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Different Reaction Modes for the Oxidative Dimerization of Epoxyquinols and Epoxyquinones. Importance of Intermolecular Hydrogen-Bonding

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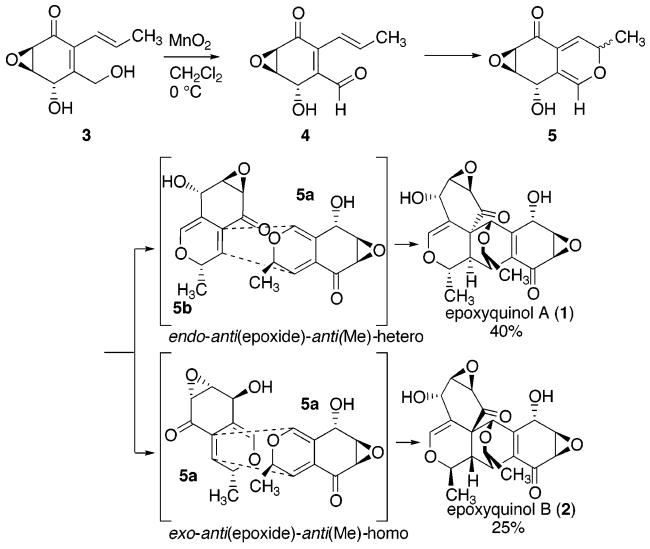
An oxidative dimerization reaction, involving the three successive steps of oxidation, 6π-electrocyclization, and Diels−Alder reaction, has been experimentally and theoretically investigated for the three 2-alkenyl-3-hydroxymethyl-2-cyclohexen-1-one derivatives epoxyquinol **3**, epoxyquinone **6**, and cyclohexenone **10**. Of the sixteen possible modes of the oxidation/6π-electrocylization/Diels−Alder reaction cascade for the epoxyquinone **6**, and eight for the cyclohexenone **10**, only the *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *endo*-*anti*(Me)-hetero modes are, respectively, observed, while both *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *exo*-*anti*(epoxide)-*anti*(Me)-homo reaction modes occur with the epoxyquinol **3**. Intermolecular hydrogen-bonding is found to be the key cause of formation of both epoxyquinols A and B with **3**, although epoxyquinone **6** and cyclohexenone **10** both gave selectively only the epoxyquinol A-type product. In the dimerization of epoxyquinol **3**, two monomer 2*H*-pyrans **5** interact with each other to afford intermediate complex **28** or **29** stabilized by hydrogen-bonding, from which Diels−Alder reaction proceeds. Theoretical calculations have also revealed the differences in the reaction profiles of epoxyquinone **6** and cyclohexenone **10**. Namely, the rate-determining step of the former is the Diels−Alder reaction, while that of the latter is the 6π-electrocyclization.

We have recently isolated and determined the structures of epoxyquinols A (**1**)[1] and B (**2**),[2] which are novel angiogenesis inhibitors with a highly functionalized and complicated heptacyclic ring system containing 12 stereocenters. Although these structures are very complex, we have proposed that they arise biosynthetically from the rather simple epoxyquinol **3** via an oxidation/6π-electrocyclization/Diels−Alder reaction cascade (Scheme 1). Recently we have accomplished the first asymmetric total synthesis of these molecules and determined their absolute stereochemistry.[3] Key steps of this synthesis are the $HfCl_4$-mediated Diels−Alder reaction of furan with the acrylate of Corey's chiral auxiliary[4] and a biomimetic, oxidative Diels−Alder reaction of monomer **3**. We have also established a practical synthetic route to both

SCHEME 1. Key Steps for the Synthesis of Epoxyquinols A and B



enantiomers of epoxyquinols A and B using the chromatography-free preparation of an iodolactone and a lipase-mediated kinetic resolution as key steps.[5] Soon after our first synthesis, Porco et al. published a synthesis of

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(1) Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496.
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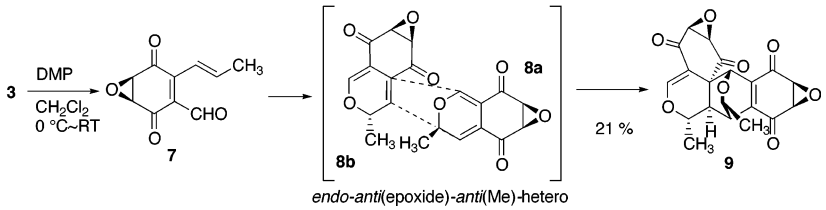
SCHEME 2. Oxidative Dimerization of Hydroxyepoxyquinone 3 with DMP



epoxyquinols A and B,[6] and just recently Mehta et al. have also reported the synthesis of racemic epoxyquinols A and B.[7]

While epoxyquinols A and B are epoxyquinol dimers, torreyanic acid, isolated from an endophytic fungus, *Pestalotiopsis microspra*, is an epoxyquinone dimer.[8] The proposed biosynthesis of torreyanic acid also involves an oxidation/6π-electrocyclization/Diels−Alder reaction cascade, and Porco et al. have developed an elegant biomimetic total synthesis, backed up by theoretical calculations, in which only the epoxyquinol A-type dimer is selectively formed.[9]

In the course of our total synthesis of epoxyquinols A and B, we examined carefully the oxidation of monomer **3** and observed the following interesting phenomenon: When monomer **3** was treated with the Dess−Martin periodinane (DMP),[10] both primary and secondary hydroxy groups were oxidized, affording cyclized 2*H*-pyran derivatives **8a**/**b**, which gave epoxyquinol A-type product **9** in 21% yield without formation of the epoxyquinol-B type product (Scheme 2). The yield of **9** was increased to 70% when isolated epoxyquinone **6** was treated with DMP (vide infra, Scheme 6).

