Electrochemically-Induced Spirolactonization of α-(Methoxyphenoxy)alkanoic Acids into Quinone Ketals

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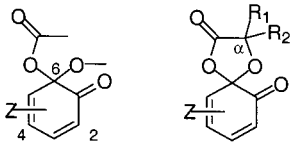
Anodic oxidation of two series of α-(2)- and α-(4-methoxyphenoxy)alkanoic acids were studied both at the analytical and preparative scales in order to delineate mechanistic aspects of electrochemically induced spirolactonization and to develop synthetically useful orthoquinone bis- and monoketals. Although α-monomethylated carboxylic acids and acetic acid derivatives do not undergo any spiroannulation, α-dimethylated carboxylic acids furnished spirolactones in high yields. A *gem*-dimethyl effect is invoked to explain these differences in cyclization capacity. Electrooxidation conditions can be selected to furnish either quinone spirolactone bis- or monoketals. Chemoselective monohydrolysis of bisketals can also be accomplished in a stepwise fashion to furnish the corresponding spirolactone monoketals, but the ortho compound unfortunately dimerized in situ via a Diels−Alder process. An ECEC pathway is proposed to rationalize the observed spirolactonizations on the basis of cyclic voltammetry analyses.

Introduction

Orthoquinone monoketals are synthetically useful cyclohexa-2,4-dienone derivatives that can serve in the rapid elaboration of complex structural motifs.[1] The methods most commonly used today to generate such synthons rely on chemically induced oxidative alkoxylation or acyloxylation of 2-alkoxyarenols. Metallic oxidants such as lead tetraacetate (LTA)[2] and hypervalent iodine(III)-based reagents such as phenyliodine(III) diacetate (PIDA)[3] are the chemical reagents most frequently used today to promote such oxidative dearomatizations of arenols.[1,4] Orthoquinone monoketals are generally more capricious in their synthetic uses than their para cyclohexa-2,5-dienone counterparts, mainly because of the capability of the 2,4-dienone unit to behave both as a diene and as a dienophile in Diels−Alder processes. It is nevertheless possible to harness the reactivity of these 6,6-dioxocyclohexa-2,4-dienone systems by choosing an appropriate substitution pattern.[1] It has, for example, been observed that 6-acetoxy derivatives (e.g., **1**, Chart 1) are less prone to undergo spontaneous cycloaddition processes than their 6,6-dialkoxy analogues,[5] and numerous specimens have been isolated as stable monomers.[1,6]

These observations on nondimerizing orthoquinol acetates such as **1** led us to envisage the preparation of cyclic 6-acyloxy analogues such as **2**. The main incitement to this objective was the access to a more conformationally rigid 6-acyloxy unit in which α-substitution could be exploited to better control both the formation and the reactivity of the cyclohexa-2,4-dienone system. The α-carbon center could, for example, be armed with groups of various types and sizes to block undesirable cycloaddition processes and to induce stereoselective formation and subsequent transformations. Another incentive to the investigation of the chemistry of *O*-spirolactone 2,4-dienones such as **2** was the fact that there are very few reports on their utilization in synthesis.[7]

Chart 1



Z = various substituents
R_1, R_2 = alkyl or H

The question then arose as to which tactic to follow in order to set in place this spirolactone dienone arrangement. An intramolecular ipso-attack of an oxo-tethered carboxylate unit on an oxidatively activated arene ring would appear to be a logical approach. Oxidative dearomatization of α-(2-hydroxyphenoxy)alkanoic acids with *N*-bromosuccinimide was the method used in previous preparations of *O*-spirolactone 2,4-dienones.[7] In this

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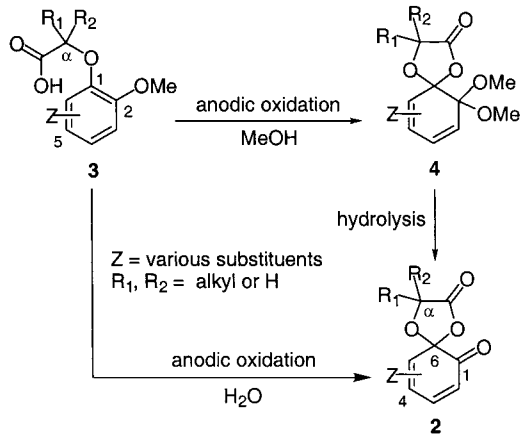
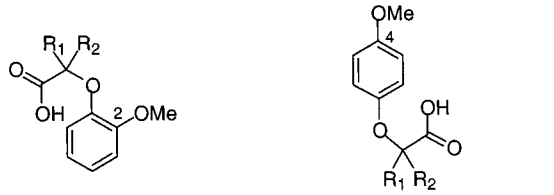
Scheme 1



study, we decided to take advantage of the capability of mild and environmentally friendly anodic oxidation to mediate single electron transfer reactions and choose readily accessible α-(2-alkoxyphenoxy)alkanoic acids such as **3** as starting materials (Scheme 1). Again, 1,2-bisalkyl aryl ethers such as **3** have been much less studied under anodic oxidation conditions than their 1,4-counterparts. To the best of our knowledge, the only reported case in the benzenoid series is the anodic oxidation of 1,2-dimethoxybenzene to 5,5,6,6-tetramethoxycyclohexa-1,3-diene, which thus demonstrated the feasibility of making orthoquinone bisketals by electrolysis aryl alkyl ethers in an alcoholic solvent.[8]

We envisaged two electrochemically induced approaches to the desired orthoquinone spirolactone monoketals **2** (Scheme 1). The first approach is an anodic oxidation−hydrolysis sequence, originally developed by Swenton and co-workers for building paraquinone monoketals via monohydrolysis of bisketal parents.[9] Selective hydrolysis of the dimethyl ketal function of electrochemically generated **4** should furnish **2**. The second approach would directly give rise to the desired 2,4-dienone **2** by simply performing the anodic oxidation

Chart 2



3a $R_1 = R_2 = Me$ (60%)
3b $R_1 = H$, $R_2 = Me$ (43%)
3c $R_1 = R_2 = H$ (48%)

5a $R_1 = R_2 = Me$ (70%)
5b $R_1 = H$, $R_2 = Me$ (60%)
5c $R_1 = R_2 = H$ (65%)

of **3** in the presence of water. Precedents for electrochemically induced spirolactonizations of α-(methoxyphenoxy)alkanoic acids can be found in the literature, but they only concern the preparation of *O*-spirolactone paraquinone ketals from 4-methoxyphenoxy derivatives.[10]

This article describes in detail the initial phase of our own investigation on the electrooxidation of α-(methoxyphenoxy)alkanoic acids. Two analogous series of three α-(2)- **3a**−**c** and three α-(4-methoxyphenoxy)alkanoic acids **5a**−**c** were comparatively studied both at the analytical and preparative scales with the aim of identifying reaction conditions most appropriate for the preparation of synthetically useful *O*-spirolactone orthoquinone ketals **2** and **4**.

