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Electrochemical Synthesis of Dimerizing and Nondimerizing Orthoquinone Monoketals

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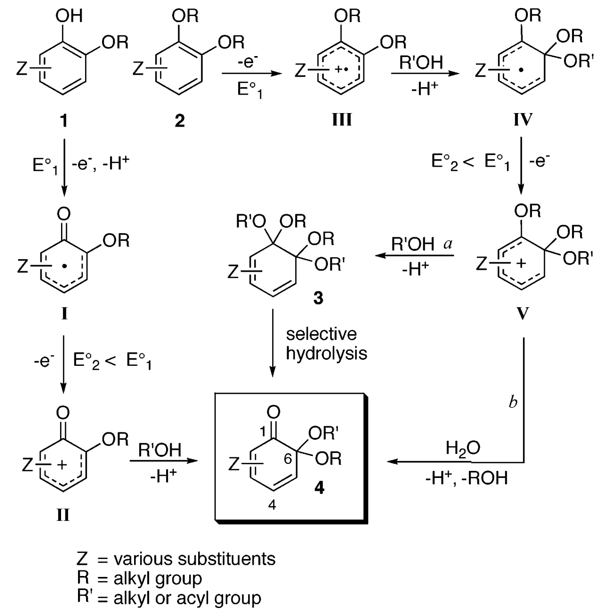
Anodic oxidation of appropriately substituted 2-methoxyphenols or α-(2-methoxyphenoxy)-2-methylpropionic acids in the presence of methanol furnishes stable orthoquinone monoketals, and thus constitutes a valuable alternative to the use of chemical oxidants that are often based on toxic metallic species. The propionic acid derivatives are initially converted into *O*-spirolactonic quinone bisketals that are then selectively hydrolyzed into the desired monoketal compounds. In the absence of blocking substituents, orthoquinone monoketals spontaneously undergo Diels–Alder dimerizations into tricyclododecadienedienones with extraordinary site selectivity, regioselectivity, and stereoselectivity. Suggestions are made to open up a new track for a long awaited rationalization of these controls on the basis of the intramolecular [2 + 2] reactivity of these orthoquinone monoketal-derived cyclodimers.

Introduction

Orthoquinone monoketals and their orthoquinol variants (i.e., **4**, Scheme 1) are synthetically useful cyclohexa-2,4-dienone derivatives that can serve in the rapid elaboration of complex structural motifs of tremendous value for natural products synthesis.[1] The most direct and efficient methods used to generate these synthons rely on the oxidative dearomatization of 2-alkoxyphenols (e.g., **1**, Scheme 1).[1,2] The two-electron oxidants lead tetraacetate (LTA)[3,4] and λ^3-iodane (diacetoxy)iodobenzene (DIB)[5,6] are the two chemical reagents most commonly used nowadays to perform such a task. Single-electron transfer sequences can also be exploited to perform similar dearomatization events using either 2-alkoxyphenols **1** or 2-alkoxyphenyl alkyl ethers **2** as

SCHEME 1



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starting materials. Initiating these one-electron oxidation reactions under appropriate electrochemical conditions constitutes an attractive alternative to the use of chemical reagents, notably because of the possibility of performing selective oxidation under environmentally friendly conditions. Inspired by the work of Swenton, Thomas, and co-workers on the electrochemical generation of paraquinone ketals,[7] we recently reported for the first time similar anodic oxidations of 2-alkoxyphenyl alkyl ethers of type **2** for the preparation of orthoquinone bisketals **3** and monoketals **4** by using either methanol or water, respectively, as a reaction cosolvent in acetonitrile (i.e., **2** → **III** → **IV** → **V** → **3/4**, Scheme 1).[8a] Bisketals **3** are easily transformed into their corresponding monoketals **4** by selective monohydrolysis.[8a] Monoketals can also be directly generated via anodic oxidation of 2-alkoxyphenols in methanol (i.e., **1** → **I** → **II** → **4**, Scheme 1). This approach was judiciously exploited by Yamamura and co-workers for the synthesis of asatone and other propenylphenol-derived asatone-type neolignans,[9] which were obtained by simply letting anodically generated orthoquinone dimethyl monoketals undergo Diels–Alder dimerizations upon standing at room temperature (vide infra). To the best of our knowledge, the only two examples of this electrochemical approach that led to nondimerizing orthoquinone monoketals are the ones reported by Swenton and co-workers and us.[8b,c]

Indeed, orthoquinone monoketals of type **4** are generally not very stable, and they rapidly succumb to Diels–Alder dimerization processes, leading to bicyclo[2.2.2]-octenones, because of the capability of their 2,4-dienone unit to behave both as a diene and as a dienophile. The lack of control over this cycloaddition chemistry is undoubtedly one of the main reasons why the use of such potentially useful building blocks has not yet been generalized in organic synthesis. It is nevertheless possible to harness the reactivity of these 6,6-dioxocyclohexa-2,4-dienone systems by choosing an appropriate substitution pattern.[1a,b] The presence of a single substituent on their ring system can drastically influence their stability. For example, a bromine or an iodine substituent at the 4-position of 6,6-dimethoxycyclohexa-2,4-dienones (i.e., **4**, R = R′ = Me)[8b,10] or a small electron-releasing group such as an alkyl or an alkoxy group at their 5-position[10b,11] are particularly efficient at retarding Diels–Alder dimerization. The presence of a bulky carbon-based substituent at their 4-position also stabilizes these orthoquinone monoketals.[8c,11b,c,12a] It has furthermore been observed that their 6-acetoxy derivatives or orthoquinol acetates (i.e., **4**, R = Me, R′ = Ac) are much less prone to undergo dimerization than their 6,6-dimethoxy analogues.[6,13]