The reaction modes for the Diels−Alder reaction initiated by oxidation of epoxyquinol **3** can be classified as follows: Consider the diene part first. The reacting face of the diene is either *anti* or *syn* to the epoxide and *anti* or *syn* to the methyl group, which we designate as *anti*(epoxide) or *syn*(epoxide) and *anti*(Me) or *syn*(Me) additions, respectively. When the diene and dienophile molecules are the same, we call it homocoupling, while heterocoupling is the reaction in which the diene and dienophile components are different. *Endo* addition is an addition in which the secondary orbital interaction between the carbonyl of the dienophile and the diene is present, while *exo* addition is an addition without such an interaction. According to this classification, epoxyquinols A and B are dimers of *endo-anti*(epoxide)-*anti*(Me)-hetero addition and *exo-anti*(epoxide)-*anti*(Me)-homo addition, respectively. In the dimerization of epoxyquinol **3**, the only two reaction modes observed are the *endo-anti*(epoxide)-*anti*(Me)-hetero and *exo-anti*(epoxide)-*anti*(Me)-homo modes, while the dimerization of epoxyquinone **6** proceeds via a single mode, the *endo-anti*(epoxide)-*anti*(Me)-hetero mode.

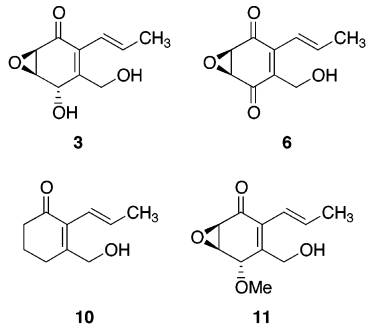


FIGURE 1. Monomers **3**, **6**, **10**, and **11**.

To understand the difference in reaction modes between epoxyquinol **3** and epoxyquinone **6**, the oxidative dimerization of a parent monomer, **10**, without epoxide and hydroxy groups, has been examined. The methoxycyclohexenone **11** was also investigated to shed light on the effect of the hydroxy group in **3**. In this paper we describe our investigation of the oxidation/6π-electrocyclization/Diels−Alder reaction by systematic comparison using the four monomers **3**, **6**, **10**, and **11** together with theoretical calculations (Figure 1).[11]

Results and Discussion

Synthesis of Monomers. Synthesis of the epoxyquinol monomer **3** has already been described.[3,5] The epoxyquinone monomer **6** was prepared from epoxyquinol monomer **3** according to Scheme 3, by protection of the primary alcohol with TBS, followed by oxidation with DMP and deprotection. The methoxy monomer **11** was prepared from **12** by methyl ether formation[12] and deprotection of the TBS group as shown in Scheme 4. The cyclohexenone monomer **10** with neither epoxy nor hydroxy functionalities was prepared according to Scheme 5. 3-Ethoxy-2-cyclohexene-1-one (**15**)[13] was treated with $LiCH_2SPh$[14] to afford 3-(phenylthiomethyl)-2-cyclohexen-1-one (**16**), which was converted to 3-formyl-2-cyclohexen-1-one (**18**) via Pummerer rearrangement.[15] Reduction with $CeCl_3$−$NaBH_4$,[16] protection of the primary hydroxy group, and

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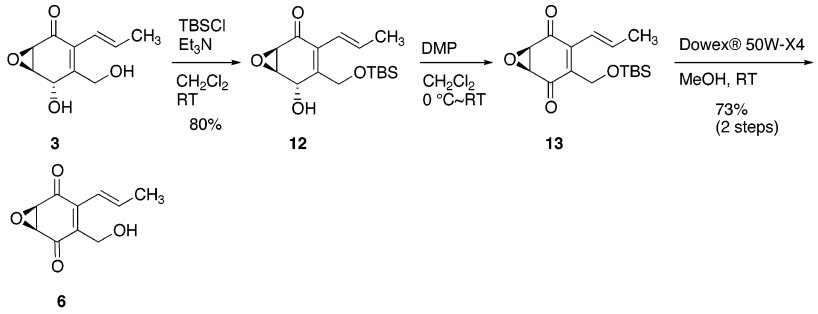
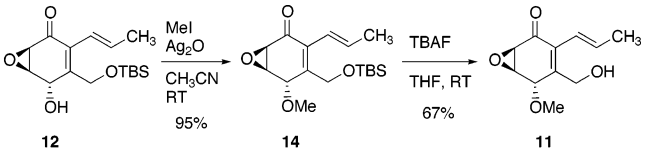
SCHEME 3. Preparation of Monomer 6



SCHEME 4. Preparation of Monomer 11



oxidation with MnO_2[17] gave 3-(*tert*-butyldimethylsiloxymethyl)-2-cyclohexen-1-one (**21**). The desired 3-hydroxymethyl-2-propenyl-2-cyclohexen-1-one (**10**) was obtained by α-iodination of ketone **21**, a Suzuki coupling reaction, and deprotection via the method developed for the synthesis of monomer **3**.[3,5]

Experimental Results for the Oxidation/6π-Electrocyclization/Diels−Alder Reaction. The results for the oxidation/6π-electrocyclization/Diels−Alder reaction of the monomers **6**, **10**, **3**, and **11** are summarized in Schemes 6−9, respectively. Though oxidation of alcohol **6** with MnO_2 did not proceed owing to the neighboring electron-withdrawing substituent, **6** was smoothly oxidized within 15 min by DMP in $CDCl_3$. ^{1}H NMR (400 MHz) showed that 2*H*-pyran **8** was formed while the corresponding aldehyde **7** could not be detected, and that epoxyquinol A-type product **9** had been formed in 50% yield with some 2*H*-pyran **8** remaining. When the crude reaction mixture was left neat for 1 h, 2*H*-pyran **8** was completely converted to the epoxyquinol A-type product **9** in 70% yield without formation of any other diastereomers (Scheme 6). These results indicate that the 6π-electrocyclization is fast, and that aldehyde **7** is readily converted to 2*H*-pyran **8**. The Diels−Alder reaction is also a fast process, proceeding only via the *endo*-*anti*(epoxide)-*anti*(Me)-hetero mode to afford epoxyquinol A-type adduct **9** in good yield. Although 2*H*-pyran **8** could be regarded as a poor diene because the two electron-withdrawing groups would decrease its HOMO energy, the dimerization is fast, which indicates that **8** acts as a reactive dienophile in the Diels−Alder reaction.

