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Chemistry of Epoxyquinols A, B, and C and Epoxytwinol A

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The asymmetric total synthesis of epoxyquinols A, B, and C and epoxytwinol A, and computational analysis of the key biomimetic oxidative dimerization procedure are described. In the first-generation synthesis, a $HfCl_4$-mediated diastereoselective Diels–Alder reaction of furan with Corey's chiral auxiliary has been developed. In the second-generation synthesis, a chromatography-free preparation of an iodolactone using acryloyl chloride as the dienophile in the Diels–Alder reaction of furan and a lipase-mediated kinetic resolution of a cyclohexenol derivative have been developed. This second-generation synthesis is suitable for large-scale synthesis. A biomimetic cascade reaction involving oxidation, 6π-electrocyclization, and then Diels–Alder dimerization is the key reaction in the formation of the complex heptacyclic structure of epoxyquinols A, B, and C. Epoxytwinol A is synthesized by the cascade reaction involving oxidation, 6π-electrocyclization, and formal [4+4] cycloaddition reactions. A 2*H*-pyran, generated by oxidation/6π-electrocyclization, acts as a good diene, reacting with several dienophiles to afford polycyclic compounds in one step.

1. Introduction

The inhibition of angiogenesis is a promising method for treating angiogenesis-related diseases such as cancer and rheumatoid arthritis.[1] Kakeya, Osada and co-workers have isolated and determined the structures of epoxyquinols A (**1**),[2] B (**2**),[3] and C (**3**)[4] and epoxytwinol A (**4**)[5] from an unknown soil fungus, and azaspirene[6] and RK-805[7] from the fungus *Neosartorya* sp. (Figure 1). With the exception of RK-805, these small natural products have structures quite distinct from those of known angiogenesis inhibitors, making their mechanism of action a matter of considerable interest. Sufficient quantities of the natural products are needed for biological investigations, and the study of their structure–reactivity relationships requires the formation of their derivatives. For these purposes efficient and flexible total syntheses are highly desirable. Recently we have accomplished the first total synthesis of epoxyquinols A and B,[8] azaspirene,[9] and RK-805.[10]

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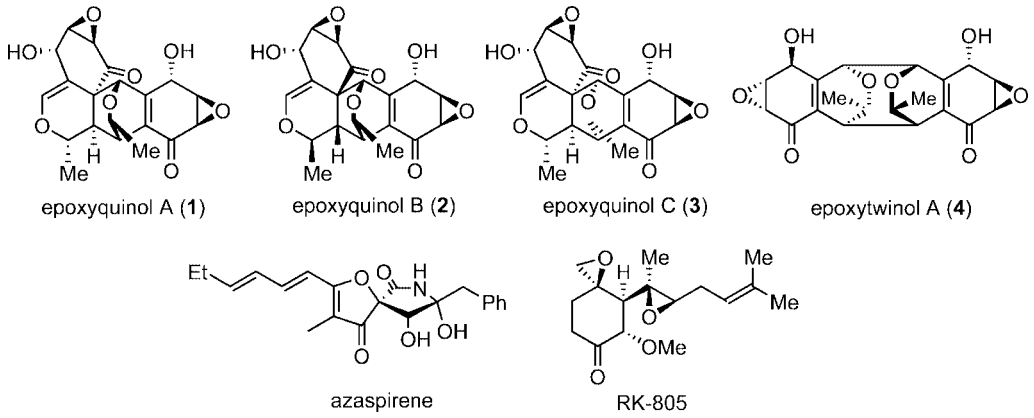


Figure 1. Epoxyquinols A (**1**), B (**2**), and C (**3**), epoxytwinol A (**4**), azaspirene, and RK-805.

Epoxyquinols A, B, and C are novel pentaketides with complex, highly-oxygenated, heptacyclic structures containing 12 chiral centers which are postulated to be biosynthetically generated from the epoxyquinol monomer **18**[11] by a cascade reaction sequence of oxidation, 6π-electrocyclization,[12] and Diels–Alder reaction.[2,3] That is, diol monomer **18** is oxidized to aldehyde **17**, which undergoes 6π-electrocyclization to afford 2*H*-pyran derivative **16** (Scheme 1). Diels–Alder dimerization of 2*H*-pyran **16** proceeds to provide epoxyquinols A (**1**), B (**2**), and C (**3**). Several other diastereomers have also been isolated along with **1**, **2**, and **3** from the same soil fungus, the structure determination of which will be the subject of future studies. Not only Diels–Alder dimers, but also epoxytwinol A (**4**) has been isolated from the same fungus.[5] Epoxytwinol A (**4**) possesses the 3,8-dioxatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene skeleton, a completely different structure from those of epoxyquinols A, B, and C. It is postulated that epoxytwinol A is biosynthetically generated by a formal [4+4] cycloaddition reaction, as used in the construction of the same key 2*H*-pyran intermediate **16** in the synthesis of epoxyquinols A, B, and C (vide infra). Since these compounds have important biological properties and synthetically challenging structures, several research groups, including ours,[8] have investigated the total synthesis of these compounds.

