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Regio- and stereoselectivities in Diels–Alder cyclodimerizations of orthoquinonoid cyclohexa-2,4-dienones

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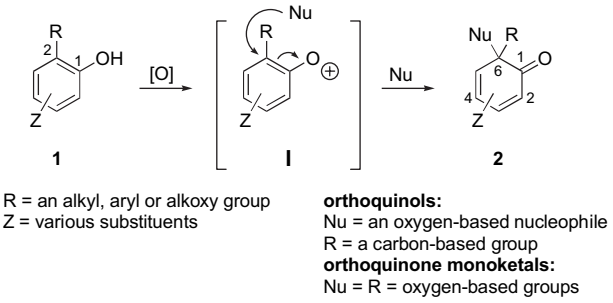
Abstract—The [4+2] cyclodimerization of cyclohexa-2,4-dienone derivatives of the orthoquinone monoketal and orthoquinol types has been the topic of numerous investigations over the last 50 years in the aim of rationalizing the extraordinary level of regio-, site-, and stereoselectivities observed in these processes. In particular, the double diastereo-π-facial differentiation expressed in cyclodimerizations of chiral orthoquinols (i.e., 6-alkyl-6-hydroxycyclohexa-2,4-dienones) is an important aspect of these transformations, for they relate to the construction of several natural products. The experimental and theoretical results that are described in this article offer a comprehensive understanding of the factors controlling these site-specific regio- and diastereoselectivities. Our interpretation of these results relies on a combination of Woodward–Hoffmann and Salem–Houk secondary orbital interactions and Cieplak-type hyperconjugative effects in bispericyclic C_2-symmetric transition states.

1. Introduction

Arene compounds are attractive starting materials for the rapid preparation of synthetically useful cyclohexadiene derivatives by various methods that are essentially based on oxidative, reductive, and transition metal-mediated dearomatization approaches.[1] Available in a variety of substitution patterns, arenes can be chosen to access selectively a particular type of cyclohexadiene derivatives by using the chemical method that is most appropriate to their reactivity and functionality. For example, electron-rich arenes generally express a reactivity well suited for dearomatization by oxidative means and, among this class of arenes, phenols are ideally functionalized to furnish cyclohexadienones.[2] Moreover, phenols of type **1** bearing electron-releasing substituents at their *ortho*-position(s) can be easily oxidized into electron-deficient intermediates of type **I**, or equivalents, and hence be regioselectively dearomatized into cyclohexa-2,4-dienones of type **2** in the presence of a suitable nucleophile (Scheme 1).



Scheme 1.

During the last eight years, we have investigated the chemistry of such cyclohexa-2,4-dienones bearing one or two oxygen-based substituent(s) at their 6-position.[3] These compounds are referred to as orthoquinols or orthoquinone monoketals. What makes these compounds useful building blocks for organic synthesis is their oxygenated six-membered ring structure composed of a five-carbon conjugated dienone unit linked to a sixth carbon center that is tetrahedral, quaternary, and possibly chiral (Scheme 1). When considering such structural features and the large number of possible transformations that can be envisaged on these compounds in regio- and stereoselective manners, one can easily understand why reports on their chemistry are so abundant in the literature.[3,4] Despite this plethora of information already available, orthoquinols or orthoquinone monoketals continue to stimulate the interest of synthetic

Keywords: Phenol dearomatization; Orthoquinone monoketals; Orthoquinols; Cyclohexa-2,4-dienones; Cycloaddition; Diels–Alder reaction; Bispericyclism; Anodic oxidation; Hypervalent iodine.
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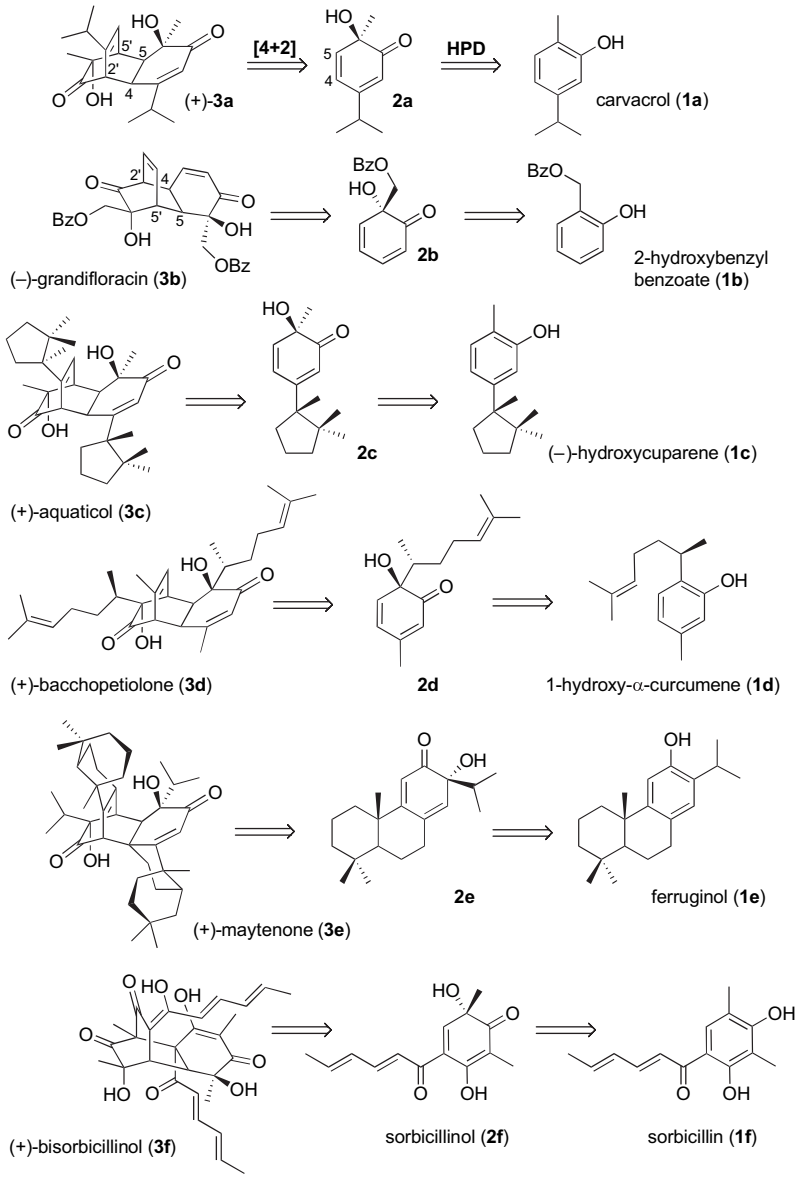
organic chemists, as evidenced by numerous reports recently published on the applications of their chemistry to the synthesis of natural products.[5] Indeed, many natural products of various biosynthetic origins do feature orthoquinol units, and many others can be made by taking advantage of their reactivity in synthetic routes that often constitute biomimetic approaches to these natural products.[3a,c,4a,5j]

The most characteristic aspect of the chemical reactivity of orthoquinols and orthoquinone monoketals is unarguably their ability to dimerize easily through [4+2] cycloaddition reactions. This propensity toward Diels–Alder processes is evidently due to the reactivity of their dienone unit that can behave either as a diene or as a dienophile. This dimerization often occurs spontaneously at ambient temperature, and can only be blocked, or at least retarded, if the cyclohexa-2,4-dienone core of the monomer bears some substituents at some specific positions. For example, the presence of a small alkyl or alkoxy group at its carbon-5 position,[6] a large electron-releasing group at the carbon-2 or -4 position,[7] a large halogen atom (i.e., bromine or iodine) at the carbon-4 position,[8] or an acetoxy group at the tetrahedral carbon-6 position[9] efficiently reduces its propensity toward [4+2] cyclodimerization and hence enables the exploitation of other facets of the reactivity of these cyclohexa-2,4-dienone derivatives. However, it is their Diels–Alder cyclodimerization that has been the topic of most studies over the years, since Wessely's pioneering work 50 years ago.[9] The reasons of this continuous interest in the investigation of this reaction are its extraordinary level of selectivity and its probable implication in the construction of several natural products. A series of examples of such natural products (**3a–f**) that can potentially be made in one chemical step from dimerizing orthoquinol intermediates (i.e., **2a–f**), which can themselves be, respectively, derived from the phenolic precursors **1a–f** by hydroxylative phenol dearomatization (HPD), are shown in Scheme 2. There is little doubt that this sequence of events corresponds to the final steps by which these terpenes and vertinoid polyketides are biosynthetically produced.[10]



