Iodane-mediated and electrochemical oxidative transformations of 2-methoxy- and 2-methylphenols

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Dedicated to Professor Anastasios Varvoglis on his 65th birthday
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Abstract
A series of 2-methoxy and 2-methylphenols have been submitted to oxygenative oxidation reactions using (1) the λ^3-iodane DIB, (2) a non-explosive and non-moisture sensitive version of the λ^5-iodane IBX, named SIBX for Stabilized IBX, and (3) anodic oxidation with the aim of identifying the best reaction conditions for preparing orthoquinonoid cyclohexadienone synthons. Both the use of DIB and anodic oxidation appeared equally valuable for making orthoquinone dimethyl ketals, but the λ^3- and λ^5-iodane reagents are more appropriate to induce *ortho*-oxygenation of 2-methylphenols. In particular, SIBX emerged as a useful reagent for mediating *ortho*-hydroxylation into dimerizing orthoquinols, a tactic that can be applied to the synthesis of natural bis(monoterpenoids) such as aquaticol.

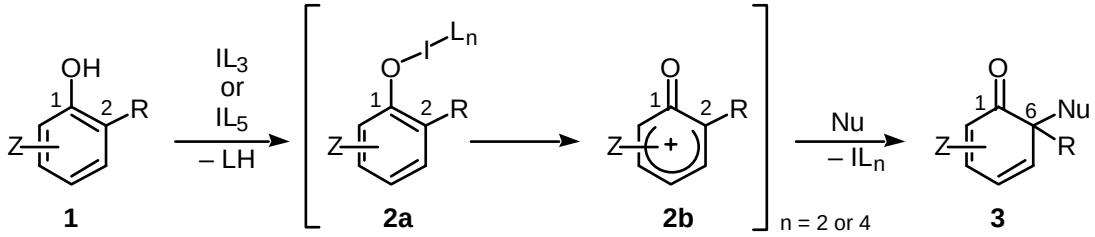
Keywords: Iodanes, arenols, oxidation, electrochemistry, orthoquinols, Diels–Alder

Introduction

Hypervalent iodine reagents are used for mediating a wide variety of synthetic transformations including halogenation, azidation, sulphenylation, arylation and other carbon ligand transfer, carbene insertion, carbocyclization, epoxidation and numerous oxygenative or dehydrogenative oxidation reactions.[1-7] In particular, both iodine(III) and iodine(V) compounds of the IL_3 and IL_5 types in which L is a monovalent electronegative ligand (i.e., λ^3-iodanes and λ^5-iodanes) can advantageously replace heavy metal-based reagents as inexpensive, non-toxic and yet efficient oxidants. The λ^3-iodanes most commonly used today in oxidation reactions, including

oxygenation reactions such as acetoxylation, methoxylation, hydroxylation, tosyloxylation and epoxidation, are (diacetoxyiodo)benzene (DIB), [bis(trifluoroacetoxy)iodo]benzene (BTI), [hydroxy(tosyloxy)iodo]benzene (HTI or "Koser's reagent")[8] and iodosylbenzene (PhIO, IOB). The Dess-Martin periodinane (DMP)[9,10] and its benziodoxole oxide precursor, 2-iodoxybenzoic acid (IBX),[11] are among the cyclic λ^5-iodanes that have found the broadest practical applications in organic synthesis, especially as mild and selective reagents for the oxidation of alcohols.[1,12] Depending on substrates and reaction conditions, both radical and ionic chemistries are available to λ^3- and λ^5-iodanes, which usually react in a more chemoselective manner than their higher iodine(VII) homologues such as periodic acid and periodates that are also used for oxidative transformations.[13,14]

Our research endeavor on the synthetic uses of orthoquinone monoketals and orthoquinol variants[15,16] initially led us to elect the λ^3-iodanes DIB and BTI as the reagents of choice to convert arenols, and in particular 2-alkoxy- or 2-alkylarenols, into the desired orthoquinonoid 6-oxocyclohexa-2,4-dienones.[17-19] In this article, we describe a selection of such oxidative transformations of arenols, which encompasses not only the use of DIB but also that of a newly developed λ^5-iodane reagent, named SIBX[20] for Stabilized IBX that otherwise decomposes violently.[21-23] Furthermore, results from certain of these iodane-mediated oxidations are compared to those obtained by anodic oxidation, a technique we are also evaluating as another environmentally benign means for the synthesis of orthoquinonoid cyclohexadienone synthons.