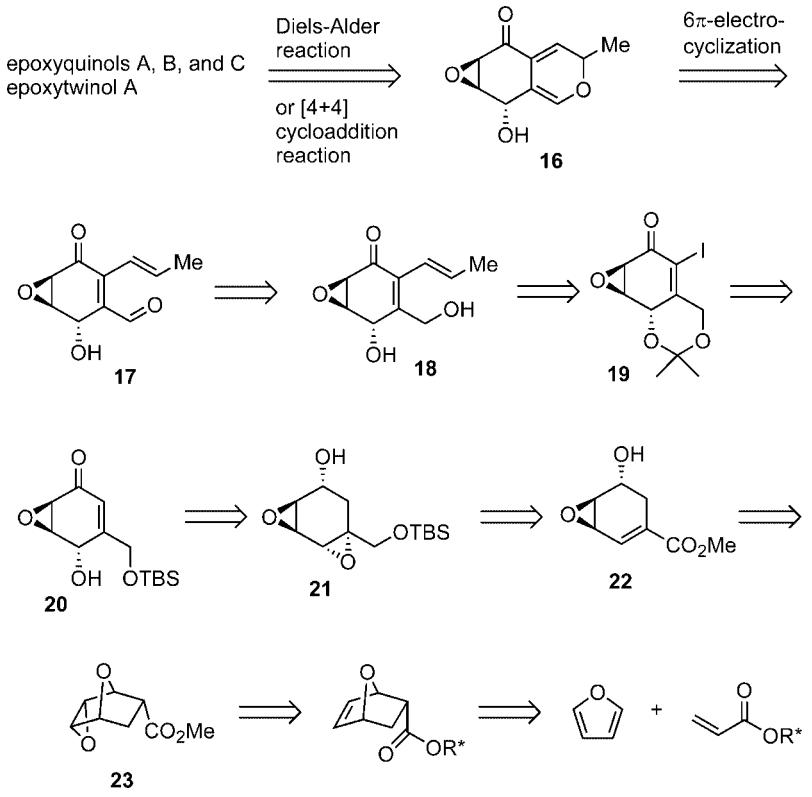
Our group has accomplished the first total synthesis of epoxyquinols A (**1**) and B (**2**), employing the biomimetic oxidative dimerization of the monomer **18** as a key step, and has determined their absolute configurations.[8] Other groups also employed the same biomimetic dimerization.[13] Starting from 2,5-dihydroxybenzaldehyde, Porco and co-workers have reported the elegant synthesis of the monomer **18** via diisopropyl tartrate mediated asymmetric epoxidation of cyclohexadienone derivative **5** [Equation (1)].[14] Mehta and Islam used lipase-mediated kinetic resolution of diol **8** to obtain optically pure **9** [Equation (2)][15] and Kuwahara and Imada employed Evans' asymmetric aldol reaction of **10** with a chiral auxiliary and 3-methyl-2-butenal [Equation (3)].[16] All these synthetic schemes provided the monomer **18** with high enantioselectivities. Ours and Mehta's groups oxidized the monomer **18** with MnO_2, while Porco's and Kuwahara's groups used TEMPO/CuCl/O_2 for the oxidative dimerization to afford epoxyquinols A (**1**) and B (**2**).

Li and Porco have reported the elegant, alkoxysilanol-facilitated total synthesis of epoxytwinol A [Equation (4)].[17]

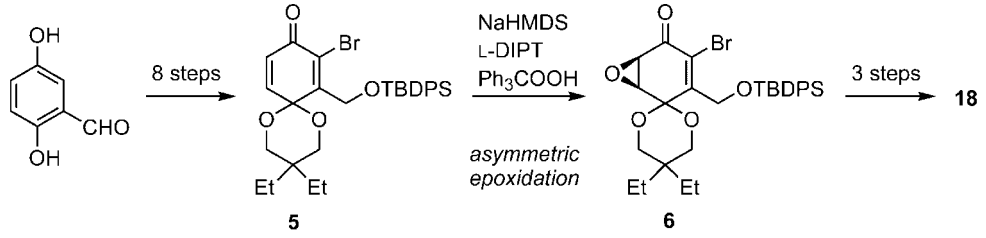
The related epoxyquinoid Diels–Alder dimer, (+)-torreyanic acid (**15**), with selective cytotoxicity against human cancer cell lines,[18] was isolated by Lee and co-workers from fungus *Pestalotiopsis,* and has been synthesized by Porco and co-workers [Equation (5)].[19] (±)-Torreyanic acid has been synthesized by Mehta's group.[20]

In our first asymmetric total synthesis of epoxyquinols A and B,[8a] an $HfCl_4$-mediated Diels–Alder reaction of furan with an acrylate bearing Corey's chiral auxiliary[21] and a biomimetic oxidative dimerization were developed as the key reactions. We uncovered the importance of hydrogen bonding in the Diels–Alder reaction forming epoxyquinol B by the combined use of synthetic organic chemistry and theoretical chemistry.[22] We have also developed a practical total synthesis involving lipase-mediated kinetic resolution as a key step.[8b] In a study of the large-scale preparation of epoxyquinols A and B, we carefully investigated the minor isomers of the key oxidative dimerization process and isolated and identified epoxyquinol C and epoxytwinol A from the crude reaction mixture.

