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INTRAMOLECULAR CYCLIZATION OF 2'-OLEFINIC SIDE-CHAINS ON ANODICALLY OXIDIZED 4-PHENYLPHENOLS. THE EFFECT OF OLEFIN SUBSTITUENTS ON CARBON-CARBON BOND FORMATION

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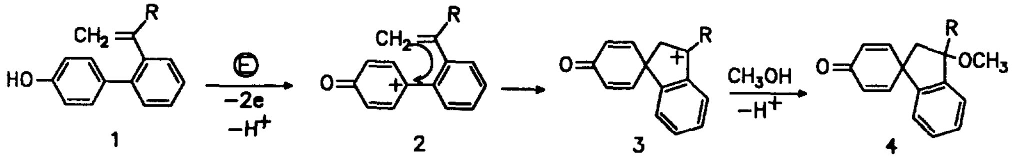
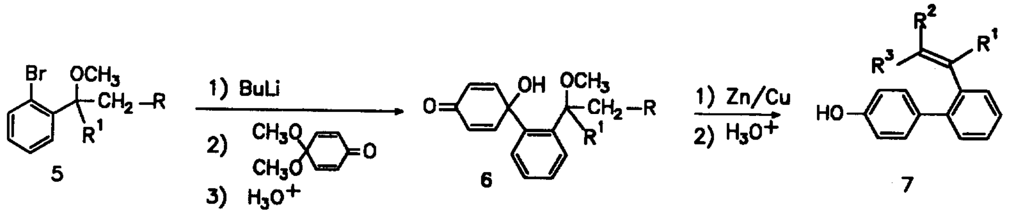
Summary: The anodic oxidation of 4-(2'-alkenylphenyl)phenols in acetonitrile/methanol affords spirodienones arising from cyclization of the olefinic side-chain to the 4-position of the phenol and reaction of the resulting benzylic cation with methanol. The efficiency of this carbon-carbon bond-forming reaction is dependent upon the olefinic substituents.

Anodic oxidation of oxygen- and nitrogen-substituted aromatic systems often serves as a very useful method for preparing compounds not conveniently available via conventional chemistry, e.g., 1,4-dimethoxy aromatics to quinone bisketals[1] and anilides to acylated quinone imine ketals.[2] However, except for some phenolic coupling reactions[3] and cycloadditions,[4] carbon-carbon bond-forming reactions arising from anodic oxidation of aromatic systems have not been extensively developed. We chose to study the anodic oxidation of 4-(2'-alkenylphenyl)phenols, **1**, as a model system for anodic carbon-carbon bond-forming reactions (see Scheme I).[5] This choice was based on several considerations. First, the proximity of the 2-alkenyl group to the 4-position of the phenol would maximize opportunity for carbon-carbon bond formation between the terminal carbon of the alkene and the reactive intermediate generated from the phenol oxidation (i.e., **2**). Second, a good intramolecular reaction could hopefully compete with known processes arising from phenol oxidation:[3,6] dimerization and reaction of nucleophilic solvents at the *o*- and *p*-positions of the phenol. Finally, the carbon-carbon bond would result in formation of spirofused-2,5-cyclohexadienones--compounds which would be useful synthetic intermediates to the many natural products which contain this type of quaternary carbon-carbon bond. In this paper we report the details of our initial studies on this new carbon-carbon bond-forming reaction.



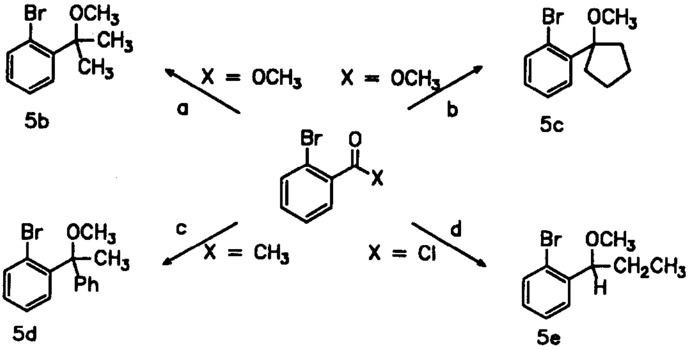
Scheme I. Carbon-Carbon Bond Formation from Anodic Oxidation of 4-(2'-Alkenylphenyl)phenols

The compounds used for investigating this anodic oxidation chemistry were prepared via the chemistry outlined in general form in Scheme II. The key synthetic step is reaction of the lithium derivative



Scheme II. The General Route to 4-(2'-Alkenylphenyl)phenols from Benzoquinone Monoketal

derived from a functionalized *o*-bromoaromatic compound with 4,4-dimethoxycyclohexa-2,5-dienone.[7] The resulting quinol ketal was hydrolyzed to the quinol **6**, which was reduced to the biphenyl ether using zinc/copper couple.[7b] Acid-catalyzed elimination of methanol from the methyl ether furnished the olefin **7**. The 4,4-dimethoxycyclohexa-2,5-dienone is easily available from anodic oxidation of 1,4-dimethoxybenzene followed by mild acid hydrolysis.[7] Scheme III details the preparation of the *o*-bromoaromatic compounds. This chemistry not only furnished the compounds required for this study but also serves as a general route to functionalized 4-phenylphenols.



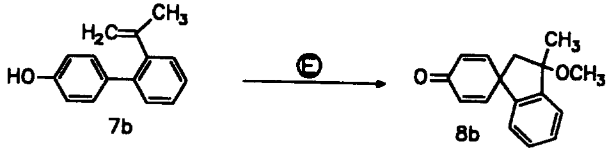
a. CH_3MgBr (2 equiv); NaH; CH_3I (42% overall). b. $BrMgCH_2CH_2CH_2CH_2MgBr$; NaH; CH_3I (57% overall). c. PhMgBr; NaH; CH_3I (27% overall). d. Et_2AlCl (1 equiv); $NaBH_4$; NaH; CH_3I (71% overall).

Scheme III. Preparation of Functionalized *o*-Bromobenzene Derivatives

Our initial investigations focused on the anodic oxidation of **7b** under a variety of experimental conditions; the most pertinent results from this research are presented in Table I. The first series of these oxidations were conducted using a platinum anode and a copper wire cathode (entries 1-7), and this study established several important variables in this reaction. The yield for the cyclization product **8b** is a function of the solvent system (entry 1 vs. 7), current density (entries 4-7), and anode material (entry 3). A mild acidic medium is especially beneficial to the yield of **8b** (compare entry 1 vs. 6 and 7). The increased yield of spirodienone in acidic media may be due to suppression of phenolic coupling processes.[8] These experiments established that high yields of spirodienones can be obtained from the oxidation of 4-(2'-alkenylphenyl)phenols under well-defined experimental conditions.