With this knowledge on dimerizing and nondimerizing orthoquinone monoketals and related orthoquinols in mind, we decided to further examine the scope of their preparation by anodic oxidation of both 2-alkoxyphenols of type **1** and 2-alkoxyphenyl alkyl ethers of type **2**. Herein we describe our results obtained with a series of differently substituted 2-methoxyphenols **1a**–**g** and a series of spirolactonizable α-(2-methoxyphenoxy)-2-methylpropionic acids **2b**–**f**. Suggestions are also made to explain the extremely high regioselectivity of the Diels–Alder dimerization of orthoquinone monoketals on the basis of the intramolecular [2 + 2] reactivity of their dimers.

Results and Discussion

Anodic oxidation of 2-alkoxyphenols **1** in the presence of a nucleophilic entity is the most direct method of electrochemically generating orthoquinone monoketals **4** (Scheme 1), if these reactive species can withstand the reaction conditions used. The first series of compounds we submitted to anodic oxidation comprised the 2-methoxyphenols **1a**–**g**. Reactions were conducted in a single cell at a constant current in methanol containing lithium perchlorate as a supporting electrolyte (Table 1). Methanol played both the role of reaction solvent and of the nucleophilic entities necessary to trap cation intermediates of type **II** into 6,6-dimethoxycyclohexa-2,4-dienones **4** (i.e., R = R′ = Me). We were pleased to isolate such

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(6) For examples of synthetic applications of nondimerizing orthoquinol acetates from our own work, see: (a) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. *Tetrahedron* **2001**, *57*, 319–329. (b) Quideau, S.; Pouységu, L.; Looney, M. A. *J. Org. Chem.* **1998**, *63*, 9597–9600. (c) Quideau, S.; Looney, M. A.; Pouységu, L.; Ham, S.; Birney, D. M. *Tetrahedron Lett.* **1999**, *40*, 615–618. (d) Quideau, S.; Pouységu, L.; Avellan, A.-V.; Whelligan, D. K.; Looney, M. A. *Tetrahedron Lett.* **2001**, *42*, 7393–7396. (e) Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 3425–3436.

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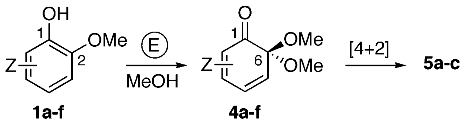
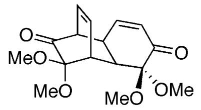
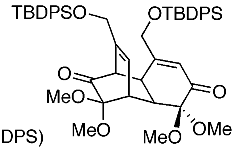
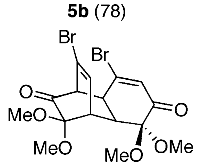
TABLE 1. Anodic Oxidation of a Series of 2-Methoxyphenols

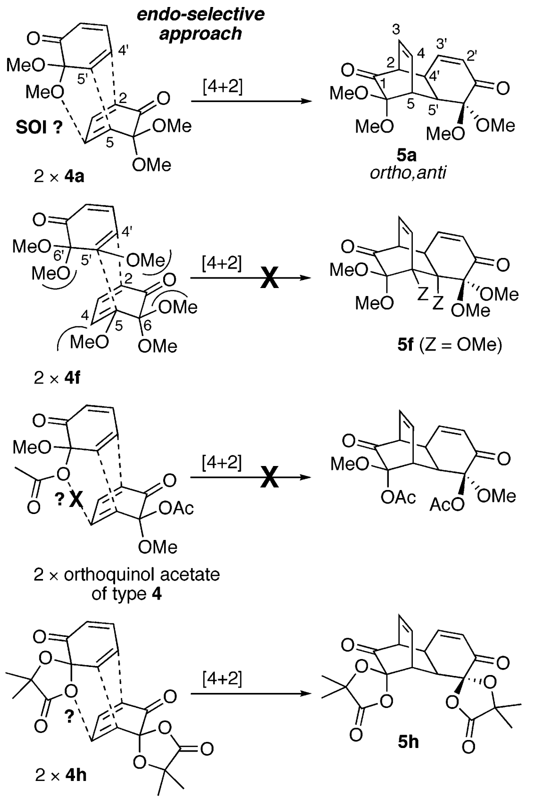


entry	phenols[a]	OQMK[b,c]	DAD[b,d]
1	**1a** (Z = H)	**4a**, n.o.[e]	 **5a** (92)
2	**1b** (Z-5 = CH$_2$OTBDPS)	**4b**, n.o. (Z-3 = CH$_2$OTBDPS)	 **5b** (78)
3	**1c** (Z-5 = Br)	**4c**, n.o. (Z-3 = Br)	 **5c** (100)
4	**1d** (Z-4 = CH$_2$OTBDPS)	**4d** (100) (Z-4 = CH$_2$OTBDPS	**5d**, n.o.
5	**1e** (Z-4 = Br)	**4e** (64) (Z-4 = Br)	**5e**, n.o.
6	**1f** (Z-3= OMe)	**4f** (100) (Z-5= OMe)	**5f**, n.o.