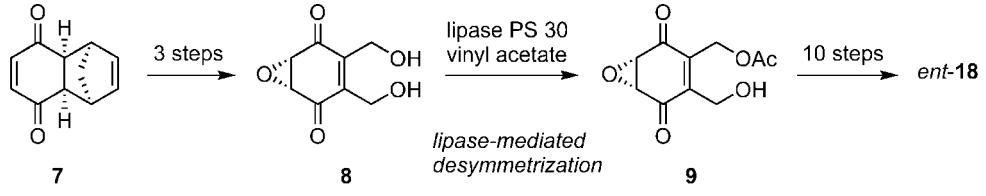
In the course of the oxidative dimerization of the monomer derivatives such as **32** and **36**, epoxyquinol A type dimers were predominantly obtained (vide infra, Scheme 6). To understand the differences in the reaction modes of epoxyquinol **18** and epoxyquinone **32**, the oxidative dimerization of a parent monomer **36**, without epoxide and ring hydroxy groups, was examined. Methoxycyclohexenone **40** was also investigated to shed light on the effect of the hydroxy group in **18**. In this paper we describe our investigation of the oxidation/6π-electrocyclization/Diels–Alder reaction by systematic comparison using the four monomers **18**, **32**, **36**, and **40** and also our theoretical calculations.



Scheme 1. Retrosynthetic analysis of epoxyquinols A (**1**), B (**2**), and C (**3**) and epoxytwinol A (**4**).



(1)



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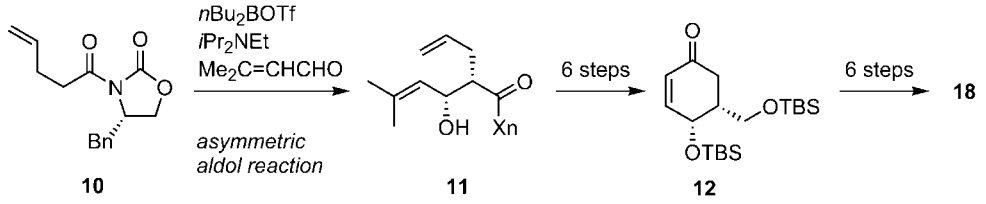

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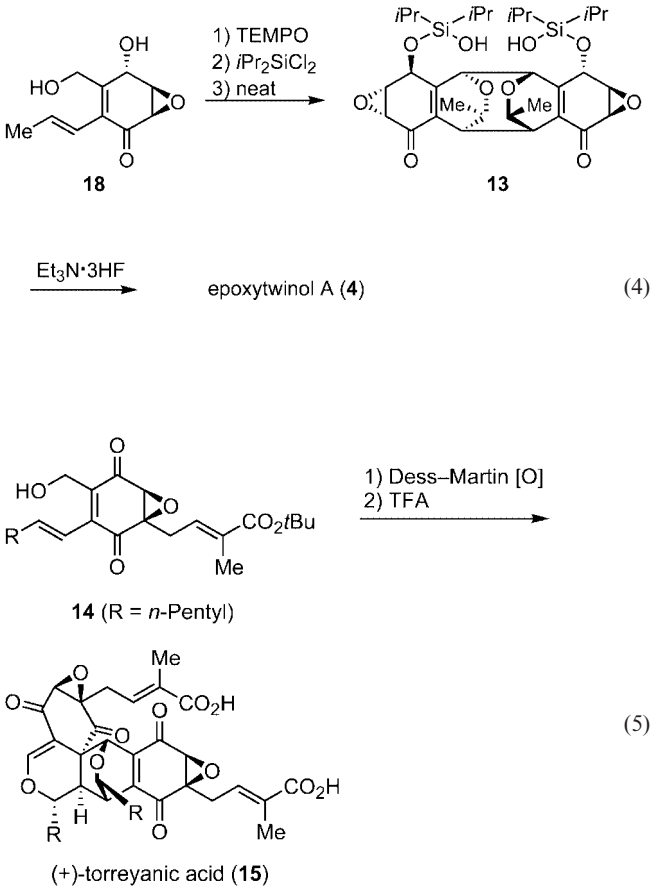


In the key oxidative dimerization step, oxidation of dienol **18** and subsequent 6π-electrocyclization affords 2*H*-pyran derivative **16**, which dimerizes to afford epoxyquinols A and B. 2*H*-Pyran derivatives are seldom employed in organic synthesis and their reactivity has not been systematically investigated because of the difficulty of generating them owing to their easy isomerization to dienals.[23] As we found a simple method for the generation of 2*H*-pyran intermediates by oxidation and 6π-electrocyclization during the synthesis of epoxyquinols A and B, we also investigated their reactivity as the diene component in Diels–Alder reactions and these results will also be presented in this paper.

