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Diels–Alder Cycloadditions of Masked *o*-Benzoquinones with Alkenes

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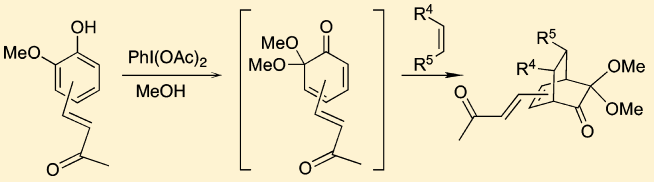
Supporting Information

ABSTRACT: Diels–Alder cycloadditions of 3-oxobut-1-enyl substituted orthoquinone monoketals with olefinic dienophiles furnished functionalized *ortho–endo* bicyclo[2.2.2]octenone derivatives with high regio- and stereoselectivities. The competition between self-dimerization and Diels–Alder cycloaddition with an external dienophile usually exists, except in the case of 5-substituted orthoquinone monoketal.



INTRODUCTION

Bicyclo[2.2.2]octenones[1] can be obtained via the Diels–Alder reactions of suitably substituted cyclohexa-2,4-dienones with appropriate dienophiles. These useful bicyclic synthons can be converted into polysubstituted cyclohexanes,[2] bicyclo[3.2.1]-octenones,[3] bicyclo[4.2.0]octenones,[4] fused triquinanes,[5] *cis*-decalins,[6] and bicyclo[4.2.2]decenones.[7] 6,6-Dialkoxycyclohexa-2,4-dienones,[8] named as orthoquinone monoketals or masked *o*-benzoquinones (MOBs), are a synthetically useful class of 2,4-cyclohexadienones. The presence of an *s–cis* diene unit constrained in the six-membered ring together with a conjugated carbonyl group at C-1 confers remarkable diene and dienophilic reactivity on these structures and results in facile dimerization during their preparation from the oxidation of simple and easily accessible 2-methoxyphenols with (diacetoxy)iodobenzene. In view of their propensity to undergo facile dimerization, these short-lived reactive species are usually trapped in situ by reactive dienes or dienophiles to provide highly functionalized bicyclic and tricyclic ring systems via inter- and intramolecular Diels–Alder reactions, respectively. It should be pointed out that, quite often, these Diels–Alder processes were a key step in total syntheses of natural products.[9]

We have been interested in investigating the effect of an electron-withdrawing substituent on the stability and reactivity of the in situ generated masked *o*-benzoquinone by placing the same electron-withdrawing substituent on each available position of the aromatic ring of the starting *o*-methoxyphenol **1** (Figure 1). Perhaps, this should result in a competition between the self-dimerization reaction of the masked *o*-benzoquinone **2** and the desired Diels–Alder cycloaddition with the external dienophile in varying extent.

We wish to address in this paper a detailed account of our investigations on the intermolecular Diels–Alder reactions of extremely unstable masked *o*-benzoquinone **2a**, moderately unstable masked *o*-benzoquinone **2b–c**, and their stable isomer **2d** with olefinic dienophiles to synthesize bicyclo[2.2.2]-octenones.

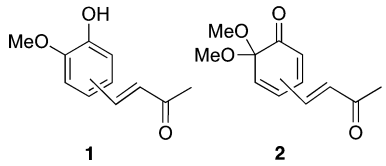


Figure 1. *o*-Methoxyphenol **1** and the corresponding masked *o*-benzoquinones **2**.

RESULTS AND DISCUSSION

The oxidation of 6-[(1*E*)-3-oxobut-1-enyl]-2-methoxyphenol[10] (**1a**) was carried out with (diacetoxy)iodobenzene at room temperature. The in situ generated 6,6-dimethoxy-2-[(1*E*)-3-oxobut-1-enyl]cyclohexa-3,5-dienone (**2a**) was highly reactive and dimerized more rapidly than cycloadding with the external dienophile (Scheme 1). To circumvent this problem, the retro-Diels–Alder/Diels–Alder sequence[11] was applied for the synthesis of the desired cycloadducts. Thus, a mixture of dimer **3a** with excess dienophile **4** in *o*-xylene was heated at 200 °C in a sealed test tube until the complete disappearance of the starting dimer (TLC monitoring). The bicyclo[2.2.2]octenones **5a–d** were isolated by flash chromatography on silica gel in good yields (48–90%) (Table 1).

Cycloadduct **5a**, was obtained as the major diastereomer, in 79% yield, when styrene **4a** was allowed (at 200 °C for 15 h) to undergo reaction with dienone **2a**, generated by the thermolysis of dimer **3a** in *o*-xylene (Table 1, entry 1). The reaction with methyl acrylate **4b** was also considered. Dienone **2a**, generated by thermolysis of dimer **3a**, reacts with methyl acrylate **4b** to give the corresponding cycloadduct **5b**, in 48% yield (Table 1, entry 2). Phenylthioethylene **4c**, an electron-rich dienophile,

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Scheme 1

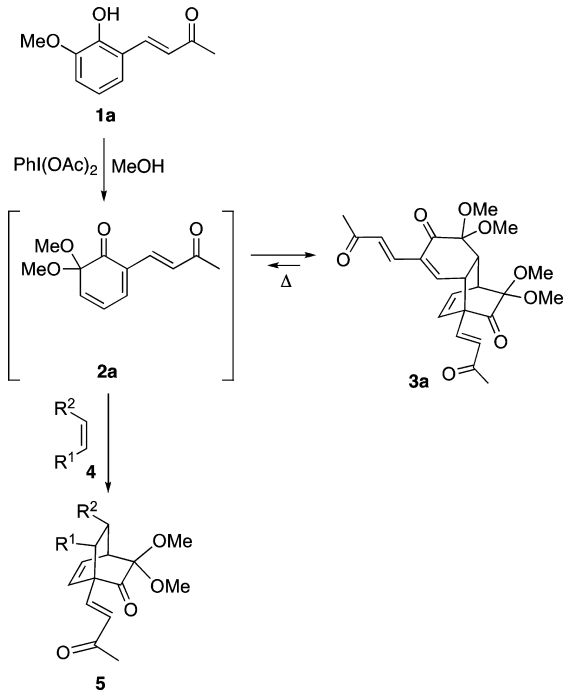

Table 1. Synthesis[a] of Bicyclo[2.2.2]octenones 5a−d

entry	R^1	R^2	product	yield (%)[b]
1	Ph	H	**5a**	79
2	MeO_2C	H	**5b**	48
3	PhS	H	**5c**	90
4	$C_6H_4CH_2$		**5d**	65

[a]All reactions were run by heating at 200 °C, in a sealed test tube, a mixture of dimer **3a** (0.59−0.86 mmol), and excess dienophile (7.35−22.09 mmol) in *o*-xylene (3 mL) for 2−15 h. [b]Yield of isolated product after flash chromatography.

also underwent highly regioselective cycloaddition with dienone **2a** at 200 °C, affording bicyclo[2.2.2]octenone **5c** in 90% yield (Table 1, entry 3). Even if indene **4d** was expected to be less reactive as a dienophile, bicyclo[2.2.2]octenone **5d** was isolated in 65% yield, when dienone **2a**, generated by thermolysis of dimer **3a**, reacted for 15 h at 200 °C with excess indene **4d** (Table 1, entry 4).