Results and Discussion

The starting acid **3a** was prepared from guaiacol (2-methoxyphenol) in a single step by reaction with 1,1,1-trichloro-2-methyl-2-propanol in the presence of sodium hydroxyde in acetone as previously described for the synthesis of α-4-tolyloxyisobutyric acid.[11] The α-(2-methoxyphenoxy)alkanoic acids **3b** and **3c** were obtained by standard nucleophilic substitution reactions between guaiacol and the commercially available α-halogenoesters, methyl chloroacetate, and ethyl 2-bromoproproniate, followed in situ by saponification.[12] The α-(4-methoxyphenoxy)alkanoic acids **5a**−**c** were prepared similarly but in higher yields from 4-methoxyphenol (Chart 2).

Preliminary cyclic voltammetric analyses were carried out to measure the oxidation potential (Epa) of the starting acids **3a**−**c** and **5a**−**c** at a voltage sweep rate of 0.2 V/s both in the absence and in the presence of the base 2,6-lutidine (Table 1). Cyclic voltammograms obtained at different sweep rates for the oxidation of **5a** in the absence of a base are displayed in Figure 1a. These voltammograms are typical examples of quasi-reversible one-electron transfers. The ratio Ipa/Ipc was closed to 1 and the peak separation for anodic and cathodic processes (Epa − Epc) approached 60 mV at a voltage sweep rate of 1.0 V/s.

Results obtained for the oxidation of **3a** are displayed in Figure 1b. The observed voltammograms show an irreversible two-electron wave. No trace of reversibility was observed even at a sweep rate up to 10 V/s. The acids **3b/c** and **5b/c** exhibited voltammetric behaviors similar to those of **3a** and **5a**, respectively (Figure 1). These

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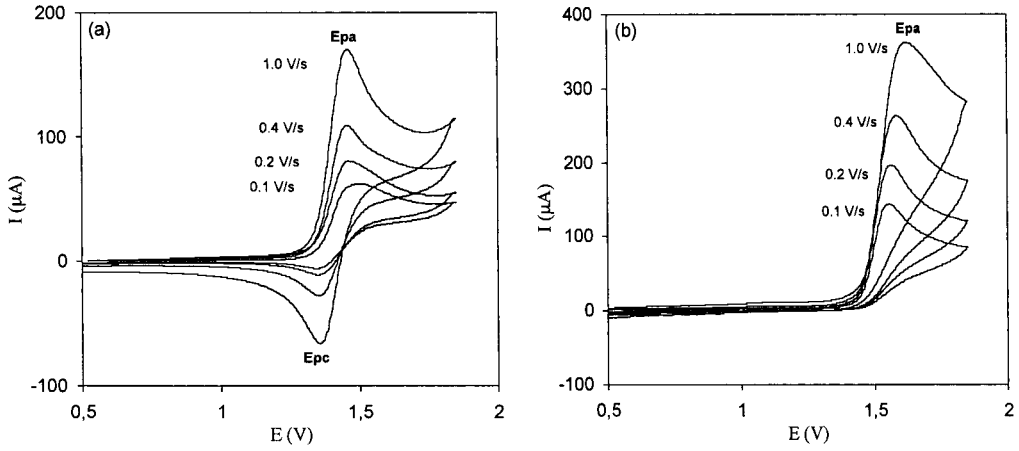

Figure 1. Cyclic voltammograms of **5a** (a) and **3a** (b) at a concentration of 2 mM in MeCN containing NBu_4BF_4 (0.1 M) and methanol (10 equiv) in the absence of a base using a platinum working electrode and a Ag/AgCl reference electrode, $v = 0.1$, 0.2, 0.4, and 1.0 V/s.

Scheme 2

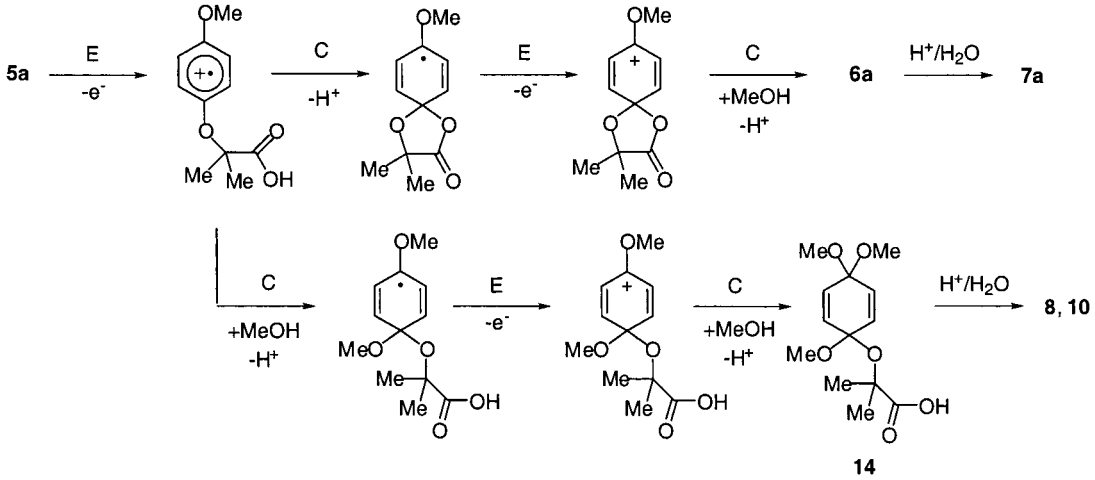

Table 1. Peak Potentials[a] from Cyclic Voltammetry[b]

compd	Epa	Epc	Epa[c]	Epc[c]
5a	1.285	-	1.450	1.360
5b	1.295	-	1.445	1.350
5c	1.300	-	1.445	1.365
1,4-DMB	1.405	1.295	1.405	1.305
3a	1.520	-	1.565	-
3b	1.535	-	1.500	-
3c	1.470	-	1.550	-
1,2-DMB	1.585	-	1.585	-

