or toluene), and bases (triethyl or tributylamine) led to poorer results.

Subsequent vinylation[29] of the cyclopalladated phenolic benzylamines **8a–8d** with excess methyl vinyl ketone in cold chloroform–glacial acetic acid, in the presence of excess triethylamine, took place smoothly (24–48 h), thus providing **1a–1d** in medium to good yields.[25] Competitive protonolysis of the highly hindered σ-aryl palladium compounds was minimized but not totally avoided. Addition of methyllithium (1.6 M in hexane) to a cold benzene solution of the unsaturated ketones **1a–1d** uneventfully afforded the desired tertiary cinnamyl alcohols **2aa–2ad**.

As illustrated in Scheme I, the key step in our initial plan (route A) called for inducing reductive cleavage of the C–O bond of the tertiary cinnamyl alcohols **2** with simultaneous isomerization of the double bond. Birch early recognized that metal–ammonia-promoted hydrogenolysis of cinnamyl alcohols could be a potentially powerful method for obtaining allyl-substituted aromatics.[30] In subsequent work, he was able to demonstrate that 2,2-dimethylchrom-3-enes furnish the corresponding *o*-(dimethylallyl)phenols on treatment with lithium in liquid ammonia. In spite of the importance of these preliminary studies, this area has remained largely unexplored.[31]

Following our recent experience with hydrogenolysis of closely related phenolic benzyl alcohols,[32] compounds **2aa–2ad** were first converted into their corresponding bis(trialkylsilyl) derivatives. The crude bis-silylated material (minor amounts of starting material and monosilylated derivatives were also detected by GLC/MS in the crude extracts) was treated with lithium in liquid ammonia for a short period of time (10–15 min) followed by quenching with solid ammonium chloride. Much to our delight, ^{1}H NMR analysis of the crude reaction mixtures revealed that the only observable compounds were the desired substituted dimethylallyl phenols **3aa–3ad** (Scheme I), thus proving that the reductive isomerization of tertiary cinnamyl alcohols is a highly promising methodology for the introduction of isoprenyl side chains into aromatics. As expected,[18] stereochemistry at Δ^2 cannot be controlled (see below) in the reductive isomerization (VIBIHY) step.[33]

Fremy's salt promoted oxidative degradation of phenolic Mannich bases **3aa–3ad** under the conditions previously described[15] yielded the desired quinones **4aa–4ad** (Scheme I) in good to excellent yields. For phenolic benzylamines having larger isoprenyl chains such as **3bd** (see below) oxidation under these conditions was found to be extremely slow because of the poor solubility of **3bd** in the aqueous phase. The oxidation was significantly accelerated in the presence of a phase-transfer catalyst,[34] such as Adogen,[35] thereby furnishing **4** in good to excellent yields.

The second successful plan (metalation method) to the desired **2** derives from a series of interesting observations by Talley[36] and Rapoport.[3,10] According to Talley's report, the reaction of the dilithio derivative of 2-bromophenol with unsaturated aldehydes gives rise directly to the corresponding phenolic cinnamyl alcohols as a result of the facile acid-catalyzed rearrangement of the initially formed (not isolated) adducts. Similar behavior was also noted by Rapoport in his synthetic efforts towards menaquinone and closely related materials,[3,10] but, in this

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(27) Cyclopalladation of 3-hydroxy-4-methoxy-*N*,*N*-diethylamine has been reported. See: Holton, R. A.; Davis, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 4175.

(28) Compounds **5a** and **5d** were reluctant to give correct elemental analysis. Crystallization from acetone gave crystals shown to contain acetone by ^{1}H NMR and elemental analysis (also confirmed by X-ray).

(29) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.

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(32) Saá, J. M.; Llobera, A. *Tetrahedron Lett.* **1987**, *28*, 5045.

(33) For the complete reduction of some cinnamyl alcohols under metal–ammonia conditions (no alcohol added), see: Hall, S. S. *J. Org. Chem.* **1973**, *38*, 1738. See also: Flisak, J. R.; Hall, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 7219.

(34) Olson, G. L.; Chenng, H.-C.; Morgan, K.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 803.

(35) Adogen is a registered trademark of Ashland Chemical Co.

(36) Talley, J. J. *Synthesis* **1983**, 845.

case, the primary adduct (a naphthylallyl alcohol) was first isolated and subsequently rearranged in the presence of acid.