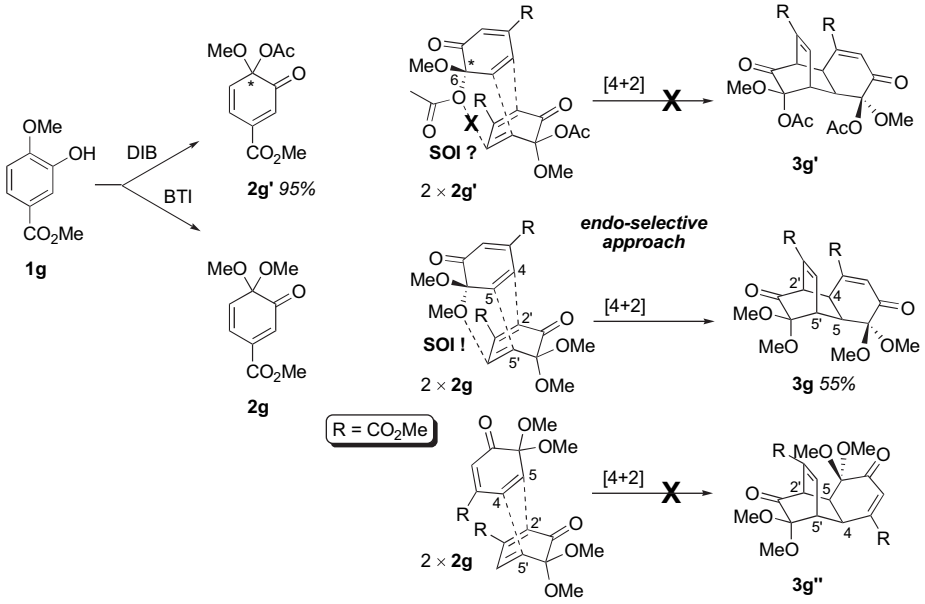
Scheme 2. Examples of natural [4+2] cyclodimers of orthoquinols; HPD=hydroxylative phenol dearomatization.

These constructions of natural products by cyclodimerization of orthoquinols would follow an *endo*-selective Diels–Alder process during which the orthoquinol acting as the dienophile would exclusively react through its Δ-4,5 bond. To the best of our knowledge, no natural dimer resulting from an *exo*-process and/or from an alternative participation of the Δ-2,3 bond of the dienophilic orthoquinol has been isolated. These selectivities already provide food for thought, but the most intriguing aspects of these [4+2] cycloadditions remain the facts that they express an even more specific regioselectivity and an extraordinary level of double diastereofacial selectivity. Indeed, these natural cyclodimers result from a back-to-back combination during which the orthoquinol monomers connect to each other by joining their carbon-5 atoms and approach one another with their carbon-6 hydroxy groups oriented towards each other. Enzymatic control is certainly not at play in these transformations, for such cyclodimerizations have been performed in the course of the synthesis of several natural products with the same selectivities.[5k,10b,11,12] Numerous model compound studies have been undertaken during the last 50 years in the aim of providing a sound rationale for the unique site-specific regioselectivity and the diastereofacial selectivity always observed in these reactions, but these investigations felt short of delivering a general explanation.[7,13,14]

Our work on oxidative dearomatization of phenols into orthoquinone monoketals and orthoquinol variants led us to revisit these [4+2] cyclodimerizations, and we recently disclosed our own thoughts on these selectivity issues in the context of the total synthesis of (+)-aquaticol (**3c**) from (−)-hydroxycuparene (**1c**) (Scheme 2).[11] We wish to describe herein a comprehensive view of the experimental and theoretical results that we gathered to delineate further the different reactivity and structural features controlling the outcome of these Diels–Alder dimerizations in a more general context.

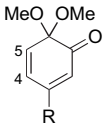
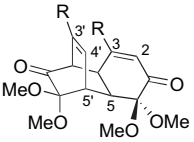
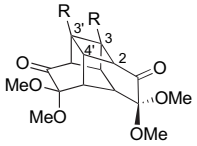
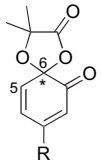
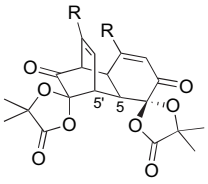
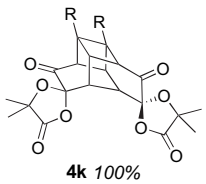
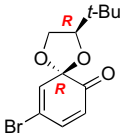
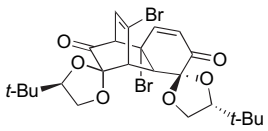
2. Results and discussion

The first set of experiments that stirred our interest in the Diels–Alder dimerization of orthoquinone monoketals and orthoquinol variants had to do with the oxidative dearomatization of phenol **1g** using λ^3-iodane reagents.[15] Depending upon the reaction conditions used, two different products were obtained. On one hand, using [bis(trifluoroacetoxy)iodo]-benzene (BTI) in a MeOH–CH_3CN (2:1) solvent mixture according to the method originally conceived by Tamura and Kita to access paraquinone monoketals,[16] the only observed product, isolated in 55% yield, was the cyclodimer **3g** (Scheme 3 and Table 1).[15] This dimer resulted from a spontaneous [4+2] *endo*-cyclodimerization of the orthoquinone monoketal **2g** that was generated in situ by the BTI-mediated oxidative methoxylation of **1g**. On the other hand, using (diacetoxyiodo)benzene (DIB) in a CH_2Cl_2–AcOH (3:1) solvent mixture according to our own method,[17] the only observed product was the orthoquinol acetate **2g′**. This orthoquinol resulted from the DIB-mediated oxidative acetoxylation of **1g** and was stable enough to be isolated as such in 95% yield (Scheme 3).[15] These initial observations led us to reason why the cyclodimerization was involving bond formations during which the carbon-5 atoms of each orthoquinol monomer **2g** get exclusively connected to each other. Furthermore, the fact that the substitution of a methoxy group by an acetoxy group on the carbon-6 ketal function of **2g** was sufficient to block so efficiently the cyclodimerization process raised additional questions. This acetoxy group blocking effect is well known,[9,14a,18] but it still awaits an explanation. Liao and co-workers suggested that one of the two carbon-6 methoxy groups of dienophilic orthoquinone dimethyl ketals such as **2g** participates, thanks to its oxygen lone pairs, in secondary orbital interactions (SOIs) in the *endo*-selective transition states (TSs), with the consequence of enhancing the propensity of such monoketals to self-dimerize.[7] A downward modulation of this orbital control in analogues such as **2g′** bearing instead an



Scheme 3.

Table 1. [4+2] Cyclodimerization of orthoquinone monoketals and intramolecular [2+2] photoannelation of their [4+2] dimers

Orthoquinone monoketal[a]	[4+2] Cyclodimer	[2+2] Cage[b]
		
2g: R = CO_2Me **2h**: R = $CH_2OTBDPS$ **2i**: R = H **2j**: R = Br	**3g** *55%* **3h** *78%* **3i** *92%* **3j** *100%*	**4g** *55%* **4h** *78%* **4i** *96%* **4j** *94%*
		
2k: R = H **2l**: R = Pr **2m**: R = Br	**3k** *100%* **3l** *78%* **3m** *78%*	**4k** *100%* **4l** *83%* —
		—
2n	(–)-**3n** *54%*	

[a] These monoketals were generated as racemates, except **2n**.
[b] Compounds **3m/n** were not submitted to irradiation.

electron-withdrawing acetoxy group at the same position could perhaps be put forward to propose a beginning of an explanation of their resistance toward dimerization (Scheme 3). What is clearly known from work carried out on many orthoquinol acetates is that, once the acetate is hydrolyzed, the resulting 6-hydroxylated product then readily self-dimerizes.[9,10b,14a,18] This experimental approach has, inter alia, been followed by Corey and Nicolaou in their biomimetic synthesis of bisorbicillinoid natural products, such as bisorbicillinol (**3f**), from sorbicillinol (**2f**) (Scheme 2).[5k,12,19] This recovery of the capability of dimerizing spontaneously when going from 6-acetoxylated to 6-hydroxylated compounds is in line with the aforementioned modulation of SOIs, to which could perhaps be added a reduced steric effect.[20] But then another question comes to mind! Why would the acetoxy group of the dienophilic component of the Diels–Alder cyclodimerization systematically orient itself toward the dienic component of the reaction? Needless to say that we were still intrigued by these reactivity differences, site selectivity, and apparent facial recognition expressed by these orthoquinone monoketals as well as their orthoquinol variants in their [4+2] transformations.