Later in our studies it was established that the yield of the cyclization product could be slightly improved by substituting a platinum wire for the copper cathode. As indicated by entries 8-12, this change affords a somewhat higher yield of **8b** and a cleaner reaction mixture. However, the beneficial effect of a slightly acidic media and the dependence of product yield on current density were also noted when using the platinum wire cathode. Thus, the most favorable conditions for performing this anodic carbon-carbon bond-forming reaction involve anodic oxidation in slightly acidic media using a platinum anode, platinum cathode, and current densities of about 1 mA/cm^2.

Table I. Effect of Experimental Variables on the Yields of Anodic Cyclization of 7b[a,b]



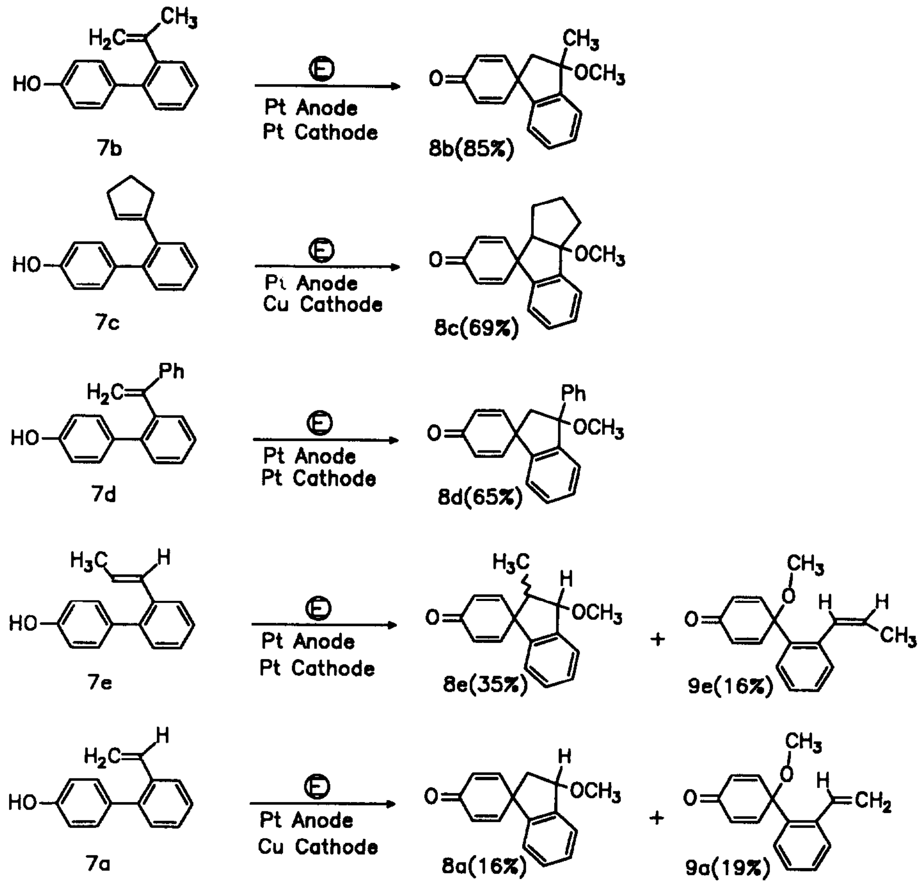
Entry	Solvent	Current Dens. (mA/cm^2)	Anode	Cathode	Additive	Yield (HPLC) (%)
1	CH_3OH	0.84	Pt	Cu	none	38
2	CH_3OH	0.84	Pt	Cu	2,6-lutidine	29
3	CH_3OH	0.84	C	Cu	AcOH (5 equiv)	37
4	CH_3CN/CH_3OH (4:1)	6.72	Pt	Cu	AcOH (5 equiv)	13
5	CH_3CN/CH_3OH (4:1)	3.40	Pt	Cu	AcOH (5 equiv)	26
6	CH_3CN/CH_3OH (4:1)	1.70	Pt	Cu	AcOH (5 equiv)	76
7	CH_3CN/CH_3OH (4:1)	0.84	Pt	Cu	AcOH (5 equiv)	83
8	CH_3OH	0.84	Pt	Pt	none	73
9	CH_3CN/CH_3OH (4:1)	0.84	Pt	Pt	AcOH (5 equiv)	91
10	CH_3CN/CH_3OH (4:1)	0.84	Pt	Pt	AcOH (10 equiv)	94
11	CH_3CN/CH_3OH (4:1)	0.84	Pt	Pt	AcOH (30 equiv)	97
12	CH_3CN/CH_3OH (4:1)	8.40	Pt	Pt	AcOH (5 equiv)	44
13	CH_3CN/CH_3OH (4:1)	0.84	Pt	Pt	KOH (5 equiv)	0

a. Oxidations were performed until > 95% of the starting phenol had reacted and current efficiencies were generally 70-90%. b. The concentrations of [**7b**] were 3-4 x 10^{-3} M.

Having established conditions for the high-yield anodic cyclization **7b** → **8b**, the effect of olefinic substituents on the yield of the spirodienone was investigated: these results are collected in Table II. Some of this work was done with a copper wire cathode; the yields for these reactions would probably be improved if a platinum cathode were used. Most surprising was the dramatic dependence of the spirodienone yield on olefin substitution. As shown in Table II, the cyclization proceeds in good yield for compounds in which the double bond is substituted at the benzylic carbon. Terminal substitution as in **7e** also favors cyclization versus 1,4-addition, as the **cis** and **trans** products of **8e** are produced in greater yield than the 1,4-addition product **9e**. However, the yield of both types of products is only about 50%. For the unsubstituted system **7a**, the reaction leads to a poor accounting of material and equal amounts of **8a** and **9a**.

Under these solvent/electrolyte conditions, the limitation of the **7** → **8** transformation may be related to the nucleophilicity of the alkenyl side-chain and/or the stabilization of the resulting benzylic carbonium ion (see Scheme I). For compounds **7b**, **7c**, **7d**, and **7e**, which have at least one substituent at the benzylic carbon, the cyclization yields are good. Even a terminal methyl substituent appears to favor the cyclization product. However, the unsubstituted compound **7a** gave a poor yield of cyclization product under a variety of reaction conditions.