2. Retrosynthesis

Our retrosynthetic analysis of epoxyquinols A, B, and C and epoxytwinol A is summarized in Scheme 1. Epoxyquinols A, B, and C and epoxytwinol A would be synthesized from the same monomer **18** by the postulated biosynthetic pathway involving an oxidation/6π-electrocyclization/Diels–Alder reaction cascade for epoxyquinols A, B, and C or an oxidation/6π-electrocyclization/[4+4] cycloaddition cascade for epoxytwinol A. The monomer **18** could be synthesized from iodocyclohexenone **19** by the Suzuki coupling reaction. Iodocyclohexenone **19** would be prepared by the α-iodination of cyclohexenone **20**, which should be available from diepoxycyclohexenol **21**. Chiral cyclohexenol **22** would be formed from the Diels–Alder reaction between furan and a chiral acrylate derivative, followed by functional group transformations.

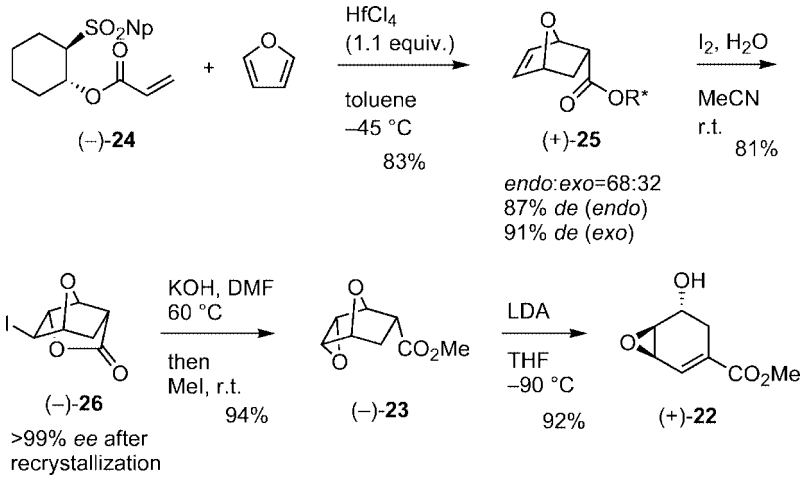
In this retrosynthetic analysis, there are several noteworthy features which should be pointed out. Derivatives with different side-chains should be accessible because the side-chain is introduced at a late stage of the monomer synthesis by a Suzuki coupling reaction. All the carbon atoms except those of the side-chain are introduced in the first Diels–Alder reaction, and the remainder of the reactions are functional group transformations except for the Suzuki coupling reaction. Chirality is introduced in the initial Diels–Alder reaction, and highly diastereoselective synthesis of the monomer would be possible by exploiting neighboring-group participation.

3. Results and Discussion

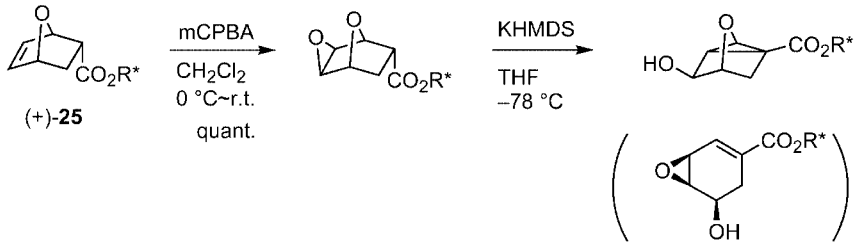
3.1 First-Generation Monomer Synthesis

Based on the above retrosynthetic analysis, the Diels–Alder reaction of furan[24] is the first step of our total synthesis, which is regarded to be a difficult cycloaddition owing to the facile retro-Diels–Alder reaction and low reactivity of furan as a diene due to its aromatic character. Although there are a number of methods for the diastereoselective Diels–Alder reaction of a chiral acrylate ester with furan,[25] few of these are synthetically useful with high *endo*/*exo*- and/or diastereoselectivities. Recently we found that $HfCl_4$ is a highly efficient Lewis acid in the Diels–Alder reaction of furan which enables the reaction to proceed at low temperature, affording the kinetically favorable *endo* isomer selectively.[26] The $HfCl_4$-mediated Diels–Alder reaction of furan was performed with chiral acrylate esters, and the choice of the chiral auxiliary was found to be important. While a chiral Evans acrylate derivative, 3-acryloyl-4-benzyl-1,3-oxazolidin-2-one,[27] gave poor diastereoselectivity, high selectivity was obtained with the acrylate ester derived from Corey's chiral auxiliary [(–)-(1*R*,2*R*)-2-(2-sulfonylnaphthyl)cyclohexanol].[21] That is, in the presence of 1.1 equivalent of $HfCl_4$, the acrylate ester (–)-**24** reacted with furan in toluene at low temperature (–45 °C) for 34 h, giving the cycloadducts (+)-**25** in good yield with moderate *endo*/*exo*- and high diastereoselectivities (Scheme 2).