2.1. Site selectivity

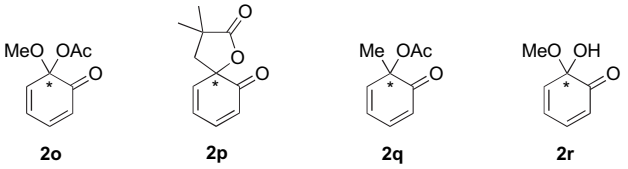
We produced several analogues of **3g** in the course of our investigation on oxidative phenol dearomatization methods based on the use of hypervalent iodine reagent as well as on anodic oxidation.[13,21] A selection of these *endo*-cyclodimers **3h–n** is displayed in Table 1. They were obtained in good to excellent isolated yields, and all of them exclusively resulted from the same site selectivity than that observed for **3g** (Scheme 3), as well as for all of so far reported cases of orthoquinone monoketal and orthoquinol dimerizations, including those leading to the natural products shown in Scheme 2. This selectivity of connection by which the two monomers join their two C_5 atoms together and the carbon-4 atom of the dienophilic partner to the carbon-2 atom of the dienic one would thus be independent of the nature of the substituents on the cyclohexadienone core of the system, as long as these substituents do not block the dimerization process (vide supra). However, this connectivity first appears counterintuitive when considering the probable polarization of the cyclohexa-2,4-dienone system. The more electron-deficient carbon-5 atom at the end of the dienone unit could be expected to join with the more electron-rich carbon-2 atom adjacent to the carbonyl function. These simple-minded considerations evidently do not allow any prediction of site selectivity in these Diels–Alder reactions. Cyclodimers resulting from such a combination, such as **3g″** from **2g** (Scheme 3), have never been observed. As we previously discussed,[13] calculations of atomic coefficients of either dienic or dienophilic HOMOs and LUMOs that have been performed on unperturbed orthoquinone monoketal reactants by using semiempirical (PM3) or ab initio RHF (3-21G*) procedures are no better to provide any clear-cut rationale. Suggestions were made on the possibility of having SOIs controlling these cyclodimerizations at the transition state level,[7,13] and this possibility is in fact backed-up by an important feature of the inherent reactivity of these cyclodimers. They readily undergo intramolecular [2+2] cycloaddition reactions upon irradiation to furnish C_2-symmetric pentacyclododecanedione derivatives.[22] Cyclodimers **3g–l** were indeed converted into such cage compounds **4g–l** in high yields by irradiating them at room temperature using a medium-pressure mercury lamp (Table 1).[13]

This facility by which these [4+2] cyclodimers further react upon irradiation is a key element of the understanding of the factors controlling the manner by which their monomers combine with each other during the [4+2] cycloaddition process. Thus, it constitutes a sound chemical evidence of the *endo*-selectivity of the process,[22] since *exo*-cyclodimers could not have the orbitals of the two reacting carbon–carbon double bonds properly lined up for the [2+2] cyclobutanation. One can thus argue with confidence that the *endo*-mode of [4+2] cycloaddition is under the influence of p-orbital interactions taking place between the two C_3's of each monomer, and between C_2 of one monomer and C_4 of the other monomer (see Table 1). These SOIs are then allowed to engage in intramolecular bond formations during the [2+2] photoannelation process. Consequently, they certainly play an important role in the kinetic selection of the [4+2] TSs, but their establishment still does not explain the site-specific regioselectivity of the reaction. The exclusive participation of the Δ-4,5 bond as a dienophilic component can be simply explained by noting the loss of enone conjugation energy that would impede the reaction TS if the Δ-2,3 bond was instead involved. However, it is still not clear why *endo*-dimers, such as **3g″** for which C_4 and C_5 of the preferred dienophilic double bond would instead, respectively, connect with C_5 and C_2 of the dienic partner, are not observed. The p-orbitals of their remaining carbon–carbon double bonds should still be able, at least

Table 2. Activation energies in kcal/mol[a]

Geometry	6-31G(d)	6-31G(d)	6-31G(d)
Wave function	6-31G(d)	6-311+G(d,p)	MP2/6-31G(d)
Reaction	*RR*/*RS*[b]	*RR*/*RS*[b]	*RR*/*RS*[b]
2g→**3g**	27.05	31.38	2.97
2g′→**3g′**	41.12/44.44	45.30/48.96	20.88/22.87
2i→**3i**	26.76	30.70	8.03
2i′→**3i′**	32.19	35.85	13.25
2k→**3k**	26.18/25.64	28.96/28.65	7.35/7.14
2o→**3o**	38.93/42.46	43.21/46.96	22.92/25.95
2p→**3p**	26.22/30.33	29.23/33.44	5.10/9.98
2q→**3q**	38.93/51.22	43.82/55.16	20.72/34.01
2r→**3r**	23.67/32.00	28.54/35.66	5.59/14.85

[a] Calculations were performed using the B3LYP functional, unless otherwise noted.
[b] For reactions involving chiral monomers, TSs of both *RR** and *RS** combinations were calculated.



2o **2p** **2q** **2r**

to some extent, to interact with each other (e.g., see **3g″** vs **3g** in Scheme 3).

We thus decided to perform a search of a selection of the TSs involved in these [4+2] cycloadditions, including those leading to dimers **3g**, **3i**, and **3k**. In order to gain further insight into these reactions, TSs of dimers not observed experimentally, such as **3g′**, **3g″** and those resulting from a different facial selectivity (vide infra), were also calculated, as well as those of other cyclodimerization systems derived from model monomers **2o–r**. These calculations were carried out using different levels of theory (see Section 4). Activation energies of these different reactions are shown in Table 2. The most striking geometrical characteristic of TSs leading to observed dimers is that they all display a C_2-axis of symmetry. This can be viewed, for example, on the representation of the TS leading to **3i** from **2i** (Fig. 1). Interestingly, the alternative combination that would result by connecting instead C_5 of one monomer with C_2 and C_4 with C_5 of the other monomer led to a TS (Fig. 1) that is about 5 kcal/mol higher in energy than the TS leading to **3i**, whatever the level of calculation is (Table 2). This alternative combination is obtained by flipping over one monomer and leads to a TS that is not C_2-symmetric anymore. The loss of the C_2-symmetry is also at the origin of significant changes in bond length alternation between the reactive centers of the two monomers. However, the bond length values (Fig. 1) do not clearly evidence a better efficiency of the overall π-conjugation in the cyclohexadienone moiety of TS-**3i** as compared to that of TS-**3i′**. Nevertheless, the stabilization of the C_2-symmetric structure TS-**3i** likely originates from a better overlap of the π electronic clouds of the two partners, hence maximizing SOIs (vide infra).

We thought of finding an explanation for this preference of bond formation between the two C_5 centers of each monomer by looking at the atomic coefficients of the perturbed HOMO and LUMO at the TS level, but this analysis, like the one performed on the unperturbed HOMO and LUMO of the orthoquinone monoketal reactant **2i**, did not unveil any diagnostic information. A comparative examination of the above asynchronous two TSs reveals that TS-**3i** is globally much more compact than TS-**3i′**, which rather adopts a V-shape (Fig. 1). The distances between the atoms involved in the first forming bond are about the same ($d_{C5'-C5}$=2.036 Å vs $d_{C5'-C2}$=1.986 Å), but the distance between $C_{4'}$ and C_5 in TS-**3i′** is rather long (i.e., 3.574 Å) for enabling efficient

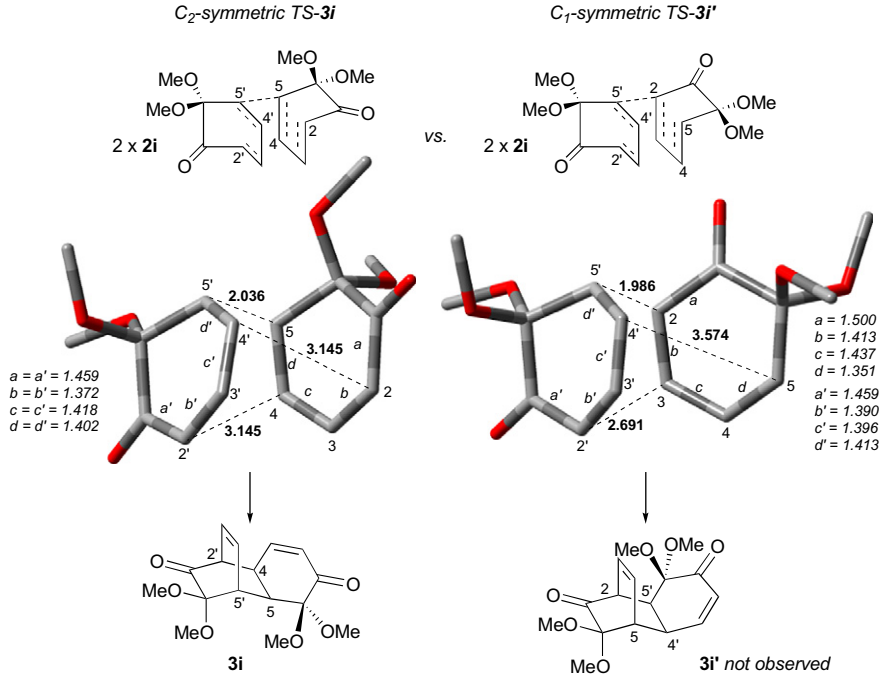


Figure 1. B3LYP/6-31G(d) TS structures with interatomic distances (Å) of *endo*-dimers **3i** and **3i′** in which C_4 and C_5 of the preferred dienophilic double bond connect with C_2 and C_5 (TS-**3i**) and with C_5 and C_2 (TS-**3i′**) of the dienic partner.