The reaction profile of cyclohexenone monomer **10** is rather different from that of epoxyquinone **6**. Unlike epoxyquinone **6**, the oxidation of **10** proceeds efficiently with MnO_2, and the ^{1}H NMR spectrum of the reaction suggests the presence of aldehyde **23**, 2*H*-pyran **24** not being observed. Generation of the Diels−Alder adduct **25** was slow, and aldehyde **23** was gradually converted into epoxyquinol A-type product **25** without detection of the 2*H*-pyran intermediate **24**. Eventually epoxyquinol A-type product **25** was gradually formed in 70% yield without formation of epoxyquinol B-type product after aldehyde **23** was allowed to stand neat for 10 h (Scheme 7). These results indicate that formation of the dimerized product is slow, and that only the *endo*-*anti*(Me)-hetero mode occurs. This phenomenon, namely, that the observed intermediate (aldehyde or 2*H*-pyran) is completely different for the reactions of epoxyquinone **6** and cyclohexenone **10**, is quite puzzling (vide infra).

The oxidation of epoxyquinol **3** was successfully carried out using MnO_2 without protection of the secondary alcohol.[3] The intermediate aldehyde **4** thus generated was not detected but was rapidly and smoothly converted to 2*H*-pyran **5**. The Diels−Alder dimerization takes 4 h to go to completion, and epoxyquinols A and B are formed in yields of 40% and 25%, respectively (Scheme 8). 6π-Electrocyclization is a fast process, and the Diels−Alder reaction is slower than that of the epoxyquinone **6**. The reaction proceeds via both *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *exo*-*anti*(epoxide)-*anti*(Me)-homo modes, generating both epoxyquinols A and B, while no other diastereomers are formed.

The methoxy derivative **11**, however, gave results quite different from those of epoxyquinol **3**. When **11** was oxidized with MnO_2, aldehyde **26**, which was not detected by ^{1}H NMR, was smoothly and completely converted into 2*H*-pyran derivatives **27** in a 4.5:1 diastereomer ratio after 1.5 h, although which isomer predominates has not been determined. As the Diels−Alder reaction of methoxy-2*H*-pyran **27** does not proceed even under more forcing reaction conditions, the single process of 6π-electrocyclization can be monitored in this system. The diastereomer ratio of **27** changed from 4.5:1 to 1.2:1 after 10 h (Scheme 9). This result clearly indicates the existence of an equilibrium[18] between *anti*- and *syn*-2*H*-pyrans **27**.

The present oxidative dimerization is composed of the three successive cascade reactions oxidation, 6π-electrocyclization, and Diels−Alder dimerization. Oxidation of the primary alcohol proceeds smoothly for all the substrates examined, while the next two reactions are dependent on the substituents. The 6π-electrocycylization and Diels−Alder reactions were separately investigated using theoretical calculations.

Theoretical Study of the 6π-Electrocyclization. Theoretical calculations were carried out to understand the reaction profile of the 6π-electrocyclization and Diels−Alder dimerization. The geometries of all stationary points were fully optimized at the B3LYP/6-31G*

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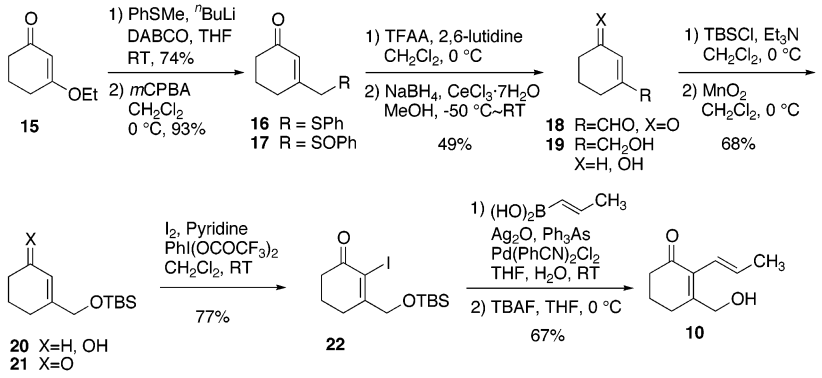
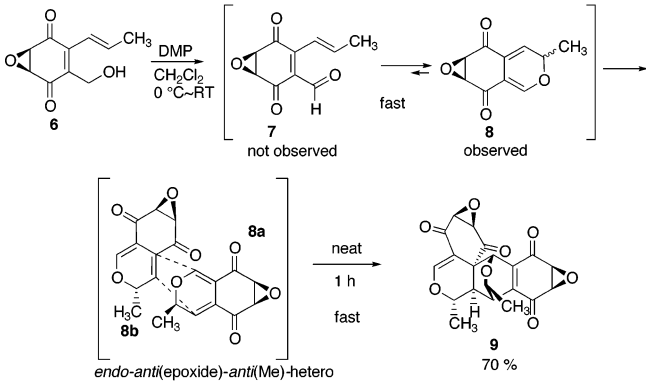
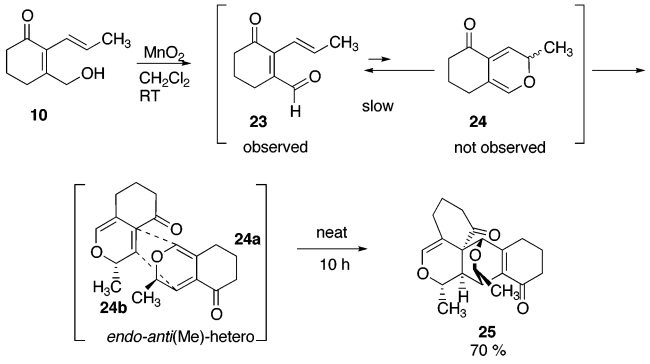
SCHEME 5. Preparation of Monomer 10



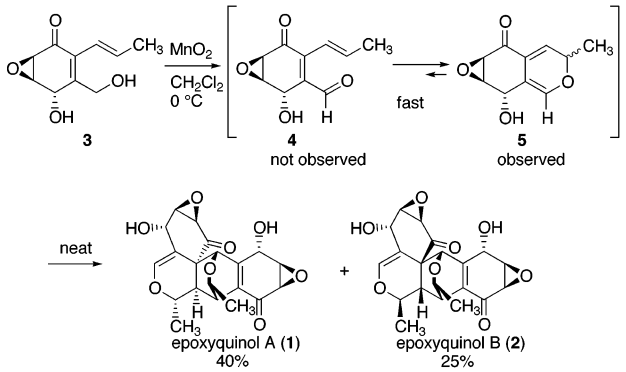
SCHEME 6. Dimerization of Epoxyquinone 6



SCHEME 7. Dimerization of Cyclohexenol 10



SCHEME 8. Dimerization of Epoxyquinol Monomer 3



level, and the properties of the molecules were also calculated at the same level.[19] All points were characterized as minima or saddle points by calculation of the harmonic vibrational frequencies, using analytical second derivatives.