Direct epoxidation of (+)-**25** with mCPBA gave stereoselectively the *exo* epoxide,[28] which, when reacted with KHMDS, afforded an undesired cyclopropane derivative [Equation (6)].[29] As a result, it was necessary to find an alternative route that would provide the *endo* epoxide isomer. After some experimentation, selective formation of the *endo* epoxide was accomplished via iodolactone (–)-**26**. Treatment of *endo* Diels–Alder adduct (+)-**25** with I_2 in aqueous MeCN afforded iodolactone (–)-**26** in 81% yield with recovery of the chiral auxiliary in 94% yield (Scheme 2). After recrystallization, optically pure lactone (–)-**26** was obtained and its absolute stereochemistry was determined by comparing its optical rotation with that re-



Scheme 2. Synthesis of (+)-**22**.



(6)

ported in the literature.[30] Although the direct transformation of iodolactone (–)-**26** to epoxy methyl ester (–)-**23** in MeOH under a variety of basic conditions was unsuccessful, a two-step conversion worked well. That is, hydrolysis and epoxide formation occurred on treatment of (–)-**26** with KOH in DMF at 60 °C for 10 h and subsequent esterification with MeI under sonication conditions for 1 h furnished epoxy ester (–)-**23** in one pot and high yield (94%).

Exposure of (–)-**23** to LDA at –90 °C for 30 minutes led to β-elimination, affording hydroxy ester (+)-**22**. A low temperature and an exact equivalent of LDA are both essential for a high yield in this step otherwise Michael addition of diisopropylamine to (+)-**22** occurs, generating a β-amino ester as a side-product.

The first total synthesis of epoxyquinols A and B was accomplished using (+)-**22** (vide infra). Although our $HfCl_4$-mediated, highly diastereoselective Diels–Alder reaction using a chiral auxiliary is suitable for the construction of optically active cyclohexenol derivatives, at least an equimolar amount of the auxiliary and $HfCl_4$ are necessary. To circumvent this problem, we have developed a more efficient and practical synthetic route to this key intermediate (+)-**22** in the synthesis of epoxyquinols A, B, and C and epoxytwinol A.