overlap of the corresponding p-orbitals. The second shortest distance in this TS is between $C_{2'}$ and C_3 (i.e., 2.691 Å), but such a connection would imply the participation of the Δ-2,3 of the monomer acting as a dienophile and a consequent loss of enone conjugation energy (vide supra). It then remains to explain why TS-**3i** is more stable than TS-**3i′** and to identify plausible factors capable of thus cementing TS-**3i** in its more compact C_2-symmetric geometry. A relevant explanation has been put forward early on to differentiate dimers of cyclohexa-2,4-dienones on the basis of the principle of the lowest dipole moment.[23] Dimers such as **3i** display a lower dipole moment than those analogous to **3i′**. This argument holds at the TS level (TS-**3i** ⇒ 2.35 D vs TS-**3i′** ⇒ 3.67 D), but the C_2-symmetric structure of TS-**3i** versus the C_1-symmetric V-shaped structure of TS-**3i′** allows another explanation based on the resulting better alignment of the TS-**3i** interacting p-orbitals already invoked to rationalize the *endo*-selectivity of the process (vide supra).

These interactions between $C_{3'}$ and C_3 and between $C_{2'}$ and C_4 or between $C_{4'}$ and C_2, respectively, correspond to the Woodward–Hoffmann (WH) SOI, classically invoked to explain the preference of *endo*- over *exo*-TSs in Diels–Alder reactions, and to the Salem–Houk (SH) SOI.[24] In fact, in all C_2-symmetric TSs leading to observed dimers, such as TS-**3i**, it is not possible to differentiate the diene from the dienophile, the $C_{2'}$/C_4 and $C_{4'}$/C_2 orbitals interactions are equivalent (Fig. 1). One will lead to the second bond formation in the Diels–Alder process, the other will play its stabilizing role as a SH SOI, or vice versa (Figs. 1 and 2). In other words, the [4+2] and the [2+4] cycloaddition reaction pathways are equivalent. Such TSs are said to be bispericyclic, as recently discussed by Caramella for butadiene and cyclopentadiene models.[25] All known dimerizations of orthoquinone monoketals and orthoquinols, including those leading to natural products (Scheme 2), follow this theoretical bispericyclism principle and their respective TSs are all further stabilized by this combination of WH and SH SOIs, which are allowed to engage in [2+2] bond-forming events upon irradiation to give rise to the observed cage compounds (see Tables 1 and 3). Remarkably, TSs of [4+2]/[2+4] cyclodimerizations of orthoquinone monoketals or orthoquinols can be viewed as the 'fingerprints' of the [2+2] products of the photoannelation of the Diels–Alder products to which they lead to (Fig. 2).

2.2. The 'acetate effect'

Observations on the resistance of C_6-acetoxylated derivatives of orthoquinone monoketals and orthoquinols toward cyclodimerization led us to analyze this phenomenon in greater details. As mentioned above, a SOI-based stereoelectronic explanation of this blocking effect would imply that the faces of the monomers orienting themselves toward each other are those bearing the acetoxy group (e.g., see **2g′** in Scheme 3). We will come back to this facial selectivity issue in the next section, but first, we wanted to exploit this 'acetate effect' in cyclic variants of the acyl/methyl C_6-ketal function of the monomers. We thought that we could prepare non-dimerizing *O*-spirolactonic orthoquinone monoketals with the possibility of accessing them in a stereoselective manner by equipping the carbon center α to the lactonic carbonyl group with different substituents.[21b] This enterprise failed simply because the *O*-spirolactonic cyclohexa-2,4-dienone system does in fact readily dimerize, as observed for the conversion of **2k–m** into **3k–m** (Table 1). The reasons of such a difference of behavior between these cyclic and acyclic monoketals were not obvious, but computational modeling of these systems gave us some clues. In agreement with our experimental observations, calculations performed on the dimerization of **2k** and **2o** indicate a much lower energy barrier for the dimerization of the *O*-spirolactone **2k** (Table 2). However, a closer examination of the corresponding TS structures does not reveal any significant difference neither in the distances between the reactive centers of the two partners nor in the orientations of the C_6–O bond of the carboxy units of the two systems (Fig. 3).

It is the comparison of the geometrical structures of the unperturbed reactants **2k** and **2o** that turned out to be more informative (Fig. 3). In the acyclic ketal **2o**, the carbonyl group of the acetate points towards the center of the cyclohexadienone core. A systematic conformational analysis confirmed that this acetate orientation is quite optimal, and corresponds to a stabilization of approximately 5 kcal/mol with respect to structures in which the acetate adopts an external position. This important stabilization of acetate reactants such as **2o**, which cannot exist for geometrically constrained cyclic ketals such as the *O*-spirolactone **2k**, could thus be the origin of their higher activation energies and, hence, it constitutes a valid explanation of the blocking 'acetate effect' always

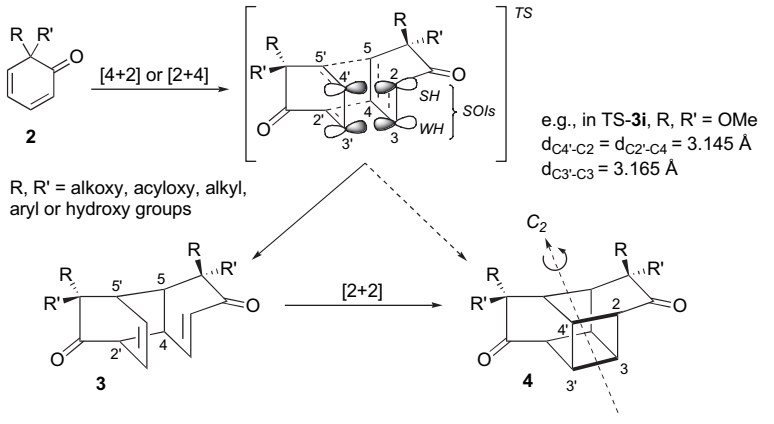


Figure 2.

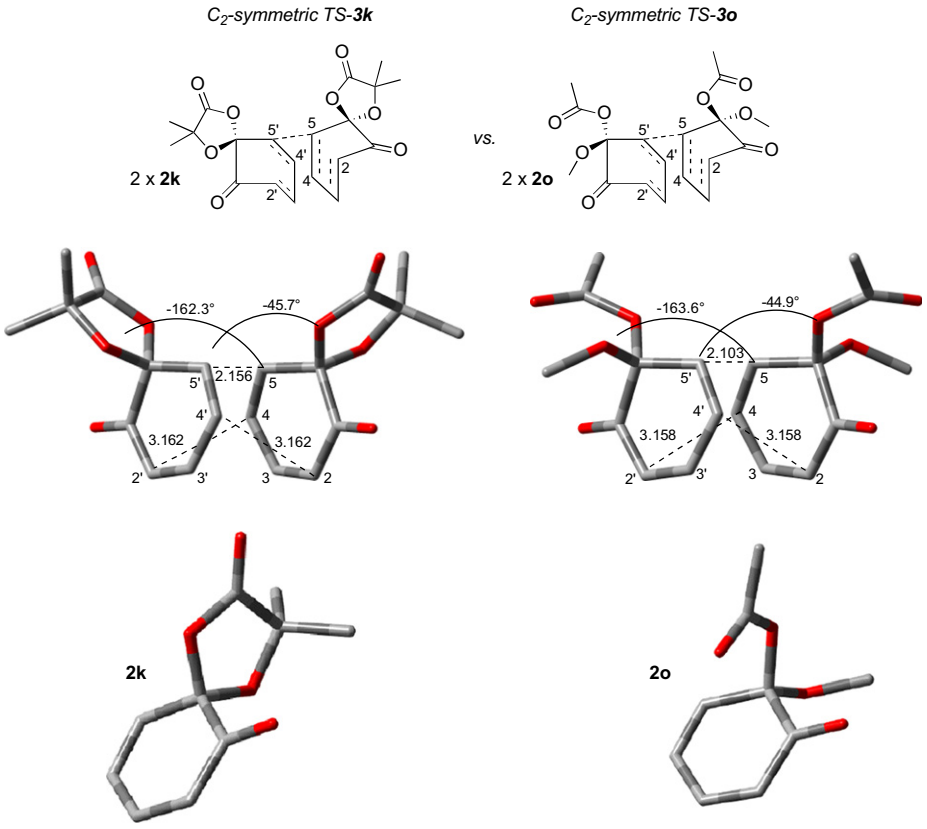


Figure 3. B3LYP/6-31G(d) structures of TS-**3k** (top left) and TS-**3o** (top right) with dihedral angles and interatomic distances (Å), and of their respective unperturbed reactants **2k** (bottom left) and **2o** (bottom right).

observed in attempted dimerizations of orthoquinol and orthoquinone ketal acetates, such as **2g′** (Scheme 3), under kinetic conditions.[9,14a,18,20] This 'acetate effect' was similarly predicted by comparing the activation energies related to the dimerization of the model orthoquinol acetates **2p** and **2q** (Table 2).