Table II. Anodic Oxidation of 4-(2'-Alkenylphenyl)phenols



In all of these oxidations, the crude weight recovery was good, but for reactions involving **7a,e** the remaining material was a mixture of higher molecular weight products. Phenolic coupling and solvent addition at the *o*-position of the phenol are two reactions probably competing with the production of **8** and **9**. Higher molecular weight phenolic coupling products would be difficult to characterize. In addition, anodic addition of solvent at the 2-position, followed by aromatization and further oxidation would yield an *o*-quinone monoketal. The *o*-quinone monoketal moiety, unless appropriately substituted, is known to be unstable.[9] Thus, formation of either or both of these products[5] could be responsible for the low accounting of material for some of these systems.

This study establishes that intramolecular nucleophilic capture of the reactive intermediate generated from anodic oxidation of *p*-aryl phenols leads to formation of the spirodienones of structure **8**. This reaction proceeds in good yield with alkenyl groups substituted at the benzylic carbon. Without this substitution, other unknown reactions constitute the major reaction pathway. The formation of quaternary carbon-carbon bonds between an aryl ring and an alkenyl substituent is rare and could have important synthetic implications. Although the strategy outlined in Scheme I has lead to a successful carbon-carbon bond-forming reaction, this portrayal of the reaction should be regarded as tentative. Since the system is conjugated, the chemistry could be viewed as intramolecular attack of the phenol portion of the molecule on an anodically oxidized styrene moiety. Further experimental work is required before details of the reaction can be more clearly defined. Future efforts will focus on effecting this transformation in high yield for compounds having less nucleophilic side chains and the bimolecular version of this reaction using both *p*-alkyl- and *p*-arylphenols.

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Experimental Section

General Procedures. Melting points were determined in capillaries in a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Infrared spectra (IR) were determined on a Perkin-Elmer Model 283B spectrometer. Unless stated otherwise ^{1}H nuclear magnetic resonance spectra (NMR, signals reported in ppm) were determined at 80 MHz on an IBM NR 80 spectrometer using deutereochloroform as solvent and residual chloroform as standard. All ^{13}C NMR spectra were determined at 20 MHz on the above instrument. Spectra at 200 MHz were determined on a Bruker AC-200 Spectrometer. Mass spectral and exact mass measurements were obtained by Mr. Richard Weisenberger on a Kratos MS-30 spectrometer connected to a DS-55 data system. High pressure liquid chromatography analyses (HPLC) were conducted using an Altec Model 110-A pump, a 10 cm x 250 cm Lichrosorb SI-60 column and an Altec Model 153 Analytical UV detector at 254 nm or an IBM Model 9560 Analytical HPLC using a 4.5 x 250 mm C_{18} reverse-phase column with detection at 260 nm. Trifluorotoluene was used as internal standard for analyses involving **7b** with 70% CH_3OH/H_2O as eluant. Combustion analyses were performed by Scandanavian Microanalytical Laboratory, Herlev, Denmark. All reagents or compounds not explicitly referenced were obtained from the Aldrich Chemical Co. Alumina and silica gel were obtained from E. Merck Co. Tetrahydrofuran (THF) was purified by distillation from benzophenone ketyl. Throughout the experimental the following abbreviations are used: PE (petroleum ether, bp 35-60 °C), *p*-TsOH (*p*-toluenesulfonic acid), and TLC (thin-layer chromatography).

Preparation of 5b. To a 1.0 M ethereal solution of methyl magnesium iodide (214 mmol) prepared in the usual fashion was added over 30 min dropwise methyl 2-bromobenzoate (20.0 g, 93.0 mmol) in Et_2O (50 mL), and the resulting mixture was stirred for 16 h at room temperature. After hydrolysis with a saturated NH_4Cl solution (75 mL), extractive workup and distillation gave the alcohol (9.5 grams, 48%) as a water-white oil, bp 95-100 °C/0.4 mm Hg: IR (neat, cm^{-1}) 3600-3300 (br, m), 2990 (m), 1470 (m), 1430 (m), 1370 (m), 1270 (m), 1170 (m), 1120 (m), 950 (m), 755 (m), 725 (m); ^{1}H NMR (80 MHz) δ 7.7-7.0

(highly struc m, 4 H), 2.78 (s, 1 H), 1.75 (s, 6 H); mass spectrum, exact mass calcd for $C_9H_{11}OBr$ *m/e* 213.9993, obsd 214.0002.

To a suspension of NaH [60% by wt in mineral oil (2.7 g, 66 mmol)] in THF (50 mL) was added the product from above (9.5 g, 44 mmol) in THF (30 mL), and the resulting mixture was stirred and heated at reflux for 16 h. Next, methyl iodide (12.5 g, 5.5 mL) was added dropwise, and the resulting mixture was heated at reflux for 2 h. After cooling, the reaction was quenched by addition of water (25 mL). Extractive workup and distillation gave **5b** (8.8 g, 87%) as a clear oil, bp 82-85 °C/0.45 mm Hg: IR (neat, cm^{-1}) 3000 (m), 2942 (m), 2880 (m), 1472 (m), 1430 (m), 1387 (m), 1370 (m), 1280 (m), 1250 (m), 1180 (s), 1080 (s), 1025 (s), 760 (s), 730 (m), 650 (m); ^{1}H NMR (80 MHz) δ 7.58-7.18 (struc m, 4 H), 3.10 (s, 3 H), 1.67 (s, 6 H); mass spectrum, exact mass calcd for $C_{10}H_{13}OBr$ *m/e* 228.0149, obsd 228.0134.