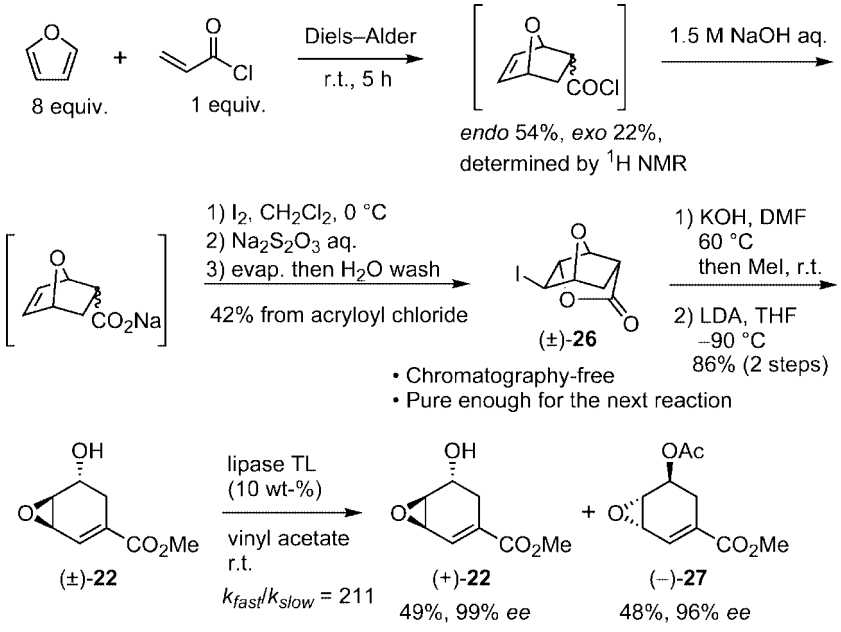
3.2 Second-Generation Monomer Synthesis

We chose as the key reaction of our new strategy the lipase-mediated kinetic resolution[31] of racemic cyclohexenol (±)-**22** as such reactions are known to be readily scaleable. However, preparation of this intermediate itself proved to be difficult because, while the Diels–Alder reaction of furan and acrylate derivatives is a powerful means of synthesizing this class of compound,[24,32] no method suitable for the large-scale preparation of the *endo* isomer has yet been described. Establishing such a route was our first goal. Instead of using a Lewis acid to promote the Diels–Alder reaction, we focused on the use of acryloyl chloride as a reactive dienophile which is reported to react with furan in the presence of a hydrogen chloride scavenger, propylene oxide, over 48 h, providing the Diels–Alder adducts in 76.5% overall yield after conversion of the adduct to the corresponding ester.[32a] Under these conditions the thermodynamically stable, *exo* isomer predominates (*endo*/*exo* = 3:7). After careful experimentation, it was found that the kinetically favored *endo* isomer was generated predominately in the early stages of the reaction. The Diels–Alder reaction of acryloyl chloride and furan (8 equiv.) proceeds in 5 h at room temperature, providing the *endo* and *exo* cycloadducts in 54 and 22% yields, respectively (^{1}H NMR yield, Scheme 3). Although at this stage the starting material, acryloyl chloride, still remained, the yield of the *endo* isomer did not increase further owing to its conversion into the thermodynamically more stable *exo* isomer after longer reaction times. Hydrolysis of the acid chloride to the sodium salt of the acid was carried out by treatment with aqueous 1.5 M NaOH. On addition of I_2 and CH_2Cl_2 to the aqueous phase, iodolactonization proceeded efficiently. By

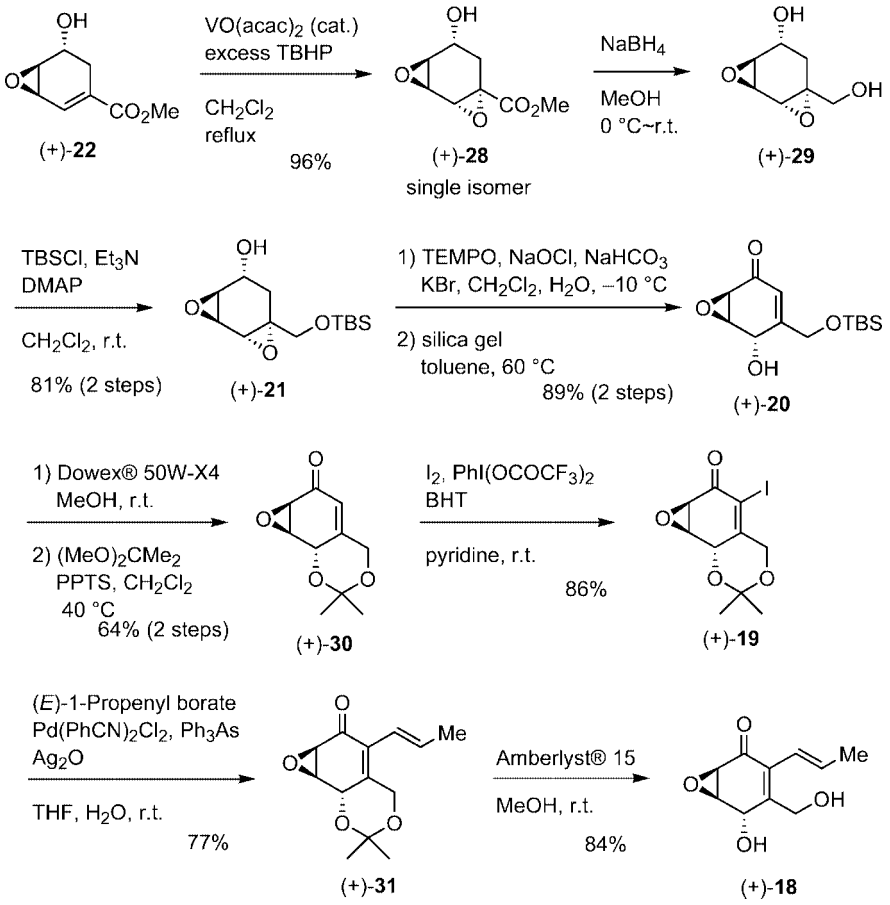
removal of excess furan and CH_2Cl_2 under reduced pressure, (±)-**26** was precipitated from the reaction mixture in 42% yield as a white solid which was pure enough to be used in the next experiment. Unreacted acryloyl chloride and the *exo* Diels–Alder adduct could be easily separated from iodolactone (±)-**26** as they both remained in the aqueous phase as the sodium salts of the corresponding acids. Although the yield was moderate, an efficient, chromatography-free procedure without extraction has been developed for the synthesis of iodolactone (±)-**26**,[33] and the reaction could easily be scaled up to 110 g. Iodolactone (±)-**26** was converted into cyclohexenol (±)-**22** by the same procedure described in Scheme 2. After screening of the lipases, the *Pseudomonas stutzeri* lipase (Meito TL) was found to be the most efficient. Kinetic resolution proceeded efficiently only with 10 wt-% of the lipase TL to afford acetate (–)-**27** in 48% yield with 96% *ee*, while the desired alcohol (+)-**22** was recovered in 49% yield with 99% *ee*, indicating a very high selectivity (k_{fast}/k_{slow} = 211). The recovered lipase worked as efficiently as that of fresh batches, showing its activity had not decreased. The absolute configuration of (+)-**22** was determined by comparison of its optical rotation with that of previously synthesized (+)-**22**, as well as by using Mosher's advanced MTPA method.[34] As acetate (–)-**27** was easily converted into alcohol (–)-**22** on treatment with K_2CO_3 in MeOH, providing (–)-**22** in 97% yield, both enantiomers of alcohol **22** could be synthesized in large quantities and with high optical purity. This kinetic resolution is suitable for producing both optically active cyclohexenols (+)-**22** and (–)-**22** on a gram-scale, not only because high selectivity is achieved, but also because only a catalytic amount of lipase is necessary and can be recycled (Scheme 3).