[a] V vs Ag/AgCl reference electrode measured using a platinum working electrode at a sweep rate of 0.2 V/s. [b] 2.0 mM of starting acid in MeCN containing NBu_4BF_4 (0.1 M), 2,6-lutidine (2 equiv) and methanol (10 equiv). [c] Without 2,6-lutidine.

behaviors were also found similar to those of 1,2- and 1,4-dimethoxybenzene in the absence of a base. Peak potentials of these reference compounds are indeed very close to those of the corresponding acids **3a**−**c** and **5a**−**c** (Table 1), which suggested an initial electron departure from the aromatic nucleus. Cyclic voltammetry of 2-methoxy-2-methylpropanoic acid, an α-methoxy analogue of **3**a and **5a**, confirmed such regiochemistry inasmuch as no significant oxidation peak was observed over the 0.5−1.8 V potential range for this carboxylic acid bearing no electroactive arene unit.

These voltammogams are in agreement with an oxidation process consisting of an overall two-electron transfer from the aromatic nucleus in a generally accepted ECEC mechanism.[8a,13] Such a mechanism is thus initiated by a reversible electron tranfer (E) giving rise to an aryl radical cation which is irreversible trapped by a nucleophile such as the carboxylic unit of the substrate or methanol (C). The resulting radical, which should be more easily oxidized than the starting compound, is then immediately oxidized (E) to furnish an arenoxenium ion eventually quenched by a second nucleophilic trapping (C) (Scheme 2). For the para acid **5a**, the first electron transfer gave a cation radical that is observed during the reverse cycle on the time scale of the experiment (Figure 1a), whereas the ortho acid **3a** is more rapidly quenched by nucleophilic addition (Figure 1b).

Both cyclic voltammetry of **5a**−**c** and **3a**−**c** show a new less anodic irreversible peak whose height increases upon addition of increasing amounts of 2,6-lutidine. Therefore, this peak was attributed to an electron transfer from the carboxylate anion form of the starting acid. In the presence of 2 equiv of the base at a voltage sweep rate of 0.2 V/s, this broad irreversible peak indicates complex electron-transfer reactions as depicted in Figures 2a and 2b for **5a** and **3a**, respectively. The observation of a more anodic shoulder in the oxidation wave of **5a** can conceivably be the consequence of a partial regeneration of its

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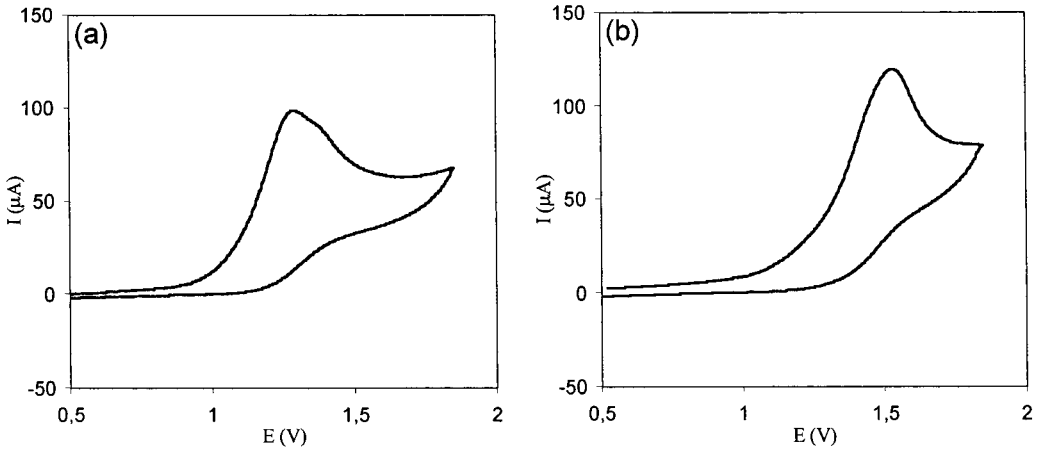

Figure 2. Cyclic voltammograms ($v = 0.2$ V/s) of **5a** (a) and **3a** (b) at a concentration of 2 mM in MeCN containing NBu_4BF_4 (0.1 M) in the presence of 2,6-lutidine (2.0 equiv) and methanol (10 equiv) using a platinum working electrode and a Ag/AgCl reference electrode.

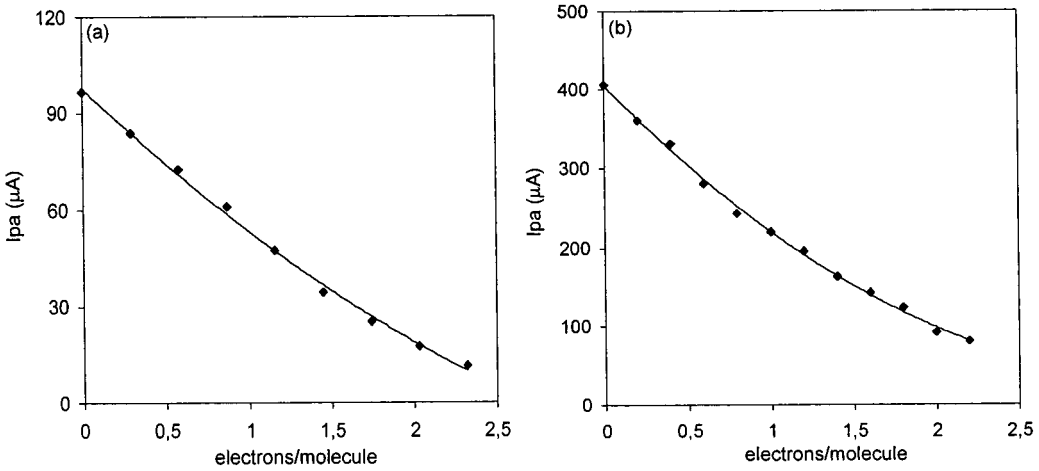

Figure 3. Peak current (Ipa) as a function of theoretical number of electrons exchanged per oxidized molecule of (a) **5a** (2 mM) and (b) **3a** (10 mM) in MeCN containing NBu_4BF_4 (0.1 M), 2,6-lutidine (2 equiv) and methanol (10 equiv) measured using a platinum working electrode and a Ag/AgCl reference electrode.

carboxylic acid form at the vicinity of the electrode. Oxonium species produced during nucleophilic trapping of cationic intermediates by methanol could serve as proton sources for this regeneration. Similar phenomena have been observed by Savéant and co-workers during cyclic voltammetry studies of aromatic carboxylic acids.[14] We then verified by coulometry at controlled potential that the irreversible peak observed with both **3a** and **5a** resulted from an overall two-electron process. Experiments were carried out, using 2 mM and 10 mM solutions of **5a** and **3a**, respectively. The anode potential was set at 300 mV anodic of the peak potential (Epa) that has been measured by cyclic voltammetry (Table 1). In both cases, the number of electrons exchanged during the electrolysis reached an approximate value of two electrons as depicted in Figure 3.