The oxidation of 5-[(1*E*)-3-oxobut-1-enyl]-2-methoxyphenol[12] (**1b**) was carried out with (diacetoxy)iodobenzene at room temperature (Scheme 2). In the absence of an external dienophile, the reaction produced exclusively dimer **3b**. However, in the presence of a dienophile, the aromatic oxidation produced the desired cycloadduct **6** along with substantial amounts of dimer **3b** (Table 2). A solution of phenol **1b** in methanol was slowly added to a solution of (diacetoxy)iodobenzene and styrene **4a** in methanol at room temperature. The reaction was continued for another hour at room temperature. The usual workup and flash chromatography afforded Diels−Alder cycloadduct **6a**, as a single diastereomer, in 19% yield along with 62% yield of dimer **3b** (Table 2, entry 1). When an even larger excess of dienophile **4a** was employed (19.13 mmol vs 9.66 mmol), then cycloadduct **6a** was isolated in 27% yield along with 51% yield of dimer **3b** (Table 2, entry 2). Since masked *o*-benzoquinone **2b** could be tlc-detected at room temperature, the reaction mixture, after

Scheme 2

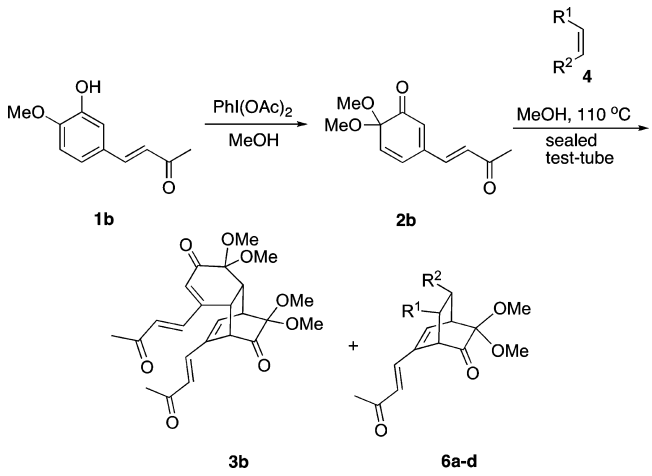

Table 2. Diels−Alder Cycloadditions[a] of Masked *o*-Benzoquinone 2b

entry	R^1	R^2	method	product	yield (%)[b]
1	Ph	H	A	**6a**	19
2	Ph	H	B	**6a**	27
3	Ph	H	C	**6a**	25
4	MeO_2C	H	A	**6b**	5
5	MeO_2C	H	B	**6b**	8
6	MeO_2C	H	C	**6b**	30
7	PhS	H	A	**6c**	33
8	PhS	H	C	**6c**	41
9	$C_6H_4CH_2$		A	**6d**	45
10	$C_6H_4CH_2$		C	**6d**	62

[a]All reactions were run by the addition of a solution of phenol **1b** (1.98 mmol) in methanol (10 mL) to a solution of (diacetoxy)-iodobenzene (2.04 mmol) and alkene **4** (7.35−11.04 mmol) in methanol (10 mL) at room temperature (method A) or by the addition of a solution of phenol **1b** (1.98 mmol) in methanol (10 mL) to a solution of (diacetoxy)iodobenzene (2.04 mmol) and alkene **4** (19.13−55.23 mmol) in methanol (10 mL) at room temperature (method B), or by the addition of a solution of phenol **1b** (1.98 mmol) in methanol (10 mL) to a solution of (diacetoxy)iodobenzene (2.17 mmol) and alkene **4** (7.35−55.23 mmol) in methanol (5 mL) at room temperature and heating the resulting mixture at 110 °C for 20−30 min (method C). [b]Yield of isolated product after flash chromatography.

the addition of the solution of phenol was complete, was transferred into a sealed test tube and heated at 110 °C for 30 min. The usual workup and flash chromatography afforded Diels−Alder cycloadduct **6a** as a single diastereomer, in 25% yield along with 37% yield of dimer **3b** (Table 2, entry 3). Even if methyl acrylate **4b** was expected to be a good dienophile for a normal Diels−Alder cycloaddition, it leads only to an 8% yield of the desired cycloadduct **6b**, along with 76% yield of dimer **3b**, despite the employment of a large excess (55.23 mmol) of **4b** (Table 2, entry 5). The yield of the cycloadduct **6b** was improved, when the reaction mixture was heated at 110 °C, in a sealed test tube, for 20 min (Table 2, entry 6). Under similar conditions, phenylthioethylene **4c** proved to be a better dienophile in the Diels−Alder cycloaddition with dienone **2b**; cycloadduct **6c** was isolated in 33% yield along with 65% yield of dimer **3b** (Table 2, entry 7). Again, the yield of the desired cycloadduct **6c** was improved, when the reaction mixture was

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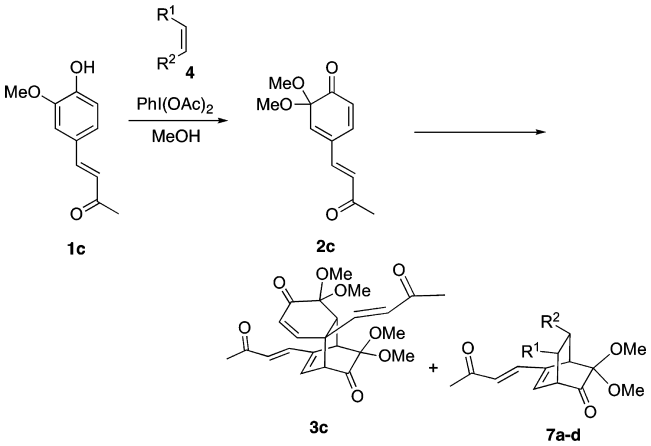
heated at 110 °C, in a sealed test tube for 20 min (Table 2, entry 8). Even if indene **4d** was expected to be less reactive, it proved to be the best dienophile in the Diels–Alder reaction with dienone **2b**; bicyclo[2.2.2]octenone **6d** was isolated in 45% yield along with 45% yield of dimer **3b** (Table 2, entry 9). When the reaction mixture was transferred in a sealed test tube and heated at 110 °C for 30 min, the yield of cycloadduct **6d** was improved to 62% (Table 2, entry 10). It appears that the low yields of the desired cycloadducts are mainly due to the rapid dimerization of the in situ generated dienone **2b** under the reaction conditions. Attempts to use the retro-Diels–Alder/Diels–Alder sequence failed, since dimer **3b** is rather stable at 200 °C even for a prolonged period of time.

The oxidation of 4-[(1*E*)-3-oxobut-1-enyl]-2-methoxyphenol[13] (**1c**) was carried out with (diacetoxy)iodobenzene at room temperature (Scheme 3). In the presence of an external

Scheme 3



dienophile, the aromatic oxidation produced the desired Diels–Alder cycloadducts **7a–d** along (Table 3) with substantial

Table 3. Diels–Alder Cycloadditions[a] of Masked *o*-Benzoquinone 2c

entry	R^1	R^2	product	yield (%)[b]
1	Ph	H	**7a**	48
2	MeO_2C	H	**7b**	18
3	PhS	H	**7c**	32
4	$C_6H_4CH_2$		**7d**	44

[a]All reactions were run by the addition of a solution of phenol **1c** (1.98 mmol) in methanol (10 mL) to a solution of (diacetoxy)-iodobenzene (2.17 mmol) and alkene **4** (7.35–55.23 mmol) in methanol (10 mL). [b]Yield of isolated product after flash chromatography.

amounts of dimer **3c**. Therefore, bicyclo[2.2.2]octenone **7a** was obtained, as a single diastereomer, in 48% yield along with a 52% yield of dimer **3c**, when a methanol solution of phenol **1c** was slowly added into a solution of (diacetoxy)iodobenzene and styrene **4a** in methanol (Table 3, entry 1). When methyl acrylate **4b** was utilized as an external dienophile, cycloadduct **7b**, as a single diastereomer, was isolated in 18% yield along with 82% yield of dimer **3c** (Table 3, entry 2). Phenylthioethylene **4c**, an electron-rich dienophile, yields cycloadduct **7c** in 32% yield along with 68% yield of dimer **3c** (Table 3, entry 3). Indene **4d** leads to the isolation of bicyclo[2.2.2]octenone **7d** in 44% yield along with a 45% yield of dimer **3c** (Table 3, entry 4). Attempts to use the retro-Diels–Alder/Diels–Alder sequence with dimer **3c** failed, since dimer **3c** is also stable at 200 °C even for a prolonged period of time.

The Diels–Alder cycloadditions of orthoquinone monoketals **2a–c** with olefinic dienophiles **4** showed excellent regio- and stereoselectivity. Structures of all cycloadducts **5–7** were unambiguously identified with IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and HRMS spectra. All the cycloadducts exhibited IR absorptions at 1732–1747 cm^{-1} due to the characteristic features of the carbonyl functional group adjacent to a *gem*-dimethoxy group in a functionalized bicyclo[2.2.2]octenone skeleton. All the cycloadducts **5–7** showed two ^{13}C resonances at about δ 201.8–197.6 ppm, revealing the presence of a carbonyl group and an unsaturated keto group as well as the peak corresponding to the quaternary carbon bearing two methoxy groups at about δ 94.3–93.3 ppm.