R = alkyl or alkoxy group; Z = various substituents; Nu = external or internal nucleophile from iodine ligand (L) or ring substituent (Z)

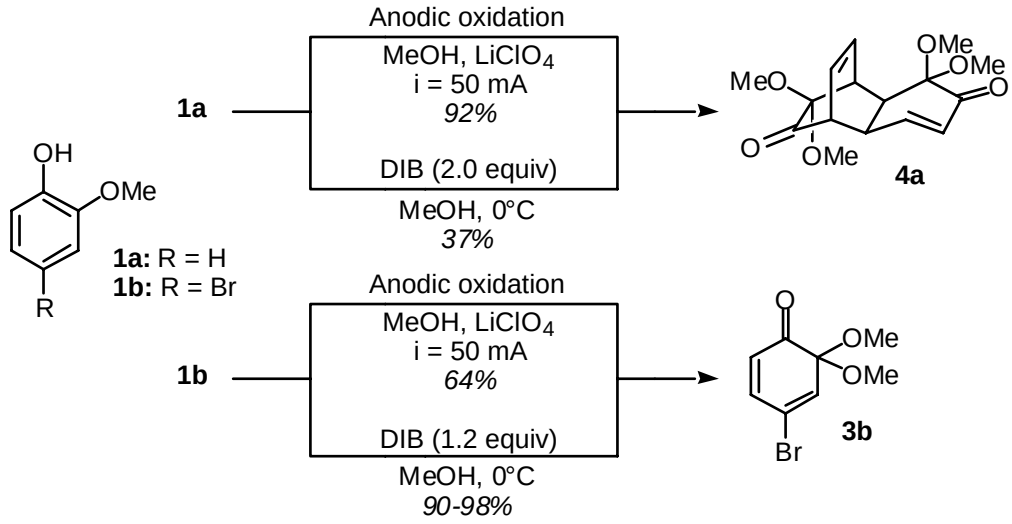
Scheme 1

Results and Discussion

The oxidative activation of 2-alkoxy- and 2-alkylarenols of type **1** is a valuable tactic for the synthesis of oxygenated carbo- and heterocyclic motifs of natural products.[15,16,24] This activation can easily find expression in the displacement of two ring electrons through the aryloxyiodane intermediate of type **2a**, which is generally thought to evolve into the arenoxenium ion of type **2b**, with concomitant loss of the phenol hydrogen (Scheme 1).[15,16] In the presence of a nucleophile (Nu), this electrophilic species can be trapped in an either concerted or stepwise

fashion to give rise to synthetically useful cyclohexadienone derivatives of type **3**, if the group at the 2-position of the starting arenol **1** can efficiently control the regiochemistry of the attack at that position (Scheme 1).

The λ^3-iodane DIB in CH_2Cl_2 is particularly efficient at performing oxidative acetoxylation of 2-methoxyarenols into 6-acetoxy-6-methoxycyclohexa-2,4-dienones of type **3** (R = OMe, Nu = OAc), also called orthoquinol acetates. We have already reported several examples of this alternative to the lead tetraacetate-mediated Wessely oxidation.[17,18,25-27] Of particular significance is the fact that the orthoquinol acetates do not succumb to Diels-Alder dimerization processes as easily as their 6,6-dimethoxy analogues (R = Nu = OMe), and hence can be exploited in various synthetic schemes.[15] The 6,6-dimethoxycyclohexa-2,4-dienone derivatives, or orthoquinone monoketals, are most conveniently prepared by oxidative methoxylation using DIB in MeOH and can be trapped in situ by either dienophiles or, in some instances, dienes to construct rapidly complex carbocyclic systems.[15,16] Their propensity to dimerize via [4+2] cycloaddition can be significantly diminished by having either a bromine substituent at the 4-position or a small alkyl or alkoxy group at the 5-position[28] of the cyclohexa-2,4-dienone core.[15,29-31] For example, the orthoquinone dimethyl monoketal **3a** (Z = H, R = Nu = OMe) derived from guaiacol **1a** spontaneously dimerizes into the *endo*-cycloadduct **4a**, as first observed by Andersson and Berntsson[32] when submitting **1a** to the periodate-mediated Adler oxidation in MeOH.

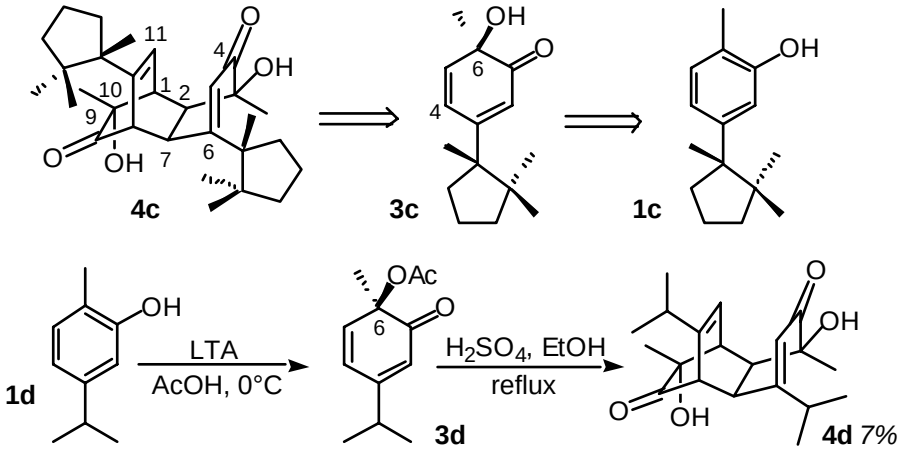


Scheme 2

We observed the same dimerization in 37% via DIB-mediated oxidative methoxylation of **1a**[27] and improved the yield of this dimerization up to 92% by anodic oxidation at constant current under neutral conditions (Scheme 2). Under these conditions, electrooxidation of a phenol is expected to give rise to a phenoxenium ion intermediate of type **2b** (Scheme 1). In contrast, the 4-bromo derivative **3b** is stable enough to be isolated as such. Anodic oxidation of