The absence of reversibility for **5a** in the presence of 2,6-lutidine indicates that the first electron transfer (E) is not reversible anymore (Scheme 2). Experimental evidence of the fact that the electron-rich aromatic ring is more easily oxidized than the carboxylate anion was again deduced from cyclic voltammetric analysis of 2-methoxy-2-methylpropanoic acid in a basic medium.

The anodic oxidation−hydrolysis sequence was the first approach that we implemented at the preparative scale. Reaction conditions were similar to the ones previously implemented by Yamamura and co-workers in their synthesis of asatone and analogues by anodic oxidation of eugenol and other related phenols.[15,16] The undivided cell used for this purpose was equipped with a platinum-coated titanium grid anode, an Ag/AgCl reference electrode, and a coiled platinum wire cathode. Oxidation of α-methoxyphenoxyalkanoic acids was carried out in a solvent mixture ranging from 9:1 to 7:3 in acetonitrile−methanol containing lithium perchlorate at a concentration of 0.1 M. Higher volumes of methanol were necessary for complete solubility of starting compounds **3b/c** and **5b/c**. The current potential was set in a range from 200 mV to 300 mV anodic of the first peak potential (Epa) measured by cyclic voltammetry (Table 1). The electrolysis was terminated after the current decayed smoothly to background with passage of 2 to 5 $F \cdot mol^{-1}$. In some

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Chart 3. Products from α-(4-Methoxyphenoxy)alkanoic Acids (I). Products from α-(2-Methoxyphenoxy)alkanoic Acids (II)

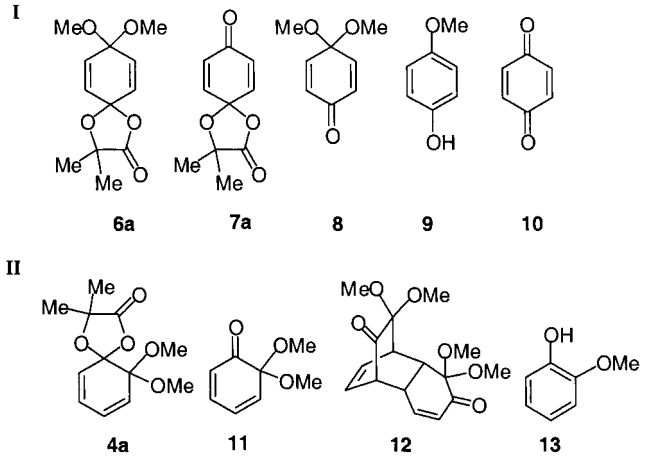

Table 2. Oxidation Products from α-(Methoxyphenoxy)alkanoic Acids[a]

entry	compd	applied potential[b]	faraday current/mol	products (GC yield %)
1[e]	**5a**	1.50	2.4 F/mol	**6a** (7), **7a** (24), **8** (23), **10** (7)
2	**5a**	1.50	2.6 F/mol	**6a** (69),[c] **9** (8), **10** (3)
3[d]	**5b**	1.50	4.5 F/mol	**8** (16), **9** (17), **10** (13)
4[d]	**5c**	1.50	4.0 F/mol	**8** (49), **9** (23), **10** (12)
5	**3a**	1.80	5.0 F/mol	**4a** (78)[c]
6[d]	**3b**	1.80	4.5 F/mol	**11** (13), **12** (40), **13** (7)
7[d]	**3c**	1.80	3.4 F/mol	**11** (5), **12** (16), **13** (25)

[a] Platinum-coated titanium grid anode, acetonitrile−methanol (9:1), 2,6-lutidine (2 equiv), $LiClO_4$ (0.1 M). [b] V vs Ag/AgCl. [c] Yield of isolated product. [d] Acetonitrile−methanol (7:3). [e] Without 2,6-lutidine.

cases, the amount of electric current passed through the solution was higher than the theoretical two electrons needed per molecule, probably because of unselective electrochemical processes. Products were isolated, purified, and characterized by standard chromatographic and spectroscopic techniques (Chart 3).

Preparative anodic oxidation of **5a** conducted under base-free conditions was found to be rather ineffective and led to a mixture of the corresponding spirolactone bisketal **6a**, the monoketal **7a**, and the paraquinone monoketal **8** in low yields (Table 2, entry 1). The electrooxidative transformation of **5a** is depicted in Scheme 2 according to the ECEC mechanism. The monoketal sideproduct **8** can probably arise from hydrolysis of some reaction intermediates such as **14** rather than **6a**, since hydrolysis of **6a** quantitatively furnished **7a** (vide infra). In this scenario, the bisketal **14** would result from the addition of methanol in competition with intramolecular trapping of the initially formed radical cation by the carboxylic function of the substrate during the first chemical step (C, Scheme 2).