The observed selectivities have literature precedents.[14] The stereo- and regioselectivities of the bicyclo[2.2.2]oct-5-en-2-ones **5–7** determined by 2D NMR studies are exemplified for cycloadduct **5a** (Figure 2). The ^{1}H NMR chemical shift of H_c

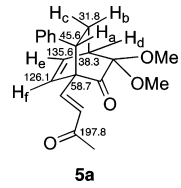
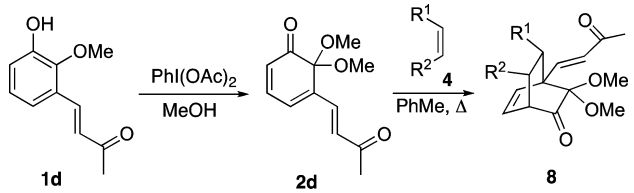


Figure 2. Selected ^{13}C NMR signals of cycloadduct **5a**.

was observed at δ 1.74, whereas, due to the deshielding effect exerted by the methoxy group, methylenic proton H_b appeared at δ 2.72–2.61 ppm. The coupling constants $J_{(H_a-H_c)}$ = 6.8 Hz and $J_{(H_a-H_b)}$ = 9.6 Hz, showing the *trans* and *cis* relation, respectively, could confirm the assigned stereochemistry. The HMBC signals between carbon atoms at δ 38.8 and 94.0 ppm with H_b and H_c as well as of carbon atoms at δ 58.7 and 126.1 ppm with H_a confirm the assigned *ortho* regiochemistry. The existence of NOESY signals between the phenyl group with the olefinic proton H_f further confirms the assigned *endo* stereochemistry.

The aromatic oxidation of 3-[(1*E*)-3-oxobut-1-enyl]-2-methoxyphenol[15] (**1d**) was carried out with (diacetoxy)-iodobenzene at room temperature, leading to the isolation of the stable masked *o*-benzoquinone **2d** in 83% yield, without any traces of the corresponding dimer (Scheme 4). Dienone **2d** is stable at 20 °C for 24 h without any significant decomposition or at least for 1 month at −20 °C (monitored by ^{1}H NMR). A solution of the isolated dienone **2d** and excess dienophile **4** in toluene was refluxed for 15–48 h. The usual workup and flash

Scheme 4



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chromatography afforded bicyclo[2.2.2]octenones **8a–d**, in moderate to good yields (Table 4).

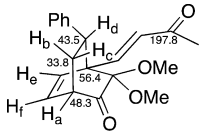
Table 4. Diels–Alder Cycloadditions[a] of Dienone 2d

entry	R^1	R^2	time (h)	product	yield[b] (%)
1	Ph	H	36	**8a**	72
2	MeO_2C	H	15	**8b**	61
3	PhS	H	48	**8c**	41
4	$C_6H_4CH_2$		48	**8d**	73

[a]All reactions were run by heating at reflux, a solution of dienone **2d** (0.77–0.80 mmol) and excess alkene **4** (4.04–55.2 mmol) in toluene (10 mL) for 15–48 h. [b]Yield of isolated product after flash chromatography.

Bicyclo[2.2.2]octenone **8a** was isolated in 72% yield, when a solution of dienone **2d** and excess styrene **4a** in toluene was refluxed for 36 h (Table 4, entry 1). Employment of a large excess (55.23 mmol) of methyl acrylate **8b** as an external dienophile results in the isolation of cycloadduct **6b** in 61% yield (Table 4, entry 2). Phenylthioethylene **8c**, an electron-rich dienophile, leads to the isolation of bicyclo[2.2.2]octenone **6c** in 41% yield (Table 4, entry 3). Bicyclo[2.2.2]octenone **8d** was isolated in 73% yield when a solution of dienone **2d** and excess indene **4d** in toluene was refluxed for 48 h (Table 4, entry 4).

The stereo- and regioselectivities of the bicyclo[2.2.2]oct-5-en-2-ones **8** determined by 2D NMR studies are exemplified for cycloadduct **8a** (Figure 3). The ^{1}H NMR chemical shift of H_b



8a

Figure 3. Selected ^{13}C NMR signals of cycloadduct **8a**.

was observed at δ 2.65–2.60 ppm, whereas, due to the magnetic anisotropy of the C=O group, methylenic proton H_c appeared at δ 1.98 ppm. The coupling constants $J_{(H_c-H_d)}$ = 10.0 Hz and $J_{(H_b-H_d)}$ = 5.5 Hz showing the *cis* and *trans* relation, respectively, could confirm the assigned stereochemistry. The HMBC signals between the carbon atom at δ 202.1 ppm with H_a, H_b, and H_c and carbon atoms at δ 95.6 and 56.4 with H_d confirm the assigned *ortho* regiochemistry (as to 3-oxobut-1-enyl substituent). The existence of NOESY signals between the phenyl group and the olefinic protons H_e and H_f further confirms the assigned *endo* stereochemistry.

The Diels–Alder cycloaddition of 3-oxobut-1-enyl substituted orthoquinone monoketals with olefinic dienophiles exhibits high regioselectivity and stereoselectivity. There are four possible cycloadducts as well as corresponding transition states (Figure 4), but only one isomer is formed as the sole product.

This extraordinary selectivity may be explained by invoking secondary orbital interactions. Competitive steric interactions developed at the *exo* transition states **B**, **D** between the substituent of the dienophile and the dimethoxy acetal group on the ethano bridge of the orthoquinone monoketal can destabilize the *exo* approach, favoring the *endo* transition states **A**, **C**. The FMO model and ab initio calculations predict[16] that the *ortho–endo* transition state **A** is more stable than the *meta–*

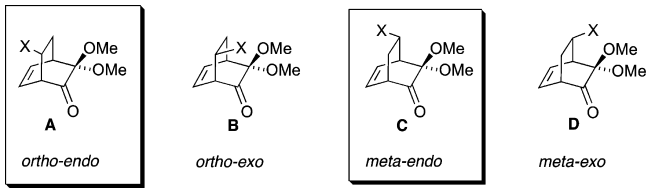


Figure 4. Four possible transition states for the cycloaddition of orthoquinone monoketals **2** with alkenes **4**.

endo transition state **C** and shows that the cycloaddition takes place along a polar stepwise mechanism. However, when two different carbonyl substituents are present, one works as regiodirector and controls the regiochemistry of the reaction. Apparently, when the keto- and 3-oxobut-1-enyl substituents are at the same dienic carbon atom, i.e., orthoquinone monoketal **2a**, both substituents direct the *ortho* addition while the dimethoxy acetyl group at the other dienic end favors the *endo* addition. Thus, the main cycloadduct, obtained from the retro-Diels–Alder/Diels–Alder sequence between dimer **3a** and olefinic dienophiles **4**, has the *ortho–endo* stereochemical orientation. When the keto- and 3-oxobut-1-enyl substituents are at adjacent carbon atoms, i.e., orthoquinone monoketal **2b**, the C1 keto substituent of the 2,4-cyclohexadienone core directs the *ortho* addition since stabilizing secondary orbital interactions developed at the transition state between the substituent of the dienophile and the C3 3-oxobut-1-enyl substituent of the 2,4-cyclohexadienone core (Figure 5).

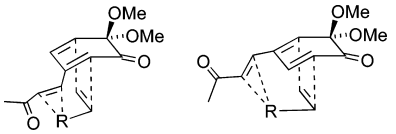


Figure 5. Secondary orbital interactions developed at the transition state.

Again, the dimethoxy acetal group at the other end of the diene favors the *endo* addition. Thus, the cycloadduct obtained from the Diels–Alder reaction of phenol **1b** with alkenes **4** has the *ortho–endo* stereochemical orientation. Similarly, when the 3-oxobut-1-enyl substituent is adjacent to the dimethoxy acetal group, i.e., orthoquinone monoketal **2c**, the C1 keto substituent of the 2,4-cyclohexadienone core directs the *ortho* addition since stabilizing secondary orbital interactions developed at the transition state between the substituent of the dienophile and the C4 3-oxobut-1-enyl substituent of the 2,4-cyclohexadienone core (Figure 5). Again, the dimethoxy acetal group at the other end of the diene favors the *endo* addition. Thus, the cycloadduct obtained from the Diels–Alder reaction of phenol **1c** with alkenes **4** has the *ortho–endo* stereochemical orientation. Finally, when the keto- and 3-oxobut-1-enyl substituents are at the opposite dienic ends, i.e., orthoquinone monoketal **2d**, the 3-oxobut-1-enyl substituent directs the *ortho* addition (*meta* to the C1 keto group) since stabilizing secondary orbital interactions developed at the transition state between the substituent of the dienophile and the new C3–C4 double bond, while the dimethoxy acetal group favors the *endo* addition. Thus, the main cycloadduct obtained from the Diels–Alder reaction of orthoquinone monoketal **2d** with alkenes **4** has the *ortho–endo* stereochemical orientation.