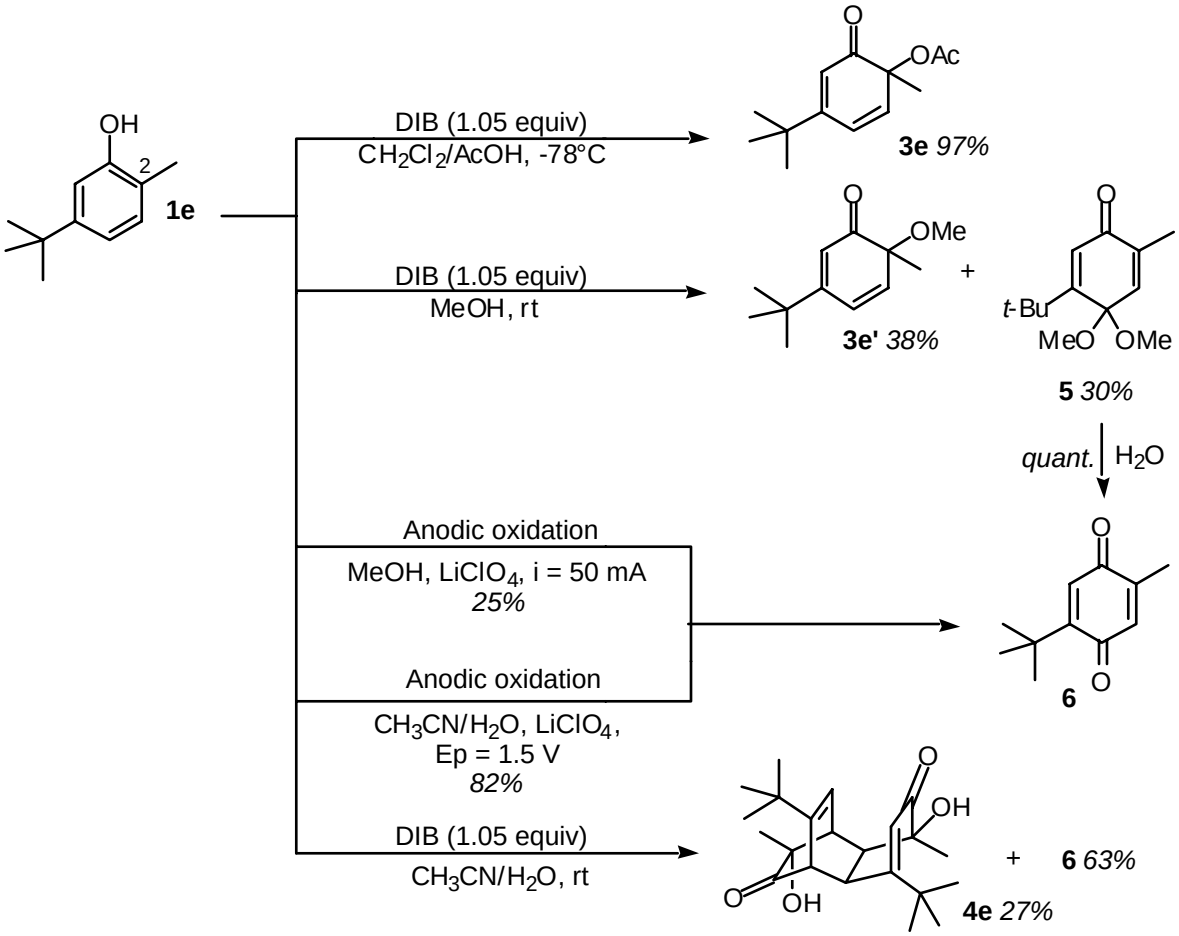
4-bromoguaiacol (**1b**) furnished **3b** in 64% yield, and DIB-mediated oxidative methoxylation of **1b** at 0°C has been reported to furnish **3b** in yields ranging from 90 to 98% (Scheme 2).[33]

Our current studies toward the total synthesis of (+)-aquaticol (**4c**), a novel bis-sesquiterpene isolated from the traditional Chinese medicine *Veronica anagallis-aquatica*,[34,35] led us to examine various oxidative *ortho*-oxygenations of 2,4-dialkylated phenols. It has been postulated that (+)-**4c** derives from a Diels-Alder dimerization of the naturally occurring sesquiterpenoid orthoquinol (*6R*)-**3c**, itself probably biosynthesized via a stereoselective oxidative hydroxylation of the (+)-cuparene-derived phenol **1c** (Scheme 3).[34,35]