The presence of a base in the reaction medium is an advantage, for it induces the chemical participation of a more nucleophilic carboxylate anion that should favor the desired spirolactonization. Therefore, preparative oxidation of α-methoxyphenoxyalkanoic acids was carried out in the presence of 2 equiv of 2,6-lutidine. Inorganic bases such as KOH or NaOH were found to be unsuitable because of the low solubility of the resulting carboxylate salts in the acetonitrile/methanol solvent system. Spirolactone *ortho*-**4a** and paraquinone **6a** bisketals were obtained in good yields from the α-(methoxyphenoxy)-alkanoic acids **3a** and **5a**, which both bear two methyl groups at the α-position of their carbonyl group (Table 2, entries 2 and 5). Ronlán and Parker had earlier mentioned the electro-oxidation of **5a** in acetonitrile containing 2,6-lutidine and methanol to give presumably **6a** in high yield.[10b] However, characterization of this bisketal was not reported and its selective hydrolysis into **7a** was not carried out by these authors. Another pertinent study is Thomas's anodic oxidation of the three α-(4-methoxyphenoxy)alkanoic acids **5a**−**c** in acetonitrile solutions containing an excess of triethylamine.[10a] *O*-spirolactone monoketals **7a**−**c** were observed in yields ranging from ca. 40% to 10%. It is not clear how the oxidative cleavage of the methyl aryl ether bond was accomplished under these apparently anhydrous conditions. Workup hydrolysis of acetamide methoxy ketals resulting from nucleophilic addition of the acetonitrile solvent during the electrosynthesis is a possible explanation.[17] In our case, all attempts to spirocyclize compounds **3b/c** and **5b/c**, which bear at least one α-hydrogen atom met with failure. Anodic oxidation of these acids instead afforded compounds **8**−**10** and **11**−**13**, respectively, as the major compounds (Chart 3 and Table 2, entries 3, 4 and 6, 7). These compounds most probably arose from methanol adducts that result from competing intermolecular nucleophilic trapping of the initially formed radical cation by the solvent at the first chemical step of the ECEC process (Scheme 2). In any event, the observed efficacy of spiroannulation of **3a** and **5a** into **4a** and **6a** indicates that the base plays a crucial role in this anodic oxidation process and confirms an overall two-electron transfer from the electron-rich arene unit in an ECEC mechanism. The fact that spirolactonization is observed for **3a** and **5a** and not for **3b**/**c** and **5b**/**c** can be further interpreted in terms of an acceleration of cyclization due to a *gem*-dialkyl effect.[18]

Hydrolysis of spirolactone quinone bisketals **4a** and **6a** was then carried out in order to prepare the desired spirolactone monoketals. Room-temperature hydrolysis of **6a** in 4% aqueous acetic acid selectively afforded the monoketal **7a** in quantitative yield (Chart 3). A simple workup treatment of **6a** using a 1 M H_3PO_4 aqueous solution also cleanly furnished ketal **7a**, as observed by GC analysis of reaction extracts. This chemoselective hydrolysis is due to the slower acidic hydrolysis rate of the *O*-spirolactone ketal unit compared to that of the dimethyl ketal. Under the same hydrolysis conditions as those described for **6a**, the ortho bisketal **4a** surprisingly remained intact. Hydrolysis conducted under more drastic conditions [10% aq HCl−acetone, (1:1)] furnished the desired monoketal **2a**, but it spontaneously dimerized to yield **15** via a Diels−Alder cycloaddition process (Scheme 3).

The formation of a single compound out of 32 possible diastereoisomers is remarkable, but not unexpected from

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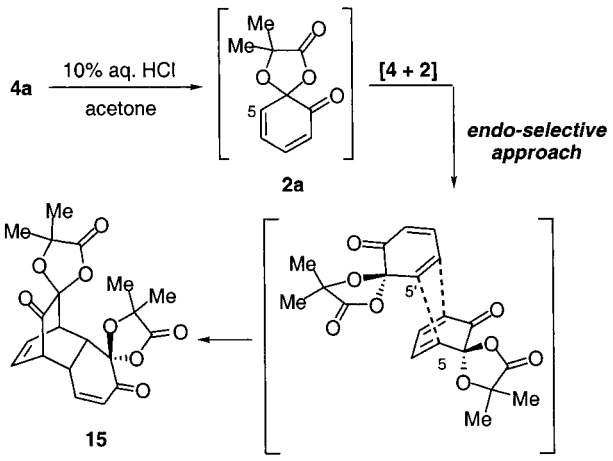
Scheme 3



this Diels−Alder cyclodimerization. All reported cases of related orthoquinol Diels−Alder cyclodimerizations have been described to be *endo*-selective as a result of a "back-to-back" mutual approach.[1,5b,c,19] An explanation for exclusive participation of the 4,5-double bond as the 2π partner in these dimerizations can be found in a report by Houk[20] who calculated that both the HOMO and the LUMO of 1-substituted electron-defficient dienes possess slightly higher atomic coefficients at the sp^2 carbon center remote from the carbonyl group, that is C-5 in the dimerizing cyclohexa-2,4-dienone units. Calculations do not however allow any clear-cut interpretation, and secondary orbital interactions have also been invoked to influence the regio- and stereochemical outcomes of these dimerizations.[21] The regio- and *endo*-stereochemistry of cyclodimer **15** was initially deduced from comparison of NMR data with those of known analogues such as dimer **12**,[19e] and unambiguously determined by an X-ray analysis (see Supporting Information). This analysis also established the configuration at the spiro-centers of **15**. The cycloaddition results from a mutual approach of two identical enantiomers of **2a** that appears to be under steric control; the most bulky spiro-substituent being away from the C-5 reaction center (Scheme 3).[5c]

The efficient electrochemical preparation of spirolactone quinone bisketals **4a** and **6a** hence prompted us to study the electrosynthesis of their monoketal versions in one single step. This second approach amounts to cleaving the methyl aryl ether bond of the starting acids by an oxidative electrolysis (Scheme 1).[22] For this second approach, electrochemical oxidation of compounds **3a** and **5a** was conducted in a mixture of acetonitrile−water (9:1) using either pyridine or 2,6-lutidine as the base (2 equiv). Both bases gave similar results, but pyridine is easier to remove during workup.[23] Monoketal **7a** was directly obtained in an isolated yield of 61%. Monoketal **2a** was also directly formed in the presence of water, but unfortunately again led to the cyclodimer **15**, a stereoisomer of which was crystallized in 21% yield from CH_2Cl_2.

Notwithstanding the fact that these results could be viewed as somewhat disappointing in light of our prime objective, that is the electrosynthesis of cyclohexa-2,4-dienones of type **2**, the fact that electrochemical *O*-spirolactonization is operational and high-yielding for α-dialkylated α-(2-methoxyphenoxy)alkanoic acids is an encouraging prelude to future successes. The difficulty that remains to overcome is not linked to the electrochemical process, but to the chemical reactivity of the cyclohexa-2,4-dienone unit of the quinone monoketal target. We are confident that solutions can be found to block cycloaddition processes by choosing more appropriate substitution patterns either on the starting arene ring (e.g., a removable bromide at the 5-position of **3**, Scheme 1)[24] or on its alkanoic acid appendage (e.g., a bulky alkyl substituent at the α-carboxyl position). We thought that the lactone acyloxy group could play a role similar to that of a 6-acetoxy group in retarding cyclodimerization.[1,5,6,25] Obviously, incorporation of the acyloxy group in a cyclic system annihilates the cause that otherwise inhibits the cycloaddition process. This observation raises some interesting questions on the factors that govern the "acetoxy effect". These factors remain to be clarified, but it appears that blocking the acyloxy group in a more conformationally constrained motif prevents it from retarding the Diels−Alder dimerization.