It is quite remarkable that all of these cycloaddition reactions proceed with absolute regio- and stereoselectivity, furnishing a

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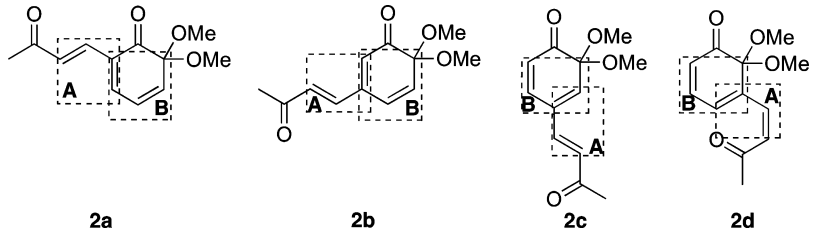

Figure 6. Inner- and outer-ring diene moieties of orthoquinone monoketals **2**.

single cycloadduct in most cases, although a number of products are possible. There are two different diene moieties when the orthoquinone monoketals **2** behaved as a 4π Diels–Alder component (Figure 6) and three electronically different double bonds, when the orthoquinone monoketals **2a–c** behaved as a 2π Diels–Alder component. In all cases examined, when orthoquinone monoketal **2** behaved as a 4π Diels–Alder component, it always reacts via diene subunit B (Figure 6). Apparently, the inner-ring *s–cis* diene subunit B is more reactive than the inner–outer-ring diene subunit A, since it leads to the more stable endocyclic olefinic cycloadduct. Similarly, in all cases examined, when the orthoquinone monoketals **2a–c** behaved as a 2π Diels–Alder component, they always reacts as a dienophile exclusively with the C4–C5 double bond, despite the existence of the adjacent bulky dimethoxy acetal group. Apparently, the *cis* stereochemistry of the C4–C5 double bond plays the crucial role.

The various orthoquinone monoketals **2** have exhibited different degrees of stability and reactivity with dienophiles to afford substituted bicyclo[2.2.2]octenones. It is known that self-dimerization occurs spontaneously at ambient temperatures; thus, there is always a competition between self-dimerization and Diels–Alder reaction with a dienophile, except in the case of orthoquinone monoketal **2d**. For example, orthoquinone monoketal **2a** is very reactive, self-dimerizing very fast at room temperature, producing dimer **3a** even in the presence of a large excess of an external dienophile. The desired bicyclo[2.2.2]octenone derivatives **5a–d** were prepared by the sequence retro-Diels–Alder/Diels–Alder of dimer **3a** with dienophiles **4**. In contrast, orthoquinone monoketal **2b** is stable enough to be detected by tlc, yielding mixtures of the desired bicyclo[2.2.2]octenone derivatives **6a–d** along with dimer **3b** to a varying degree. Similarly, orthoquinone monoketal **2c** is stable enough to be detected by tlc and has a reduced tendency to self-dimerize, thus producing mixtures of bicyclo[2.2.2]-octenone derivatives **7a–d** along with dimer **3c** at room temperature. On the other hand, orthoquinone monoketal **2d** was found to be stable at room temperature. The corresponding dimer was not even detected. Apparently, these differences in stability and reactivity should be a result of the position of the 3-oxobut-1-enyl substituent.

It is known that the self-dimerization can be blocked or at least retorted when some substituents exist. For example, a large electron-donating group at the C2 or C4 position or a halogen (iodine or bromine) at the C4 carbon atom of the 2,4-cyclohexadienone core hinders self-dimerization. When orthoquinone monoketal **2d** is generated, the existence of the 3-oxobut-1-enyl substituent at the C5 position of the 2,4-cyclohexadienone core hinders self-dimerization by its steric interaction at the transition state with the 6,6-dimethoxy acetal group of the dienophile partner, thus permitting its isolation as a liquid. Both the diene and the dienophile moieties are part of an extended conjugated system. Moreover, the dienophile moiety, i.e., the C4–C5 double bond, bears two strong electron-withdrawing substituents with *trans* stereochemical orientation as well as the bulky dimethoxy acetal group, and hence, it is impossible to behave as a dienophile in either a normal or an inverse-electron-demand Diels–Alder reaction with another orthoquinone monoketal molecule. When orthoquinone monoketal **2c** is generated, the existence of the large 3-oxobut-1-enyl substituent at the C4 carbon atom of the 2,4-cyclohexadienone core results in a minimized tendency to self-dimerize; thus, the Diels–Alder cycloaddition with an external dienophile can be performed at room temperature. Apparently, the dienophile moiety, i.e., the C4–C5 double bond of the 2,4-cyclohexadienone core, bears two strong electron-withdrawing substituents with *gem* stereochemical orientation as well as the bulky dimethoxy acetal group, and hence, it is difficult to behave as a dienophile in a Diels–Alder cycloaddition.

When orthoquinone monoketal **2b** is generated, the existence of the large 3-oxobut-1-enyl substituent at the C3 carbon atom of the 2,4-cyclohexadienone core results in reduced propensity toward self-dimerization. Apparently, at the favored *ortho–endo* transition state with a C_2-axis of symmetry, there is a steric interaction between the two large 3-oxobut-1-enyl substituents of the diene and dienophile partners, resulting in a reduced tendency to self-dimerize. In the case of orthoquinone monoketal **2a**, which spontaneously dimerized at room temperature even in the presence of a large excess of an external dienophile, there are minimal steric interactions between the substituents at the favored *ortho–endo* transition state. Thus, the chemical behavior of orthoquinone monoketal **2a** was revealed by following the retro-Diels–Alder/Diels–Alder sequence.

The Diels–Alder cycloadditions of 3-oxobut-1-enyl substituted orthoquinone monoketals with various olefinic dienophiles have been studied. These cycloadditions occur with high regio- and stereoselectivity and provide easy access to highly substituted bicyclo[2.2.2]oct-5-en-2-ones. When the 3-oxobut-1-enyl substituent exists at either end of the diene moiety of the 2,4-cyclohexadienone core, it works as regiodirector and controls the regiochemistry of the addition. In the absence of external dienophiles, the in situ generated orthoquinone monoketal usually undergoes self-dimerization in a highly regio- and stereoselective manner, one molecule acting as a diene, the other as a dienophile. In contrast, the 5-substituted orthoquinone monoketal shows no tendency to self-dimerize to the corresponding *ortho–endo* dimer and was isolated as a liquid.

■ EXPERIMENTAL SECTION

Melting points were uncorrected. IR spectra were recorded on an FT-IR spectrophotometer. ^{1}H and ^{13}C NMR were recorded on a 250 or 400 or 500 MHz instrument. The residual solvent protons (^{1}H) or the

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solvent carbon atoms (^{13}C) were used as internal standards. The ^{1}H NMR spectroscopic data are presented as follows: chemical shift in parts per million relative to tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, double of doublets; ddd, double of doublet of doublets; m, multiplet. High-resolution mass spectra were determined using ES ionization techniques. TLC analysis was conducted on precoated silica gel plates. The spots were visualized either by UV irradiation (254 nm) or with a $KMnO_4$ solution. Silica gel (0.040−0.063 μm) was used for flash chromatography. All commercial reagents were used without further purification. Solvents were dried by standard methods and purified by distillation before use.