[a] All reactions were carried out in methanol containing LiClO$_4$ as a supporting electrolyte (see Experimental Section for details). [b] Isolated yields are given in parentheses where applicable. [c] OQMK = orthoquinone monoketal. [d] DAD = Diels–Alder dimer. [e] Not observed.

orthoquinone dimethyl monoketals in good to excellent yields in cases for which the substitution pattern of their cyclohexa-2,4-dienone ring system was appropriate to block the Diels–Alder dimerization process (Table 1). All products were isolated, purified, and characterized by standard chromatographic and spectroscopic techniques. As expected, the anodic oxidation of the unsubstituted 2-methoxyphenol, guaiacol **1a** (entry 1, Z = H), furnished the known Diels–Alder dimer **5a**[10f] as the sole product. Similar high-yielding dimerizations were obtained using 2-methoxyphenols bearing either a *tert*-butyldiphenylsilyloxymethyl group (entry 2, **1b** → **5b**) or a bromine atom (entry 3, **1c** → **5c**) at their 5-position. The presence of the orthoquinone monoketal monomers **4a**–**c** were not even detected by NMR analysis of the crude products. The regio- and stereochemistry of dimers **5b** and **5c** were deduced from their NMR characterization data (see Supporting Information) and by analogy with previously established structures of related dimers. In all reported cases,[1a,b,d] the cyclodimerization takes place via an *endo*-selective "back-to-back" mutual approach of the two cyclohexa-2,4-dienone monomers with the $C_{4'}-C_{5'}$ double bond always acting as the dienophile (Scheme 2). In contrast to **1b** and **1c**, the 2-methoxyphenols **1d** and **1e** bearing the same substituents, but at their 4-position, led to the desired orthoquinone monoketals **4d** and **4e** in 100 and 64% yields, respectively (entries 4 and 5). These results are in agreement with previous observations on the stability of chemically generated orthoquinone monoketals bearing a relatively large group at their 4-position.[8c,11b,c,12a] The 2-methoxyphenol **1f**, which is equipped with a methoxy group at its 3-position, also furnished the stable orthoquinone monoketal **4f** (entry 6)[11a,c] in quantitative yield, thus confirming the stabilizing effect of a small electron-releasing group at the corresponding cyclohexa-2,4-dienone 5-position (vide infra).[11] The anodic oxidation of 2,6-dimethoxyphenol (**4g**, not shown) under the same conditions in MeOH was totally inefficient at producing an orthoquinone monoketal or its corresponding dimer, and the only isolated product was 2,6-dimethoxy-1,4-quinone in a moderated 30% yield. The most likely course of events leading to the formation of this paraquinone is the anodic generation of a stable 2,6-dimethoxycyclohexa-2,5-dienonyl cation intermediate of type II, which is trapped by methanol to furnish 2,4,6-trimethoxyphenol, followed by further oxidative methoxylation into 2,4,4,6-tetramethoxycyclohexa-2,5-dienone, and dimethyl ketal hydrolysis during the aqueous workup.

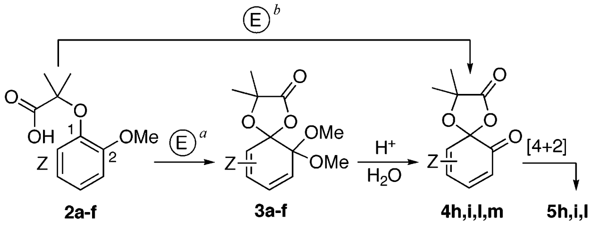
SCHEME 2

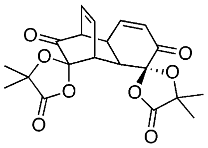
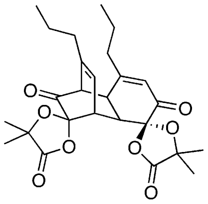
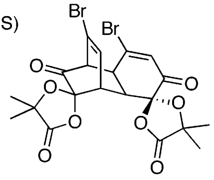


We performed calculations on molecular orbitals of **4a**–**f** at both semiempirical PM3 and ab initio RHF/3-21G levels with the aim of identifying some reasons that might explain the dimerizing and nondimerizing behaviors of these orthoquinone monoketals on the basis of HOMO–LUMO energy gaps and/or electronic effects due to the presence or lack of substituents on the atomic coefficients of their cyclohexa-2,4-dienone system. No clear-cut explanation could be drawn from the results of these calculations. In all cases, HOMO–LUMO energy gaps are similar and the relative magnitudes of the C_2, C_3, C_4, and C_5 coefficients of these FMOs are not affected by substituent electronic effects in a way that could support drastic changes in chemical reactivity (see Supporting Information). Similar calculations have been carried out by others at the same and higher levels[11b,14] in order to rationalize the reactivity and high regioselectivity observed in the case of reactions of differently substituted orthoquinone monoketals with various external dienophiles. It was also concluded that calculations based on such simple terms of FMO theory are not enough to delineate any general trends in the reactivity/selectivity profile of orthoquinone monoketals with electron-deficient dienophiles.[11b,14] These reactions are analogous to the dimerization reactions in the sense that the $C_{4'}-C_{5'}$ double bond of the orthoquinone monoketal unit acting as a dienophile is under the influence of the electron-withdrawing effect of the 2-en-1-one unit of the system (Scheme 2). Thus, the stabilizing effects observed with a bromine atom or a *tert*-butyldiphenylsilyloxymethyl group at the 4-position of the cyclohexa-2,4-dienone system, as well as with a methoxy group at the 5-position, are simply due to the size of the substituent rather than to its electronic effect. Although the methoxy group does not exhibit a large steric demand, its presence at the 5-position of the system such as in **4f** can still block the cyclodimerization by mutually interfering with the geminal groups at the sp^3-hybridized C_6 center of the other unit, as first suggested by Waring for generic cyclohexa-2,4-dienones (Scheme 2).[1d] The known blocking effect of a methyl group at the same position,[10b,11] as well as that of a bulky group at the 4-position,[8c,11b,c,12a] is probably due to the same type of steric impediment.[1d]