Both directed lithiation of phenolic benzylamines **6** and halogen–metal exchange on brominated phenolic Mannich bases **5** have been used for our purposes. Thus, directed lithiation[15] of unprotected phenolic benzylamine **6d** followed by quenching with 3-methyl-2-butenal provided the corresponding benzylallyl alcohol **7ad** as the major product (some starting material was recovered). Treatment of the crude product with phosphoric acid in dioxane furnished cinnamyl alcohol **2ad**, in quantitative yield. This two-step transformation is also applicable for the introduction of larger isoprenyl chains, as demonstrated for the reaction of the dilithio derivative of phenolic benzylamine **6d** with C_{10} α,β-unsaturated aldehydes such as the commercially available citral. The crude alcohol mixture **7*E*,*Z*-bd** when exposed to the action of phosphoric acid led to the expected trans tertiary cinnamyl alcohol **2bd** as revealed by its ^{1}H NMR. In this case, allylic isomerization was found to be somewhat slower, thereby facilitating the formation of minor byproducts of diene structure (not isolated) in the reaction mixture. Actually, all synthetic steps in this protocol were carried out with the crude reaction products, and only after Fremy's salt oxidation, the resulting quinones were purified by TLC and properly characterized. Vinylogous Birch hydrogenolysis on the bis-silylated **2b** under the above-described conditions led to an *E*/*Z* (ca. 2.4:1) mixture of prenylated phenols **3bd**. Upon Fremy's salt oxidation this mixture furnished quinones **4bd** in 15% overall yield (from **7** = **6d**) also as a c.a. 2.4:1 (70:30 = *E*:*Z*) mixture, thereby demonstrating that stereochemistry at this valuable bond cannot be properly controlled using the vinylogous Birch hydrogenolysis (VIBIHY), as was found for closely related examples.[18]

Having found that the vinylogous Birch hydrogenolysis of tertiary cinnamyl alcohols leads to *E*,*Z* mixtures of the desired prenyl derivatives, we decided to look upon the well-known Birch hydrogenolysis (BIHY) of the readily available, isomeric *E* and *Z* benzylallyl (α-vinyl benzyl) alcohols **7*E*-bd**, **7*Z*-bd** as an alternative approach to reach the prenylated phenolic benzylamines (route B, Scheme I).

To our delight, when the bis-silylated derivatives of benzyl alcohols **7*E*-bd**, **7*Z*-bd**, and **7*E*,*Z*-bd**, obtained by quenching of the dilithio derivative of **6d** with geranial, neral, or commercial citral, were subjected to Birch hydrogenolysis, followed by Fremy's salt promoted oxidative degradation, the corresponding prenylated quinones (*E*)-**4bd** and (*Z*)-**4bd** were obtained in acceptable (25–30%) overall yield. More interesting, Birch hydrogenolysis took place with almost complete control of stereochemistry as demonstrated by ^{1}H NMR and ^{13}C NMR spectroscopy on the isolated quinones **4bd**. Mainly one stereoisomer was isolated for both the case of geranyl (>90% *E* pure) and neryl (>85% *Z* pure) side chains. In this regard it should be kept in mind that the stereochemical purity of geranial and neral employed was found to be 95% and 90%, respectively, as determined by integration of their ^{1}H NMR spectra.

We have also prepared benzylallyl alcohols by means of dilithio derivatives of phenolic benzylamines generated by halogen–metal exchange on appropriate precursors. Thus, bromophenol **5b** when treated with excess *n*-BuLi at 0 °C followed by quenching with commercial 3-methyl-2-butenal afforded benzylallyl alcohol **7ab**.[37] The crude material from silylation of **7ab** was submitted to Birch hydrogenolysis conditions, thereby yielding **3ab**. Fremy's salt oxidation provided the expected quinone **4ab**, which was purified at this stage, in an 10–15% overall yield starting from bromophenol **5**. It is worth noting that, when impure, quinone **4ab** is very sensitive and needs to be prepared and handled with care.

The high stereoselectivity of the BIHY process is most surprising in light of the low stereoselectivity of the VIBIHY process. We refrain at this point to offer mechanistic explanations to these and other questions until clear-cut evidence is available.

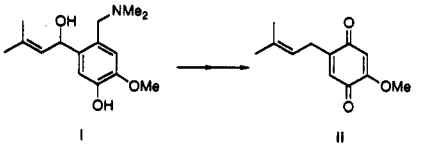
Although only a limited number of representative examples have been examined to date, route B is the one of choice for the stereocontrolled synthesis of prenylated quinones. This approach may also be of use for the preparation of prenyl-substituted aromatics and related substances. Ironically, in their synthetic work toward menaquinones, Rapoport and co-workers[3] decided to abandon a closely related route due to the difficulties found (isomerization of the Δ^2 double bond) in achieving clean hydrogenolysis of naphthylallyl alcohols by using lithium aluminum hydride/aluminum trichloride.

In summary, two novel approaches leading to prenylated quinones are now at hand. The cornerstone of our first approach, namely the vinylogous Birch hydrogenolysis (VIBIHY) of phenolic tertiary cinnamyl alcohols, yields the corresponding isoprenylated phenols in a very efficient manner. Its major disadvantage is the control of stereochemistry at the most precious double bond (Δ^2) of the isoprenyl chain. This, however, can be overcome by recourse to our second generation approach which involves Birch hydrogenolysis (BIHY) of the easily available, isomeric benzylallyl alcohols. The latter reaction takes place with almost complete control of stereochemistry (retention of configuration) at the sensitive Δ^2 double bond. Studies directed at understanding this, in principle,[38] striking result are now in progress.