Scheme 3

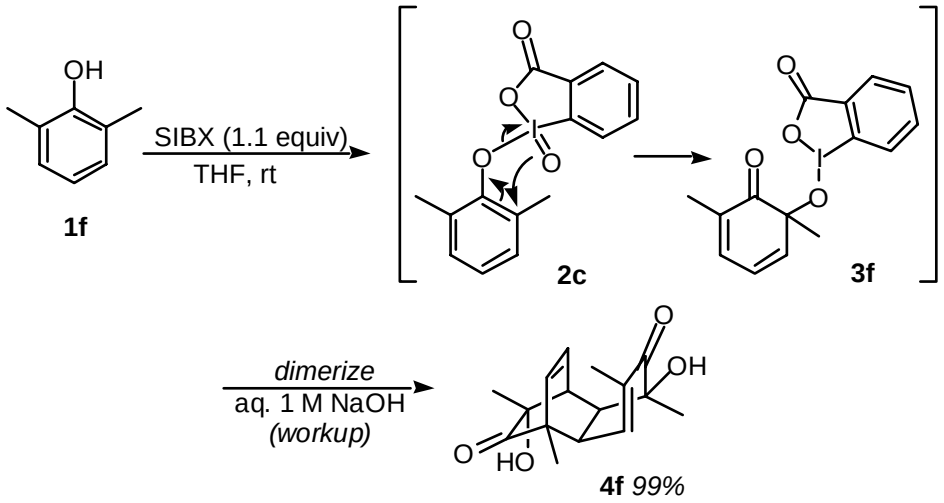
This sequence of transformations should be amenable to chemical synthesis, and 2-methyl-5-*tert*-butylphenol **1e** was selected as a model phenol to evaluate the potential of such a biomimetic approach to aquaticol. Initially, we planned to generate the stable orthoquinol acetate **3e** that would subsequently be hydrolyzed to induce dimerization. A similar approach had already been followed by Carman and co-workers in their synthesis of the *Callitris macleayana* carvacrol (2-methyl-5-*iso*-propylphenol)-derived diterpene **4d** (Scheme 3).[36,37] For both **4c** and **4d**, the Diels–Alder cyclodimerization follows an *endo*-selective back-to-back mutual approach of the face of the orthoquinol on which resides the hydroxy group with a regioselective participation of the 4,5-double bond of the 2π partner, as it is the case for all reported cyclodimerizations of orthoquinols.[15] More recently, K. C. Nicolaou's and E. J. Corey's groups exploited the relative stability of orthoquinol acetates and resolved sorbicillin-derived species by chromatographic separation. The appropriate acetate enantiomer was then hydrolyzed to induce dimerization into bisorbicillinoid natural products.[38,39] We tried to implement the same various deacetylation procedures to our racemic acetate **3e**, which was generated in quasi quantitative yield by oxidative acetoxylation of **1e** using DIB in CH_2Cl_2/AcOH at –78°C (Scheme 4), but no clean dimerization was observed.



Scheme 4

We then decided to submit **1e** to the DIB-mediated oxidative methoxylation conditions with the expectation that the orthoquinol methyl ether intermediate **3e'** would spontaneously undergo the requisite [4+2] cycloaddition at room temperature. In fact, **3e'** was isolated in 38% yield, together with the paraquinone dimethyl monoketal **5** in 30% yield (Scheme 4). This loss of regioselectivity in the trapping of a reaction intermediate of type **2** can be putatively attributed to the harder nucleophilic character of MeOH relatively to that of AcOH, and to the lack of differences in electrophilic reactivity between the methyl-substituted C-2 and the unsubstituted C-4 centers of **1e**. An attempt to dimerize **3e'** by heating it in a toluene solution was to no avail. The monoketal **5** was quantitatively converted into the paraquinone **6** upon standing in the fridge during a couple of weeks; this ketal hydrolysis was certainly engendered by residual H_2O and traces of AcOH left after workup. Anodic oxidation of **1e** in MeOH at constant current was totally inefficient in making **3e'**, and the only product isolated after an aqueous workup was the paraquinone **6** in 25% yield (Scheme 4). The anodic oxidation of **1e** was then performed in the presence of H_2O as the nucleophilic trapping agent instead of MeOH in the hope that an excess of H_2O would help in forming a product mixture composed of both the paraquinone **6** and the