This first series of reactions confirmed previous observations made by us and others on the critical and fine influence exhibited by substituent positioning and size, rather than electronic effect, on the stability of orthoquinone monoketals. A bulky substituent at their 4-position blocked the Diels–Alder process, but the same substituent at their 3-position did not (entries 4 and 5 vs entries 2 and 3), and a relatively small group at their 5-position is enough to furnish nondimerizing species (entry 6). Three new examples are reported herein (entries 2–4, Table 1). Most importantly, anodic oxidation of 2-methoxyphenols in methanol appears as a valuable alternative methodology for generating nondimerizing orthoquinone monoketals.[8b,c]

TABLE 2. Anodic Oxidation of a Series of α-(2-Methoxyphenoxy)-2-methylpropionic Acids



entry	acids	OQBK[c,d]	OQMK[c,e]	DAD[c,f]
1	**2a** (Z = H)	**3a** (78)	**4h**, n.o.[g]	 **5h**[h] (100)[a] (21)[b]
2	**2b** (Z-4 = *n*-Pr)	**3b** (50)	**4i**, n.o. (Z-3 = *n*-Pr)	 **5i** (78)[a] (31)[b]
3	**2c** (Z-4 = $CH_2OTBDPS$)	**3c** (62)	**4j**, n.o. (Z-3 = $CH_2OTBDPS$)	**5j**, n.o.
4	**2d** (Z-5 = $CH_2OTBDPS$)	**3d** (42)	**4k**, n.o. (Z-4 = $CH_2OTBDPS$)	**5k**, n.o.
5	**2e** (Z-4 = Br)	**3e** (70)	**4l**, n.o. (Z-3 = Br)	 **5l** (78)[a] (24)[b]
6	**2f** (Z-5 = Br)	**3f** (53)	**4m** (71)[a] (52)[b] (Z-4 = Br)	**5m**, n.o.

[a] Reactions were carried out in $CH_3CN-MeOH$ (9:1) containing $LiClO_4$ as a supporting electrolyte. [b] Reactions were carried out in CH_3CN-H_2O (9:0) containing $LiClO_4$ as a supporting electrolyte. [c] Isolated yields are given in parentheses where applicable. [d] OQMK = orthoquinone monoketal. [e] OQBK = orthoquinone bisketal. [f] DAD = Diels–Alder dimer. [g] Not observed. [h] See ref 8a.

We then applied similar anodic oxidation conditions to a series of 2-alkoxyphenyl alkyl ethers of type **2**. For this, we used α-(2-methoxyphenoxy)-2-methylpropionic acids **2b**–**f** for which the first nucleophilic entities (i.e., R′OH) trapping the radical cation intermediate of type III into a radical of type IV are tethered to one of the alkoxy groups (Scheme 1). The incentive for this choice was initially based on the fact that 6-acetoxy-6-methoxycyclohexa-2,4-dienones (i.e., **4**, R = Me, R′ = Ac, Scheme 1) do not dimerize.[6,13] The reasons for this efficient blocking effect of a 6-acetoxy group are not known. Liao and co-workers suggested that one methoxy group in 6,6-dimethoxy derivatives participates in secondary orbital interactions (SOIs) through its oxygen lone pair to enhance the propensity of these species to self-dimerize (e.g., **4a** → **5a**, Scheme 2).[11b] A downward modulation of this orbital control with an adequately oriented acetoxy group in which the oxygen lone pair is now conjugated with the adjacent carbonyl group certainly opens up a track for further theoretical investigations (Scheme 2). In any event, we thought that having a cyclic version of the same ketal functionality would allow the generation of nondimerizing *O*-spirolactone cyclohexa-2,4-dienones (e.g., **4h**, Scheme 2), with the added advantage of introducing chiral centers next to the carbonyl group for asymmetric induction in subsequent transformations. Unfortunately, as we previously reported,[8a] the conformational constraint brought about by the cyclic structure counteracts any Diels–Alder blocking effect of the lactonic acyloxy unit and cyclodimers are readily produced (Scheme 2 and Table 2, entry 1). Furthermore, only α-dialkylated carboxylic units undergo the desired intramolecular spirocyclization thanks to the

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(14) (a) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856–866. (b) Gao, S.-Y.; Ko, S.; Lin, Y.-L.; Peddinti, R. K.; Liao, C.-C. *Tetrahedron* **2001**, *57*, 297–308. (c) Arjona, O.; Medel, R.; Plumet, J.; Herrera, R.; Jiménez-Vázquez, H. A.; Tamariz, J. *J. Org. Chem* **2004**, *69*, 2348–2354.

help of a *gem*-dialkyl Thorpe–Ingold effect, in contrast to α-monomethylated carboxylic acids and acetic acid derivatives that do not cyclize.[8a] Notwithstanding, we here wanted to identify an appropriate substitution pattern on α-(2-methoxyphenoxy)-2-methylpropionic acids that would permit the generation of stable *O*-spirolactone cyclohexa-2,4-dienones.