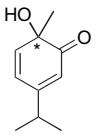
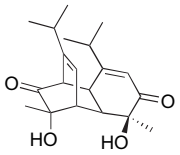
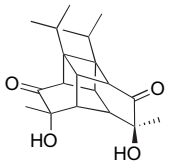
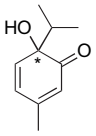
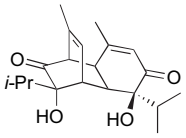
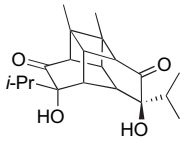
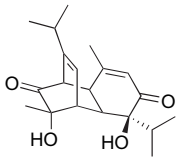
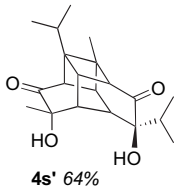
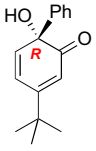
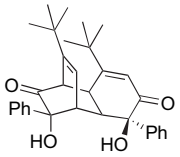
2.3. Facial selectivity

The most striking aspect of the manner by which *O*-spirolactonic orthoquinone monoketals **2k**–**m** dimerize is that they do so by orienting their lactonic C_6–O bonds towards each other (Table 1 and Fig. 3). The chirality of the ketal C_6-center thus strongly influences the outcome of the dimerization. Not only the two faces of the dienophile are differentiated, but also those of the monomer behaving as a diene. Starting from racemic *O*-spirolactone dienones such as **2k**–**m**, only two enantiomers of eight possible *endo*-cyclodimers are made. The two starting ketal enantiomers recognize each other and do not cross-react. All of the known analogous dimers generated under kinetic control also resulted only from chiral orthoquinone monoketals or orthoquinol variants displaying the same configuration at their stereogenic C_6-center. This enantiospecific pairing was confirmed by our calculations of the [4+2] TS structures of the dimerization of **2g′** and **2o**–**r** (Table 2). The calculated *RR* combinations were systematically lower in energy than their *RS* alternatives. The only exception was for the dimerization of **2k**, the TSs calculation of which indicated similar activation energies for both combinations (Table 2). This is in sharp contrast with our experimental observation, which indicated, to the limits of sensibility of both ^{1}H and ^{13}C NMR analyses, that the racemate **3k** was the only dimer formed.

The orthoquinols **2a** and **2s/t** that we generated also spontaneously dimerized to furnish exclusively the *endo*-products **3a** and **3s/t** according to the same double diastereofacial selectivity (Scheme 2 and Table 3). The structures of **3a** and **3s** (and **3s′**, vide infra) were again further confirmed by performing [2+2] photoannelation into the cage compounds **4a**, **4s**, and **4s′** (see Section 5). The dimer **3t** was refractory to photoannelation, probably because of the steric demand of the two *tert*-butyl groups. Interestingly, the mixture of racemic orthoquinols **2a** and **2s** that we generated by a λ^5-iodane-mediated hydroxylative phenol dearomatization (HPD) reaction of a mixture of the phenolic terpenoids carvacrol (**1a**) and thymol led to a racemic mixture of **3a**, **3s**, and **3s′** (see Section 5). This latter compound, isolated in a yield of 9%, resulted from [4+2] cycloaddition between **2a** behaving as a diene and **2s** behaving as a dienophile. Formation of the alternative compound that could have resulted from a switch of the dienic/dienophilic behavior of **2a** and **2s** was not observed, but that of **3s′** again results from a combination of **2a** and **2s** during which they approach one another with their C_6-hydroxy groups oriented towards each other.

To the best of our knowledge, the only reported case of dimerization showing a deviation from this double diastereofacial selection concerns the racemate of an orthoquinol acetate of type **2q** (Table 2), which, when forced to dimerize upon heating, gave rise to a cyclodimer derived from a

Table 3. [4+2] Cyclodimerization of orthoquinols and intramolecular [2+2] photoannelation of their [4+2] dimers

Orthoquinol[a]	[4+2] Cyclodimer	[2+2] Cage
 **2a**	 **3a** *48%*	 **4a** *81%*
 **2s**	 **3s** *50%*	 **4s** *90%*
2a+2s	 **3a** *21%* **3s** *12%* + **3s'** *9%*	 **4s'** *64%*
 **2t**	 (+)-**3t** *66%*	—

[a] These orthoquinols were generated as racemates, except **2t**.

cross-reaction between its two enantiomers.[14a,18] The enantiomer that behaved as the dienophile in this cyclodimerization approached its partner from its face bearing the methyl group. Apparently, the resulting dimer is thermodynamically more stable, probably because the bulkier acetoxy group is then oriented *anti* to the ethylene bridge of the bicyclo[2.2.2]octene unit. However, the TS leading to this alternative dimer must be less stable, since its formation is never observed to any significant extent when the reaction is maintained under kinetic control. The fact that the enantiomer behaving as the diene conserves the orientation of its bulkier C_6-acetoxy group toward the Diels–Alder reaction centers has been attributed to an electrostatic preference for orientation of the most polarizable substituent at C_6 (i.e., the acetoxy group) *anti* to the ethylene bridge.[14a] Such a sterically-independent preference for *anti*- over *syn*-products has been rationalized, for Diels–Alder reactions involving cyclopentadiene derivatives, in terms of attractive interactions between the diene and the dienophile due to dipole–dipole, dipole-induced dipole, and London dispersion forces.[26] The same *anti*-preference is also observed when orthoquinols, their acetates or their alkyl ethers react with dienophiles other than themselves.[6b,20,27] This issue of π-facial selectivity of Diels–Alder cycloadditions involving dienes bearing heteroatomic allylic substituents has fueled numerous studies over the years; electronic and steric forces or a combination of both have all been proposed as the dominating factors depending on the type of compounds under investigation.[28] More recently, Liao revisited this issue of π-facial selectivity in Diels–Alder reactions of orthoquinol methyl ethers with various dienophiles,[29] and outlined two possible explanations

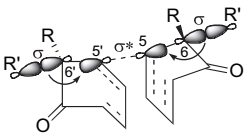


Figure 4. Proposed contribution to the stabilization of cyclohexa-2,4-dienone cyclodimerization TSs by double 'Cieplak–Fallis' hyperconjugation; R, R′=carbon-, oxygen-, sulfur-, or halogen-based groups with R′ involved in the most electron-donating σ-bond.

relying on (i) a Cieplak-type hyperconjugative stabilization of the reaction TSs by the most electron-donating σ-bond of the two C_6-substituents connecting bonds being antiperiplanar to the σ*-orbital of the incipient bond with the dienophile, as first proposed by Macaulay and Fallis,[30] or on (ii) the orbital mixing rule, which stipulates that, as a result of an out-of-phase combination of the π HOMO of the diene with the n-orbital of the oxygen atom at C_6, the out-of-phase mixing of this n-orbital with the σ-orbitals of the diene reaction centers should favor an approach of the dienophile on the face bearing the C_6-oxygen atom.[31] These suggestions are of course still open to further discussions, but they are unarguably fed by considerations that are much more advanced than those simply based on steric effects. These effects have generally been invoked to explain the double diastereofacial selectivity observed in the dimerization of orthoquinols (i.e., Me and OH groups at C_6) and their spirooxirane versions.[14,32] However, natural bond orbital analyses we carried out on TSs of the conversion of orthoquinol **2c** into (+)-aquaticol (**3c**)[11] (Scheme 2) leads us to favor an explanation based on a double 'Cieplak–Fallis' hyperconjugation as the determining factor in this stereoselectivity (Fig. 4). In all stereochemically defined cases of orthoquinone monoketal and orthoquinol kinetically-controlled dimerizations, the most electron-donating σ-bond of the two allylic C_6-substituents connecting bonds is ideally oriented to be quasi antiperiplanar to the σ*-orbital of the C_5–$C_{5'}$ incipient bond in TS structures (e.g., see TS-**3k** and TS-**3o** in Fig. 3). This is not only the case with carbon/oxygen-based C_6-substituents, but also with carbon/halogen- and sulfur/oxygen-based C_6-substituents.[33] The C_2-symmetry of all of the calculated TSs leading to products under kinetic conditions merits one final comment, as it allows hyperconjugation from each antiperiplanar C_6-allylic bond of each monomer to affect the same C_5–$C_{5'}$ incipient bond (Fig. 4). This is in contrast to the non-observed sites' connection alternative, such as that in the C_1-symmetric TS-**3i′**, in which hyperconjugation from the same C_6-allylic bonds are at best spread over two different incipient bonds (i.e., $C_{5'}$–C_2 and $C_{4'}$–C_5, see Fig. 1). Hence, we suggest that these hyperconjugative effects can also play a determining role in controlling not only the π-facial selectivity but also the regioselectivity of these cyclodimerizations, even in the case of achiral orthoquinone monoketals, such as **2i**, as well as other cyclohexa-2,4-dienones.