Experimental Section

General Methods. All melting points are uncorrected and were taken on a capillary melting point apparatus. Proton NMR spectra were obtained at 80, 200, or 300 MHz in $CDCl_3$ with TMS as internal standard, unless otherwise noted. Electron impact mass spectra were recorded at 70 eV ionizing energy. Column chromatographies were performed on Merck silica gel (Kieselgel 40). TLC was performed on silica plates purchased from Scharlau (Glasschrom Si F_{254} 0.5 mm). Phenolic benzylamines **7a–7d** were obtained by straightforward procedures.[13] Commercial Li_2PdCl_4 was dried at 100 °C, under vacuo, for 24 h. The resulting purple red material was kept in a desiccator prior to use for cyclopalladations (see below). Geranial and neral were prepared from the corresponding commercial alcohols (Aldrich) by Swern

(37) Under these conditions the expected isomeric benzylallyl alcohol **i** was detected as a minor product (<10%) in the reaction mixture by ^{1}H NMR. After the full sequence of operations was carried out, its structure was further confirmed by isolation of the corresponding quinone **ii**, previously obtained by us. See ref 15.



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(38) Gassman, P. G.; Singleton, D. A.; Kageshita, H. *J. Am. Chem. Soc.* **1991**, *113*, 6271.

oxidation,[40] and their purity was checked by ^1H NMR and ^{13}C NMR spectroscopy.

THF was distilled from sodium benzophenone ketyl. Dry methanol was obtained by refluxing with a limited amount of sodium and subsequent distillation.[39] Organolithium reagents purchased from Fluka were used as received. All operations involving organolithium compounds were carried out under Ar.

The standard workup procedure employed throughout involved extraction of the aqueous solution with three to five 25-mL portions of CH_2Cl_2 or Et_2O, followed by drying of the organic phases over Na_2SO_4 and evaporation in vacuo. The residue was usually flash chromatographed on silica gel prior to crystallization or bulb-to-bulb distillation.

Unless otherwise noted, the purity of new compounds for which combustion analysis could not be obtained was judged to be ≥90% on the basis of its ^1H NMR spectrum (available as supplementary material).

Route A. Preparation of Phenolic Tertiary Cinnamyl Alcohols 2 by the Cyclopalladation Method. General Procedure. To a cooled (0 °C) suspension of dried Li_2PdCl_4 (0.35 g, 1.34 mmol) in dry methanol (5 mL), under Ar, was added a methanol (5 mL, dry) solution containing sodium acetate (0.225 g, 2.7 mmol) and the suitable *p*-hydroxybenzylamine **6** (1.36 mmol) via syringe. After 10 min the ice bath was removed and the mixture stirred at rt for another 24 h. During this time the cyclopalladated compounds **8** separated from the reaction mixture as a precipitate, which was then filtered and washed with cold methanol (3 × 3 mL).

Cyclopalladated phenols **8a–8d** have been obtained using this procedure. Physical and spectroscopic data are provided as supplementary material.

The cyclopalladated benzylamines **8** (0.35 g, 0.54 mmol) were suspended in a mixture of glacial acetic acid (3 mL) and $CHCl_3$ (1 mL), cooled at 0 °C. TEA (0.28 g, 2.77 mmol) and MVK (0.21 g, 3 mmol) were sequentially added to the above suspension. The resulting mixture was held at 0 °C for 10 min, warmed to and stirred at rt for 24–48 h, and protected from light (flask wrapped with aluminum foil). Palladium black precipitated during this period of time. The reaction mixture was then filtered with suction through Celite, the column being washed with a saturated solution of $NaHCO_3$ (10 mL) and $CHCl_3$ (5 mL). The filtrate was concentrated to eliminate most of the acetic acid. The concentrate was basified with $NaHCO_3$ and extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on a silica gel column (or plate) using ether–triethylamine (9:1) as eluent. This operation afforded pure aryl-substituted methyl vinyl ketones **1** which were then bulb-to-bulb distilled.

β-Aryl-substituted methyl ketones **1a–1d** have been obtained using this procedure. Physical and spectroscopic data are provided as supplementary material.

A solution (hexanes) of MeLi (1.1 M, 3.2 mL, 3.5 mmol) was added, via syringe, to a benzene solution (10 mL) of β-aryl-substituted vinyl ketones **1** (1 mmol), cooled to 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h protected from light. Brine (5 mL) and 5% HCl (10 mL) were sequentially added. The aqueous layer was washed twice with ether (2 × 20 mL), basified with solid $NaHCO_3$ and extracted three times with ether (3 × 20 mL). The standard workup yielded crude tertiary cinnamyl alcohols **2** of sufficient purity to use in subsequent reactions. Analytical samples were obtained by distillation or crystallization.