Preparation of 5c. To the Grignard reagent of 1,4-dibromobutane[10] (11.4 g, 5.3 mmol) prepared in the usual fashion in THF (130 mL) was added over 30 min a solution of methyl-2-bromobenzoate (10.0 g, 46.0 mmol) in THF (40 mL) at 0 °C, and the resulting mixture was stirred for an additional 2 h. The reaction was hydrolyzed by addition of saturated NH_4Cl (75 mL). Extractive workup gave the crude carbinol (11.0 g) which was used without further purification in the next step. The carbinol was dissolved in THF (30 mL) and added to a suspension of NaH [60% by wt. in mineral oil (3.0 g, 75.0 mmol)] in THF (50 mL), and the mixture was heated at reflux for 2 h. Methyl iodide (6.2 mL) was added, and heating was continued for an additional 2 h, after which time the reaction mixture was poured into H_2O (50 mL). Extractive workup and distillation gave **5c** (6.7 g, 57%) as a water-white oil, bp 105-110 °C/0.5 mm Hg: IR (neat, cm^{-1}) 2970 (br, s), 2882 (m), 2830 (m), 1470 (m), 1437 (m), 1120 (m), 1070 (br, s), 1025 (m), 785 (m); ^{1}H NMR (80 MHz) δ 7.7-7.0 (struc m, 4 H), 2.9 (br s, 3 H), 2.7-1.6 (highly struc m, 8 H); mass spectrum, exact mass calcd for $C_{12}H_{15}OBr$ *m/e* 254.0306, obsd 254.0289.

Preparation of 5d. To a solution of phenyl magnesium bromide (16.6 mmol) prepared in the usual fashion in THF (10 mL) was added dropwise 2'-bromoacetophenone[11] (3.0 g, 15.1 mmol) in THF (5 mL). The resulting mixture was heated at reflux for 2 h and cooled to room temperature, and the reaction was quenched by addition of saturated NH_4Cl solution (10 mL). Extractive workup gave the crude carbinol (3.4 g). This material was dissolved in dry THF (10 mL), and added to a suspension of NaH [0.91 g of 60% by wt in mineral oil, washed with hexane (3 x 5 mL)] in THF (15 mL), and the resulting mixture was stirred at reflux for 2 h. Methyl iodide (1.9 mL) was added and heating was continued for an additional 2 h. Extractive workup gave a dark oil (2.9 g) which was chromatographed on silica gel (6" x 1/2" column, hexane as eluant) to give **5d** (1.08 g, 27% overall) as a water-white oil: IR (neat, cm^{-1}) 2980 (m), 2940 (m), 1465 (m), 1450 (m), 1430 (m), 1130 (m), 1090 (br, m), 1060 (m), 1020 (m), 752 (s), 695 (s); ^{1}H NMR (80 MHz) δ 7.8-7.0 (struc m, 4 H), 7.25 (br s, 5 H), 3.07 (s, 3 H), 1.94 (s, 3 H); mass spectrum, exact mass calcd for $C_{15}H_{15}OBr$ *m/e* 290.0306, obsd 290.0304.

Preparation of 5e. To a solution of 2-bromobenzoic acid chloride (12 g, 55 mmol) in toluene (100 mL) at 0 °C was added dropwise over 20 min a solution of diethylaluminum chloride (55 mL of a 1 M solution in hexane). The resulting solution was stirred at room temperature for 2 h, and then the reaction was quenched by addition of H_2O (15 mL). Extractive workup using $CHCl_3$ gave a brown oil, which was purified by a Kugelrohr distillation (80-100 °C bath/0.5 mm Hg) to afford *o*-bromopropiophenone[12] as a clear oil (10.29 g, 88%).

To a solution of this product (9.78 g, 46 mmol) in EtOH/H_2O (3:1, 150 mL) was added a slurry of $NaBH_4$ (2.92 g, 92 mmol) in EtOH (150 mL). The resulting suspension was stirred at room temperature for 3 h, then concentrated in vacuo. Extractive workup using $CHCl_3$ gave a clear oil, which was then purified by a Kugelrohr distillation (60-80 °C bath/ 0.6 mm Hg) to afford the alcohol as a clear oil (8.98 g, 91%): IR (neat, cm^{-1}) 3340 (s, br), 2958 (s), 2922 (m), 1462 (s), 1435 (s), 1041 (m), 1013 (s), 968 (s), 742 (s); ^{1}H NMR (200 MHz) δ 7.55-7.06 (m, 4 H), 5.04-4.96 (m, 1 H), 1.97-1.95 (d, J = 3.6 Hz, 1 H), 1.93- 1.62 (m, 2 H), 1.03-0.95 (t, J = 7.4 Hz, 3 H); exact mass calcd for $C_9H_{11}OBr$ *m/e* 215.9973, obsd 215.9970.

To a suspension of NaH [60% dispersion in mineral oil (3.2 g, 80 mmol)] in THF (150 mL) was added a solution of the alcohol (8.1 g, 39 mmol) in THF (50 mL). The resulting solution was stirred and heated at reflux for 5 h and then was cooled to room temperature. A solution of CH_3I (11.4 g, 80 mmol) in THF (25 mL) was then added via a syringe, and the resulting mixture was stirred at room temperature for 14 h. Extractive workup using $CHCl_3$ gave a light yellow clear oil (9.3 g) as the crude product. This product was purified via a Kugelrohr distillation (60-80 °C bath/0.6 mm Hg) to give pure **5e** as a clear oil (8.0 g, 89%): IR (neat, cm^{-1}) 2958 (s), 2922 (s), 2863 (m), 1460 (s), 1430 (s), 1350 (m), 1115 (s), 1102 (s), 1075 (s), 1013 (s), 743 (s); H^{1}NMR (200 MHz, $CDCl_3$) δ 7.53-7.06 (m, 4 H), 4.53-4.47 (m, 1 H), 3.22 (s, 3 H), 1.73-1.61 (m, 2 H), 0.9 (t, J = 7.4 Hz, 3 H); exact mass calcd for $C_{10}H_{13}OBr$ *m/e* 228.0150, obsd 228.0137.

Preparation of 7a. To a solution of 2'-bromostyrene (4.0 g, 21.9 mmol) in THF (60 mL) at -78 °C was added dropwise over 10 min *n*-BuLi (15 mL of a 1.6 M solution), and the resulting mixture was stirred at this temperature for 3 h. Next, a solution of 4,4-dimethoxy-2,5-cyclohexadienone (3.4 g, 3.0 mL) in THF (15 mL) was added dropwise over 10 min, and the resulting solution was stirred for 1 h at -78 °C and then allowed to warm to room temperature over 16 h. The reaction was then quenched by addition of 5% HOAc (25 mL), and the mixture was stirred for 30 min. Extractive workup gave the crude *p*-quinol (4.5 g) which was dissolved in THF (26 mL) and added to a suspension of zinc-copper couple (2.6 g) in 5% HOAc (26 mL), and the mixture was stirred and heated to reflux for 1 h. Extractive workup gave a thick orange oil which was chromatographed on silica gel (8" x 1" column, CH_2Cl_2 as eluant) to give **14** (2.27 g, 53% overall) as a clear oil: IR (neat, cm^{-1}) 3600-3150 (br, m), 1620 (m), 1520 (m), 1480 (m), 1260 (m), 1230 (br, m), 1180 (m), 910 (m), 838 (m), 760 (m); ^1H NMR (80 MHz) δ 7.8-7.2 (m, 6 H), 7.0-6.5 (AB overlapping X component of AMX, 3 H), 5.7 (d of d, J = 1.5, 17.5 Hz, 1 H), 5.18 (d of d of AMX, J = 1.5, 11 Hz, 1 H), 4.7 (br s, 1 H); mass spectrum, exact mass calcd for $C_{14}H_{12}O$ *m/e* 196.0888, obsd 196.0892.