Rodriguez-Otero has studied a series of 6π-electrocyclizations of (*Z*)-hexa-1,3,5-triene and its heterosubstituted analogues at various levels of theory and found that the reaction is slightly endothermic, the required TS energy for the 6π-electrocyclization of (2*Z*)-2,4-pentadienal being calculated as 21.52 kcal/mol at the B3LYP/6-31G**//B3LYP/6-31G** level.[20] Porco et al. studied the 6π-electrocyclization of epoxyquinone derivatives in their torreyanic acid synthesis. Their computational study indicates that this reaction is highly exothermic and that the TS energy is 5.0 kcal/mol for the *syn*-isomer and 10.2 kcal/mol for the *anti*-isomer at the B3LYP/6-31G*//AM1 level.[9b] As there has been no systematic study of substituent effects on 6π-electrocyclizations,[18] the 6π-electrocyclizations of the methyl ether epoxyquinol derivative **26**, epoxyquinone **7**, epoxyquinol **4**, and cyclohexenone **23** have been investigated in detail. Scheme 10 represents the transition structures leading to both *syn*- and *anti*-2*H*-pyrans along with the TS energies and distances of the newly formed O_1-C_2 bond (2*H*-pyran numbering).

The methoxy derivative **26** is an ideal substrate as there is no subsequent Diels–Alder reaction and hence the electrocyclization itself can easily be monitored experimentally. Therefore, the 6π-electrocyclization of this compound was examined first. 6π-Electrocyclization of **26** is exothermic, and both *syn*- and *anti*-2*H*-pyrans **27** are calculated to be more stable than the parent aldehyde **26**, by 4.18 and 4.16 kcal/mol, respectively. The TS energies leading to the two diastereomers of the 2*H*-pyran are low (15.50 and 17.74 kcal/mol), and the TS energies of retro-6π-electrocyclization are under 22 kcal/mol (19.68 and 21.90 kcal/mol). The TS energy for the reaction leading to *syn*-2*H*-pyran **27a** is lower than that of the reaction leading to *anti*-isomer **27b**, while the *anti*- and *syn*-isomers have the same stability.

These calculations are in good agreement with the experimental results as follows: (1) After oxidation, 2*H*-pyran **27** was observed without detection of intermediate aldehyde **26**. This is because on formation aldehyde **26** was immediately converted into 2*H*-pyran **27** as the TS energy is low and 6π-electrocyclization is exothermic. (2)

(19) All calculations were performed with the program package TITAN 1.0.5 of Schrodinger, Inc. (http://www.schrodinger.com) and Wavefunction Inc. (http://www.wavefun.com).

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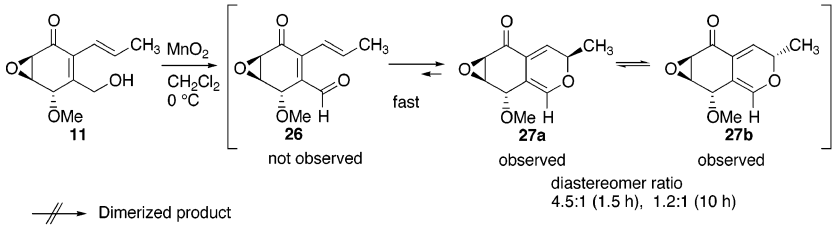
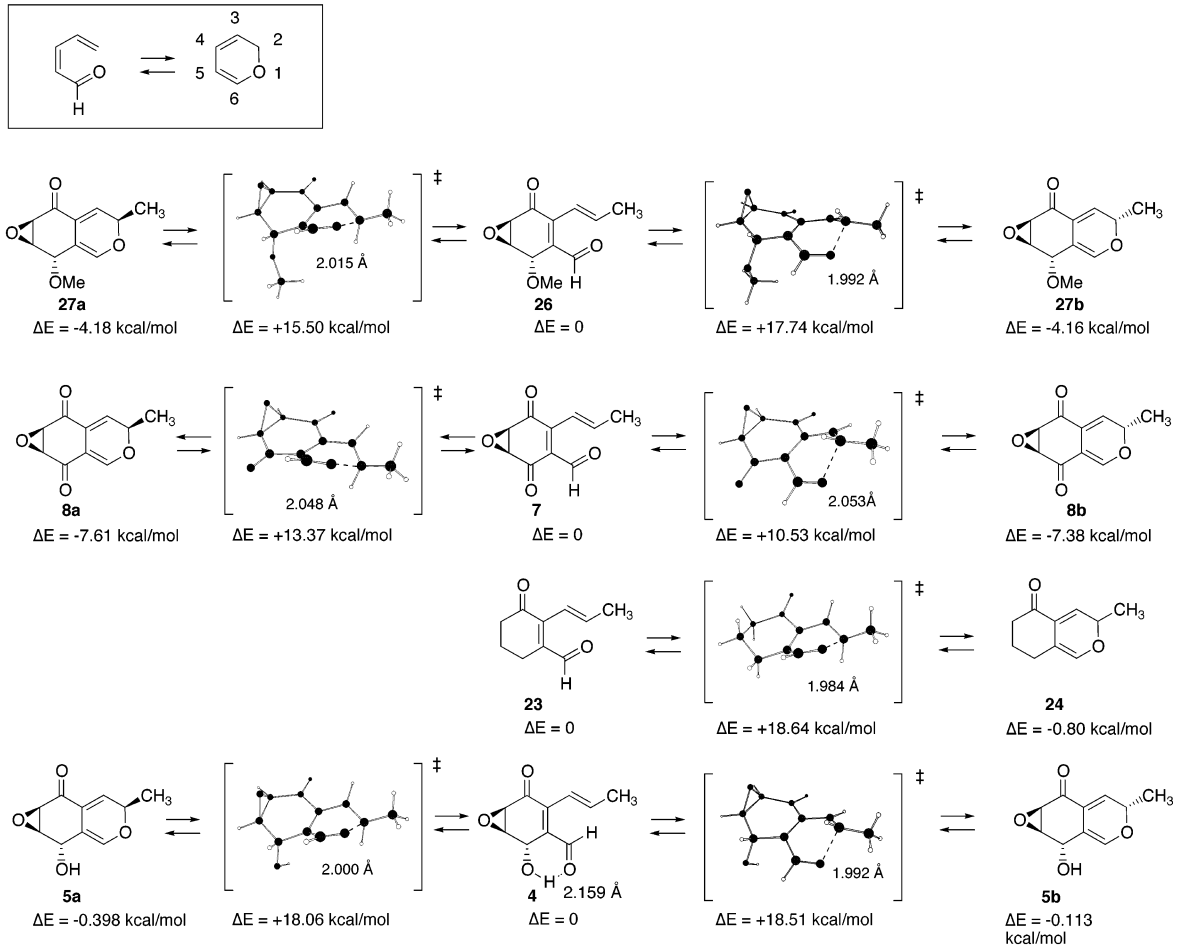
SCHEME 9. 6π-Electrocyclization of 11