3-(3′-Hydroxy-3′-methylbutenyl)-4-[(dimethylamino)-methyl]phenol (2aa). Colorless oil, bp 187–192 °C (0.12 mmHg). ^1H NMR: 7.03 (d, J = 8.1 Hz, 1 H), 6.87 (d, J = 16 Hz, 1 H), 6.77 (broad s, 1 H), 6.59 (dd, J = 8, 2.3 Hz, 1 H), 6.04 (d, J = 16 Hz, 1 H), 3.42 (s, 2 H), 2.25 (s, 6 H), 1.34 (s, 6 H) ppm. ^{13}C NMR: 156.09, 138.89, 137.92, 132.36, 126.46, 123.56, 114.86, 112.92, 70.99, 60.92, 44.87 (2 C), 29.42 (2 C) ppm. IR (film): 3500–3100 (broad), 2960, 2870, 2810, 2780, 1685, 1600, 1580, 1460, 1450, 1360, 1290, 1240, 1160 cm^{-1}. MS *m/e* (%): 235 (M^+, 5), 234 (3), 220 (2), 192 (1), 177 (13), 176 (100), 161 (8), 133 (65). HRMS: calcd for $C_{14}H_{21}O_2N$ 235.1572, obsd 235.1564.

5-(3′-Hydroxy-3′-methylbutenyl)-2-methoxy-4-[(dimethylamino)methyl]phenol (2ab). Colorless oil, bp 210–212 °C (0.12 mmHg). ^1H NMR: 7.01 (s, 1 H), 6.80 (s, 1 H), 6.42 (d, J = 15.8 Hz, 1 H), 6.03 (d, J = 15.8 Hz, 1 H), 3.86 (s, 3 H), 3.39 (s, 2 H), 2.23 (s, 6 H), 1.40 (s, 6 H) ppm. ^{13}C NMR: 146.12, 145.01, 137.78, 129.91, 127.03, 123.04, 112.98, 112.02, 70.74, 60.58, 55.80, 44.90 (2 C), 29.73 (2 C) ppm. IR (film): 3445–3150 (broad), 2860, 2820, 2780, 1605, 1580, 1510, 1500, 1470, 1450, 1445, 1360, 1250, 1145, 1100 cm^{-1}. MS *m/e*: 265 (M^+, 15), 206 (100), 163 (62), 149 (25), 131 (32), 103 (13), 59 (45). HRMS: calcd for $C_{15}H_{23}O_3N$ 265.1677, obsd 265.1672.

3-(3′-Hydroxy-3′-methylbutenyl)-2,6-dimethoxy-4-[(dimethylamino)methyl]phenol (2ac). Isolated as a colorless solid, mp 78–80 °C. ^1H NMR: 6.74 (s, 1 H), 6.68 (d, J = 16.3 Hz, 1 H), 6.29 (d, J = 16.3 Hz, 1 H), 3.89 (s, 3 H), 3.75 (s, 3 H), 3.41 (s, 2 H), 2.26 (s, 6 H), 1.43 (s, 6 H) ppm. ^{13}C NMR: 146.07, 145.25, 142.27, 137.78, 127.41, 123.91, 119.17, 109.06, 70.89, 61.27, 59.66, 55.94, 44.91 (2 C), 29.58 (2 C) ppm. IR (CCl_4): 3560, 2980, 2965, 2825, 2780, 1610, 1490, 1460, 1300, 1170, cm^{-1}. MS *m/e*: 295 (M^+, 15), 236 (66), 193 (100), 178 (23), 161 (22). HRMS: calcd for $C_{16}H_{25}O_4N$ 295.1783, obsd 295.1783.

3-(3′-Hydroxy-3′-methylbutenyl)-2-methoxy-4-[(dimethylamino)methyl]-6-methylphenol (2ad). Isolated as a colorless solid, mp 91–3 °C. ^1H NMR: 6.81 (s, 1 H), 6.75 (d, J = 16.4 Hz, 1 H), 6.38 (d, J = 16.4 Hz, 1 H), 3.70 (s, 3 H), 3.43 (s, 2 H), 2.29 (s, 6 H), 2.22 (s, 3 H), 1.43 (s, 6 H) ppm. ^{13}C NMR: 146.31, 144.50, 142.65, 128.34, 128.00, 127.56, 122.62, 119.60, 70.97, 61.64, 59.84, 45.00 (2 C), 29.60 (2 C), 15.31 ppm. IR (film): 3570–3150, 2960, 2930, 2860, 2820, 2780, 1610, 1460, 1360, 1300, 1240 cm^{-1}. MS *m/e*: 279 (M^+, 9), 220 (54), 177 (39), 162 (12), 145 (27), 71 (20), 59 (82), 43 (100). HRMS: calcd for $C_{16}H_{25}O_3N$ 279.1834, obsd 279.1819.

Vinylogous Birch Hydrogenolysis. Preparation of Prenylated Phenolic Benzylamines 3. General Procedure. Silylation Procedure. Freshly distilled trimethylchlorosilane (3 mmol) was added to a solution of the tertiary cinnamyl alcohols **2** (1 mmol) in anhydrous THF (3 mL) and TEA (3 mL). The mixture, protected from light with an aluminum foil, was stirred for 2 h at rt. Brine (10 mL) was added and the aqueous layer extracted with ether (3 × 20 mL). The standard workup furnished crude benzylamines **2**, which were used without further purification for the following step.