Preparation of 7b. To a -78 °C solution of **5b** from above (8.5 g, 37.0 mmol) in THF (125 mL) was added dropwise over 10 min *n*-BuLi (25.5 mL of a 1.6 M solution). The resulting mixture was stirred at this temperature for 3 h, then a solution of 4,4-dimethoxy-2,5-cyclohexadienone (5.7 g, 5.15 mL) in THF (15 mL) was added dropwise over 15 min. After being stirred for 1 h at -78 °C, the reaction mixture was allowed to warm to room temperature over 16 h, and the reaction was then quenched by adding a saturated NH_4Cl solution (50 mL). The material obtained from extractive workup was dissolved in $(CH_3)_2CO$ (350 mL), 5% HOAc (60 mL) was added, and the mixture was stored at 0 °C overnight. The bulk of the solvent was removed in vacuo, and the residue was poured into a saturated $NaHCO_3$ solution (50 mL). Extractive workup CH_2Cl_2 (3 x 75 mL) gave the *p*-quinol (9.5 g, 99%) suitable for use in the next step.

The *p*-quinol from above was dissolved in THF (50 mL) and was added to a suspension of zinc-copper couple (4.5 g) in 5% HOAc (50 mL), and the resulting mixture was heated at reflux for 1 h. After being cooled, the mixture was poured into 5% HCl (50 mL). Extractive workup gave the phenol ether (8.4 g, 94%) as a light tan solid, mp 134-137 °C, which was deemed suitable for use in the next step without further purification. Recrystallization of a portion from Et_2O/PE gave the analytical sample as white needles: mp 143.5-145 °C; IR (KBr, cm^{-1}) 3280-3190 (br, m), 1520 (m), 1480 (m), 1440 (m), 1265 (m), 1230 (m), 1160 (m), 840 (m), 765 (m); ^1H NMR (80 MHz) δ 7.6-7.2 (m, 4 H), 6.9 (AB q, $\Delta\nu$ = 28 Hz, J_{AB} = 9 Hz, 4 H), 5.19 (s, 1 H), 3.04 (s, 3 H), 1.36 (s, 6H); mass spectrum, exact mass calcd for $C_{16}H_{18}O_2$ *m/e* 242.1337, obsd 242.1322.

The *p*-arylphenol methyl ether from above (2.3 g, 9.5 mmol) was dissolved in $CHCl_3$ (150 mL), *p*-TsOH (0.04 g) was added, the mixture was heated to reflux for 20 min, and then the reaction mixture was poured into a saturated $NaHCO_3$ solution (50 mL). Extractive workup and chromatography on silica gel (6" x 1/2" column, CH_2Cl_2 as eluant) gave **7b** (1.6 g, 80%) as a crystalline solid: mp 65-66 °C; IR (neat, cm^{-1}) 3600-3150 (br, m), 1600 (m), 1520 (m), 1485 (m), 1250 (br, m), 1180 (m), 840 (m), 760 (m); ^1H NMR (80 MHz) δ 7.19 (s, 4 H), 6.9 (AB q, $\Delta\nu$ = 38 Hz, J_{AB} = 9 H), 4.96 (d of d, further coupled, 2 H), 1.59 (br s, 3 H); mass spectrum, exact mass calcd for $C_{15}H_{14}O$ *m/e* 210.1044, obsd 210.1044.

Preparation of 7c. To a solution of **5c** (2.5 g, 10.0 mmol) in THF (25 mL) at -78 °C was added dropwise *n*-BuLi (6.4 mL of a 1.4 M solution), and the resulting milky yellow solution was stirred for 1 h. Next, a solution of 4,4-dimethoxy-2,5-cyclohexadienone (1.4 mL) in THF (5 mL) was added dropwise, and the mixture was stirred at -78 °C for 2 h and then allowed to warm to room temperature over 16 h. The reaction was quenched by addition of saturated NH_4Cl (10 mL). The crude product obtained from extractive workup was dissolved in $(CH_3)_2CO$ (75 mL), 5% HOAc (15 mL) was added, and the mixture was stored at 0 °C for 16 h to effect the hydrolysis to the *p*-quinol. The mixture was then poured into saturated $NaHCO_3$ (50 mL). Extractive workup gave the crude quinol which was then dissolved in THF (13 mL) and added to a suspension of zinc-copper couple (1.2 g) in 5% HOAc. This mixture was heated at reflux for 1 h and then poured into 5% HCl (50 mL). Extractive workup gave an oil which was chromatographed on silica gel (6" x 1/2" column, 4:1 PE/EtOAc as eluant). The *p*-arylphenol methyl ether (0.565 g, 21% overall) was obtained as a white solid, mp 139-143 °C, suitable for use in the next step. Repeated crystallization from Et_2O/PE gave the analytical sample: mp 157-158.5 °C; IR (KBr, cm^{-1}) 3500-3200 (br, m), 1521 (m), 1271 (m), 1228 (m), 1050 (m), 770 (m); ^1H NMR (80 MHz) δ 7.5-7.3 (struc m, 4 H), 7.0 (AB q, $\Delta\nu$ = 31 Hz, J_{AB} = 8 Hz with lower-field component partially obscured, 4 H), 4.88 (br s, 1 H), 3.0 (s, 3 H), 2.2-1.4 (m, 8 H); mass spectrum, exact mass calcd for $C_{18}H_{20}O_2$ *m/e* 268.1474, obsd 268.1481.