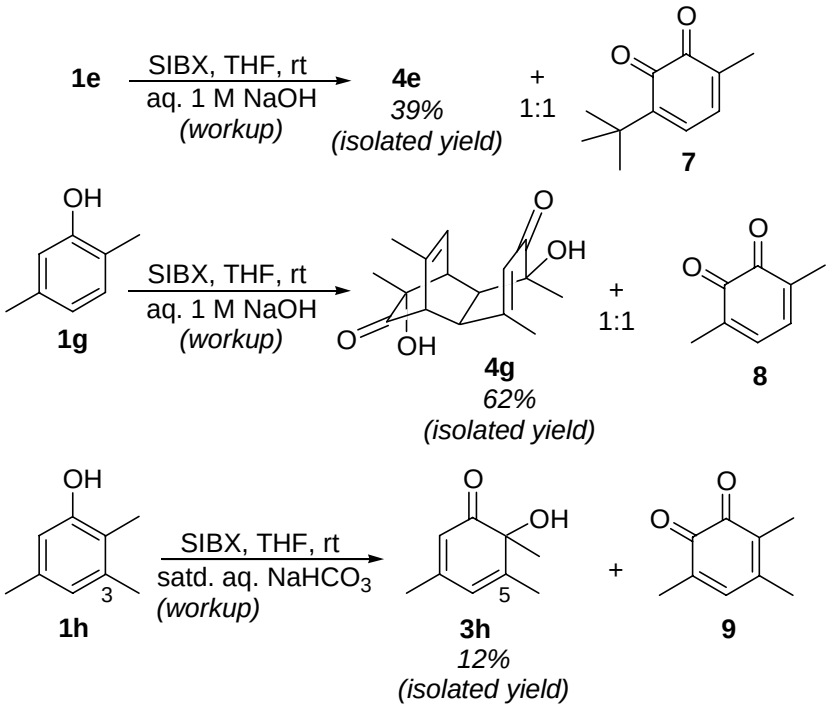
orthoquinol-derived dimer **4e**. The electrooxidation of **1e** was this time carried out at controlled potential in order to minimize the concomitant oxidation of water that would occur during constant current electrolysis. The anode potential was set 100 mV anodic of the peak potential value for **1e** (Ep = 1.411 V *vs.* Ag/AgCl), as measured by cyclic voltammetry.[40] The electrolysis was stopped after passage of 2.5 F/mol. Surprisingly, the only product generated under these conditions was the paraquinone **6** (Scheme 4). Notwithstanding this failure of the anodic oxidation reaction, a DIB-mediated oxidative hydroxylation was attempted using again a CH_3CN/H_2O solvent mixture. The desired *endo*-cyclodimer **4e** was thus obtained in 27% yield, together with the paraquinone **6** (63%) and some recovered starting phenol **1e** (8%). This result, which constitutes an almost four-fold yield improvement relatively to Carman's two-step dimerization of the *iso*-propyl analogue **1d** (Scheme 3), was quite encouraging, even though the *para*-selectivity of the H_2O attack and its electrochemical emphasis remain difficult to explain. In search of a solution to futher improve the dimerization yield, it appeared that a reagent capable of delivering an oxygen atom after being fixed on the phenolic oxygen would be ideal for *ortho*-selective oxygenation. The diphenylseleninic anhydride-mediated Barton oxidation[41,42] was an obvious method to try, but a recent report by Pettus and co-workers[43] on the use of IBX for regioselective *ortho*-oxygenation of phenols brought us to select this λ^5-iodane reagent. These authors actually reported a yield of 51% for the conversion of 2,6-dimethylphenol **1f** into the dimer **4f** (Scheme 5).[43,44]



Scheme 5

We first repeated this reaction with a few modifications; the Stabilized IBX, or SIBX,[20] was used in THF at room temperature, and a final workup step with aqueous 1M NaOH instead of aqueous sodium dithionite furnished pure **4f** in quasi quantitative yield (Scheme 5). The same reaction conditions were then applied to **1e** to furnish a clean 1:1 mixture of the dimer **4e** and the double-oxidized orthoquinone **7** (Scheme 6). Roughly, two thirds of the starting phenol **1e** has

thus reacted at its methylated C-2 position despite the higher steric impediment at that position relatively to the other *ortho*-position. The development of a partial positive charge at C-2, which would be stabilized by the attached methyl group, may be proposed as an explanation for this regioselectivity, assuming that the reaction follows an oxidative nucleophilic substitution pathway. Separation of the product mixture by silica gel chromatography gave pure **4e** in 39% yield. 2,5-Dimethylphenol (**1g**) also gave rise to an analogous 1:1 mixture composed of the orthoquinone **8**[45] and the dimer **4g**, which was this time isolated in 62% yield. This dimer has previously been synthesized by Adler and Holmberg[46] in only 12% via the periodate-mediated Adler oxidation.



Scheme 6

Finally, the SIBX-mediated oxidation of 2,3,5-trimethylphenol (**1h**) was carried out to verify the fact that a small alkyl substituent at the C-5 position of the cyclohexa-2,4-dienone core is sufficient to block the [4+2] cyclodimerization.[15,28] Indeed, no dimer was observed and a clean 1:1 mixture of the orthoquinol **3h**[47] and the orthoquinone **9** was obtained in *ca*. 83% yield. The orthoquinol **3h** was separated from **9** by silica gel chromatography in a mere yield of 12%. Of particular note is the fact that, in contrast to the use of DIB (Scheme 2), SIBX-mediated oxygenation of guaiacol (**1a**) and 4-bromoguaiacol (**1b**) led to intractable mixtures, and 2-methoxyphenols bearing an electron-withdrawing group such as vanillin and isovanillin failed to undergo any oxidation. The latter remark confirms observations already made by Pettus and co-workers.[43]

Conclusions

This comparative study of iodane-mediated and electrochemical oxidations revealed the newly developed SIBX reagent,[20] an environmentally safe version of IBX, as an efficient λ^5-iodane alternative for promoting *ortho*-oxygenation of 2-methylarenols. This regioselectivity is a consequence of the intramolecular delivery of an oxygen atom from the iodine(V) center of the aryloxyiodane intermediate (**2c**) to the carbon-2 center of the aryloxy unit with concomitant reduction into an orthoquinoxy-λ^3-iodane species (**3f**). This one-pot synthesis of orthoquinols from 2-methylarenols will be applied to the synthesis of aquaticol (**4c**). This work and other synthetic applications of SIBX are currently in progress and will be reported in due course.