SCHEME 10. Theoretical Calculations on the 6π-Electrocyclization



Though the major isomer of **27** has not been determined, the diastereomer ratio of 2*H*-pyrans **27a**,**b** changed from 4.5:1 (1.5 h) to 1.2:1 (10 h). We can surmise that this is because of an equilibrium occurring between 2*H*-pyrans **27a**,**b** and aldehyde **26**, a result of the low TS energies of both the 6π-electrocyclization and its retro reaction.

As calculated results for the methoxy derivative **26** proved to be in good agreement with experimental findings, the other 6π-electrocyclizations of **4**, **7**, and **23** have also been examined, and the following noteworthy features have been found from comparison of the four reactions: (1) The lone pair of the formyl oxygen is involved to a great extent in the TS as shown by the loss of planarity in the dihedral angles of $C_2O_1C_6C_5$ (2*H*-pyran numbering), and this is consistent with the calculations of Rodriguez-Otero on the parent 2,4-pentadienal.[20] (2) As the TS energies of both the 6π-electrocyclization and retro-6π-electrocyclization are below 22 kcal/mol for all the substrates, there is equilibrium among the *anti*- and *syn*-2*H*-pyrans and aldehyde at rt. (3) As the substituent becomes more electron-withdrawing, the TS energy becomes lower, indicating that 6π-electrocyclization becomes easier. (4) The order of the length of the newly formed O_1-C_2 bond in the transition state is epoxyquinone **7** > epoxyquinol **4** = methoxy derivative **26** > cyclohexenone **23**. As the substituent becomes more electron-withdrawing, the length O_1-C_2 in the TS becomes longer, indicating that the new bond has formed to a considerably lesser extent, and that the transition state is closer to the starting material. (5) As the substituent becomes more electron-withdrawing, the reaction becomes more exothermic, and the stability of the 2*H*-pyran over the aldehyde increases except in the case of epoxyquinol **4**. (6) The reaction of epoxyquinol **4** is a special case, in which aldehyde **4** and 2*H*-pyrans **5a**,**b** are of almost the same energy, while for the corresponding methoxy derivative 2*H*-pyrans **27a**,**b** are more stable than aldehyde **26** by ca. 4 kcal/mol. This is because there

TABLE 1. TS Energy of the Reaction Modes of Dimerization of Epoxyquinone 8

entry	reaction mode	diene	dienophile	TS energy/kcalmol^{-1}
1	*endo-anti*(epoxide)-*anti*(Me)-hetero	**8a**	**8b**	13.52
2	*endo-syn*(epoxide)-*syn*(Me)-hetero	**8a**	**8b**	27.55
3	*exo-syn*(epoxide)-*syn*(Me)-hetero	**8a**	**8b**	18.76
4	*exo*-anti(epoxide)-anti(Me)-hetero	**8a**	**8b**	17.24
5	*exo-anti*(epoxide)-*anti*(Me)-homo	**8a**	**8a**	15.43
6	*exo-syn*(epoxide)-*syn*(Me)-homo	**8a**	**8a**	20.56
7	*endo-anti*(epoxide)-*anti*(Me)-homo	**8a**	**8a**	25.04
8	*endo-syn*(epoxide)-*syn*(Me)-homo	**8a**	**8a**	18.38
9	*exo-anti*(epoxide)-*syn*(Me)-homo	**8b**	**8b**	19.04
10	*exo-syn*(epoxide)-*anti*(Me)-homo	**8b**	**8b**	15.93
11	*endo-syn*(epoxide)-*anti*(Me)-homo	**8b**	**8b**	20.40
12	*endo-anti*(epoxide)-*syn*(Me)-homo	**8b**	**8b**	21.79
13	*endo-anti*(epoxide)-*syn*(Me)-hetero	**8b**	**8a**	23.19
14	*endo-syn*(epoxide)-*anti*(Me)-hetero	**8b**	**8a**	18.60
15	*exo-syn*(epoxide)-*anti*(Me)-hetero	**8b**	**8a**	18.25
16	*exo-anti*(epoxide)-*syn*(Me)-hetero	**8b**	**8a**	20.98

TABLE 2. Frontier Orbital Energies of 8, 24, and 5

entry	orbital	orbital energy/eV	entry	orbital	orbital energy/eV
1	HOMO of **8a**	−6.22730	6	LUMO of **24**	−1.60257
2	LUMO of **8a**	−2.25359	7	HOMO of **5a**	−5.80672
3	HOMO of **8b**	−6.25759	8	LUMO of **5a**	−1.97206
4	LUMO of **8b**	−2.27970	9	HOMO of **5b**	−5.88086
5	HOMO of **24**	−5.46902	10	LUMO of **5b**	−1.99471

SCHEME 11. Reaction Modes of 2*H*-Pyran

is a hydrogen-bond interaction between the hydroxy group and formyl group in **4** (2.159 Å) as shown in Scheme 10, and this stabilizes the aldehyde **4**, so a higher TS energy is required for the conversion into 2*H*-pyrans **5** than for conversion of the corresponding methyl ether **26** into **27**.