The *p*-aryl phenol methyl ether (2.33 g, 8.7 mmol) was dissolved in $CHCl_3$ (150 mL) containing *p*-TsOH (0.035 g), the solution was stirred and heated at reflux for 20 min, and then the mixture was poured into saturated $NaHCO_3$ (50 mL). Extractive workup and rapid chromatography of the crude product on silica gel (4" x 1/2" column, CH_2Cl_2 as eluant) gave **7c** (1.56 g, 76%) as a waxy white solid, mp 105-108 °C, suitable for use in the next step. Recrystallization of a portion from Et_2O/PE gave the analytically pure material: mp 107.5-109 °C; IR (KBr, cm^{-1}) 3400-3100 (br, m), 1520 (m), 1455 (m), 1250 (s), 835 (m), 758 (m); ^1H NMR (80 MHz) δ 7.2 (s, 4 H), 6.95 (AB q, $\Delta\nu$ = 44 Hz, J_{AB} = 9 Hz, with lower-field component partially obscured, 4 H), 5.55 (m, 1 H), 4.66 (s, 1 H), 2.5-1.5 (m, 6 H): mass spectrum, exact mass calcd for $C_{17}H_{16}O$ *m/e* 236.1201, obsd 236.1217.

Preparation of 7d. To a solution of **5d** (1.04 g, 3.57 mmol) in THF (15 mL) at -78 °C was added dropwise over 10 min *n*-BuLi (2.6 mL of a 1.45 M solution). After being stirred for an additional 2 h, a solution of 4,4-dimethoxy-2,5-cyclohexadienone (0.55 g) in THF (5 mL) was added dropwise, and the resulting mixture was stirred at -78 °C for 1 h and then allowed to warm to room temperature over 12 h. Extractive workup gave a white foam which was dissolved in THF (5 mL); 5% HOAc was added (5 mL), followed by addition of zinc-copper couple (0.5 g). The mixture was stirred and heated at reflux for 1 h. Extractive workup and chromatography on silica gel (6" x 1/2" column, 1:1 Et_2O/hexane as eluant) gave 0.325 g, (30% overall), mp 152-155 °C. Recrystallization of a portion from Et_2O/hexane gave the analytical sample: mp 155-157 °C; IR (KBr, cm^{-1}) 3320 (m), 1615 (m), 1518 (m), 1278 (m), 1212 (m), 1079 (m), 1060 (m), 829 (m), 765 (m), 700 (m); ^1H NMR (80 MHz) δ 7.9-6.8 (m, 9 H), 6.46 (s, 4 H), 4.52 (s, 1 H), 3.04 (s, 3 H), 1.70 (s, 3 H); mass spectrum, exact mass calcd for $C_{21}H_{20}O_2$ *m/e* 304.1463, obsd 304.1463.

To a solution of the above *p*-phenylphenol methyl ether (0.285 g, 0.937 mmol) in $CHCl_3$ (75 mL) was added *p*-TsOH (10 mg), and the resulting mixture was heated at reflux for 1 h. Extractive workup and chromatography on silica gel (6" x 1/2" column, CH_2Cl_2 as eluant) gave **7d** (0.242 g, 95%) as a clear oil: IR (neat, cm^{-1}) 3500-3300 (br, m), 1612 (m), 1518 (m), 1448 (m), 1121 (m), 830 (m), 760 (m); ^1H NMR (80 MHz) δ 7.42 (s, 4 H), 7.16 (s, 5 H), 6.9 (AB q, $\Delta\nu$ = 41 Hz, J_{AB} = 9 Hz, 4 H), 5.65 (d, J = 1 Hz, 1 H), 5.28 (d, J = 1 Hz, 1 H), 5.09 (s, 1 H); mass spectrum, exact mass calcd for $C_{20}H_{16}O$ *m/e* 272.1201. obsd 272.1205.

Preparation of 7e. To a solution of **5e** (5.0 g, 21.7 mmol) and THF (80 mL) at -78 °C was added dropwise a solution of n-BuLi (9.0 mL of a 2.4 M solution). The resulting solution was stirred at -78 °C for 40 min, then a solution of 4,4-dimethoxy-2,5-cyclohexadienone (3.35 g, 21.7 mmol) in THF (20 mL) was added dropwise over 5 min. After stirring at this temperature for 1 h the reaction was warmed to room temperature and stirred overnight. After addition of H_2O (15 mL), extractive workup gave a solid (7.61 g) which was chromatographed on silica gel (1" x 10 " column, 5-12% Et_2O/hexane, then 12-50 % EtOAc/hexane as eluant) to afford pure quinol (4.99 g, 89%): mp: 200.5-201.5 °C; IR (KBr, cm^{-1}) 3280 (s, br), 2958 (s), 2922 (s), 1670 (s), 1625 (m), 1445 (m), 1385 (s), 1100 (s), 1070 (s), 1056 (m), 1030 (m), 956 (s), 908 (s), 856 (s), 776 (s); H^1NMR (200 MHz) δ 7.47-6.91 (m, 6 H), 6.27-6.22 (m, 2 H), 4.55 (m, 1 H), 3.94 (s, 1 H), 3.25 (s, 3 H), 1.92-1.61 (m, 2 H), 1.00 - 0.92 (t, J = 7.4 Hz, 3 H).

The above *p*-quinol (0.45 g, 1.8 mmol) in THF (30 mL) and 5% HOAc (28 mL) was added to a suspension of zinc/copper couple (0.36 g, 2.8 mmol) in THF (10 mL), and the solution was heated at reflux for 1 h. Extractive workup gave a light brown solid which was chromatographed on silica gel (8" x 0.2 " column, 10% EtOAc/hexane as eluant) to afford the phenol as a white crystalline solid (0.391 g, 88%): mp 134.5-135.5 °C; IR (KBr, cm^{-1}) 3252 (s, br), 2962 (m), 2928 (m), 1614 (m), 1538 (s), 1478 (s), 1464 (m), 1443 (m), 1270 (s), 1215 (s), 1170 (m), 1098 (m), 1060 (s), 930 (m), 912 (m), 840 (m), 818 (m), 765 (s); ^1H NMR (200 MHz) δ 7.51-7.1 (m, 6 H), 6.87-6.83 (m, 2 H), 5.15 (s, 1 H), 4.22 - 4.15 (m, 1 H), 3.11 (s, 3 H), 1.75-1.59 (m, 2 H), 0.82-0.74 (t, J = 7.4 Hz, 3 H); exact mass calcd for $C_{16}H_{18}O_2$ *m/e* 242.1307, obsd 242.1336.