Experimental Section

General Procedures. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from sodium/benzophenone under N_2 immediately before use. Dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), and methanol (MeOH) were distilled under N_2 prior to use from CaH_2, P_2O_5, and $CaCl_2$, respectively. Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N_2. Evaporations were conducted under reduced pressure at temperatures less than 45 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 40-63 μm silica gel (Merck) and the indicated solvents. Further drying of the residues was accomplished under high vacuum. Melting points are uncorrected. NMR spectra of samples in the indicated solvent were run at 200, 250, 300 or 400 MHz. Carbon multiplicities were determined by DEPT135 experiments. Electron impact (50-70 eV) and liquid secondary ion mass spectrometry low and high resolution (EIMS, and LSIMS, HRMS) were obtained from the mass spectrometry laboratory at the CESAMO, Université Bordeaux 1.

General procedure for SIBX-mediated oxidation

To a stirred solution of starting phenol (*ca*. 100 mg) in dry THF (*ca*. 0.4 M) was added 1.1 equivalent of stabilized *o*-iodoxybenzoic acid (SIBX, Simafex, France) in one portion. After stirring at room temperature for 18 h, the reaction mixture was poured into a stirred ice-cold mixture of CH_2Cl_2 (3 mL) and H_2O (5 mL), treated dropwise with ice-cold 1 M NaOH until pH 8, and extracted with CH_2Cl_2 (2 × 5 mL). The combined extracts were then washed with water (3 × 10 mL), dried over Na_2SO_4, filtered and evaporated to afford products of good to excellent purity. When deemed necessary, further purification and/or product separation were carried out by silica gel column chromatography.

General procedure 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 (available from Magneto-Chemie) and a copper wire (0.5 mm diameter) as the cathode. Lithium perchlorate ($LiClO_4$, purchased from Acros, 1.5 g, 14.0 mmol) was added as a supporting electrolyte to dry MeOH (50 mL). The starting material was introduced, and the electrolysis was then performed at 50 mA, provided by a Sodilec SDRL02-120 regulated DC power supply, until the desired charge passed (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.* Constant potential electrolyses were performed according to the method we previously described.[40]

3,3,10,10-Tetramethoxytricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (4a). Electrooxidation of a solution of guaiacol **1a** (211 mg, 1.70 mmol) was performed according to the procedure A. The reaction mixture was then processed as described above, and the residue was purified by column chromatography, eluting with pentanes/Et_2O [(2:1) → (1:1)], to furnish pure dimer **4a** as fine off-white crystals (241 mg, 92%). All spectroscopic data were identical to those previously reported.[32,40]

4-Bromo-6,6-dimethoxycyclohexa-2,4-dienone (3b). Electrooxidation of a solution of 4-bromo-2-methoxyphenol (**1b**, 171 mg, 0.84 mmol)[48] was performed according to the procedure A. The reaction mixture was then processed as described above, and the oily residue was purified by column chromatography, eluting with pentanes/Et_2O (2:1), to furnish the pure orthoquinone monoketal **3b** as a yellow oil (126 mg, 64%): IR (NaCl) 1689, 1631 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.37 (s, 6H), 5.96 (d, J = 10.1 Hz, 1H), 6.66 (d, J = 1.8 Hz, 1H), 6.87 (dd, J = 1.8, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 192.8, 143.2, 135.3, 126.6, 119.4, 92.9, 50.2; EIMS *m/z* (rel intensity) 234 (M^+, 22), 232 (M^+, 22), 219 (4), 217 (4), 204 (9), 203 (21), 202 (9), 201 (21), 153 (52), 125 (100).

6-Acetoxy-3-*tert*-butyl-6-methylcyclohexa-2,4-dienone (3e). 5-*tert*-Butyl-2-methylphenol (**1e** 100 mg, 0.61 mmol)[49] was submitted to the DIB-mediated oxidative acetoxylation method we previously described[18] to furnish **3e** as an orangish oil (131 mg, 97%): IR (NaCl) 1750, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.18 (s, 9H), 1.37 (s, 3H), 2.07 (s, 3H), 6.05 (d, J = 1.5 Hz, 1H), 6.22 (d, J = 10.1 Hz, 1H), 6.37 (dd, J = 1.5, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 199.3, 169.4, 163.8, 140.9, 122.3, 119.4, 113.6, 78.0, 30.1, 23.8, 20.4; EIMS *m/z* (rel intensity) 222 (M^+, 3), 180 (67), 165 (35), 163 (6), 57 (18), 43 (100); HRMS (EI) calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1254.