Lithium/Ammonia Reaction. Small pieces of lithium wire (6 mmol, 42 mg) washed with hexanes were placed in a three-necked round-bottomed flask, cooled to −78 °C, and equipped with a dry ice condenser and an argon inlet. As ammonia (10 mL) was distilled into the flask a dark blue solution immediately formed. The crude bis-silylated derivatives of benzylamines **2** obtained in the previous step were dissolved in THF (5 mL) and added via syringe to the above solution. Stirring was maintained for 15 min at −78 °C. The reaction was then quenched by addition of solid NH_4Cl until the blue color disappeared. Ammonia was allowed to evaporate in the hood, and the solid residue was dissolved in brine (10 mL). The standard workup yielded crude **3** of sufficient purity to use in the subsequent oxidation step. Analytically pure samples were obtained by chromatography (TLC) on commercial silica gel plates (ether–triethylamine (9:1)) followed by bulb-to-bulb distillation.

3-(3′-Methyl-2′-butenyl)-4-[(dimethylamino)methyl]phenol (3aa). Isolated in 55% yield as a colorless oil, bp 170–2 °C. ^1H NMR: 7.11 (d, J = 7 Hz, 1 H), 6.63 (s, 1 H), 6.59 (d, J = 7 Hz, 1 H), 5.23 (broad t, J = 7.1 Hz, 1 H), 3.40 (d, J = 7.1 Hz, 2 H), 3.37 (s, 2 H), 2.26 (s, 6 H), 1.74 (s, 6 H) ppm. IR (film): 3600–3100 (broad), 2985, 2855, 1610, 1580, 1560, 1460, 1450, 1330, 1320, 1250, 840 cm^{-1}. MS *m/e*: 219 (M^+, 3), 174 (48), 159 (100). HRMS: calcd for signal $C_{12}H_{14}O$ 174.1049, obsd 174.1044.

2-Methoxy-5-(3′-methyl-2′-butenyl)-4-[(dimethylamino)-methyl]phenol (3ab). Isolated in 62% yield as a colorless oil, bp 140–2 °C. ^1H NMR: 6.89 (s, 1 H), 6.72 (s, 1 H), 5.19 (broad t, J = 7.8 Hz, 1 H), 3.84 (s, 3 H), 3.32 (s, 2 H), 3.29 (d, J = 7.8 Hz, 2 H), 2.22 (s, 6 H), 1.71 (bs, 6 H) ppm. ^{13}C NMR: 144.74 (2 C), 133.49, 131.68, 126.90, 123.29, 115.39, 112.91, 60.31, 55.84, 44.86 (2 C), 30.52, 25.48, 17.67 ppm. IR (film): 3530–3200 (broad), 2960, 2850, 2820, 1610, 1570, 1510, 1470, 1450, 1290, 1250, 1090,

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(40) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

1020, 840 cm^{-1}. MS *m/e*: 249 (M$^+$, 3), 204 (77), 189 (100), 178 (40). HRMS: calcd for $C_{15}H_{23}NO_2$ 249.1681, obsd 249.1676.

2,6-Dimethoxy-3-(3′-methyl-2′-butenyl)-4-[(dimethylamino)methyl]phenol (3ac). Isolated in 43% yield as a colorless oil, bp 156–160 °C (0.15 mmHg). ^{1}H NMR: 6.73 (s, 1 H), 5.05 (broad t, J = 7.6 Hz, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.34 (s, 2 H), 3.39 (d, J = 7.6 Hz, 2 H), 2.24 (s, 6 H), 1.78 (bs, 3 H), 1.68 (bs, 3 H) ppm. ^{13}C NMR: 145.44, 137.63, 130.41, 127.57, 126.94, 123.81 (2 C), 108.40, 60.87, 60.29, 55.94, 45.15 (2 C), 25.43, 24.59, 17.71 ppm. IR (CCl_4): 3525, 2960, 2920, 2840, 2805, 2725, 1610, 1510, 1490, 1460, 1305, 1235, 1115, 1020 cm^{-1}. MS *m/e*: 279 (M$^+$, 3), 234 (87), 219 (100), 187 (48), 159 (24). HRMS: calcd for $C_{16}H_{25}NO_3$ 279.1834, obsd 279.1829.