Hydroxy-directed epoxidation of homoallylic alcohol (+)-**22** using a catalytic amount of $VO(acac)_2$ and excess *tert*-butyl hydroperoxide (TBHP) under reflux in CH_2Cl_2[35] proceeded to give diepoxide (+)-**28** as a single isomer in high yield. Although reduction of ester (+)-**28** with DIBAL proceeded smoothly, the recovered yield of the diol (+)-**29** was quite low owing to its water solubility. Thus, a non-aqueous work up was examined: reduction with $NaBH_4$ in MeOH at room temperature for 15 minutes, removal of solvent in vacuo, and flash column chromatography afforded the diol (+)-**29**. The primary hydroxy group of (+)-**29** was selectively protected with TBSCl, affording (+)-**21** in 81% yield over two steps. Although the oxidation of (+)-**21** with SO_3·pyridine[36] afforded 2-[(*tert*-butyldimethylsilyloxy)-methyl]-5,6-epoxy-2-cyclohexene-1,4-dione by oxidation of (+)-**20** TEMPO oxidation[37] gave the desired β,γ-epoxy ketone without formation of this byproduct. Isomerization occurred on treatment of the β,γ-epoxy ketone with silica gel at 60 °C in toluene for 4 h,[38] affording α,β-unsaturated ketone (+)-**20** in 89% yield over two steps. The α-iodination of cyclohexenone (+)-**20** was problematic, and the choice of diol protecting group and iodination reagent was found to be important for the success of this reaction: None of the desired product was obtained on treatment of hydroxy ketone (+)-**20** with I_2/DMAP,[39] I_2/$TMSN_3$,[40] or NaN_3/ICl,[41] while the secondary alcohol was oxidized affording epoxyquinone in the reaction using I_2/$PhI(OCOCF_3)_2$/pyridine.[42]

The low reactivity and side-reaction of (+)-**20** can be attributed to steric hindrance caused by the *tert*-butyldimethylsiloxymethyl group at the C3 position and the unprotected hydroxy group at the C4 position, respectively, and so a sterically smaller protecting group had to be employed. Acetonide derivative (+)-**30** was prepared in 64% yield from (+)-**20** over two steps by removal of the TBS group with Dowex® 50W-X4 in MeOH and protection of the resulting 1,3-diol with 2,2-dimethoxypropane. Unlike with (+)-**20**,



Scheme 3. Synthesis of (±)-**22** using lipase-medated kinetic resolution.