3. Conclusion

The interpretation of the experimental and theoretical results described therein constitutes a comprehensive understanding of the factors that control the regio- and stereoselectivities at play in kinetically-controlled [4+2] dimerizations

of orthoquinonoid cyclohexa-2,4-dienones. The dimerization blocking 'acetate effect' has been rationalized, and sterically-independent explanations of both the site-specific regioselectivity and double diastereo-π-facial selectivity of the process are proposed on the basis of the establishment of asynchronous, bispericyclic, and C_2-symmetric reaction transition states. These transition states would be held together through a combination of both Woodward–Hoffmann and Salem–Houk secondary orbital interactions. Their resulting geometry enables hyperconjugation between the σ-bond linking the antiperiplanar allylic C_6-substituent of each monomer and the first-formed bond. These stabilizing hyperconjugative effects could thus also contribute to the site-specific regioselectivity observed in the dimerization of orthoquinonoid and other cyclohexa-2,4-dienones. In the same line of thought, the double diastereo-π-facial selectivity observed with chiral orthoquinonoid cyclohexa-2,4-dienones could then be due to a preference for Cieplak-type hyperconjugative effects, since the σ-bond linking the antiperiplanar allylic C_6-substituent is always the most electron-donating bond. The various aspects of the hypothesis discussed in this article obviously still need to be exposed to other in-depth investigations and further theoretical refinements before being confirmed or not, but it is, at this stage, unarguably attractive to admit that these aspects all appear to converge toward a single all-embracing explanation of the regio-, site-, *endo*-, and π-facial selectivities of this [4+2] cyclodimerization process involved in the biosynthetic elaboration of many natural products.

4. Computational

Geometry optimizations were carried out in vacuum using the density functional theory (DFT) with the three-parameter hybrid functional B3LYP[34] and the 6-31G(d) basis set. Thermal corrections were calculated from the unscaled harmonic vibrational frequencies using standard temperature and pressure conditions. Every transition state was characterized by a single imaginary frequency in the diagonalized mass-weighted Hessian matrix. In several significant cases, intrinsic reaction coordinates' (IRC) calculations were performed to determine an unambiguous path connecting transition structures with reactants and products. Electronic energies were further refined by using the larger 6-311+G(d,p) basis set, as well as by using the second order-Møller–Plesset (MP2) level of theory within the 6-31G(d) basis set. These procedures are referred to as B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) and MP2/6-31G(d)//B3LYP/6-31G(d), respectively. All calculations were performed using Gaussian03.[35]

5. Experimental

5.1. General

All moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N_2. Tetrahydrofuran (THF) was purified immediately before use either by distillation from sodium/benzophenone under N_2, or by filtration through alumina under N_2. Acetonitrile (CH_3CN), methanol (MeOH), and 2,2,2-trifluoroethanol (CF_3CH_2OH) were used as received. λ^5-Iodane, i.e., stabilized *o*-iodoxybenzoic acid (SIBX),[36] and λ^3-iodanes, i.e., [bis(trifluoroacetoxy)iodo]-benzene (BTI) and (diacetoxyiodo)benzene (DIB), were furnished by SIMAFEX and were used as received. Evaporations were conducted under reduced pressure at temperatures less than 30 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 40–63 μm silica gel (Merck) and the indicated solvents. Melting points were measured in open capillary tubes and are uncorrected. NMR spectra of samples in the indicated solvent were run at 250, 300 or 400 MHz and calibrated using residual solvent as an internal standard. Carbon multiplicities were determined by either DEPT135 or *J*-Mod experiments. Electron impact (EIMS, 50–70 eV), chemical ionization (CIMS), electrospray (ESIMS), and liquid secondary ion mass spectrometry (LSIMS) low- and/or high-resolution (HRMS) mass spectrometric analyses were obtained from either the mass spectrometry laboratory at the Centre d'Etude Structurale et d'Analyse des Molécules Organiques (CESAMO), Université Bordeaux 1, or the Centre Régional de Mesures Physiques de l'Ouest (CRMPO), Université Rennes 1, France. Elemental analyses were carried out at the Service Central d'Analyses du CNRS, Vernaison. The X-ray crystallographic analyses were performed at the Institut Européen de Chimie et Biologie (IECB), and X-ray diffraction data were collected on a crystal sealed in a Lindemann-glass using Cu Kα radiation on a CAD4 diffractometer.

5.1.1. 3,3,10,10-Tetramethoxy-6,12-dimethoxycarbonyl-tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (3g).[15] To a stirred solution of methyl 3-hydroxy-4-methoxybenzoate (322 mg, 1.77 mmol) and K_2CO_3 (488 mg, 3.34 mmol) in dry MeOH (10 mL) at −42 °C was added a solution of BTI (761 mg, 1.77 equiv) in CH_3CN (5 mL). The reaction mixture immediately became bright yellow, and after 2 h, TLC monitoring [hexanes–EtOAc (1:1)] indicated complete consumption of the starting material. The mixture was then allowed to warm up to room temperature, and was kept under stirring for 30 min, after which it was poured into water (10 mL), extracted with Et_2O (3×10 mL), washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated. The resulting brown oil was purified by column chromatography, eluting with hexanes–EtOAc (4:1→1:1), to furnish the cyclodimer **3g** as an amorphous yellowish solid. Further crystallization from pentanes–CH_2Cl_2 afforded pure **3g** as amber needles (207 mg, 55%): mp 166–168 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.94 (s, 3H), 3.10 (s, 3H), 3.19 (br d, *J*=6.9 Hz, 1H), 3.25 (dd, *J*=1.2, 8.3 Hz, 1H), 3.30 (s, 3H), 3.36 (s, 3H), 3.56 (s, 3H), 3.73 (ddd, *J*=1.3, 2.8, 8.3 Hz, 1H), 3.75 (s, 3H), 3.86 (dd, *J*=1.9, 2.8 Hz, 1H), 6.64 (d, *J*=1.2 Hz, 1H), 6.96 (dd, *J*=1.8, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 200.1, 193.6, 164.7, 163.2, 144.2, 140.5, 132.6, 132.2, 98.4, 94.2, 52.7, 51.9, 51.5, 50.4, 50.1, 49.8, 49.0, 40.9, 38.2, 38.1; EIMS *m/z* (rel intensity) 424 (M^+, 8), 396 (64), 381 (14), 336 (17); Anal. Calcd for $C_{20}H_{24}O_{10}$: C, 56.60; H, 5.70; O, 37.70. Found: C, 56.39; H, 5.83; CCDC 636463.

5.1.2. 7*R*,11-Dibromo-3*R*,10*R*-bis(2′-*tert*-butyl-1′,4′-dioxaspirocyclopentane)-tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (3n). A stirred solution of (+)-2-[(*R*)-2-hydroxy-3,3-dimethylbutoxy]-4-bromophenol (50 mg, 0.173 mmol) in CF_3CH_2OH (6 mL) was cooled at −35 °C,

and was treated dropwise, over 5 min, with a solution of DIB (57 mg, 0.176 mmol) in CF_3CH_2OH (1 mL). The reaction mixture immediately became pale yellow and then slowly changed to yellow-pink. After 20 min, TLC monitoring [cyclohexane–acetone (2:1)] indicated complete consumption of the starting material. Powdered $NaHCO_3$ was added in one portion to the reaction mixture, which was kept under stirring at −35 °C for 15 min. After CF_3CH_2OH removal in vacuo, the residue was taken up with CCl_4 (3×15 mL), filtered, and evaporated. Further drying under high vacuum allowed complete removal of the iodobenzene by-product and afforded an orange oily mixture of the corresponding ortho-quinone monoketal **2n** and its cyclodimer **3n**. Proton NMR monitoring of the mixture in a $CDCl_3$ solution (ca. 0.3 M) indicated that quasi complete [4+2] cyclodimerization of **2n** into **3n** was achieved after 15 days at room temperature. Subsequent purification by column chromatography, eluting with cyclohexane–acetone (5:1), gave pure cyclodimer **3n** as a pale orange oil (27 mg, 54%): $[\alpha]_D^{20}$ −161.7 (*c* 0.35, $CHCl_3$); IR (NaCl) 1748, 1708, 1194, 1107, 1008 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (s, 9H), 0.95 (s, 9H), 3.45–3.49 (m, 2H), 3.66–3.98 (m, 4H), 4.29 (dd, *J*=7.3, 14.2 Hz, 2H), 4.39 (br t, *J*=6.7 Hz, 1H), 6.04 (d, *J*=10.2 Hz, 1H), 6.19 (dd, *J*=2.4, 6.8 Hz, 1H), 6.49 (d, *J*=10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 200.6, 189.6, 146.5, 127.9, 127.3, 125.1, 102.4, 100.5, 85.9, 85.5, 67.7, 66.2, 63.2, 55.8, 53.9, 53.8, 33.4, 32.8, 25.3, 25.2; CIMS *m/z* (rel intensity) 594 (MNH_4^+, 39), 592 (MNH_4^+, 77), 590 (MNH_4^+, 39), 577 (MH^+, 24), 575 (MH^+, 46), 573 (MH^+, 24), 467 (100); HRMS (ESI) calcd for $C_{24}H_{30}O_6{}^{79}Br_2Na$ 595.0307, found 595.0308.