The two electrochemical tactics here available to us for carrying out such a task are the anodic oxidation-selective hydrolysis sequence to orthoquinone monoketals of type **4** (route *a*, Scheme 1) and their in situ generation by performing the anodic oxidation in the presence of water (route *b*, Scheme 1). Both approaches were implemented, and anodic oxidations of **2b**–**f** were carried out at a controlled potential in order to minimize the concomitant oxidation of water that would otherwise occur during constant-current electrolysis. The anode potential was set at 1.8 V vs Ag/AgCl. The electrolysis was stopped after passage of 2.5 F/mol. The anodic oxidation–hydrolysis sequence was first applied by performing the reaction in a CH_3CN–MeOH (9:1) solvent mixture. The *O*-spirolactone quinone bisketals **3b**–**f** were all obtained in yields ranging from 42 to 78% (Table 2). Selective hydrolysis of these bisketals led to different results depending on the nature and positioning of the substituents on the cylohexadienone ring. Treatment of bisketal **3a** with 10% aq HCl in acetone (1:1) for 30 min was sufficient to selectively hydrolyze it into the monoketal **4h**, which spontaneously dimerized into **5h** in quantitative yield. The structure of **5h** has been unambiguously determined by an X-ray analysis.[8a] Stronger acidic conditions (i.e., 2 N aq H_2SO_4 in acetone at room temperature for 30 min) had to be used to convert bisketal **3b** into the monoketal **4i**, which again quickly dimerized to furnish **5i** in 78% yield, indicating that the presence of the electron-releasing *n*-propyl group at the 3-position of the lactonic monoketal **4i** does not block the Diels–Alder process (Table 2, entry 2). It is already known from the work of Yamamura and co-workers that the presence of secondary alkyl groups or alkenyl groups with similar steric demand at the 4-position of orthoquinone monoketals does not prevent their dimerization.[9] Bisketal **3e** was hydrolyzed under the same conditions as for **3a**[8a] to furnish the dimer **5l** in 78% yield (Table 2, entry 5), indicating that a bromine atom at the 3-position of the lactonic monoketal **4l** does not express any retarding effect on the Diels–Alder dimerization process, as already observed for **4c** (Table 1, entry 3). However, monoketal **4m** was isolated in a good yield of 71% after selective hydrolysis of its bisketal parent **3f** under the same conditions (Table 2, entry 6), showing again the efficacy of a bromine atom at the 4-position in stabilizing the cyclohexadienone unit.

Direct evidence of this importance of the bromine atom positioning in the control of the Diels–Alder dimerization was obtained when a 1:1 mixture of the two regioisomers **3e** and **3f** was monohydrolyzed to cleanly furnish the dimer **5l** (46%) and the nondimerizing ketal **4m** (41%), respectively. Monohydrolysis attempts on bisketals **3c** and **3d** bearing a *tert*-butyldiphenylsilyloxymethylenyl group at their 4- and 5-positions, respectively, only led to untractable mixtures (Table 2, entries 3 and 4). The same disappointing observations were made when attempting to generate directly their monoketal versions by performing the anodic oxidation in the presence of water (route *b*, Scheme 1 and Table 2). For this approach, electrolyses of the α-(2-methoxyphenoxy)-2-methylpropionic acids **2b**–**f** were carried out at a constant current in a CH_3CN–H_2O (9:1) solvent mixture, still containing $LiClO_4$ as a supporting electrolyte. Under these conditions, the *O*-spirolactone quinone monoketals **4h/i** and **4l/m** behaved in a similar manner, but overall yields were consistently lower than those obtained by the two-step electrolysis-hydrolysis procedure (Table 2). All together, these results validate the anodic oxidation approach as an alternative to chemical means to transform either 2-alkoxyphenols of type **1** or 2-alkoxyphenyl alkyl ethers of type **2** into orthoquinone monoketals, which can be isolated as such if equipped with appropriate substituents at appropriate positions to prevent their cyclohexa-2,4-dienone unit from engaging in cyclodimerization. Furthermore, it is worth noting that these electrooxidations were carried out using a convenient single-cell system with electrolytic media compatible with the reduction events. In particular, no side-reduction of aryl bromides was observed in these reactions.

The [4 + 2] cyclodimerization of orthoquinone monoketals and related orthoquinols has been extensively studied over the last 50 years. Ample chemical evidence supported by a few crystallographic analyses has been gathered early on, in particular by Adler and coworkers,[11d,13,15] to confirm the structures of such dimers, but the extraordinary selectivity of this chemistry has not yet been thoroughly rationalized. Indeed, this Diels–Alder-type reaction exhibits extremely high site selectivity, regioselectivity, and stereoselectivity. The orthoquinone monoketal unit acting as a dienophile always engages its $C_{4'}$–$C_{5'}$ double bond, never its $C_{2'}$–$C_{3'}$ double bond, and the dimerization always furnishes dimers with ortho regiochemistry and anti stereochemistry (i.e., the $C_{3'}$–$C_{2'}$ double bond is adjacent and anti to the C_1 carbonyl group, Scheme 2).[14a] The anti selectivity can be classically explained as resulting from an *endo* transition state that is preferred over the *exo* alternative because it is stabilized by SOIs between the $C_{2'}$–$C_{3'}$ double bond of the monomer acting as a dienophile and the olefinic double bonds of the monomer acting as a diene. However, the ortho regioselectivity of the process remains puzzling. Again, calculations of atomic coefficients of both the HOMO and LUMO we performed on the dimerizing orthoquinone monoketals **4a** and **4c** do not provide any clear-cut rationale (see Supporting Information). For the HOMOs, coefficients at C_2 and C_5 are both the largest ones but are nearly the same, with a somewhat larger coefficient at C_2, and for the LUMOs, the largest coefficients are at $C_{3'}$, so the observed regioselectivity cannot be explained on this basis, since it would at best favor a participation of the $C_{2'}$–$C_{3'}$ double bond as a dienophile.