Theoretical Study of the Diels−Alder Dimerization. Theoretical calculations on the homo-Diels−Alder reaction of 2*H*-pyran indicate the regiochemistry should be one of those shown in Scheme 11 according to the frontier orbital theory.[21,22] For this regiochemistry, there are 16 possible reaction modes[23] of the Diels−Alder reaction of both epoxyquinone **6** and epoxyquinol **3**. Of these, only the *endo-anti*(epoxide)-*anti*(Me)-hetero mode is observed with epoxyquinone **6**, while both the *endo-anti*(epoxide)-*anti*(Me)-hetero and *exo-anti*(epoxide)-*anti*(Me)-homo modes are detected with epoxyquinol **3**. In the case of cyclohexenone **10**, of the eight possible reaction modes[24] only the *endo-anti*(Me)-hetero mode was observed.

All 16 reaction modes for epoxyquinone **6** (**8a**,**b**) were investigated by theoretical calculations, and the TS energies of these reaction modes are summarized in Table 1. The frontier orbital energies of 2*H*-pyran derivatives **8a**,**b**, **24**, and **5a**,**b** and the HOMO−LUMO energy gap of **8a**,**b** have been summarized in Tables 2 and 3, respectively.

TABLE 3. Energy Gap of Frontier Orbitals of 8

entry	frontier orbital	energy gap/ eV
1	HOMO of **8a**−LUMO of **8a**	3.9737
2	HOMO of **8a**−LUMO of **8b**	3.9476
3	HOMO of **8b**−LUMO of **8b**	3.9779
4	HOMO of **8b**−LUMO of **8a**	4.0040

Calculations indicate that the orientation of the methyl groups is very important. That is, the three reaction modes with the lowest TS energy are the *endo-anti*-(epoxide)-*anti*(Me)-hetero (Table 1, entry 1), *exo-anti*-(epoxide)-*anti*(Me)-homo (entry 5), and *exo-syn*(epoxide)-*anti*(Me)-homo (entry 10) modes, in which the two methyl groups are oriented on opposite sides of the approaching dienophile and diene. That is to say, the steric hindrance caused by the methyl groups is so large that the methyl group of the diene monomer should be oriented *anti* to its reacting face, and that of the dienophile monomer oriented *anti* to its reacting face; otherwise the TS energies are over 16 kcal/mol.

Of the 16 reaction modes, the TS energy of the *endo-anti*(epoxide)-*anti*(Me)-hetero mode is found to be the lowest, 13.52 kcal/mol, indicating that this reaction is a facile process (entry 1). Scheme 12 indicates that steric hindrance is minimized through the two methyl groups, occupying axial positions. This is orbitally preferable in terms of the lowest HOMO−LUMO energy gap (Table 3, entry 2), and also because of its secondary orbital interactions (*endo* rule). The next lowest reaction mode is *exo-anti*(epoxide)-*anti*(Me)-homo, which would lead to the epoxyquinol B-type product (Table 1, entry 5). As this second lowest TS energy is 15.43 kcal/mol, which is 1.91

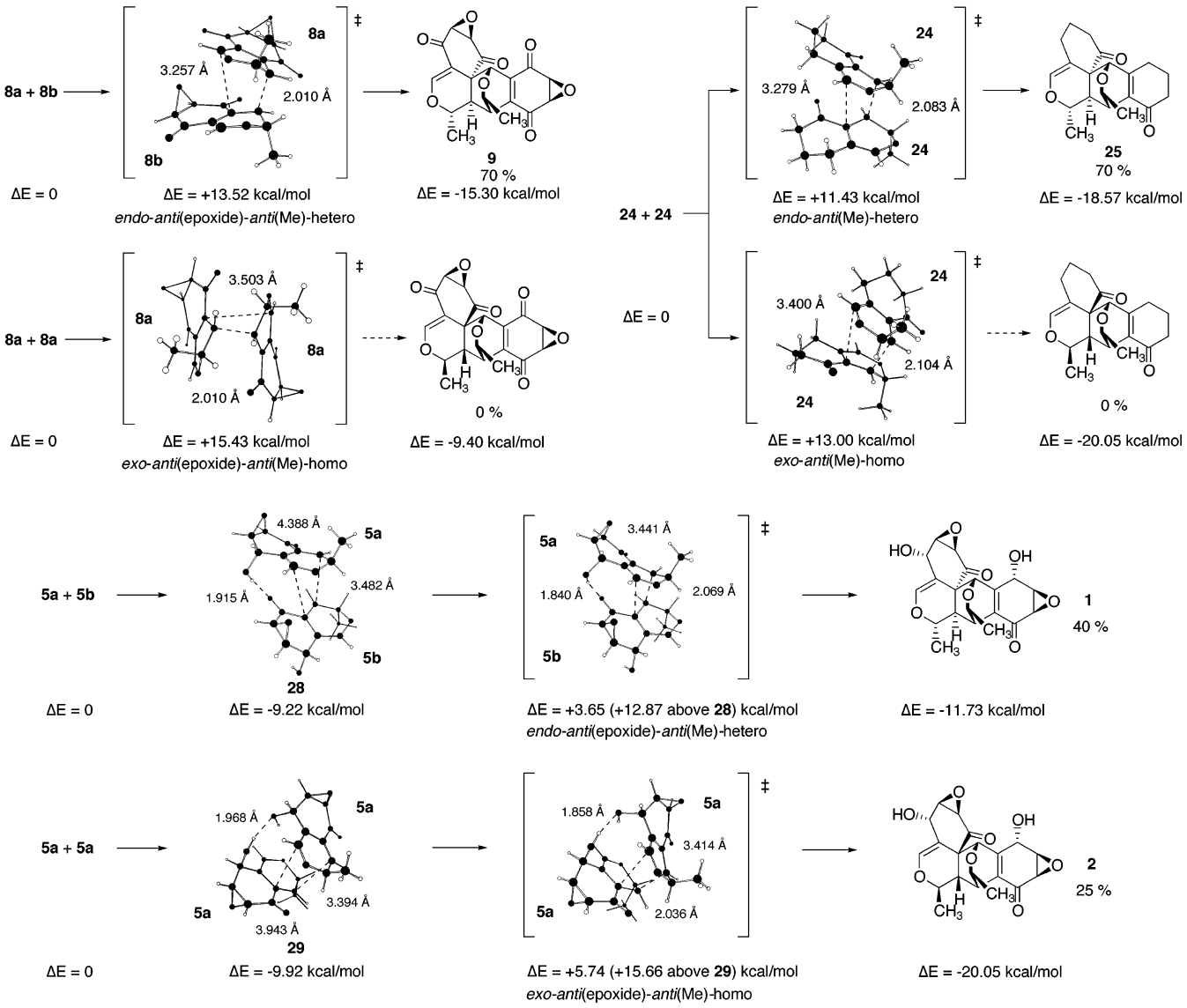
(21) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: Chichester, U.K., 1976.