2-Methoxy-3-(3′-methyl-2′-butenyl)-4-[(dimethylamino)-methyl]-6-methylphenol (3ad). Isolated in 43% yield as a colorless oil, bp 140–2 °C (0.15 mmHg). ^{1}H NMR: 6.82 (s, 1 H), 5.17 (broad t, J = 6.1 Hz, 1 H), 3.75 (s, 3 H), 3.45 (d, J = 6.1 Hz, 2 H), 3.27 (s, 2 H), 2.21 (s, 9 H), 1.77 (bs, 3 H), 1.68 (bs, 3 H) ppm. ^{13}C NMR: 147.88, 146.81, 132.75, 132.30, 129.67, 125.17, 123.62, 62.34 (2 C), 46.52 (2 C), 26.85, 26.45, 16.65, 16.27 ppm. IR (film): 3550–3100 (broad), 2965, 2930, 2860, 2805, 2780, 1580, 1485, 1460, 1420, 1370, 1305, 1070 cm^{-1}. MS *m/e*: 263 (M$^+$, 1), 218 (12), 203 (17), 171 (13), 153 (100), 125 (43), 110 (73). HRMS: calcd for signal $C_{14}H_{18}O_2$ 218.1307, obsd 218.1305.

Preparation of Prenylated Quinones 4 by Fremy's Salt Oxidative Degradation of 3. General Procedure. Method A. As previously described.[15] **Method B.** Adogen (a catalytic amount) and 2 mL of a buffered (pH = 5.7) solution (6.5 mL of 2 M Na_2HPO_4 and 93.5 mL of 2 M NaH_2PO_4) of Fremy's salt was added to a solution of **3** (1 mmol) in Cl_2CH_2 (2 mL). The reaction mixture was vigorously stirred at rt until no starting material was detected by TLC. The standard workup yielded crude benzoquinones **4**. Purification by TLC on silica gel (hexanes–ethyl acetate (9:1)) afforded pure isoprenyl quinones **4**.

2-(3′-Methyl-2′-butenyl)-1,4-benzoquinone (4aa). Isolated in 75% yield as a yellow solid, mp 30–2 °C (lit.[41] mp 30.5 °C). ^{1}H NMR ($CDCl_3$): 6.70 (s, 1 H), 6.67 (d, J = 10 Hz, 1 H), 6.47 (dt, J = 1 and 1.5 Hz, 1 H), 3.09 (m, 2 H), 5.15 (m, 1 H), 1.77 (m, 3 H), 1.68 (m, 3 H). IR (film): 3320, 3280, 1665, 1603, 1300, 903 cm^{-1}.

2-Methoxy-5-(3′-methyl-2′-butenyl)-1,4-benzoquinone (4ab). Isolated in 80% yield as a yellow solid, mp 106–8 °C. ^{1}H NMR: 6.46 (t, J = 1.7 Hz, 1 H), 5.91 (s, 1 H), 5.12 (broad t, J = 7 Hz, 1 H), 3.81 (s, 3 H), 3.11 (broad d, J = 7 Hz, 2 H), 1.74–1.50 (m, 6 H) ppm. IR (film): 1660, 1645, 1595, 1480, 1360, 1205, 970, 890, 867 cm^{-1}. MS *m/e* 206 (M$^+$, 35), 191 (100), 177 (32), 163 (26), 135 (12), 95 (18), 69 (100). HRMS: calcd for $C_{12}H_{14}O_3$ 206.0943, obsd 206.0936.

2,6-Dimethoxy-3-(3′-methyl-2′-butenyl)-1,4-benzoquinone (4ac). Isolated in 73% yield as a yellow oil, bp 75–81 °C (0.12 mmHg). ^{1}H NMR: 5.82 (s, 1 H), 5.04 (broad t, J = 7.5 Hz, 1 H), 3.96 (s, 3 H), 3.79 (s, 3 H), 3.14 (broad d, J = 7.5 Hz, 2 H), 1.73 (s, 3 H), 1.67 (s, 3 H) ppm. ^{13}C NMR: 186.99, 186.81, 157.17, 153.91, 133.51, 132.57, 119.84, 106.78, 60.76, 56.19, 25.57, 22.50, 17.68 ppm. IR (film): 2920, 2840, 1675, 1640, 1595, 1455, 1440, 1300, 1270, 1230, 1180, 1100 cm^{-1}. MS *m/e*: 236 (M$^+$, 50), 221 (100), 193 (73), 181 (39). HRMS: calcd for $C_{13}H_{16}O_4$ 236.1058, obsd 236.1053.

2-Methoxy-3-(3′-methyl-2′-butenyl)-6-methyl-1,4-benzoquinone (4ad). Isolated in 86% yield as a yellow oil, bp 47–49 °C (0.12 mmHg). ^{1}H NMR: 6.49 (q, J = 1.6 Hz, 1 H), 5.05 (broad t, J = 7.6 Hz, 1 H), 3.98 (s, 3 H), 3.11 (broad d, J = 7.6 Hz, 2 H), 2.01 (d, J = 1.6 Hz, 3 H), 1.72 (broad s, 3 H), 1.65 (broad s, 3 H) ppm. ^{13}C NMR: 187.63, 184.00, 155.50, 143.46, 133.21, 132.97, 131.79, 119.96, 60.64, 25.48, 22.19, 17.55, 15.01 ppm. IR (film): 2910, 1655, 1600, 1440, 1380, 1360, 1330, 1290, 1280, 1205, 1095, 915, 890 cm^{-1}. MS *m/e*: 220 (M$^+$, 14), 205 (36) 191 (14), 190 (31), 177 (42), 167 (31), 149 (100). HRMS: calcd for $C_{13}H_{16}O_3$ 220.1099, obsd 220.1086.