6,6-Dimethoxy-5-[(1*E*)-3-oxobut-1-enyl]cyclohexa-3,5-dienone (2d). A solution of the phenol **1d** (0.194 g, 1.01 mmol) in methanol (10 mL) was slowly added to a solution of (diacetoxy)-iodobenzene (0.323 g, 1.00 mmol) in methanol (10 mL). The resulting red solution was stirred at room temperature for 1.0 h. The solvent was evaporated under reduced pressure, and the residue was flash chromatographed [silica gel; CH_2Cl_2, (8:1) CH_2Cl_2−EtOAc, (4:1) CH_2Cl_2−EtOAc] to afford dienone **2d** as a colorless oil (0.185 g, 83% yield). IR (KBr): 3066, 2944, 2838, 1668, 1600, 1364, 1258, 1120, 1074, 980, 968, 816 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.10 (d, J = 16.2 Hz, 1H), 7.00 (dd, J = 9.8, 6.3 Hz, 1H), 6.86 (d, J = 16.2 Hz, 1H), 6.67 (d, J = 6.3 Hz, 1H), 6.13 (d, J = 9.8 Hz, 1H), 3.18 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.5, 195.8, 145.1, 139.4, 137.1, 130.8, 130.3, 127.1, 94.3, 50.8, 28.1. HRMS (ESI-TOF): MH^+, found 223.0955. $C_{12}H_{15}O_4$ requires 223.0965.

General Procedure for the Synthesis of Dimers 3a−c. A solution of the appropriate phenol **1a−c** (2.11−10.00 mmol) in methanol (10−30 mL) was slowly added to a solution of (diacetoxy)iodobenzene (2.14−10.19 mmol) in methanol (10−30 mL). The resulting red solution was stirred at room temperature for 1.0 h. The solvent was evaporated under reduced pressure, and the residue was flash chromatographed [silica gel; CH_2Cl_2, (8:1) CH_2Cl_2−EtOAc, (4:1) CH_2Cl_2−EtOAc] to afford dimers **3a−c**.

*5,5,9,9-Tetramethoxy-1,7-bis[(1E)-3-oxobut-1-enyl]-1,4a,5,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4H)-dione (**3a**).* The title compound was isolated as white crystals (1.51 g, 68% yield) by following the above-mentioned procedure in which a solution of phenol **1a** (1.92 g, 10.00 mmol) in methanol (30 mL) was slowly added into a solution of (diacetoxy)iodobenzene (3.28 g, 10.19 mmol) in methanol (30 mL). m.p = 159−160 °C (EtOAc−hexanes). IR (KBr): 2959, 1736, 1709, 1680, 1618, 1358, 1254, 1080, 1055, 987 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.06 (d, J = 16.6 Hz, 1H), 6.95 (d, J = 16.2 Hz, 1H), 6.80 (d, J = 16.2 Hz, 1H), 6.48 (d, J = 4.2 Hz, 1H), 6.34−6.21 (m, 1H), 6.23 (d, J = 16.6 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 3.49 (s, 3H), 3.45−3.42 (m, 1H), 3.43 (s, 3H), 3.40−3.38 (m, 1H), 3.23−3.20 (m, 1H), 3.22 (s, 3H), 3.06 (s, 3H), 2.39 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.8, 198.2, 196.9, 193.4, 146.7, 140.2, 136.4, 135.7, 133.6, 132.6, 129.6, 128.7, 99.0, 94.8, 58.6, 50.5, 50.4, 49.8, 49.0, 43.9, 39.8, 39.4, 28.3, 27.6. HRMS (ESI-TOF): MNa^+, found 467.1674. $C_{24}H_{28}O_8Na$ requires 467.1676.

*5,5,9,9-Tetramethoxy-2,8-bis[(1E)-3-oxobut-1-enyl]-1,4a,5,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4H)-dione (**3b**).* The title compound was isolated as white crystals (0.74 g, 67% yield) by following the above-mentioned procedure in which a solution of phenol **1b** (0.96 g, 5.00 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (1.66 g, 5.16 mmol) in methanol (20 mL). m.p = 184−186 °C (EtOAc−hexanes). IR (KBr): 2952, 1734, 1698, 1678, 1360, 1234, 1110, 1056 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00 (d, J = 16.4 Hz, 1H), 6.98 (d, J = 16.2 Hz, 1H), 6.57 (d, J = 16.4 Hz, 1H), 6.50 (d, J = 6.9 Hz, 1H), 6.17 (s, 1H), 5.83 (d, J = 16.2 Hz, 1H), 3.74 (dd, J = 8.4, 2.6 Hz, 1H), 3.58−3.57 (m, 1H), 3.49 (s, 3H), 3.44 (s, 3H), 3.39 (d, J = 8.4 Hz, 1H), 3.30 (dd, J = 6.9, 1.5 Hz, 1H), 3.25 (s, 3H), 3.05 (s, 3H), 2.39 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.3, 197.5, 196.8, 193.0, 149.5, 139.8, 138.8, 137.2, 137.0, 131.6, 131.3, 127.3, 98.4, 94.3, 52.5, 50.5, 50.1, 49.8, 48.9, 40.9, 38.4, 37.6, 28.1, 27.3. HRMS (ESI-TOF): MNa^+, found 467.1667. $C_{24}H_{28}O_8Na$ requires 467.1676.

*5,5,9,9-Tetramethoxy-3,8a-bis[(1E)-3-oxobut-1-enyl]-1,4a,5,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4H)-dione (**3c**).* The title compound was isolated as a colorless oil (0.43 g, 91% yield) by following the above-mentioned procedure in which a solution of phenol **1c** (0.40 g, 2.11 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.68 g, 2.14 mmol) in methanol (10 mL). IR (neat): 2948, 1740, 1710, 1674, 1622, 1360, 1258, 1134, 1054, 978, 736 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, J = 16.1 Hz, 1H), 6.79 (d, J = 16.3 Hz, 1H), 6.32 (d, J = 16.1 Hz, 1H), 6.26 (d, J = 16.3 Hz, 1H), 6.25 (dd, J = 6.6, 1.5 Hz, 1H), 6.22 (d, J = 10.3 Hz, 1H), 6.06 (d, J = 10.3 Hz, 1H), 3.48 (s, 3H), 3.46 (s, 3H), 3.39−3.36 (m, 2H), 3.34 (d, J = 6.6 Hz, 1H), 3.26 (s, 3H), 3.09 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.0, 198.1, 197.6, 191.4, 146.13, 146.08, 141.4, 138.6, 132.9, 130.5, 128.5, 128.3, 97.6, 94.2, 58.3, 50.6, 50.5, 50.2, 49.9, 48.8, 43.5, 40.5, 27.6, 27.5. HRMS (ESI-TOF): MNa^+, found 467.1672. $C_{24}H_{28}O_8Na$ requires 467.1676.

General Procedure for the Synthesis of Cycloadducts 5a−d. A solution of dimer **3a** (0.59−0.86 mmol), and excess alkene **4** (7.35−22.09 mmol) in *o*-xylene (3 mL) was heated, in a sealed test tube, at 190−200 °C for 2−15 h. The solvent was evaporated under reduced pressure, and the residue was flash chromatographed [silica gel; CH_2Cl_2, (8:1) CH_2Cl_2−EtOAc, (4:1) CH_2Cl_2−EtOAc] to afford cycloadducts **5a−d**.

*1-[(1E)-3-Oxobut-1-enyl]-3,3-dimethoxy-7-phenylbicyclo[2.2.2]-oct-5-en-2-one (**5a**).* The title compound was isolated as a colorless oil (0.45 g, 79% yield) by following the above-mentioned procedure in which a solution of dimer **3a** (0.38 g, 0.86 mmol), and styrene **4a** (1.0 g, 9.62 mmol) in *o*-xylene (3 mL) was heated at 200 °C, in a sealed test tube, for 15 h. IR (KBr): 3020, 2944, 2836, 1736, 1678, 1636, 1494, 1458, 1360, 1256, 1146, 1058, 770 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.24−7.03 (m, 5H), 6.82 (d, J = 16.8 Hz, 1H), 6.80−6.72 (m, 1H), 6.13 (dd, J = 8.4, 2.3, Hz, 1H), 5.65 (d, J = 16.8 Hz, 1H), 3.43 (s, 3H), 3.37 (s, 3H), 3.32−3.28 (m, 2H), 2.72−2.61 (m, 1H), 2.09 (s, 3H), 1.74 (ddd, J = 13.3, 6.8, 2.7 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.4, 197.7, 142.3, 141.8, 135.6, 132.6, 128.4, 128.2, 127.2, 126.1, 94.0, 58.7, 50.3, 49.8, 45.6, 38.8, 31.8, 26.4. HRMS (ESI-TOF): MNa^+, found 349.1412. $C_{20}H_{22}O_4Na$ requires 349.1410.