In summary, this work validates the electrochemical approach as a new alternative route to the synthesis of *O*-spirolactone orthoquinone ketals. Our comparative study between para- and ortho isomers led us to propose an electrochemical pathway based on an ECEC sequence to explain the spirolactonizations of α-dimethylated carboxylic acids **3a** and **5a** that occurred in high yields in basic media. A *gem*-dimethyl effect is invoked in the case of **3a** and **5a** to rationalize the ineffectiveness of α-monomethylated carboxylic acids **3b/5b** and acetic acid derivatives **3c/5c** in performing spirocyclizations via electrooxidation. Work is now in progress to directly transform more appropriately substituted acid arenes into spirolactone quinone monoketals via electrooxidation, a mild and environmentally friendly synthetic tactic, which does not require removal of stoichiometric amounts of spent oxidants.

Experimental Section

General. Acetonitrile (Riedel de Haën, HPLC grade), methanol (SDS, HPLC grade), 2,6-lutidine (Aldrich), and lithium perchlorate (Acros) were used as received for prepara-

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tive scale electrolyses. Acetonitrile (Riedel de Haën, HPLC grade) was distilled over P_2O_5 prior to voltammetric analyses. Tetrabutylammonium tetrafluoroborate (Fluka) was dried at 100 °C under vacuum and stored under N_2 before use. Diethyl ether (Et_2O) was purified by distillation from sodium/benzophenone under Ar immediately before use. CH_2Cl_2 was distilled from CaH_2 prior to use. Light petroleum refers to the fraction boiling in the 40−60 °C range. Column chromatography was carried out under positive N_2 pressure using 40−63 μm silica gel (Merck) and the indicated solvents. Evaporations were conducted under reduced pressure at temperatures less than 45 °C unless otherwise noted. Further drying of the residues was accomplished under high vacuum. Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Targon 1000 spectrometer. NMR spectra of samples in the indicated solvent were run at 250 MHz unless otherwise noted. Electron impact and liquid secondary ion mass spectrometry low and high-resolution mass spectrometric analyses (EIMS, and LSIMS, HRMS) were obtained from the mass spectrometry laboratory at the CESAMO, Bordeaux 1 University.

Cyclic Voltammetry. Cyclic voltammetry experiments were carried out in an acetonitrile solution containing NBu_4BF_4 or $LiClO_4$ (0.1 M) in a 20 mL three-neck round-bottom flask cell. The potentiostat used was an Autolab PGSTAT100. The working electrode was a 3 mm diameter platinum disk. The counter electrode was a platinum wire, and the reference electrode (double-junction) was a silver (Ag) wire immersed in a saturated potassium chloride (KCl) solution separated from the bulk solution by a salt bridge fine glass frit. The reference electrode was calibrated after each experiment against the ferrocene/ferrocinium couple ($E°_{Fc/Fc^+} = 0.46$ V vs the Ag/AgCl reference electrode). Feedback correction was applied in order to minimize the ohmic drop between the working and reference electrodes. The precision of the measurements was about ±5 mV.

Preparative Electrochemical Oxidation. Electrolyses were carried in a 100 mL undivided cylindrical cell, equipped with a platinum-coated titanium grid (50 g Pt/m^2, 40 × 60 mm) as the anode (available from Magneto-Chemie) and a 160 mm Pt wire (0.5 mm diameter) as the cathode. $LiClO_4$ (1.5 g, 14.0 mmol) was added as supporting electrolyte to a 100 mL mixture of acetonitrile−methanol or acetonitrile−water (9:1 or 7:3). The starting acid and the base (e.g., 2,6-lutidine, 2 equiv) were introduced, and the electrolysis was then performed at constant potential on an Autolab PGSTAT 100 potentiostat using an Ag/AgCl reference electrode until the current decayed smoothly to background. All reactions were vigorously stirred. After electrolysis, the solution was evaporated, and the residue was diluted in Et_2O (50 mL) and washed with brine (3 × 30 mL). The layers were then separated, and the aqueous layer was extracted three times with Et_2O (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to dryness.

α-(2-Methoxyphenoxy)-2-methylpropionic Acid (3a). To a stirred ice-cold solution of 2-methoxyphenol (2.0 g, 16 mmol) and 1,1,1-trichloro-2-methylpropan-2-ol $(H_2O)_x$ (7.88 g, 44 mmol)[11] in acetone (40 mL) was added powdered sodium hydroxide (6.0 g, 150 mmol) in three equal portions at 2 h intervals. After each addition, the reaction mixture was allowed to warm to room temperature. Before the last addition, an additional 40 mL of acetone was added to the thick suspension. The mixture was then stirred for 18 h at room temperature, and the solvent was evaporated to give a residue, which was diluted in water and acidified to pH 1 with 10% aq HCl. The aqueous phase was extracted three times with Et_2O (3 × 100 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give crude **3a** as light brown oil. Crystallization from benzene−hexane afforded pure **3a** (2.0 g, 60%) as white crystals, mp 42 °C (lit.[26] mp 45−47 °C). IR (NaCl) 2990, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 6H), 3.80 (s, 3H), 6.81−7.10 (m, 4H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 176.8, 152.2, 142.7, 124.9, 123.2, 120.8, 111.8, 81.6, 55.4, 24.6; EIMS *m*/*z* (relative intensity) 210 (M$^+$, 31), 165 (16), 124 (100).