3-*tert*-Butyl-6-methoxy-6-methylcyclohexa-2,4-dienone (3e′) and 5-*tert*-butyl-4, 4-dimethoxy- 2-methylcyclohexa-2,5-dienone (5). To a stirred solution of DIB (412 mg, 1.28 mmol) in dry MeOH (10 mL) was added a solution of **1e** (200 mg, 1.22 mmol)[49] in dry MeOH (2 mL). The reaction mixture immediately became bright yellow. After 30 min, TLC monitoring

[hexanes/Et_2O (4:1)] indicated complete disappearance of the starting material. The mixture was concentrated at room temperature, diluted with CH_2Cl_2 (20 mL) and poured into a 1:2 mixture of ice-cold saturated $NaHCO_3$ and H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Purification of the resulting dark oily residue by column chromatography, eluting with hexanes/Et_2O (4:1) under N_2, furnished **3e'** as a bright yellow oil (45 mg, 38 %) and **5** as an amorphous solid (41 mg, 30%). Under storage in the fridge for a couple of weeks, monoketal **5** was quantitatively converted into the paraquinone **6** (*vide infra*). Compound **3e'**: IR (NaCl) 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15 (s, 9H), 1.28 (s, 3H), 3.08 (s, 3H), 5.97 (s, 1H), 6.31 (d, J = 10.1 Hz, 1H), 6.45 (d, J = 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 203.7, 164.3, 143.3, 124.6, 119.9, 79.5, 54.1, 35.4, 28.1, 25.7; EIMS *m/z* (rel intensity) 194 (M^+, 83),179 (34), 164 (22), 163 (9), 151 (75), 149 (84), 137 (16), 119 (82), 57 (49), 43 (100); HRMS (EI) calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1310. Compound **5**: IR (NaCl) 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.28 (s, 9H), 1.92 (d, J = 1.5 Hz, 3H), 3.24 (s, 6H), 6.38 (s, 1H), 6.48 (q, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 186.9, 164.7, 140.3, 136.8, 129.3, 98.4, 50.7, 36.4, 30.9, 14.8; EIMS *m/z* (rel intensity) 224 (M^+, 39), 209 (32), 194 (21), 193 (78), 168 (100), 167 (23), 57 (43); HRMS (EI) calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1409.

2-*tert*-Butyl-5-methyl-1,4-benzoquinone (6). Electrooxidation of a solution of **1e** (113 mg, 0.69 mmol)[49] in MeOH was first performed according to the procedure A. The reaction mixture was then processed as described above, and the oily residue was purified by column chromatography, eluting with hexanes/Et_2O (8:1), to furnish paraquinone **6** as colorless crystals (31 mg, 25%).

In a second experiment, a stirred solution of **1e** (237 mg, 1.44 mmol) in CH_3CN (90 mL) and H_2O (2.6 mL, 100 equiv) containing $LiClO_4$ was electrolysed at 1.5 V using a Pt anode. The mixture slowly turned orangish. TLC monitoring [hexanes/Et_2O (9:1)] indicated complete disappearance of the starting material after 2.5 F/mol were passed. The mixture was concentrated at room temperature, diluted with CH_2Cl_2 (10 mL), and poured into ice-cold saturated $NaHCO_3$ (10 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated at room temperature. Purification of the resulting dark oily residue by column chromatography, eluting with hexanes/Et_2O (9:1), gave **6** as colorless crystals (211 mg, 82%): mp 87-88 °C (lit.[50] mp 84-85 °C); IR (NaCl) 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (s, 9H), 1.99 (d, J = 1.5 Hz, 3H), 6.49 (q, J = 1.5 Hz, 1H), 6.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 188.8, 187.7, 155.9, 144.0, 135.4, 131.5, 35.0, 29.1, 14.8; EIMS *m/z* (rel intensity) 178 (M^+, 89), 163 (91), 148 (4), 135 (100), 133 (12), 121 (19), 57 (9); HRMS (EI) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0992.

6,12-Di-*tert*-butyl-3,10-dihydroxy-3,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (4e). To a stirred solution of DIB (206 mg, 0.64 mmol) in CH_3CN/H_2O (8:1) (3 mL), was added dropwise a solution of **1e** (100 mg, 0.61 mmol)[49] in CH_3CN (2 mL). The mixture slowly

turned bright yellow. After 1 h, TLC monitoring [hexanes/Et_2O (4:1)] indicated complete disappearance of the starting material, and the mixture was poured into ice-cold saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and filtered. Evaporation of the solvent furnished a bright yellow oil, which was purified by column chromatography, eluting with hexanes/Et_2O (4:1), then with CH_2Cl_2/MeOH (6:1), to give **4e** as a beige solid (30 mg, 27%), the paraquinone **6** as colorless crystals (68 mg, 63%), and recovered starting phenol **1e** (8 mg, 8%).