5.1.3. (3*R*,10*R*)-6,12-di-*tert*-Butyl-3,10-dihydroxy-3,10-diphenyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (3t). To a stirred suspension of acidic ion-exchange resin Amberlite® IR120-H^+ (ca. 200 mg) in dry THF (4 mL) was added dropwise a solution of 2*R*,9-di-*tert*-butyl-(6*R*)-phenyl-1,4-dioxaspiro[4.(5*R*)]deca-7,9-dien-6-ol (69 mg, 0.202 mmol) in dry THF (2 mL), in the presence of 4 Å molecular sieves. After stirring overnight at room temperature, TLC monitoring [hexanes–Et_2O (4:1)] indicated complete consumption of the starting material. The reaction mixture was then filtered and evaporated to furnish a pale yellow oily residue, which was purified by column chromatography, eluting with hexanes–Et_2O (4:1), to give the cyclodimer **3t** as a colorless syrup (32.4 mg, 66%): $[\alpha]_D^{20}$ +187.9 (*c* 0.78, $CHCl_3$); IR (NaCl) 3426, 1716, 1669, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 9H), 1.16 (s, 9H), 2.88 (s, 1H), 3.68 (s, 1H), 3.72 (d, *J*=9.0 Hz, 1H), 3.78 (dd, *J*=3.0, 6.8 Hz, 1H), 3.99 (dd, *J*=3.0, 9.0 Hz, 1H), 4.93 (s, 1H), 5.80 (dd, *J*=1.9, 6.8 Hz, 1H), 5.88 (s, 1H), 7.16–7.29 (m, 10H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 199.1, 166.2, 145.3, 144.4, 143.3, 129.3, 128.1, 128.0, 127.7, 126.7, 126.6, 122.6, 54.7, 47.1, 40.4, 40.0, 37.9, 34.4, 29.6, 28.5; ESIMS *m/z* (rel intensity) 507 (MNa^+, 100), 485 (MH^+, 2), 439 (4), 265 (10); HRMS (ESI) calcd for $C_{32}H_{36}O_4Na$ 507.2511, found 507.2495.

5.2. General procedure for SIBX-mediated oxidation reaction of 2-alkylphenols

To a solution of 2-alkylphenol (10 mmol) in dry THF (25 mL) was added SIBX (6.875 g, 11 mmol) as a solid in one portion. The resulting suspension was stirred at room temperature for 24 h, after which TFA (780 μL, 10 mmol) was added and the mixture was further stirred for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and H_2O (50 mL). An aqueous 1 M solution of NaOH was added slowly and continuously with vigorous shaking until all solid material dissolved. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with aqueous 1 M NaOH (40 mL), H_2O (50 mL), and brine (2×50 mL), then shaken vigorously with a saturated aqueous solution of $Na_2S_2O_4$ (100 mL), washed again with brine (50 mL), dried over Na_2SO_4, filtered, and evaporated at room temperature to give a residue, which was then purified by column chromatography.

5.2.1. 3,10-Dihydroxy-6,12-di-*iso*-propyl-3,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (3a). SIBX-mediated oxidation of carvacrol (**1a**, 1.5 g, 1 mmol) was carried out according to the general procedure to give, after purification by column chromatography, eluting with hexanes–Et_2O (1:1), 2,3-dihydroxy-4-*iso*-propyl-1-methylbenzene (**5**) as a brown oil (398 mg, 24%) and the cyclodimer **3a** as a yellow solid (930 mg). The latter was recrystallized twice at low temperature from hexanes–CH_2Cl_2 to afford pure **3a** as white needles (795 mg, 48%). Pure **3a** was also obtained as colorless prisms from slow evaporation of $CHCl_3$.

Compound **5**:[37] IR (NaCl) 3453, 2963, 1467 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (d, *J*=6.8 Hz, 6H), 2.24 (s, 3H), 3.17 (sept, *J*=6.8 Hz, 1H), 5.31 (br s, 2H), 6.69 (d, *J*=7.9 Hz, 1H), 6.73 (d, *J*=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 141.5, 141.0, 132.5, 121.9, 121.3, 117.4, 27.1, 22.6, 15.3; EIMS *m/z* (rel intensity) 166 (M^+, 92), 151 (100), 133 (56), 105 (60).

Compound **3a**: mp 136 °C (lit.[10b] 138–139 °C); IR (KBr) 3451, 2967, 1724, 1676, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, *J*=6.8 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 3H), 1.11 (d, *J*=7.0 Hz, 3H), 1.12 (d, *J*=6.6 Hz, 3H), 1.22 (s, 3H), 1.24 (s, 3H), 1.83 (sept, *J*=6.8 Hz, 1H), 2.48 (sept, *J*=6.8 Hz, 1H), 3.12 (dd, *J*=2.5, 8.7 Hz, 1H), 3.13–3.17 (m, 1H), 3.23 (dd, *J*=1.9, 8.7 Hz, 1H), 3.35 (dq, *J*=2.4, 6.8 Hz, 1H), 5.84 (d, *J*=6.8 Hz, 1H), 5.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.3, 201.9, 166.5, 145.6, 126.1, 119.9, 73.4, 72.8, 55.8, 44.6, 41.9, 40.8, 33.2, 32.8, 32.2, 25.8, 22.9, 20.7, 20.0, 19.2; EIMS *m/z* (rel intensity) 332 (M^+, 31), 315 (16), 289 (18), 271 (40), 243 (48), 166 (42), 149 (61), 125 (100).

5.2.2. 3,10-Dihydroxy-3,10-di-*iso*-propyl-6,12-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (3s). SIBX-mediated oxidation of thymol (1.5 g, 1 mmol) was carried out according to the general procedure to give, after purification by column chromatography, eluting with hexanes–Et_2O (1:1), 2,3-dihydroxy-4-*iso*-propyl-1-methylbenzene (**5**) as a brown oil (229 mg, 14%) and the cyclodimer **3s** as a yellow solid (970 mg). The latter was recrystallized twice at low temperature from hexanes–CH_2Cl_2 to afford pure **3s** as white needles (830 mg, 50%). Pure **3s** was also obtained as colorless prisms from slow evaporation of $CHCl_3$: mp 159.5 °C (lit.[38] mp 168–170 °C); IR (KBr)

3481, 2972, 2927, 1719, 1681, 1448, 1361 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.56 (d, J=6.6 Hz, 3H), 0.81 (d, J=6.8 Hz, 3H), 0.84 (d, J=7.1 Hz, 3H), 0.95 (d, J=6.6 Hz, 3H), 1.50–1.65 (m, 1H), 1.60 (s, 3H), 1.76 (sept, J=6.8 Hz, 1H), 1.95 (s, 3H), 2.36 (br s, 1H), 3.08 (d, J=7.3 Hz, 1H), 3.16 (s, 1H), 3.26 (d, J=8.3 Hz, 1H), 3.29 (d, J=6.6 Hz, 1H), 3.79 (s, 1H), 5.82 (d, J=6.1 Hz, 1H), 5.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.8, 201.8, 155.9, 135.7, 126.6, 125.3, 78.1, 77.8, 57.2, 47.1, 41.8, 37.2, 37.1, 32.5, 22.1, 21.3, 16.7, 16.6, 16.3, 16.0; ESIMS (MeOH) m/z 333 [MH^+].