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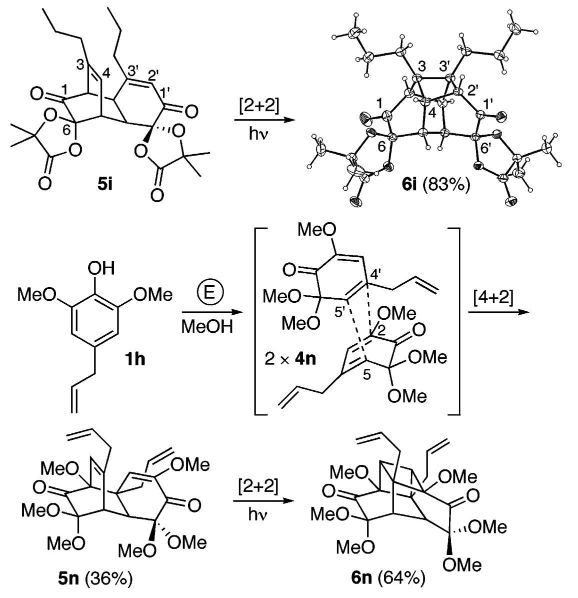
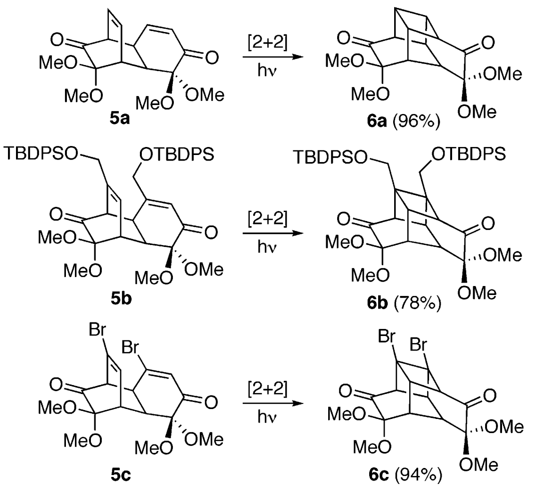
(15) (a) Adler, E.; Andersson, G.; Edman, E. *Acta Chem. Scand.* **1975**, *B 29*, 909–920. (b) Adler, E.; Holmberg, K.; Ryrfors, L.-O. *Acta Chem. Scand.* **1974**, *B 28*, 888–894. (c) Adler, E.; Holmberg, K. *Acta Chem. Scand.* **1974**, *B 28*, 465–472. (d) Adler, E.; Holmberg, K. *Acta Chem. Scand.* **1974**, *B 28*, 549–554. (e) Adler, E.; Holmberg, K. *Acta Chem. Scand.* **1971**, *25*, 2775–2776. (f) Adler, E.; Brasen, S.; Miyake, H. *Acta Chem. Scand.* **1971**, *25*, 2055–2069. (g) Adler, E.; Junghahn, L.; Lindberg, U.; Berggren, B.; Westin, G. *Acta Chem. Scand.* **1960**, *14*, 1261–1273. (h) Metlesics, W.; Wessely, W. *Monatsch. Chem.* **1957**, *88*, 108–117. For X-ray analyses, see: (i) Karlsson, B.; Kierkegaard, P.; Pilotti, A.-M.; Wiehager, A.-C.; Lindgren, B. O. *Acta Chem. Scand.* **1973**, *27*, 1428–1430.

SCHEME 3



SCHEME 4



If we compare the coefficients at C_2 and C_5 of the LUMO of one orthoquinone monoketal acting as the diene partner, the C_5 coefficient is the largest one of the two, but the slightly larger coefficient of the HOMO of the other orthoquinone monoketal unit acting as the dienophile is at $C_{2'}$. It has already been reported that Diels–Alder reactions of dienes and dienophiles terminally substituted by electron-demanding groups cannot be explained in terms of simple FMO theory when unperturbed reactants are considered but that other factors such as SOIs at the transition state level may be controlling these dimerization regioselectivities.[11b,16]

In the case of orthoquinone monoketal-derived [4 + 2] cycloadducts, their inherent reactivity might actually provide further insight into their remarkable regioselectivity. In an attempt to confirm the structure of **5i** (Table 2) by X-ray crystallography, we let a sample of this dimer (i.e., 10 mg) in CH_2Cl_2 be exposed to light on the bench. Crystallization did occur slowly, but the compound we obtained was **6i** (see the ORTEP diagram in Scheme 3), resulting from an intramolecular [2 + 2] cyclobutanation. This is a well-known process of cyclohexa-2,4-dienone photochemistry,[17,18] which has been, inter alia, judiciously exploited by Yamamura and co-workers for the synthesis of neolignan-type compounds.[9c,g,i,j,l,n] For example, isoasatone **6n** was synthesized in 64% yield by irradiating asatone **5n**,[9n] which has been prepared in 36% yield by electrolyzing at constant current (0.31 mA/cm^2) a solution of 4-allyl-2,6-dimethoxyphenol (**1h**) in methanol containing $LiClO_4$ as a supporting electrolyte to furnish the orthoquinone monoketal **4n**; this monoketal quantitatively dimerized into **5n** upon standing overnight at room temperature (Scheme 3).[9c,19] With this precedent directly related to our work in mind, we submitted **5i** in a 3:1 *n*-hexanes–Et_2O solution to irradiation at room temperature using a medium-pressure mercury lamp with a Pyrex filter. The bicyclo[2.2.2]octenone **5i** was thus cleanly converted to the pentacyclododecanedione **6i** in 83% yield (Scheme 3).