In a second experiment, SIBX-mediated oxidation of **1e** (70 mg, 0.43 mmol)[49] was carried out according to the general procedure to afford a clean 1:1 mixture of dimer **4e** and 3-*tert*-butyl-6-methyl-1,2-benzoquinone (**7**). This brown solid was submitted to column chromatography, eluting with pentanes/EtOAc (4:1) → (1:1), to give the racemic dimer **4e** as fine white crystals (30 mg, 39%): mp 178-180 °C; IR (NaCl) 3451, 1727, 1677 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 9H), 1.20 (s, 3H), 1.22 (s, 9H), 1.23 (s, 3H), 2.61 (bs, 1H), 2.99 (dd, *J* = 3.2, 9.1 Hz, 1H), 3.34 (d, *J* = 9.1 Hz, 1H), 3.38 (dd, *J* = 3.2, 7.0 Hz, 1H), 3.41 (s, 1H), 4.10 (s, 1H), 5.99 (dd, *J* = 1.6, 7.0 Hz, 1H), 6.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 211.1, 202.5, 166.9, 145.8, 128.5, 121.1, 73.9, 72.2, 53.6, 45.2, 40.7, 38.5, 37.8, 34.4, 32.7, 29.2, 28.2, 26.1; LSIMS *m/z* (rel intensity) 383 (MNa^+, 100), 361 (MH^+, 43), 360 (13), 343 (7), 303 (12); HRMS (LSIMS) calcd for $C_{22}H_{33}O_4$ 361.2379, found 361.2382.

3,10-Dihydroxy-3,5,8,10-tetramethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (4f). SIBX-mediated oxidation of 2,6-dimethylphenol **1f** (100 mg, 0.82 mmol) was carried out according to the general procedure to afford the racemic dimer **4f** as a pale orange solid (112 mg, 99%): mp 179-180 °C (lit.[41] mp 183 °C; lit.[44] mp 187-190 °C; lit.[51] mp 196 °C); IR (NaCl) 3416, 1713, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.21 (s, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.80 (d, *J* = 0.7 Hz, 3H), 2.83-2.85 (m, 1H), 3.23 (dd, *J* = 1.9, 8.3 Hz , 1H), 3.34 (d, *J* = 6.8 Hz, 1H), 4.00 (bs, 2H), 5.45 (d, *J* = 8.3 Hz, 1H), 6.19-6.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 214.6, 202.9, 139.3, 135.6, 135.3, 133.1, 73.6, 72.7, 53.7, 44.3, 43.4, 42.6, 31.6, 26.1, 16.2, 15.5; EIMS *m/z* (rel intensity) 276 (M^+, 5), 242 (3), 216 (3), 138 (42), 122 (15), 121 (33), 43 (100).

3,10-Dihydroxy-3,6,10,12-tetramethyltricyclo[6.2.2.02,7]dodeca-5,11-diene-4,9-dione (4g). SIBX-mediated oxidation of 2,5-dimethylphenol **1g** (100 mg, 0.82 mmol) was carried out according to the general procedure to afford a clean 1:1 mixture of dimer **4g** and 3,6-dimethyl-1,2-benzoquinone (**8**).[45] This dark reddish solid was purified by column chromatography, eluting with pentanes/EtOAc (4:1) → (1:1), to yield the racemic dimer **4g** as a red solid (70 mg, 62%): mp 181-185 °C (lit.[46] mp 200-201 °C); IR (NaCl) 3435, 1729, 1671, 1379, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.60 (s, 3H), 1,65 (s, 3H), 1.96 (d, *J* = 1.5 Hz, 3H), 2.35 (d, *J* = 1.2 Hz, 3H), 3.18 (bs, 1H), 3.52 (bs, 3H), 3.66 (dd, *J* = 1.5, 6.7 Hz, 1H), 4.43 (bs, 1H), 6.19-6,23 (m, 1H), 6.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 212.7, 201.4, 156.4, 136.4, 128.2, 124.8, 73.2, 72.9, 56.9, 44.7, 44.1, 41.0, 31.9, 25.8, 22.3, 21.4; EIMS *m/z* (rel intensity) 276 (M^+, 16), 216 (3), 215 (12), 188 (8), 187 (23), 159 (15), 122 (10), 121 (17), 43 (100).

6-Hydroxy-3,5,6-trimethylcyclohexa-2,4-dienone (3h) and 3,4,6-trimethyl-1,2-benzoquinone (9). SIBX-mediated oxidation of 2,3,5-trimethylphenol (**1h**, 500 mg, 3.6 mmol) was carried out according to the general procedure to afford, after a workup using saturated aqueous $NaHCO_3$, a clean 1:1 mixture of the orthoquinol **3h** and the 3,4,6-trimethyl-1,2-benzoquinone (**9,** 461 mg, *ca*. 83%). This dark reddish solid was separated by column chromatography, eluting with toluene/EtOAc (6:1), to give racemic **3h** as an orange oil (68 mg, 12%). Compound **3h**: IR (NaCl) 3456, 1667, 1642, 1572, 1161; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 3H), 1.99 (s, 3H), 2.00 (d, J = 1.5 Hz, 3H), 3.50 (s, 1H), 5.76 (bt, J = 1.5 Hz, 1H), 5.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 206.4, 155.7, 154.9, 121.3, 118.6, 77.5, 29.2, 23.0, 17.6; EIMS *m/z* (rel intensity) 152 (M^+, 26), 137 (12), 122 (100), 107 (27), 79 (95). Compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88 (s, 3H), 1.91 (m, 3H), 2.04 (s, 3H), 6.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 180.7, 179.9, 145.9, 141.5, 135.9, 132.9, 20.3, 15.0, 11.3. These NMR data were read on spectra of the crude product mixture; the *ortho*-quinone **9**, as well as **7** and **8**, did not resist silica gel chromatography.

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