5.2.3. 3,10-Dihydroxy-3,12-di-*iso*-propyl-6,10-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (3s′). SIBX-mediated oxidation of a 1:1 mixture of carvacrol (**1a**, 150 mg, 1 mmol) and thymol (150 mg, 1 mmol) was carried out according to the general procedure to give, after purification by column chromatography, eluting with hexanes–acetone (10:1), three fractions: one black and two yellow solids. Submission of the black solid residue (90 mg) to column chromatography, eluting with hexanes–Et_2O (4:1), afforded pure catechol **5** as a brown oil (40 mg, 24%) and pure thymol-based cyclodimer **3s** as a white solid (40 mg, 12%). Recrystallization at low temperature from hexanes–CH_2Cl_2 of the two yellow solids identified as the carvacrol-based cyclodimer **3a** and the cyclodimer **3s′**, respectively, furnished pure cyclodimers **3a** (68 mg, 21%) and **3s′** (31 mg, 9%) as white needles.

Compound **3s′**: mp 158–159 °C; IR (KBr) 3451, 1724, 1676, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.59 (d, J=6.6 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H), 0.90 (d, J=6.6 Hz, 3H), 0.98 (d, J=6.6 Hz, 3H), 1.22 (s, 3H), 1.58 (sept, J=6.6 Hz, 1H), 1.80–2.00 (m, 1H), 1.97 (s, 3H), 2.38 (br s, 1H), 3.09 (d, J=8.1 Hz, 1H), 3.25 (br s, 2H), 3.40 (d, J=8.6 Hz, 1H), 3.86 (br s, 1H), 5.82 (d, J=6.6 Hz, 1H), 5.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.0, 201.6, 156.4, 145.5, 126.0, 125.2, 76.7, 72.9, 55.0, 44.3, 43.9, 37.8, 36.8, 33.1, 25.9, 22.4, 20.4, 19.4, 16.7, 15.9; ESIMS (MeOH) m/z 333 (MH^+); Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25. Found: C, 71.89; H, 8.51; CCDC 636462.

5.3. General procedure for [2+2] photoannelation reaction of cyclodimers

A Pyrex tube containing a solution of cyclodimer in either dry MeOH or dry CH_2Cl_2 (ca. 0.04 M) was irradiated at room temperature using a medium-pressure mercury lamp. The reaction mixture was then evaporated and purified by column chromatography.

5.3.1. 4,4,11,11-Tetramethoxy-7,8-dimethoxycarbonylpentacyclo[6.4.0.0^{2,7}.0^{3,10}.0^{6,9}]dodeca-5,12-dione (4g). Photoannelation of cyclodimer **3g** (40 mg, 0.09 mmol) in MeOH (3 mL) was carried out over 10 h according to the general procedure. Purification by column chromatography, eluting with cyclohexane–acetone (2:1), afforded **4g** as a pale yellow oil (22 mg, 55%): IR (NaCl) 2957, 2850, 1735, 1437, 1282, 1252, 1223, 1121, 1079, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.89 (d, J=3.9 Hz, 2H), 3.21 (s, 6H), 3.35 (s, 6H), 3.68 (d, J=6.8 Hz, 2H), 3.72 (s, 8H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 200.7, 169.4, 95.5, 52.5, 50.6, 48.9, 45.8, 38.5, 36.1; EIMS m/z (rel intensity) 424 (M^+, 2), 409 (2), 393 (17), 365 (17), 306 (7), 212 (6), 174 (100); HRMS (ESI) calcd for $C_{20}H_{24}O_{10}Na$ 447.1267, found 447.1286.

5.3.2. 4,11-Bis(3′,3′-dimethyl-1′,4′-dioxaspirocyclopentan-2-one)pentacyclo[6.4.0.0^{2,7}.0^{3,10}.0^{6,9}]dodeca-5,12-dione (4k). Photoannelation of 3,10-bis(3′,3′-dimethyl-1′,4′-dioxaspirocyclopentan-2-one)tricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione[21b] (**3k**, 9 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was carried out over 20 h according to the general procedure. The reaction mixture was then evaporated to furnish **4k** as a white solid (9 mg, quantitative yield). Recrystallization from hexanes–CH_2Cl_2 afforded pure **4k** as colorless prisms: mp 310–313 °C; IR (NaCl) 2921, 1806, 1738, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 6H), 1.52 (s, 6H), 2.86 (s, 2H), 3.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 201.8, 174.0, 98.7, 78.8, 45.0, 41.2, 35.9, 35.6, 27.0, 25.0; CIMS (NH_3) 406 (MNH_4^+); HRMS (ESI) calcd for $C_{20}H_{21}O_8$ 389.1236, found 389.1219; CCDC 637238.

5.3.3. 4,11-Dihydroxy-7,8-di-*iso*-propyl-4,11-dimethylpentacyclo[6.4.0.0^{2,7}.0^{3,10}.0^{6,9}]dodeca-5,12-dione (4a). Photoannelation of cyclodimer **3a** (68 mg, 0.2 mmol) in MeOH (5 mL) was carried out over 24 h according to the general procedure. Purification by column chromatography, eluting with hexanes–acetone (3:1), gave **4a** as a colorless solid (55 mg, 81%). Further recrystallization from hexanes–CH_2Cl_2 afforded pure **4a** as colorless prisms: mp 238–239 °C (lit.[39] mp 229 °C); IR (KBr) 3469, 2974, 1702, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 6H), 1.06 (s, 6H), 1.32 (s, 6H), 2.04 (s, 2H), 2.75 (s, 2H), 2.94 (s, 4H), 2.90–3.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 215.9, 73.3, 50.7, 50.2, 40.6, 36.2, 30.0, 23.2, 19.1, 18.3; EIMS m/z (rel intensity) 332 (M^+, 10), 289 (30), 271 (32), 243 (63), 229 (29), 201 (58), 191 (32), 166 (56), 159 (84), 149 (66), 123 (100); HRMS (ESI) calcd for $C_{20}H_{28}O_4Na$ 355.1885, found 355.1891; CCDC 636464.

5.3.4. 4,11-Dihydroxy-4,11-di-*iso*-propyl-7,8-dimethylpentacyclo[6.4.0.0^{2,7}.0^{3,10}.0^{6,9}]dodeca-5,12-dione (4s). Photoannelation of cyclodimer **3s** (100 mg, 0.3 mmol) in MeOH (5 mL) was carried out over 24 h according to the general procedure. Purification by column chromatography, eluting with hexanes–Et_2O (1:1), furnished **4s** as a white solid (90 mg, 90%). Further recrystallization from hexanes–CH_2Cl_2 gave pure **4s**: mp 150 °C (lit.[39] mp 155 °C); IR (KBr) 3507, 2974, 1710, 1154, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 6H), 0.96 (s, 6H), 1.16 (s, 6H), 1.66 (s, 2H), 2.56 (s, 2H), 2.85 (s, 4H), 3.10 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 215.0, 79.1, 49.2, 44.4, 40.5, 39.6, 29.0, 16.6, 16.2, 15.7; EIMS m/z (rel intensity) 332 (M^+, 6), 314 (5), 296 (8), 271 (8), 243 (30), 225 (18), 173 (29), 166 (41), 151 (67), 135 (38), 123 (35), 105 (62), 91 (65), 71 (100); HRMS (ESI) calcd for $C_{20}H_{28}O_4Na$ 355.1885, found 355.1881.

5.3.5. 4,11-Dihydroxy-4,8-di-*iso*-propyl-7,11-dimethylpentacyclo[6.4.0.0^{2,7}.0^{3,10}.0^{6,9}]dodeca-5,12-dione (4s′). Photoannelation of cyclodimer **3s′** (25 mg, 0.075 mmol) in MeOH (2 mL) was carried out over 24 h according to the

general procedure. Purification by column chromatography, eluting with hexanes–acetone (3:1), gave **4s′** as a colorless amorphous solid (16 mg, 64%). Further recrystallization from hexanes–CH_2Cl_2 afforded pure **4s′** as colorless crystals: mp 173–175 °C; IR (KBr) 3325, 2967, 1710, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 3H), 0.87 (s, 3H), 1.00 (s, 6H), 1.29 (s, 6H), 1.71 (s, 2H), 1.83 (s, 1H), 2.51 (s, 1H), 2.79 (s, 2H), 2.92 (s, 1H), 2.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.7, 215.1, 78.9, 73.6, 51.0, 49.6, 47.2, 41.7, 41.4, 41.1, 40.7, 39.4, 30.2, 28.9, 23.1, 18.6, 18.2, 18.1, 16.4, 15.8; EIMS *m/z* (rel intensity) 332 (M^+, 6), 289 (7), 271 (20), 243 (45), 229 (21), 201 (25), 173 (44), 149 (87), 137 (52), 125 (56), 119 (64), 71 (100); HRMS (EIMS) calcd for $C_{20}H_{28}O_4$ 332.1987, found 332.1972.

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Supplementary data

X-ray data on structures **3g**, **3k**, **3s′**, **4a**, **4k**, and **4l** are available from the Cambridge Crystallographic Data Center (CCDC 636463, 178536, 636462, 636464, 637238, 245748). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.035.

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