Dimers **5a**–**c** were then submitted to the same photochemical reaction conditions and again cleanly furnished the corresponding [2 + 2] photodimers **6a**–**c** featuring two fused four-membered rings. Despite their intrinsic strain energy, these cage compounds are quite stable and they all exhibit very simple NMR signal patterns, because their structure is characterized by a 2-fold axis of symmetry, all atoms and substituents constituting equivalent pairs around this axis (see Supporting Information).[17,18] The structures of **6a**–**c** are here deduced by analogy with that of **6i**, which has been unambiguously determined by X-ray crystallography (Schemes 3 and 4). Furthermore, the X-ray structure of **6i** confirmed the structure of its [4 + 2] dimer parent, and hence those of all the dimers described therein (Tables 1 and 2) that all exhibit the same spectroscopic criteria. Of particular note is the fact that the racemic *O*-spirolactones **5h**,[8a] **5i**, and **5l** exclusively result from dimerization of **4h**, **4i**, and **4l**, respectively, in which the configuration at $C_6/C_{6'}$ is the same (*S*/*S* shown or *R*/*R*) with the two less sterically demanding acyloxy units pointing toward each other and the two *gem*-dimethyl units pointing away from each other during the Diels–Alder approach. No dimer resulting from the pairing of two enantiomers of different configuration at $C_6/C_{6'}$ is formed. This diastereoselectivity is further evidence of the extraordinary manner with which these [4 + 2] cyclodimerizations are controlled, but again, this stereoselectivity still demands to be further explained. How-

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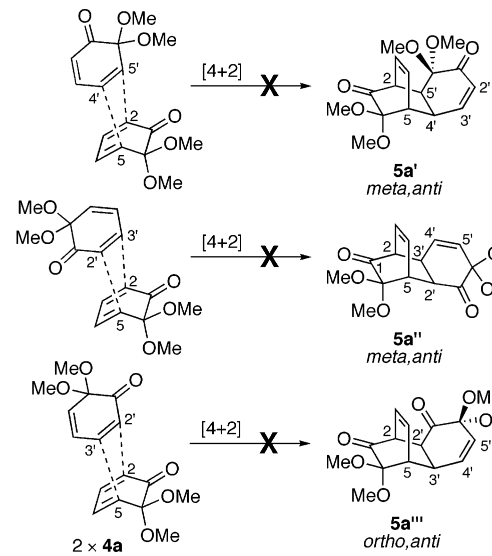
[16] (a) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092–4094. (b) Houk, K. N.; Domelsmith, L. N.; Strozier, R. W.; Patterson, R. T. *J. Am. Chem. Soc.* **1978**, *100*, 6531–6533. (c) Alston, P. V.; Ottenbrite, R. M.; Guner, O. F.; Shillady, D. D. *Tetrahedron* **1986**, *42*, 4403–4408. (d) Alston, P. V.; Ottenbrite, R. M.; Shillady, D. D. *J. Org. Chem.* **1973**, *38*, 4075–4077. (e) Fleming, I.; Michael, J. P.; Overman, L. E.; Taylor, G. F. *Tetrahedron Lett.* **1978**, *15*, 1313–1314. (f) Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523–531.

[17] (a) Hamada, T.; Iijima, H.; Yamamoto, T.; Numao, N.; Hirao, K.-i.; Yonemitsu, O. *J. Chem. Soc., Chem. Commun.* **1980**, 696–697. (b) Iwakuma, T.; Hirao, K.-i.; Yonemitsu, O. *J. Am. Chem. Soc.* **1974**, *96*, 2570–2575. (c) Iwakuma, T.; Yonemitsu, O.; Kanamaru, N.; Kimura, K.; Witkop, B. *Angew. Chem., Int. Ed.* **1973**, *12*, 72–73.

[18] (a) Becker, H.-D.; Konar, A. *Tetrahedron Lett.* **1972**, 5177–5180. (b) Antus, S.; Nogradi, M.; Baitz-gacs, E.; Radics, L.; Becker, H.-D.; Karlsson, B.; Pilotti, A.-M. *Tetrahedron* **1978**, *34*, 2573–2577.

[19] For another synthesis of asatone **5n** by oxidation of **1h** using (diacetoxy)iodobenzene, see: Kürti, L.; Szilagyi, L.; Antus, S.; Nogradi, M. *Eur. J. Org. Chem.* **1999**, 2579–2581. These authors claimed an improved synthesis of **5n**, but the corresponding yield they reported is only 22%.

SCHEME 5



ever, as alluded to above, an explanation can be proposed for their ortho regioselectivity on the basis of the facility with which orthoquinone monoketal-derived *endo*-dimers can be photochemically converted into [2 + 2] pentacyclododecanediones. This facility may be a consequence of the SOIs that can take place between their $C_{2'}$, $C_{3'}$, C_3, and C_4 sp^2-centers (Scheme 2, 2 × **4a** → **5a**). In other words, these stabilizing SOIs could be the factor that kinetically selects the transition state path leading not only to the *endo*(anti) stereochemistry[17,18] but also to the ortho regiochemistry exclusively observed for these dimers. Upon irradiation, these [4 + 2]-controlling SOIs are then allowed to engage into the bond-making events of the [2 + 2]-cyclization.