Preparation of Prenylated Benzoquinones 4ad and (*E,Z*)-4bd by the Metalation Method. General Procedure. A solution of phenolic benzylamine **6d** (0.195 g, 1 mmol) in anhydrous THF (1 mL), at 0 °C, was treated with excess commercial *n*-BuLi (2.5 M, 1.2 mL, 3 mmol). After 10 min the ice–water bath was removed and the reaction stirred for another 2 h. To the resulting brownish solution of the dilithio derivative, cooled to 0 °C, was added excess (3 mmol) 3-methyl-2-butenal or commercial citral (68:32 *E/Z* mixture) and the mixture stirred for an additional 3 h. The standard extractive workup with ether yielded crude benzylallyl alcohols **7ad** (extraction at pH = 8 gives best results) and (*E,Z*)-**7bd** (extraction at pH = 14 gives best results), respectively.

The crude benzyl alcohols **7ad** and (*E,Z*)-**7bd**, without further purification, were isomerized to the corresponding cinnamyl alcohols **2ad** and **2bd** by treating a solution of those in dioxane (10 mL) with commercial 85% phosphoric acid (2 mL). Stirring was continued for 4 h. Water was added, followed by solid $NaCO_3H$ until pH = 8–9 was reached. The standard extractive workup yielded crude **2ad** and **2bd**. Without any further purification these compounds were submitted first to the vinylogous Birch hydrogenolysis protocol and then to Fremy's salt oxidative degradation as shown above. The resulting quinones **4** were purified by thin-layer chromatography on commercial silica gel using hexanes–ethyl acetate (9:1)) as eluant.

2-Methoxy-3-(3′-methyl-2′-butenyl)-6-methyl-1,4-benzoquinone (4ad). Isolated in 20% overall yield from **6d**. Yellow oil, bp 47–49 °C (0.12 mmHg). All spectroscopic data were identical to those of **4ad** above.

(2′*E,Z*)-2-Methoxy-3-(3′,7′-dimethyl-2′,6′-octadienyl)-6-methyl-1,4-benzoquinone ((*E,Z*)-4bd). Isolated as a yellow oil in 10% overall yield from **6d**. All spectroscopic data were found to be identical to those of (*E*)-**4bd** and (*Z*)-**4bd**. Integration of the ^{1}H NMR signals at 5.04 and 5.14 ppm (or those at 3.97 ppm) revealed this to be a ca. 70:30 mixture of (*E*)-**4bd** and (*Z*)-**4bd**, respectively.

Route B. Preparation of Prenylated Benzoquinones 4ab, 4ad, (*E*)-4bd, (*Z*)-4bd, and (*E,Z*)-4bd. General Procedure. By Directed Metalation of Phenols. The dilithio derivative of **6d** prepared as described above was treated with an excess (3 mmol) of either commercial 3-methyl-2-butenal, commercial citral (68:32 *E/Z* mixture), geranial (95:5 *E/Z* mixture), or neral (10:90 *E/Z* mixture). The standard extractive workup with ether yielded crude benzylallyl alcohols **7ad** (extraction at pH = 8 gives best results), (*E*)-**7bd**, (*Z*)-**7bd**, and (*E,Z*)-**7bd** (extraction at pH = 14 for the latter three compounds), respectively.

The crude benzylallyl alcohols, without further purification, were submitted to the silylating conditions described above. The resulting crude bis-silylated materials were submitted, without purification, to Birch hydrogenolysis under identical conditions to those described above for the vinylogous Birch hydrogenolysis, thereby giving rise to the expected crude prenylated phenolic benzylamines **3ad**, (*E*)-**3bd**, (*Z*)-**3bd**, and (*E,Z*)-**3bd**, which were then submitted to Fremy's salt oxidative degradation as shown above. The crude prenylated quinones **4** thus obtained were purified by chromatography on commercial silica gel plates (hexanes–ethyl acetate (9:1)).

By Halogen–Metal Exchange of Bromophenols. A solution of bromophenol **5b** (0.26 g, 1 mmol) in anhydrous THF (1 mL), at 0 °C was treated with excess commercial *n*-BuLi (2.2 M, 1.4 mL, 3 mmol). After 10 min the ice–water bath was removed, and the reaction continued to stir for another 2 h. The resulting yellow solution of the dilithio derivative was cooled to 0 °C. To this solution excess (3 mmol) 3-methyl-2-butenal was added and the mixture stirred for an additional 3 h. The standard extractive workup yielded crude benzylallyl alcohol **7ab** which was then submitted to the same protocol as above. The crude benzoquinone **4ab** (do not concentrate to dryness when impure) was purified by chromatography on precoated plates.