*Methyl 8,8-Dimethoxy-7-oxo-1-[(1E)-3-oxobut-1-enyl]bicyclo-[2.2.2]oct-7-ene-2-carboxylate (**5b**).* The title compound was isolated as a colorless oil (0.206 g, 48% yield) by following the above-mentioned procedure in which a solution of dimer **3a** (0.31 g, 0.70 mmol), and methyl acrylate **4b** (2 mL, 22.09 mmol) in *o*-xylene (3 mL) was heated at 190 °C, in a sealed test tube, for 3.0 h. IR (KBr): 2952, 1734, 1672, 1636, 1436, 1362, 1186, 1150, 1070, 1046, 982, 888, 720 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.97 (d, J = 16.7 Hz, 1H), 6.58−6.52 (m, 1H), 6.12 (d, J = 16.7 Hz, 1H), 6.10−6.06 (m, 1H), 3.51 (s, 3H), 3.29 (s, 3H), 3.26 (s, 3H), 3.21−3.17 (m, 1H), 3.08−3.02 (m, 1H), 2.40−2.29 (m, 1H), 2.27 (s, 3H), 1.66 (ddd, J = 12.9, 6.4, 2.8 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 197.8, 197.7, 172.3, 141.6, 134.9, 132.6, 125.9, 93.8, 55.6, 51.8, 50.2, 49.8, 44.2, 38.2, 26.9, 26.7. HRMS (ESI-TOF): MK^+, found 347.0893. $C_{16}H_{20}O_6K$ requires 347.0891.

*1-[(1E)-3-Oxobut-1-enyl]-3,3-dimethoxy-7-phenylthiobicyclo-[2.2.2]oct-5-en-2-one (**5c**).* The title compound was isolated as a colorless oil (0.38 g, 90% yield) by following the above-mentioned procedure in which a solution of dimer **3a** (0.26 g, 0.59 mmol), and phenylthioethylene **4c** (1.0 g, 7.35 mmol) in *o*-xylene (3 mL) was heated at 200 °C, in a sealed test tube, for 2 h. IR (neat): 3058, 2944, 2836, 1738, 1678, 1440, 1258, 1148, 1062, 736 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.30−7.16 (m, 5H), 6.66 (d, J = 16.7 Hz, 1H), 6.61−6.55 (m, 1H), 6.25−6.21 (m, 2H), 3.74 (dd, J = 9.4, 5.6 Hz, 1H), 3.33 (s, 3H), 3.27 (s, 3H), 3.15−3.09 (m, 1H), 2.71 (ddd, J = 13.8, 9.4, 2.7 Hz, 1H), 1.95 (s, 3H), 1.52 (ddd, J = 13.8, 5.6, 3.2 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.2, 198.1, 141.7, 135.4, 135.1, 133.3, 131.4, 129.0, 127.1, 125.8, 93.7, 59.7, 50.4, 49.7, 47.8, 37.9, 31.3, 25.9. HRMS (ESI-TOF): MNa^+, found 381.1127. $C_{20}H_{22}O_4SNa$ requires 381.1131.

*4-[(1E)-3-Oxobut-1-enyl]-11,11-dimethoxy-4,4a,9,9a-tetrahydro-1H-1,4-ethanofluoren-10-one (**5d**).* The title compound was isolated

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as a colorless oil (0.37 g, 65% yield) by following the above-mentioned procedure in which a solution of dimer **3a** (0.38 g, 0.86 mmol), and indene **4d** (1.0 g, 8.62 mmol) in *o*-xylene (3 mL) was heated at 200 °C, in a sealed test tube, for 15 h. IR (neat): 3066, 2946, 2838, 1734, 1676, 1634, 1460, 1264, 1056, 884, 736 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.23 (d, J = 16.5 Hz, 1H), 7.18−6.93 (m, 4H), 6.42−6.36 (m, 1H), 6.13 (d, J = 16.5 Hz, 1H), 5.96 (d, J = 8.5 Hz, 1H), 3.79 (d, J = 8.9 Hz, 1H), 3.45 (s, 3H), 3.38−3.31 (m, 2H), 3.33 (s, 3H), 3.23−3.12 (m, 1H), 2.79−2.71 (m, 1H), 2.41 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.9, 197.6, 144.2, 142.7, 140.4, 132.9, 132.8, 127.7, 127.2, 125.9, 125.8, 124.3, 94.2, 59.0, 53.3, 50.4, 49.8, 43.5, 37.3, 36.4, 27.5. HRMS (ESI-TOF): MNa^+, found 361.1407. $C_{21}H_{22}O_4Na$ requires 361.1410.

General Procedure for the Synthesis of Cycloadducts 6a−d. A solution of phenol **1b** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added to a solution of (diacetoxy)iodobenzene (0.70 g, 2.17 mmol), and alkene **4** (7.35−55.23 mmol) in methanol (5 mL). The resulting orange solution was heated at 110 °C, in a sealed test tube, for 20−30 min. The solvent was evaporated under reduced pressure, and the residue was flash chromatographed [silica gel; CH_2Cl_2, (8:1) CH_2Cl_2−EtOAc, (4:1) CH_2Cl_2−EtOAc] to afford cycloadducts **6a−d** along with dimer **3b**.

*3,3-Dimethoxy-6-[(1E)-3-oxobut-1-enyl]-7-phenylbicyclo[2.2.2]-oct-5-en-2-one (**6a**).* The title compound was isolated as a colorless oil (0.16 g, 25% yield), along with dimer **3b** (0.16 g, 37% yield), by following the above-mentioned procedure in which a solution of phenol **1b** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.70 g, 2.17 mmol), and styrene **4a** (1.0 g, 9.62 mmol) in methanol (5 mL). The resulting orange solution was heated at 110 °C, in a sealed test tube, for 30 min. IR (neat): 3060, 2946, 1738, 1670, 1612, 1360, 1260, 1130, 1094, 1060, 974, 736 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.10 (m, 4H), 7.07−7.03 (m, 2H), 6.88 (d, J = 6.8 Hz, 1H), 5.78 (d, J = 16.0 Hz, 1H), 3.50−3.45 (m, 2H), 3.39 (s, 3H), 3.37−3.34 (m, 1H), 3.33 (s, 3H), 2.58−2.48 (m, 1H), 2.13 (s, 3H), 1.67 (ddd, J = 13.3, 6.3, 2.8 Hz, 1H) . ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.6, 198.0, 142.6, 140.5, 140.1, 134.5, 128.5, 127.1, 126.9, 126.2, 93.6, 55.2, 50.4, 49.8, 40.0, 39.2, 28.9, 27.8. HRMS (ESI-TOF): MK^+, found 365.1144. $C_{20}H_{22}O_4K$ requires 365.1150.

*Methyl 8,8-Dimethoxy-7-oxo-6-[(1E)-3-oxobut-1-enyl]bicyclo-[2.2.2]oct-2-ene-7-carboxylate (**6b**).* The title compound was isolated as a colorless oil (0.18 g, 30% yield), along with dimer **3b** (0.20 g, 45% yield), by following the above-mentioned procedure in which a solution of phenol **1b** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.66 g, 2.06 mmol), and methyl acrylate **4b** (4.75 g, 55.23 mmol) in methanol (5 mL). The resulting orange solution was heated at 110 °C, in a sealed test tube, for 20 min. IR (neat): 2950, 2837, 1745, 1666, 1612, 1587, 1434, 1359, 1205, 1095, 1054, 975, 734 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.09 (d, J = 16.1 Hz, 1H), 6.73 (d, J = 6.1 Hz, 1H), 6.23 (d, J = 16.1 Hz, 1H), 3.85−3.84 (m, 1H), 3.60 (s, 3H), 3.32 (s, 3H), 3.28 (s, 3H), 3.28−3.21 (m, 1H), 3.11 (ddd, J = 13.4, 5.6, 2.2 Hz, 1H), 2.36−2.32 (m, 1H), 2.26 (s, 3H), 1.86 (ddd, J = 13.4, 5.6, 3.1 Hz, 1H) . ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.9, 198.0, 172.4, 140.4, 139.3, 134.5, 126.8, 93.7, 52.2, 50.4, 49.72, 49.65, 39.3, 38.5, 27.5, 23.8. HRMS (ESI-TOF): MNa^+, found 331.1150. $C_{16}H_{20}O_6Na$ requires 331.1152.