α-(2-Methoxyphenoxy)propionic Acid (3b). To a stirred solution of 2-methoxyphenol (2.0 g, 16 mmol) in acetone (40 mL) were added ethyl bromopropionate (3.6 g, 20 mmol), potassium carbonate (2.76 g, 20 mmol), and potassium iodide (0.13 g, 0.8 mmol). The reaction mixture was refluxed for 22 h. After being cooled to room temperature, the potassium salts were removed by filtration. The filtrate was diluted in EtOAc−AcOH [100 mL, (100:1)] and washed with 1 M H_3PO_4 (50 mL) and brine (3 × 50 mL). After separation, the organic layer was dried over $MgSO_4$, filtered, and evaporated to give a residue which was further dried under under high vacuum overnight to give 3.8 g of crude product. To a stirring solution of this crude ester in absolute ethanol (25 mL) was added a solution of potassium hydroxide (1.0 g, 18.3 mmol) in absolute ethanol (5 mL). The mixture was refluxed for 24 h. After cooling to room temperature, the mixture was acidified with 10% aq HCl (10 mL), extracted with Et_2O (2 × 50 mL), dried over Na_2SO_4, filtered, and evaporated to give crude **3b**. Crystallization from benzene−pentane yielded pure **3b** (1.36 g, 43%) as white crystals, mp 82 °C (lit.[27] mp 85 °C). IR (NaCl) 2962, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.65 (d, J = 6.7 Hz, 3H), 3.84 (s, 3H), 4.72 (q, J = 6.7 Hz, 1H), 6.83−7.04 (m, 4H), 9.41 (bs, 1H), ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 176.4, 149.9, 146.5, 123.4, 120.9, 117.3, 112.2, 74.8, 55.7, 18.3.

α-(2-Methoxyphenoxy)acetic Acid (3c). To a stirred solution of 2-methoxyphenol (3.0 g, 24 mmol) in 5% aq sodium hydroxide (20 mL) was added methyl chloroacetate (5.2 g, 48 mmol) in 8% aq sodium hydroxide (50 mL). The mixture was heated on a steam-bath at 80 °C for 16 h. After being cooled to room temperature, the mixture was acidified with 10% aq HCl, extracted with Et_2O (2 × 50 mL), dried over Na_2SO_4, filtered, and evaporated to give crude **3c**. Crystallization from benzene−pentane yielded pure **3c** (2.1 g, 48%) as white crystals, mp 121 °C (lit.[28] mp 121.5 °C). IR (NaCl) 3014, 1745, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 4.70 (s, 2H), 6.90−7.06 (m, 4H), 9.44 (bs, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 173.4, 149.6, 146.9, 123.4, 121.0, 115.7, 112.1, 67.1, 55.8.

3,3-Dimethyl-1,4-Dioxaspiro(4.5(deca-7,9-diene-6,6-dimethoxy-2-one (4a). Electro-oxidation of a solution of **3a** (118 mg, 0.56 mmol) in acetonitrile−methanol (9:1) was performed in the presence of 2 equiv of 2,6-lutidine according to the general procedure described above for preparative electrochemical oxidation. Electrolysis was carried out at a constant potential of 1.8 V/Ag/0.1 M AgCl until the current decayed smoothly to background with passage of 5.0 F/mol. The reaction mixture was then processed as described above, and the residue was further dried overnight to give **4a** (106 mg, 78%) as a pale yellow oil. IR (NaCl) 1800 cm^{-1}; ^{1}H NMR (CDCl3) δ 1.48 (s, 3H), 1.57 (s, 3H), 3.39 (s, 3H), 3.40 (s, 3H), 5.81−6.13 (m, 4H); ^{13}C NMR (CDCl3, 62.9 MHz) δ 175.3, 130.7, 127.8, 127.3, 126.5, 106.3, 97.6, 76.4, 51.6, 51.3, 27.2, 24.5; EIMS *m*/*z* (relative intensity) 240 (M$^+$, 22), 209 (7), 154 (100), 139 (30), 123 (20), 111 (84); HRMS (EIMS) calcd for $C_{12}H_{16}O_5$ 240.0998, found 240.0994.

α-(4-Methoxyphenoxy)-2-methylpropionic Acid (5a). This acid was prepared as described for **3a**. Crystallization of the resulting crude light brown oil from benzene−pentane yielded pure **5a** (2.4 g, 70%) as beige needles, mp 54 °C (lit.[29] mp 57 °C). IR (NaCl) 2963, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 6H), 3.76 (s, 3H), 6.77−6.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 179.5, 155.7, 147.9, 122.6, 114.2, 79.8, 55.4, 24.9; EIMS *m*/*z* (relative intensity) 210 (M$^+$, 31), 165 (18), 124 (100).

α-(4-Methoxyphenoxy)propionic Acid (5b). This acid was prepared as described for **3b**. Crystallization from benzene−pentane yielded pure **5b** (1.9 g, 60%) as colorless needles, mp 86 °C (lit.[12] mp 90 °C). IR (NaCl) 2949, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (d, J = 6.7 Hz, 3H), 3.76 (s, 3H), 4.70 (q, J =

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6.7 Hz, 1H), δ 6.80−6.88 (m, 4H), 9.41 (bs, 1H), ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 178.2, 154.6, 151.2, 116.5, 114.7, 73.0, 55.6, 18.4.

α-(4-Methoxyphenoxy)acetic Acid (5c). This acid was prepared as described for **3c** to furnish pure **5c** as colorless plates (4.8 g, 65%), mp 105 °C (lit.[12] mp 110 °C). IR (NaCl) 2915, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 4.63 (s, 2H), 6.81−6.90 (m, 4H), 9.6 (bs, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 174.6, 154.7, 151.5, 115.8, 114.7, 65.7, 55.6.

3,3-Dimethyl-8,8-dimethoxy-1,4-dioxaspiro[4.5]deca-6,9-dien-2-one (6a). Electro-oxidation of a solution of **5a** (300 mg, 1.45 mmol) in acetonitrile−methanol (9:1) was performed in the presence of 2 equiv of 2,6-lutidine according to the general procedure described above for preparative electrochemical oxidation. Electrolysis was carried out at a constant potential of 1.5 V/Ag/0.1 M AgCl until the current decayed smoothly to background with passage of 2.6 F/mol. The reaction mixture was then processed as described above to give crude **6a** (257 mg), which was purified by column chromatography, eluting with hexanes−EtOAc (2:1) to furnish pure **6a** (240 mg, 69%) as a solid, mp 121 °C. IR (NaCl) 1789 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 6H), 3.28 (s, 3H), 3.29 (s, 3H), 5.97−6.02 (d, J = 10.37 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 175.2, 132.4, 130.4, 98.3, 92.2, 77.5, 50.3, 26.3; EIMS *m*/*z* (relative intensity) 240 (M^+, 1), 209 (65), 165 (27), 154 (23), 123 (100); HRMS (EIMS) calcd for $C_{12}H_{16}O_5$ 240.0998, found 240.0995.