2-Methoxy-5-(3′-methyl-2′-butenyl)-1,4-benzoquinone (4ab). This compound was obtained as a yellow solid, mp 106–8 °C, in 10% overall yield from **5**. Its spectroscopic data were identical to those described above.

2-Methoxy-3-(3′-methyl-2′-butenyl)-6-methyl-1,4-benzoquinone (4ad). Isolated in 30% overall yield from **6d**. Yellow oil, bp 47–49 °C (0.12 mmHg). All spectroscopic data were identical to those of **4ad** above.

(2′*E*)-2-Methoxy-3-(3′,7′-dimethyl-2′,6′-octadienyl)-6-methyl-1,4-benzoquinone ((*E*)-4bd). Isolated as a yellow oil in 32% overall yield from **6d**. Integration of the ^{1}H NMR signals

(41) Bohlmann, F.; Kleine, K. M. *Chem. Ber.* **1966**, *99*, 885.

at 5.04 and 5.14 ppm (or those at 3.97 ppm) revealed this to be a ca. 94:6 mixture of (*E*)-**4bd** and (*Z*)-**4bd**, respectively. ^{1}H NMR ($CDCl_3$): 6.50 (q, J = 1.5 Hz, 1 H), 5.04 (m, 2 H), 3.97 (s, 3 H), 3.12 (d, J = 7.2 Hz, 2 H), 2.1–1.9 (m, 4 H), 2.02 (d, J = 1.5 Hz, 3 H), 1.72 (d, J = 1.2 Hz, 3 H), 1.64 (d, J = 1.2 Hz, 3 H), 1.57 (br s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): 187.89, 184.21, 155.51, 143.60, 137.03, 133.09, 132.08, 131.38, 124.10, 119.87, 60.89, 39.66, 26.45, 25.64, 22.23, 17.62, 16.09, 15.32 ppm. IR (film): 2985, 2965, 2930, 1670, 1660, 1635, 1610, 1445, 1380, 1360, 1335, 1300, 1280, 1210, 1180, 1095, 1075, 1060, 930, 890, 690 cm^{-1}. MS *m/e*: 288 (M^+, 13), 273 (11), 245 (55), 217 (23), 205 (100), 187 (87), 177 (26), 159 (44), 123 (45), 117 (88), 91 (64), 67 (75). HRMS: calcd for $C_{18}H_{24}O_3$ 288.1725, obsd 288.1723.

(2′*Z*)-2-Methoxy-3-(3′,7′-dimethyl-2′,6′-octadienyl)-6-methyl-1,4-benzoquinone ((*Z*)-4bd). Isolated as a yellow oil in 33% overall yield from **6d**. Integration of the ^{1}H NMR signals at 5.04 and 5.14 ppm (or those at 3.97 ppm) revealed this to be a ca. 14:86 mixture of (*E*)-**4bd** and (*Z*)-**4bd**, respectively. ^{1}H NMR ($CDCl_3$): 6.49 (q, J = 1.65 Hz, 1 H), 5.14 (m, 1 H), 5.03 (m, 1 h), 3.97 (s, 3 H), 3.12 (d, J = 7.2 Hz, 2 H), 2.2–1.7 (m, 4 H), 2.00 (d, J = 1.65 Hz, 3 H), 1.68 (br s, 3 H), 1.65 (d, J = 1.2 Hz, 3 H), 1.62 (br s, 3 H), ppm. ^{13}C NMR ($CDCl_3$): 187.84, 184.20, 155.48, 143.57, 137.22, 133.08, 131.87, 131.60, 124.21, 120.53, 60.88, 31.85, 26.51, 25.69, 23.36, 22.03, 17.62, 15.32 ppm. IR (film): 2985, 2965, 2930, 1670, 1660, 1635, 1610, 1445, 1380, 1360, 1335, 1300, 1280, 1210, 1180, 1095, 1075, 1060, 930, 890, 690 cm^{-1}. HRMS: calculated for $C_{18}H_{24}O_3$ 288.1725, obsd 288.1714.

(2′*E*,*Z*)-2-Methoxy-3-(3′,7′-dimethyl-2′,6′-octadienyl)-6-methyl-1,4-benzoquinone ((*E*,*Z*)-4bd). Isolated as a yellow oil in 25% overall yield from **6d**. All spectroscopic data were found to be identical to those of (*E*)-**4bd** and (*Z*)-**4bd**. Integration of the ^{1}H NMR signals at 5.04 and 5.14 ppm (or those at 3.97 ppm) revealed this to be a ca 68:32 *E*/*Z* mixture.

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Supplementary Material Available: Physical and spectroscopic data of **1a–1d** and **8a–8d** and ^{1}H and/or ^{13}C NMR spectra of compounds **1a**, **1b**, **1c**, **1d**, **2aa**, **2ab**, **2ac**, **2ad**, **3aa**, **3ab**, **3ac**, **3ad**, **4ab**, **4ac**, **4ad**, (*E*)-**4db**, (*Z*)-**4db**, and (*E*,*Z*)-**4db** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.