(22) The coefficients of the HOMO and LUMO energies of the 2*H*-pyrans are described in the Supporting Information.

(23) The 16 possible reaction modes are as follows: *endo-anti*-(epoxide)-*anti*(Me)-hetero, *exo-anti*(epoxide)-*anti*(Me)-homo, *endo-anti*(epoxide)-*anti*(Me)-homo, *exo-anti*(epoxide)-*anti*(Me)-hetero, *endo-anti*(epoxide)-*syn*(Me)-hetero, *exo-anti*(epoxide)-*syn*(Me)-homo, *endo-anti*-(epoxide)-*syn*(Me)-homo, *exo-anti*(epoxide)-*syn*(Me)-hetero, *endo-syn*-(epoxide)-*anti*(Me)-hetero, *exo-syn*(epoxide)-*anti*(Me)-homo, *endo-syn*-(epoxide)-*anti*(Me)-homo, *exo-syn*(epoxide)-*anti*(Me)-hetero, *endo-syn*-(epoxide)-*syn*(Me)-hetero, *exo-syn*(epoxide)-*syn*(Me)-homo, *endo-syn*-(epoxide)-*syn*(Me)-homo, *exo-syn*(epoxide)-*syn*(Me)-hetero.

(24) Because there is no epoxide in **10**, the number of possible reaction modes is reduced from sixteen in **3** to eight.

SCHEME 12. Theoretical Calculation of the Diels–Alder Reaction



kcal/mol higher than that of the lowest, the reaction should not proceed via this mode but the via *endo-anti*(epoxide)-*anti*(Me)-hetero mode alone, which is consistent with the experimental result that epoxyquinol A-type dimer **9** was selectively obtained.

In the case of cyclohexenone **10** (**24**), two reaction modes, which would lead to epoxyquinol A- and B-type products, were investigated (Scheme 12). The TS energy of the *endo-anti*(Me)-hetero mode (11.43 kcal/mol) is lower than that of the *exo-anti*(Me)-homo mode (13.00 kcal/mol), which is consistent with the experimental result that the *endo-anti*(Me)-hetero dimer **25** (epoxyquinol A-type product) was selectively formed.

The TS energies of the 6π-electrocyclization and the Diels–Alder reaction of **3**, **6**, and **10** are summarized in Table 4. By comparing epoxyquinone **6** and cyclohexenone **10**, the aforementioned puzzling experimental results can be reasonably explained as follows: As described previously, only 2*H*-pyran **8**, but not aldehyde **7**, was detected for epoxyquinone **6**, while only aldehyde **23**, but not 2*H*-pyran **24**, was observed for cyclohexenone **10**. These contrasting results are due to the different reaction

TABLE 4. TS Energies of the 6π-Electrocyclization and Diels–Alder Reaction

	TS energy/kcalmol^{-1}	
substrate	6π-electrocyclization	Diels–Alder reaction
epoxyquinone **6** (**8**)	10.53,[a] 13.37[b]	13.52
cyclohexenone **10** (**24**)	18.64	11.43
epoxyquinol **3** (**5**)	18.51,[a] 18.06[b]	12.87,[c] 15.66[d]

[a] The TS energy to *anti*-2*H*-pyran. [b] The TS energy to *syn*-2*H*-pyran. [c] The TS energy to **1**. [d] The TS energy to **2**.

profiles of these two reactions. That is, the rate-determining step has been reversed: The rate-determining step for epoxyquinone **6** is the Diels–Alder reaction, while that for cyclohexenone **10** is 6π-electrocyclization (Table 4). For the 6π-electrocyclization, the TS energy for epoxyquinone **6** is lower than that for cyclohexenone **10** because the TS energy becomes lower as the substituent becomes more electron-withdrawing, and there are two electron-withdrawing groups in **6** compared with only one in **10**. On the other hand, the TS energy of the Diels–Alder reaction of epoxyquinone **6** is higher than that of

cyclohexenone **10** because there is steric hindrance caused by the epoxide in **6**, and also because the Diels−Alder reaction of **10** is orbitally favorable. Namely, the two electron-withdrawing groups reduce the reactivity of the diene **8** by lowering its HOMO energy, and cause a larger HOMO−LUMO energy gap for **8a**/**8b** (3.9476 eV, Table 3, entry 2) than for **24** (3.8665 eV, Table 2, entry 5 (HOMO of **24)**, entry 6 (LUMO of **24**)). As a result, the rate-determining step has been reversed.