The *p*-arylphenol methyl ether (0.380 g, 1.57 mmol) was dissolved in toluene (130 mL), *p*-TsOH (50 mg) was added, and the mixture was heated at reflux for 8 h. The cooled reaction mixture was then poured into sat. $NaHCO_3$ (50 mL). Extractive workup gave crude **7e** (0.384 g) which was chromatographed on silica gel column (10" x 0.2" column, 10% EtOAc/hexane as eluant) to give **7e** as a white crystalline solid (0.311 g, 94%): mp 100-101 °C; IR (KBr, cm^{-1}) 3212 (s, br), 3018 (m), 1612 (m), 1592 (m), 1515 (s), 1476 (s), 1436 (m), 1237 (s), 1173 (m), 958 (m), 824 (s), 752 (m); H^1NMR (200 MHz) δ 7.57-6.86 (m, 8 H), 6.42-6.34 (q of d, J = 15.7, 1.4 Hz, 1 H), 6.24-6.10 (q of d, J = 15.7, 6.4 Hz, 1 H), 4.76 (s, 1 H), 1.83-1.79 (d of d, J = 6.4, 1.4 Hz, 3 H); exact mass calcd for $C_{15}H_{14}O$ *m/e* 210.1045, obsd 210.1045.

Anodic Oxidations. These constant-current oxidations employed a Kepco Model JQE 0-36V direct-current power supply. The anode in all cases was a cylindrical, perforated platinum sheet (4.8 cm x 2.5 cm diameter) with an estimated surface area of 60 cm^2. Using a current of 0.05 A corresponded to a current density of 0.84 mA/cm^2. The cathode was either a coil of copper wire ($\simeq$ 2.5 cm length) or a platinum wire (approx. 2 cm length) as specified. All anodic oxidations were performed at 0-10 °C. The current efficiencies are based on the theoretical number of coulombs required to consume the starting phenol and are probably only accurate to ± 15%.

Anodic Oxidation of 7a. A solution of **7a** (0.5 g, 2.55 mmol) in 4:1 CH_3CN/CH_3OH (300 mL) containing HOAc (0.75 mL) and 1% by wt. $LiClO_4$ as electrolyte was anodically oxidized at 0 °C in a single cell with a perforated cylindrical platinum *sheet anode and copper wire cathode at a constant current of 0.05 A for 290 min (57% current efficiency).* The analysis indicated that the reaction was not clean, giving two major products plus numerous UV-active spots and material remaining at the origin.

Extractive workup and chromatography on silica gel (6" x 1/2" column, 10% Et_2O/hexane as eluant) gave **9a** (0.11 g, 19%) as a clear oil: IR (KBr, cm^{-1}) 2930 (m), 1671 (s), 1623 (s), 1478 (m), 1389 (m), 1261 (m), 1164 (m), 1060 (m), 939 (m), 915 (m), 852 (m), 761 (s); ^{1}H NMR δ 7.53-7.18 (m, 5 H), 6.65 (AB q, J = 10 Hz, $\Delta\nu$ 43 Hz, 4H), 5.47 (d of d, J = 16, 1.5 Hz, 1H), 5.24 (d of d, J = 11, 1.6 Hz, 1 H), 3.33 (s, 3 H); exact mass calcd for $C_{15}H_{14}O_2$ *m/e* 226.0994, obsd 226.0989.

Concentration of subsequent fractions afforded the spirodienone **8a** (0.095 g, 16%) as a light yellow oil: IR (neat, cm^{-1}) 1675 (s), 1635 (m), 1095 (m), 860 (m), 760 (m); ^{1}H NMR (80 MHz) δ 7.5-6.0 (struc m, 8 H), 4.8 (d of d of ABX, J = 6, 2 Hz, 1 H), 3.4 (s, 3 H), 2.39 (m of ABX, 2 H); mass spectrum, exact mass calcd for $C_{15}H_{14}O_2$ *m/e* 226.0993, obsd 226.1009.

Anodic Oxidation of 7b. A solution of the *p*-aryl phenol **7b** from above (0.106 g, 0.5 mmol) in 4:1 CH_3CN/CH_3OH (100 mL) containing HOAc (0.50 mL) and 2% by wt. of $LiClO_4$ as electrolyte was anodically oxidized at 0 °C in a single cell at a constant current of 0.05 A using a perforated cylindrical platinum sheet anode and platinum wire cathode for 38 min (85% current efficiency). Extractive workup gave a white crystalline solid (0.114 g, 92%) which was nearly pure by ^{1}H NMR. This crude material was triturated with Et_2O/hexane to afford pure product (0.103 g, 85%), mp 108-109 °C. Recrystallization of a portion from Et_2O/PE gave the analytically pure material: mp 110-111 °C; IR (KBr, cm^{-1}) 1665 (s), 1625 (m), 1105 (m), 855 (m); ^{1}H NMR (80 MHz) δ 7.65-6.64 (highly struc m, 6 H), 6.37-6.0 (struc m, 2 H), 3.12 (s, 3 H), 2.38 (AB q, $\Delta\nu$ = 26 Hz, J_{AB} = 4 Hz, 2 H), 1.61 (s, 3 H); ^{13}C NMR δ 186.0 (1 C), 153.9 (1 C), 153.2 (1 C), 144.8 (1 C), 143.0 (1 C), 129.4 (1 C), 128.7 (1 C), 128.2 (1 C), 126.2 (1 C), 124.9 (1 C), 124.8 (1 C), 85.0 (1 C), 52.1 (1 C), 50.6 (1 C), 49.1 (1 C), 23.3 (1 C); mass spectrum, exact mass calcd for $C_{16}H_{16}O_2$ *m/e* 240.1150, obsd 240.1178. *Anal.* Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.67. Found: C, 79.59; H, 6.77%.