*3,3-Dimethoxy-6-[(1E)-3-oxobut-1-enyl]-7-(phenylthio)bicyclo-[2.2.2]oct-5-en-2-one (**6c**).* The title compound was isolated as a colorless oil (0.29 g, 41% yield), along with dimer **3b** (0.25 g, 57% yield), by following the above-mentioned procedure in which a solution of phenol **1b** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.70 g, 2.17 mmol), and phenylthioethylene **4c** (1.00 g, 7.35 mmol) in methanol (5 mL). The resulting orange solution was heated at 110 °C, in a sealed test tube, for 20 min. IR (neat): 3053, 2943, 1745, 1614, 1587, 1439, 1360, 1057, 970, 812, 743 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.36−7.29 (m, 5H), 7.24 (d, J = 16.0 Hz, 1H), 6.79 (d, J = 6.7 Hz, 1H), 5.94 (d, J = 16.0 Hz, 1H), 3.87−3.81 (m, 1H), 3.51−3.50 (m, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 3.28−3.24 (m, 1H), 2.66−2.56 (m, 1H), 2.25 (s, 3H), 1.31−1.22 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.2, 198.0, 140.0, 135.2, 134.1, 131.6, 129.2, 128.9, 127.7, 126.7, 93.8, 51.9, 50.4, 49.8, 41.3, 39.3, 28.0, 27.8. HRMS (ESI-TOF): MH^+, found 359.1302. $C_{20}H_{23}O_4S$ requires 359.1312.

*3-[(1E)-3-Oxobut-1-enyl]-11,11-dimethoxy-4,4a,9,9a-tetrahydro-1H-1,4-ethanofluoren-10-one (**6d**).* The title compound was isolated as a colorless oil (0.42 g, 62% yield), along with dimer **3b** (0.16 g, 36% yield), by following the above-mentioned procedure in which a solution of phenol **1b** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.70 g, 2.17 mmol), and indene **4d** (1.00 g, 8.62 mmol) in methanol (5 mL). The resulting orange solution was heated at 110 °C, in a sealed test tube, for 30 min. IR (neat): 3038, 2945, 1732, 1666, 1618, 1444, 1256, 1138, 1090, 1056, 974, 750 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.18−7.16 (m, 1H), 7.12−7.07 (m, 3H), 6.88 (d, J = 16.1 Hz, 1H), 6.58 (d, J = 6.7 Hz, 1H), 6.04 (d, J = 16.1 Hz, 1H), 3.95−3.93 (m, 1H), 3.82−3.81 (m, 1H), 3.46 (s, 3H), 3.45−3.44 (m, 1H), 3.35 (s, 3H), 3.27−3.25 (m, 2H), 2.74−2.67 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 201.8, 198.2, 143.2, 141.2, 140.0, 138.1, 136.4, 127.4, 126.7, 126.2, 124.2, 123.9, 94.3, 53.0, 50.5, 49.8, 48.0, 45.1, 37.4, 35.0, 27.3. HRMS (ESI-TOF): MK^+, found 377.1148. $C_{21}H_{22}O_4K$ requires 377.1150.

General Procedure for the Synthesis of Cycloadducts 7a−d. A solution of phenol **1c** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added to a solution of (diacetoxy)iodobenzene (0.65−0.66 g, 2.02−2.05 mmol), and alkene **4** (7.35−55.23 mmol) in methanol (10 mL). The solvent was evaporated under reduced pressure, and the residue was flash chromatographed [silica gel; CH_2Cl_2, (8:1) CH_2Cl_2−EtOAc, (4:1) CH_2Cl_2−EtOAc] to afford cycloadducts **7a−d** along with dimer **3c**.

*3,3-Dimethoxy-5-[(1E)-3-oxobut-1-enyl]-7-phenylbicyclo[2.2.2]-oct-5-en-2-one (**7a**).* The title compound was isolated as a colorless oil (0.31 g, 48% yield), along with dimer **3c** (0.23 g, 52% yield), by following the above-mentioned procedure in which a solution of phenol **1c** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.66 g, 2.05 mmol), and styrene **4a** (1.00 g, 9.62 mmol) in methanol (10 mL). IR (neat): 3060, 2946, 2836, 1744, 1684, 1618, 1458, 1360, 1256, 1090, 976, 762 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.25−7.13 (m, 4H), 7.04−7.00 (m, 2H), 6.42−6.33 (m, 2H), 3.52 (d, J = 2.3 Hz, 1H), 3.46−3.39 (m, 1H), 3.36 (s, 3H), 3.35−3.31 (m, 1H), 3.26 (s, 3H), 2.60−2.53 (m, 1H), 2.30 (s, 3H), 1.51 (ddd, J = 13.4, 6.7, 2.6 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.7, 198.4, 143.6, 143.1, 139.8, 131.8, 128.4, 127.1, 126.7, 126.6, 93.3, 56.1, 50.4, 49.7, 40.5, 38.8, 29.5, 27.1. HRMS (ESI-TOF): MNa^+, found 349.1407. $C_{20}H_{22}O_4Na$ requires 349.1410.

*Methyl 8,8-Dimethoxy-7-oxo-5-[(1E)-3-oxobut-1-enyl]bicyclo-[2.2.2]oct-2-ene-7-carboxylate (**7b**).* The title compound was isolated as a colorless oil (0.108 g, 18% yield), along with dimer **3c** (0.36 g, 82% yield), by following the above-mentioned procedure in which a solution of phenol **1c** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.66 g, 2.06 mmol), and methyl acrylate **4b** (1.02 g, 11.86 mmol) in methanol (10 mL). IR (neat): 2952, 1732, 1676, 1616, 1436, 1360, 1044, 976 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.12 (d, J = 16.2 Hz, 1H), 6.45−6.42 (m, 1H), 6.29 (d, J = 16.2 Hz, 1H), 3.66 (s, 3H), 3.66−3.62 (m, 1H), 3.49−3.42 (m, 1H), 3.34 (s, 3H), 3.27 (s, 3H), 3.16−3.08 (m, 1H), 2.36 (ddd, J = 13.4, 10.1, 2.9 Hz, 1H), 2.31 (s, 3H), 1.69 (ddd, J = 13.4, 6.1, 2.9 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.3, 198.5, 172.8, 143.6, 139.8, 131.4, 127.1, 93.4, 52.3, 51.0, 50.7, 49.8, 39.5, 38.1, 27.0, 24.4. HRMS (ESI-TOF): MH^+, found 309.1321. $C_{16}H_{21}O_6$ requires 309.1333.

*3,3-Dimethoxy-5-[(1E)-3-oxobut-1-enyl]-7-(phenylthio)bicyclo-[2.2.2]oct-5-en-2-one (**7c**).* The title compound was isolated as a colorless oil (0.23 g, 32% yield), along with dimer **3c** (0.30 g, 68% yield), by following the above-mentioned procedure in which a solution of phenol **1c** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.66 g, 2.05 mmol), and phenylthioethylene **4c** (0.72 g, 5.29 mmol) in methanol (10 mL). IR (neat): 3053, 2943, 1747, 1583, 1470, 1435, 1360, 1257,

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972, 744 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 5H), 7.18 (d, J = 16.2 Hz, 1H), 6.45 (d, J = 6.3 Hz, 1H), 6.28 (d, J = 16.2 Hz, 1H), 3.70−3.62 (m, 1H), 3.42−3.39 (m, 2H), 3.31 (s, 3H), 3.24 (s, 3H), 2.66−2.56 (m, 1H), 2.31 (s, 3H), 1.26−1.17 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.4, 198.4, 143.0, 139.8, 133.8, 132.0, 131.9, 129.2, 127.7, 127.2, 93.5, 53.8, 50.7, 49.9, 42.7, 38.3, 28.3, 27.1. HRMS (ESI-TOF): MNa^+, found 381.1110. $C_{20}H_{22}O_4NaS$ requires 381.1131.