Compared with the above two substrates, the epoxyquinol **3** (**5a**,**b**) had a different profile: Though the two 2*H*-pyran monomers **8** and **24** react to afford dimerized product, monomer **5** from epoxyquinol **3** was not directly transformed into the Diels−Alder products **1** and **2**. Calculations suggest that initially the two monomers **5a**,**b** preassociate to give intermediate complexes **28** and **29**, which are more stable than the parent **5a** + **5b** and **5a** + **5a** by 9.22 and 9.92 kcal/mol, respectively. This stabilization can be ascribed to a hydrogen-bond interaction as shown in Scheme 12. The hydroxy group of **5a** coordinates the carbonyl lone pair of **5b** in **28**, at a distance of 1.915 Å, while two OH groups of two different **5a** molecules interact with each other in **29**, at a distance of 1.968 Å. From the intermediates **28** and **29**, the dimerization proceeds to afford Diels−Alder products **1** and **2**. As the TS energies for the *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *exo*-*anti*(epoxide)-*anti*(Me)-homo modes are 12.87 and 15.66 kcal/mol, respectively, the former mode would be theoretically more favorable than the latter, and this is consistent with the experimental result that **1** was formed predominantly. However, the large difference between the TS energies of the two modes (2.79 kcal/mol) is not in good agreement with the experiment, in which **2** was also formed in 25% yield. This discrepancy could be the result of neglecting solvent effects in the calculation, which would be detrimental owing to the existence of hydrogen-bonding. The hydrogen-bonding effect is found to be operative not only in the ground state, but also in the transition state. As shown in Scheme 12, the hydrogen-bond activates the ketone function in the *endo*-*anti*(epoxide)-*anti*(Me)-hetero mode, whereas there is hydrogen-bonding stabilization of the TS in the *exo*-*anti*(epoxide)-*anti*(Me)-homo mode.

This hydrogen-bonding interaction, which is found to be important in the transition state in the theoretical calculations, is also found in the crystal structure of the final product, epoxyquinol B, in which a hydrogen-bond between the two OH groups has in fact been observed.[25] Moreover, if these transition-state hydrogen-bonds exist, the distribution of epoxyquinols A and B should be affected by the solvent, which is found to be the case. As shown in Table 5, **1** was formed predominantly in neat conditions or in benzene solution, while **2** was the major product in toluene and CH_2Cl_2. Lewis acids such as $LiClO_4$[26] accelerate the reaction, affording epoxyquinol A predominantly via the orbitally preferable *endo* mode and in short reaction time. This is in a marked contrast with the dimerization of cyclohexenone **10**, in which the product distribution is not affected at all by the solvent (Table 6). That is, epoxyquinol A-type product **25** was selectively obtained as the sole product, irrespective of the solvent. Another interesting observation is that the reaction of **10** in MeOH is much faster than that in benzene, toluene, and CH_2Cl_2, while the reaction of epoxyquinol **3** is slower in MeOH than that in benzene and toluene. Hydrogen-bonding activation by MeOH, which has been observed in the reaction of **10**, cannot be realized in the reaction of **3** owing to strong intermolecular hydrogen-bonding. This is further evidence for the importance of hydrogen-bonding in the oxidative dimerization of **3**. Moreover, the predominant formation of epoxyquinol B in toluene is synthetically useful, because epoxyquinol B is a more potent angiogenesis inhibitor than epoxyquinol A.[2]

TABLE 5. Solvent Effect on the Oxidative Dimerization of 3

			yield[a]/%	
entry	solvent	time/h	**1**	2
1	neat	4	40	25
2	$LiClO_4/Et_2O$	2.5	46	25
3	benzene	12	39	32
4	toluene	12	25	45
5	CH_2Cl_2	33	21	38
6	Et_2O	46	25	21
7	MeOH	94	21	21
8	CH_3CN	140	14	21

[a] Isolated yield.

TABLE 6. Solvent Effect on the Oxidative Dimerization of 10

entry	solvent	time/h	yield[a]/%
1	neat	10	70
2	MeOH	25	73
3	benzene	43	30
4	toluene	43	35
5	CH_2Cl_2	72	25

[a] Isolated yield of **25**.

The importance of the hydroxy group is also demonstrated by the following experiment. Diels−Alder dimerization of the methyl ether **11**, in which there is no hydrogen-bonding interaction, does not proceed, though the 6π-electrocyclization does (vide supra, Scheme 9). This is another piece of evidence supporting the importance of the hydroxy group in the dimerization of epoxyquinol **3**. The steric hindrance caused by the methoxy groups of **27** would prevent the Diels−Alder reaction.

There are literature precedents in which intermolecular hydrogen-bonding can be successfully utilized for the control of the stereochemistry of a Diels−Alder reaction.[27] In this oxidative dimerization, nature has also successfully employed hydrogen-bonding in the Diels−Alder reaction for the formation of epoxyquinol B.

Conclusions

In the oxidative dimerization of epoxyquinone **6** and cyclohexenone **10**, the preferred reaction modes are *endo*-

(25) See footnote 18 of ref 6.
(26) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.

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anti(epoxide)-*anti*(Me)-hetero and *endo*-*anti*(Me)-hetero, respectively, while both epoxyquinols A and B are formed via the *endo*-*anti*(epoxide)-*anti*(Me)-hetero and *exo*-*anti*-(epoxide)-*anti*(Me)-homo modes in the dimerization of epoxyquinol **3** because of intermolecular hydrogen-bonding, which has been proved to exist by theoretical calculations and several experimental results. Other noteworthy features are as follows: The existence of an equilibrium between the 2*H*-pyran and aldehyde has been theoretically and experimentally demonstrated in the case of the methoxy derivative **11**. In the dimerization of epoxyquinol **3**, monomer 2*H*-pyrans **5** preassociate to afford complexes **28** and **29**, from which the Diels−Alder reaction proceeds. Theoretical calculations have also clarified the difference in reaction profiles between epoxyquinone **6** and cyclohexenone **10**. Namely, the rate-determining step of the former is the Diels−Alder reaction, while that of the latter is 6π-electrocyclization.

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Supporting Information Available: Complete experimental procedures, full characterization, copies of ^{1}H and ^{13}C NMR and IR of all new compounds, and Cartesian coordinates for calculated transition states of 6π-electrocyclization and Diels−Alder reaction (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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