Anodic Oxidation of 7c. A solution of **7c** (0.5 g, 2.11 mmol) in 4:1 CH_3CN/CH_3OH (300 mL) containing HOAc (0.75 mL) and 1% by wt. of $LiClO_4$ as the electrolyte was anodically oxidized at 0 °C in a single cell with a platinum anode and copper wire cathode at a constant current of 0.05 A for 145 min (95% current efficiency), after which time no starting material remained by TLC (2:1 PE/Et_2O). Extractive workup gave a yellow-orange oil (0.552 g) which was chromatographed on silica gel (6" x 3/4" column, 2% Et_2O/CH_2Cl_2 as eluant) to afford the spirodienone **8c** (0.389 g, 69%) as an off-white solid, mp 111-115 °C. Recrystallization of a portion from Et_2O/PE gave the analytically pure material: mp 118-120 °C; IR (KBr, cm^{-1}) 1672 (s), 1630 (m), 1090 (m), 1080 (m), 775 (m); ^{1}H NMR (500 MHz) δ 7.42 (d, J = 7 Hz, 1 H), 7.35 (t, J = 7 Hz, 1 H), 7.29 (t, J = 7 Hz, 1 H), 6.93 (d, J = 7 Hz, 1 H), 6.67 (AB q, $\Delta\nu$ = 225 Hz, J_{AB} = 10.2 Hz, 2 H), 6.62 (AB q, $\Delta\nu$ = 450 Hz, J_{AB} = 9.9 Hz, 2 H), 3.24 (s, 3 H), 2.91 (t, 1 H), 2.29 (struc m, 1 H), 2.11 (struc m, 1 H), 1.89 (struc m, 2 H), 1.67 (struc m, 2 H); mass spectrum, exact mass calcd for $C_{18}H_{18}O_2$ *m/e* 266.1307, obsd 266.1312. *Anal.* Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.76. Found: C, 80.98; H, 6.82%.

Anodic Oxidation of 7d. A solution of **5d** (0.107 g, 0.39 mmol) in 4:1 CH_3CN/CH_3OH (100 mL) containing HOAc (0.4 mL) and 2% by wt. $LiClO_4$ as electrolyte was anodically oxidized at 0 °C in a single cell with a platinum sheet anode and a platinum wire cathode at a constant current of 0.05 A for 29 min (86% current efficiency). The crude reaction mixture was poured into a saturated $NaHCO_3$ solution (50 mL) and worked up to afford a thick yellow oil (0.142 g). The ^{1}H NMR spectrum of this material indicated it was > 90% pure. Chromatography of this material on silica gel (6" x 1/4" column, 5-7% Et_2O/hexane as eluant) gave crystalline **8d** (0.8 g, 65%). Recrystallization from Et_2O/hexane gave the spirodienone as white crystals: mp 147-149 °C; IR (KBr, cm^{-1}) 1672 (s), 1092 (m), 860 (m), 768 (m), 701 (m); ^{1}H NMR (80 MHz) δ 7.5-7.2 (m, 9 H), 7.2-6.1 (highly struc m, 4 H), 3.13 (s, 3 H), 2.61 (AB q, $\Delta\nu$ = 18 Hz, J_{AB} = 14 Hz, 2 H); mass spectrum, exact mass calcd for $C_{21}H_{18}O_2$ *m/e* 302.1307, obsd 302.1314.

Anodic Oxidation of 7e. A solution of **7e** (0.235 g, 1.12 mmol) in 4:1 CH_3CN/CH_3OH (170 mL) containing HOAc (0.7 mL) and 1% by wt. $LiClO_4$ as electrolyte was anodically oxidized at 0 °C in a single cell with a platinum sheet anode and a platinum wire cathode at a constant current of 0.05 A for 50 min (90% current efficiency). The progress of the reaction was monitored by hplc which indicated three products were formed. The crude reaction mixture was poured into a saturated $NaHCO_3$ solution (60 mL) and worked-up to yield a light brown oil (0.3 g). The products were separated on base-washed silica gel (12" x 1/4" column, 3% EtOAc/hexane as eluant). The stereochemistry for **8e** was assigned assuming a large coupling constant for the *cis* versus the *trans* hydrogens.[13]

The 1,4-adduct **9e** was obtained as a white solid (0.042 g, 16%) having: mp 53-54 °C; IR (KBr, cm^{-1}) 2950 (m), 2930 (m), 1666 (s), 1622 (m), 1466 (m), 1448 (m), 1276 (m), 1062 (s), 942 (m), 851 (m), 745 (m); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54-6.86 (m, 7 H), 6.45-6.37 (m, 2 H), 5.99-5.81 (d of q, J = 15.5 , 6.6 Hz, 1 H), 3.32 (s, 3 H), 1.84-1.79 (d of d, J = 6.6, 1.8 Hz, 3 H); exact mass calcd for $C_{16}H_{16}O_2$ *m/e* 240.1150, obsd 240.1155.

The *trans* compound **8e-*t*** was obtained as a white solid (0.048 g, 18%) showing: mp 112-113 °C IR (KBr, cm^{-1}) 2986-2830 (m), 1660 (s), 1626 (m), 1478 (m), 1462 (m), 1406 (m), 1095 (s), 1082 (s), 759 (s); H^{1}NMR (200 MHz, $CDCl_3$) δ 7.50-6.98 (m, 5 H), 6.76-6.70 (d of d, J = 10, 2.8 Hz, 1 H), 6.50-6.44 (d of d, J = 10, 1.9 Hz, 1 H), 6.23-6.17 (d of d, J = 10.1, 1.9 Hz, 1 H), 4.58-4.55 (d, J = 5.3 Hz, 1 H), 3.42 (s, 3 H), 2.74-2.61 (d of q, J = 5.3, 7.3 Hz, 1 H), 1.04-1.00 (d, J = 7.3 Hz, 3 H); exact mass calcd for $C_{16}H_{16}O_2$ m/e 240.1150, obsd 240.1154.

The *cis* compound **8e-c** was obtained as a white solid (0.44 g, 17%) having: mp 70-71 °C; IR (KBr, cm^{-1}) 2922 (m), 2822 (m), 1660 (s), 1618 (s), 1595 (m), 1468 (s), 1405 (s), 1358 (m), 1264 (m), 1182 (s), 1165 (m), 1092 (s), 972 (m), 931 (m), 851 (s), 765 (s); ^1H NMR (200 MHz, $CDCl_3$) δ 7.49-6.85 (m, 5 H), 6.69-6.62 (d of d, J = 10.1, 2.9 Hz, 1 H), 6.44-6.38 (d of d, J = 10.0, 1.9 Hz, 1 H), 6.31-6.25 (d of d, J = 10.1, 1.9 Hz, 1 H), 4.71-4.67 (d, J = 7.8 Hz, 1 H), 3.63 (s, 3 H), 2.68-2.60 (d of q, J = 7.8, 7.1 Hz, 1 H), 1.15-1.11 (d, J = 7.1 Hz, 3 H); exact mass calcd for $C_{16}H_{16}O_2$ m/e 240.1151, obsd 240.1151.

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