3,3-Dimethyl-1,4-dioxaspiro[4.5]deca-6,9-diene-2,8-dione (7a). Procedure A. Monohydrolysis of spirolactone bisketal **6a** (40 mg, 0.17 mmol) in acetone (2 mL) was carried out at room temperature by treatment with 4% aq acetic acid (5 mL). The reaction mixture was stirred for 30 min and then poured over a 5% aq $NaHCO_3$ solution. The organic product was extracted with Et_2O, dried over Na_2SO_4, filtered, and evaporated to give **7a** quantitatively (33 mg) as pale yellow crystals. **Procedure B.** Electro-oxidation of a solution of **5a** (220 mg, 1.05 mmol) in acetonitrile−water (9:1) was performed in the presence of 2 equiv of pyridine according to the general procedure described above for preparative electrochemical oxidation. Electrolysis was carried out at a constant potential of 1.5 V/Ag/0.1 M AgCl until the current decayed smoothly to background with passage of 2.4 F/mol. The reaction mixture was then processed as described above to give **7a** (123 mg, 61%) as pale yellow crystals, mp 105 °C (lit.[10a] mp 103.5 °C. IR (NaCl) 1796, 1676, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 6H), 6.24−6.28 (d, 2H, J = 10.1 Hz), 6.61−6.65 (d, 2H, J = 10.1 Hz); EIMS *m*/*z* (relative intensity) 166 [$(M - CO)^+$, 9], 150 (45), 43 (100).

1,4a,5,8a-Tetrahydro-5,5,9,9-tetramethoxy-1,4-ethanonaphthalene-6,10(4*H*)-dione (12). Electro-oxidation of a solution of **3b** (132 mg, 0.67 mmol) in acetonitrile−methanol (9:1) was performed in the presence of 2 equiv of 2,6-lutidine according to the general procedure described above for preparative electrochemical oxidation. Electrolysis was carried out at a constant potential of 1.8 V/Ag/0.1 M AgCl until the current decayed smoothly to background with passage of 4.5 F/mol. The reaction mixture was then processed as described above to give a residue which was submitted to column chromatography, eluting with EtOAc−hexane (4:1), to furnish the dimer **12** (17 mg, 16%) as fine off-white crystals, mp 180 °C (lit.[19e] mp 187−190 °C). IR (NaCl) 1739, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz); δ 3.05 (s, 3H), 3.21 (s, 3H), 3.38 (s, 3H), 3.42 (s, 3H), 3.0−3.45 (m, 4H), 5.90 (ddd, J = 7.8, 6.2, 1.4 Hz, 1 H), 6.02 (dd, J = 10.1, 1.6 Hz, 1H), 6.24 (ddd, J = 7.9, 6.7, 1.2 Hz, 1H), 6.41 (dd, J = 10.1, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 202.2, 193.8, 146.4, 132.3, 129.0, 128.5, 98.6, 94.8, 52.6, 50.5, 50.1, 49.7, 48.8, 40.2, 39.3, 39.0; LSIMS *m*/*z* (relative intensity) 309 (MH^+, 11), 277 (63), 246 (87), 217 (100).

Bis(spirolactone) Dimer (15). Procedure A. Monohydrolysis of spirolactone bisketal **4a** (40 mg, 0.17 mmol) in acetone (5 mL) was carried out at room temperature by treatment with 10% aq HCl (5 mL). The reaction mixture was stirred for 30 min and then poured over a 5% aq $NaHCO_3$ solution. The organic product was extracted with Et_2O, dried over Na_2SO_4, filtered, and evaporated to give **15** quantitatively (32 mg) as an off-white solid. **Procedure B.** Electro-oxidation of a solution of **3a** (219 mg, 1.04 mmol) in acetonitrile−water (9:1) was performed in the presence of 2 equiv of pyridine according to the general procedure described above for preparative electrochemical oxidation. Electrolysis was carried out at a constant potential of 1.8 V/Ag/0.1 M AgCl until the current decayed smoothly to background with passage of 4.8 F/mol. The reaction mixture was then processed as described above to give a residue. Purification of this residue by column chromatography, eluting with hexanes−EtOAc (4:1 → 1:1), gave an off-white solid which was crystallized from CH_2Cl_2 to furnish pure **15** (42 mg, 21%) as small opaque flakes, mp 227 °C. IR (NaCl) 1820, 1754, 1742, 1706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (s, 3H), 1.53 (s, 6H), 1.58 (s, 3H), 3.17 (dd, J = 8.3, 1.9 Hz, 1 H), 3.36 (dt, J = 6.7, 1.8 Hz, 1H), 3.43 (ddd, J = 3.8, 2.4, 1.3 Hz, 1H), 3.50 (m, 1H), 6.08 (ddd, J = 7.8, 6.4, 1.6 Hz, 1H), 6.24 (dd, J = 10.3, 1.6 Hz, 1H), 6.41 (dddd, J = 7.8, 6.5, 1.8, 0.5 Hz, 1H), 6.60 (dd, J = 10.2, 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 199.5, 188.9, 174.2, 146.5, 131.6, 129.7, 128.7, 100.9, 98.6, 78.9, 78.3, 51.1, 44.3, 42.9, 37.7, 27.0, 26.7, 25.3, 24.0; EIMS *m*/*z* (relative intensity) 388 (M^+, 0.12), 360 (17), 274 (26), 160 (100); HRMS (EIMS) calcd for $C_{20}H_{20}O_8$ 388.1158, found 388,1160.

X-ray Analysis of 15. Crystals of **15**, suitable for an X-ray structure determination (0.2 × 0.025 × 0.4 mm.) were obtained in dimethylformamide by slow evaporation. X-ray diffraction data were collected on a crystal sealed in a Lindemann-glass using CuKα radiation on a CAD4 diffractometer. The structure was solved by direct methods and refined to final reliability factor of R = 28% for 4146 reflections.

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Supporting Information Available: Proton and carbon NMR spectra of compounds **4a**, **6a**, and **15**. ORTEP diagram and CIF file (CCDC 178536) of the X-ray structure of **15**. This material is available free of charge via the Inernet at htpp://pubs.acs.org.

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