The presence of additional substituents on the dimerizing orthoquinone monoketals does not appear to have any major deleterious effects on the facility with which the [2 + 2] cycloaddition occurs, since dimers **5a**–**c** and **5i** were here all readily and cleanly converted to their corresponding pentacyclododecanedione photodimers (Schemes 3 and 4). For the sake of simplicity, only the three alternative *endo* approaches of two orthoquinol monoketal units **4a** are depicted in Scheme 5, including those for which the $C_{2'}-C_{3'}$ double bond acts as a dienophile that would give rise to the meta/anti dimers **5a″** and the ortho/anti dimer **5a‴**. These two possibilities can be ruled out on the basis that the remaining $C_{4'}-C_{5'}$ double bond loses its conjugation with the electronic-demanding $C_{1'}$ carbonyl group in the process, thus probably affecting the extent of any participation of this double bond in SOIs with the C_3 and C_4 *p*-orbitals of the other **4a** unit (Scheme 5). Could this trivial hypothesis constitute a premise for a theoretical rationalization of the yet unexplained site-selectivity observed in these orthoquinone monoketal Diels–Alder dimerizations? Turning our attention back to the ortho regioselectivity observed in the participation of the $C_{4'}-C_{5'}$ double bond as a dienophile, a simple comparative examination of molecular models of the [4 + 2] cycloadducts resulting from (1) the operational approach during which the $C_{4'}-C_{5'}$ double bond of one unit respectively connects with the C_2 and C_5 sp^2-centers of the other unit (Scheme 2) and (2) the alternative approach during which the same double bond would respectively connect with the C_5 and C_2 sp^2-centers of the other unit (Scheme 5) indicates that the latter [4 + 2] approach does not permit the most adequate sp^2 orbitals' alignment for extra stabilization from SOIs and, hence, subsequent photocyclization during which the same orbital interactions are involved in the observed [2 + 2] bond-making events. In both cases, the $C_{2'}-C_{3'}$ double bond remains conjugated with the $C_{1'}$ carbonyl group that can hence behave as an effective intramolecular triplet sensitizer in the process;[20] however, the orbitals alignment differences are in favor of the case resulting in product formation, that is, **5a** (Scheme 2) and not **5a′** (Scheme 5). The only other explanation that has been put forward early on to rationalize this remarkable regioselectivity in the [4 + 2] cycloaddition of cyclohexa-2,4-dienones relied on an agreement to the principle of the lowest dipole moment of the transition state: dimers of type **5a** displaying a lower dipole than dimers of type **5a′**.[21] Such an argument is certainly valid, but our hypotheses deserve to be examined with the help of computer-based molecular modeling, as they constitute new premises for such theoretical investigations.

In conclusion, this work has demonstrated that anodic oxidation of 2-methoxyphenols of type **1** and α-(2-methoxyphenoxy)-2-methylpropionic acids of type **2** is a valuable alternative to the use of chemical oxidants to generate orthoquinone monoketals, which are stable if properly equipped with substituents to block their [4 + 2] cyclodimerization. When formed, the corresponding dimers can be readily converted to C_2-symmetric cage photodimers. Suggestions were made on the basis of this [2 + 2] reactivity to explain the extraordinary site selectivity, regioselectivity, and stereoselectivity observed in the [4 + 2] cyclodimerization of orthoquinone monoketals. Computational work is in progress with the aim of providing a sound rationalization of this chemistry at the theoretical level, and results will be reported in due course.

Experimental Section

General Procedures for Electrochemical Oxidation. *Procedure A.* Constant-current electrolyses were carried out 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 and a copper wire (0.5 mm diameter) as the cathode. Lithium perchlorate ($LiClO_4$, 1.5 g, 14.0 mmol) was added as a supporting electrolyte to anhydrous MeOH (50 mL). The starting material was introduced ,and the electrolysis was then performed at 50 or 100 mA using a regulated DC power supply until the desired charge passed (ca. 2.5 F/mol). All reactions were vigorously stirred. After electrolysis, the solution was evaporated, and the residue was diluted in CH_2Cl_2 (50 mL) and washed with H_2O (3 × 30 mL). The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to dryness. *Procedure B.* Controlled-potential electrolyses were carried out 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 and a copper wire (0.5 mm diameter) as the cathode. Lithium perchlorate ($LiClO_4$, 1.5 g, 14.0 mmol) was added as supporting

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[20] de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41.

[21] Brown, T. L.; Curtin, D. Y.; Fraser, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 4339–4341.

electrolyte to a 50 mL mixture of acetonitrile–methanol or acetonitrile–water (9:1). The starting acid and the base (e.g., 2,6-lutidine or pyridine, 2 equiv) were introduced, and the electrolysis was then performed at constant potential on a 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 CH_2Cl_2 (50 mL) and washed with H_2O (3 × 30 mL). The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to dryness.

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Supporting Information Available: Detailed descriptions of experimental procedures, ^{1}H and ^{13}C NMR spectra of compounds **1b**–**d**,**g**, **2b**–**f**, **3b**–**f**, **4d**–**f**,**m**, **5a**–**c**,**i**,**l**, and **6a**–**c**,**i**, an ORTEP diagram and a CIF file (CCDC 245748) of the X-ray structure of **6i**, and HOMO/LUMO energies, atomic coefficients, and computational data of compounds **4a**,**c**,**e**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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