*2-[(1E)-3-Oxobut-1-enyl]-11,11-dimethoxy-4,4a,9,9a-tetrahydro-1H-1,4-ethanofluoren-10-one (**7d**).* The title compound was isolated as a colorless oil (0.30 g, 44% yield), along with dimer **3c** (0.20 g, 45% yield), by following the above-mentioned procedure in which a solution of phenol **1c** (0.38 g, 1.98 mmol) in methanol (10 mL) was slowly added into a solution of (diacetoxy)iodobenzene (0.65 g, 2.02 mmol), and indene **4d** (1.06 g, 9.14 mmol) in methanol (10 mL). IR (neat): 3048, 2946, 2836, 1736, 1668, 1620, 1460, 1360, 1258, 1086, 982, 830, 736 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.18−7.11 (m, 4H), 7.08−7.03 (m, 1H), 6.31 (d, J = 16.2 Hz, 1H), 6.18 (dd, J = 6.4, 1.3 Hz, 1H), 3.87−3.83 (m, 1H), 3.62 (dd, J = 6.4, 2.7 Hz, 2H), 3.44 (s, 3H), 3.30 (s, 3H), 3.26−3.25 (m, 1H), 3.23−3.12 (m, 1H), 2.48 (dd, J = 16.1, 4.5 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 201.2, 198.8, 143.4, 142.2, 141.9, 140.7, 133.5, 127.4, 126.9, 126.8, 124.5, 124.0, 94.0, 55.1, 50.7, 49.9, 48.1, 43.6, 36.6, 34.5, 26.9. HRMS (ESI-TOF): MNa^+, found 361.1411. $C_{21}H_{22}O_4Na$ requires 361.1410.

General Procedure for the Synthesis of Cycloadducts 8a−d. A solution of dienone **2d** (0.171 g, 0.77 mmol), and the appropriate alkene **4** (4.00 4.90 mmol) in toluene (10 mL) was refluxed for 15−48 h. The solvent was evaporated under reduced pressure, and the residue was flash chromatographed [silica gel; CH_2Cl_2, (8:1) CH_2Cl_2−EtOAc, (4:1) CH_2Cl_2−EtOAc] to afford cycloadducts **8a−d**.

*3,3-Dimethoxy-4-[(1E)-3-oxobut-1-enyl]-8-phenylbicyclo[2.2.2]-oct-5-en-2-one (**8a**).* The title compound was isolated as a colorless oil (0.182 g, 72% yield), by following the above-mentioned procedure in which a solution of dienone **2d** (0.171 g, 0.77 mmol), and styrene **4a** (0.51 g, 4.90 mmol) in toluene (10 mL) was refluxed for 36 h. IR (neat): 3060, 3028, 2946, 2838, 1736, 1676, 1628, 1458, 1260, 1102, 1002, 752, 730 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.17−7.13 (m, 3H), 7.04−7.02 (m, 2H), 6.89 (d, J = 16.6 Hz, 1H), 6.53−6.50 (m, 1H), 6.34 (d, J = 8.3 Hz, 1H), 5.69 (d, J = 16.6 Hz, 1H), 3.70 (dd, J = 10.0, 5.5 Hz, 1H), 3.52 (s, 3H), 3.35−3.32 (m, 1H), 3.22 (s, 3H), 2.65−2.60 (m, 1H), 2.08 (s, 3H), 1.98 (ddd, J = 13.7, 5.5, 3.4 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 202.1, 197.8, 144.8, 142.7, 134.3, 131.3, 129.3, 128.2, 127.7, 126.8, 95.6, 56.4, 53.6, 52.1, 48.3, 43.5, 33.8, 26.8. HRMS (ESI-TOF): MNa^+, found 349.1414. $C_{20}H_{22}O_4Na$ requires 349.1410.

*Methyl 7,7-Dimethoxy-8-oxo-1-[(1E)-3-oxobut-1-enyl]bicyclo-[2.2.2]oct-2-ene-7-carboxylate (**8b**).* The title compound was isolated as a colorless oil (0.147 g, 61% yield), by following the above-mentioned procedure in which a solution of dienone **2d** (0.171 g, 0.77 mmol), and methyl acrylate **4b** (5 mL) in toluene (10 mL) was refluxed for 15 h. IR (neat): 2949, 2841, 1745, 1732, 1574, 1487, 1454, 1435, 1360, 1198, 1173, 1107, 986, 710 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.06 (d, J = 16.4 Hz, 1H), 6.43−6.34 (m, 2H), 6.27 (d, J = 16.4 Hz, 1H), 3.54 (s, 3H), 3.48 (dd, J = 10.1, 4.8 Hz, 1H), 3.42 (s, 3H), 3.29−3.24 (m, 1H), 3.22 (s, 3H), 2.36−2.25 (m 1H), 2.31 (s, 3H), 1.97 (dd, J = 13.3, 4.6, 3.6 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.3, 198.0, 173.4, 144.0, 133.9, 131.4, 127.1, 95.3, 54.2, 54.0, 52.1, 51.5, 47.4, 44.0, 28.3, 27.1. HRMS (ESI-TOF): MNa^+, found 331.1150. $C_{16}H_{20}O_6Na$ requires 331.1152.

*3,3-Dimethoxy-4-[(1E)-3-oxobut-1-enyl]-8-(phenylthio)bicyclo-[2.2.2]oct-5-en-2-one (**8c**).* The title compound was isolated as a colorless oil (0.118 g, 41% yield), by following the above-mentioned procedure in which a solution of dienone **2d** (0.178 g, 0.80 mmol), and phenylthioethylene **4c** (0.55 g, 4.04 mmol) in toluene (10 mL) was refluxed for 48 h. IR (neat): 3057, 2943, 1738, 1676, 1580, 1479, 1360, 1269, 1099, 1001, 916, 735 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.31−7.25 (m, 5H), 6.80 (d, J = 16.6 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 6.38 (dd, J = 8.3, 6.7 Hz, 1H), 6.36 (d, J = 16.6 Hz, 1H), 4.05 (dd, J = 9.3, 3.5 Hz, 1H), 3.40 (s, 3H), 3.32−3.23 (m, 1H), 3.18 (s, 3H), 2.73 (ddd, J = 14.1, 9.3, 1.7 Hz, 1H), 2.07 (s, 3H), 1.98−1.89 (m, 1H) . ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.0, 198.2, 143.6, 136.2, 134.3, 132.7, 130.7, 129.0, 127.6, 126.6, 95.7, 56.8, 54.2, 52.0, 47.9, 47.6, 33.7, 26.5. HRMS (ESI-TOF): MH^+, found 359.1306. $C_{20}H_{23}O_4S$ requires 359.1312.

*1-[(1E)-3-Oxobut-1-enyl]-11,11-dimethoxy-4,4a,9,9a-tetrahydro-1H-1,4-ethanofluoren-10-one (**8d**).* The title compound was isolated as colorless crystals (0.19 g, 73% yield), by following the above-mentioned procedure in which a solution of dienone **2d** (0.171 g, 0.77 mmol), and indene **4d** (0.51 g, 4.40 mmol) in toluene (10 mL) was refluxed for 48 h. m.p = 179−180 °C ($CHCl_3$−hexanes). IR (neat): 3064, 2924, 2848, 1730, 1674, 1358, 1258, 1116, 1064, 1000, 756 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.35 (d, J = 16.6 Hz, 1H), 7.16−7.13 (m, 1H), 7.10 (d, J = 7.4 Hz, 1H), 7.07−7.02 (m, 2H), 6.34 (d, J = 16.6 Hz, 1H), 6.22 (d, J = 8.3 Hz, 1H), 6.16 (dd, J = 8.3, 6.5 Hz, 1H), 4.18−4.17 (m, 1H), 3.53 (s, 3H), 3.40−3.38 (m, 1H), 3.28−3.22 (m, 2H), 3.26 (s, 3H), 2.73 (d, = 12.7 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 200.9, 197.8, 144.9, 144.2, 141.6, 135.0, 132.0, 127.1, 125.9, 125.4, 125.1, 124.0, 95.9, 56.5, 54.12, 54.05, 52.2, 51.2, 38.5, 37.6, 27.8. HRMS (ESI-TOF): MNa^+, found 361.1406. $C_{21}H_{22}O_4Na$ requires 361.1410.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01755.

^1H and ^{13}C spectra of **2d**, **3a−c**, **5a−d**, **6a−d**, **7a−d**, and **8a−d**, and 2D NMR spectra of **5a**, **6a**, **7a**, and **8a** (PDF)

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Notes

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