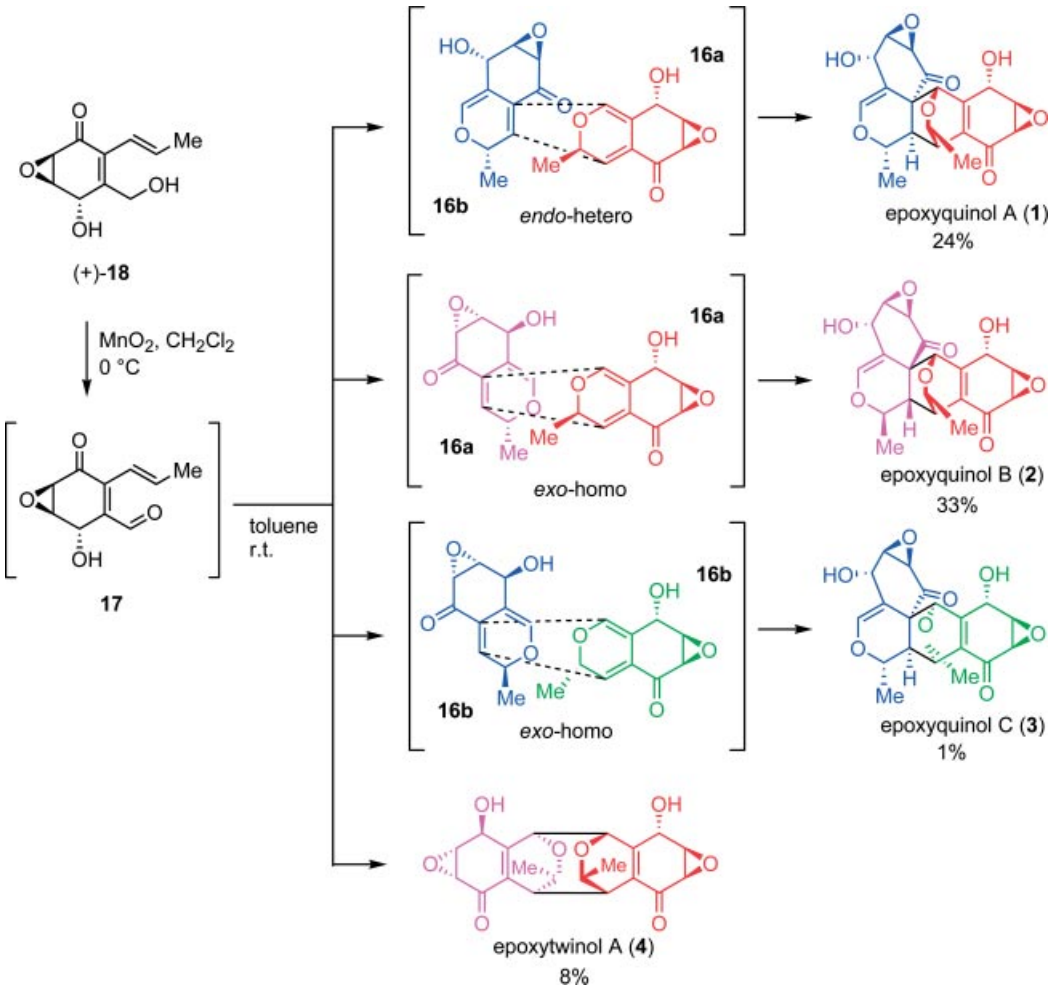
Scheme 4. Synthesis of the monomer (+)-**18**.

the reaction of (+)-**30** proceeded in the presence of I_2/PhI-$(OCOCF_3)_2$/pyridine, affording (+)-**19**, but irreproducibly. After careful examination it was found that the iodination proceeded only after a certain induction period and that once generated, (+)-**19** began to decompose after a further induction period. Based on our speculation that the side-reaction was radical in nature, we carried out the reaction in the dark in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger (5 mol-%), conditions which gave reproducible results, providing (+)-**19** in 86% yield. As iodinated cyclohexenone (+)-**19** is labile, it was immediately subjected to a Suzuki coupling reaction with (*E*)-1-propenyl borate[43] under Johnson's conditions,[44] affording dienone (+)-**31** in 77% yield. Cleavage of the acetonide under acidic conditions provided monomer (+)-**18** in 84% yield (Scheme 4).

3.3 Biomimetic Oxidative Dimerization of the Monomer

With the monomer (+)-**18** in hand, we examined its oxidative dimerization. In order to accomplish the preliminary oxidation, it was necessary to distinguish the two allylic alcohols. After several experiments it was found that (+)-**18** could be directly oxidized without protection of the secondary hydroxy group. That is, the oxidation proceeded on treatment of 0.03 mmol of (+)-**18** with excess MnO_2 in CH_2Cl_2 at 0 °C, affording hydroxy aldehyde **17** and 2*H*-pyran derivatives **16a**,**b**, formed by 6π-electrocyclization reaction of **17** (Scheme 5). The dimerization proceeded when the crude oxidized mixture was allowed to stand at room temperature without solvent. After 4 h, epoxyquinols A (**1**) and B (**2**) were isolated in 40 and 25% yields, respectively.[8a] Epoxyquinol A (**1**) is a heterodimer of **16a** and **16b** which would be generated by an *endo* intermolecular Diels–Alder reaction with *anti* stereochemistry at the C9 and C19 methyl positions to reduce the steric hindrance.[2] On the other hand, epoxyquinol B (**2**) is a homodimer of **16a** which would be generated by an *exo* intermolecular Diels–Alder reaction also with the sterically favored *anti* stereochemistry at the C9 and C19 methyl positions.[3] In their recent elegant total synthesis of torreyanic acid[19] and the jesterone dimer (unnatural product),[45] Porco and co-workers demonstrated the oxidative dimerization of epoxyquinones in which only heterodimers were formed. As shown by the dimerization of (+)-**18**, not only epoxyquinones, but also epoxycyclohexenones can be oxidatively dimerized to form highly functionalized heptacyclic ring systems by both hetero- and homodimerization.

In order to search for other diastereomers in the crude reaction mixture, we scaled up the reaction to a 0.4 mmol scale. Since we have found that there is a large solvent effect in this oxidative Diels–Alder reaction,[22b] the investigation



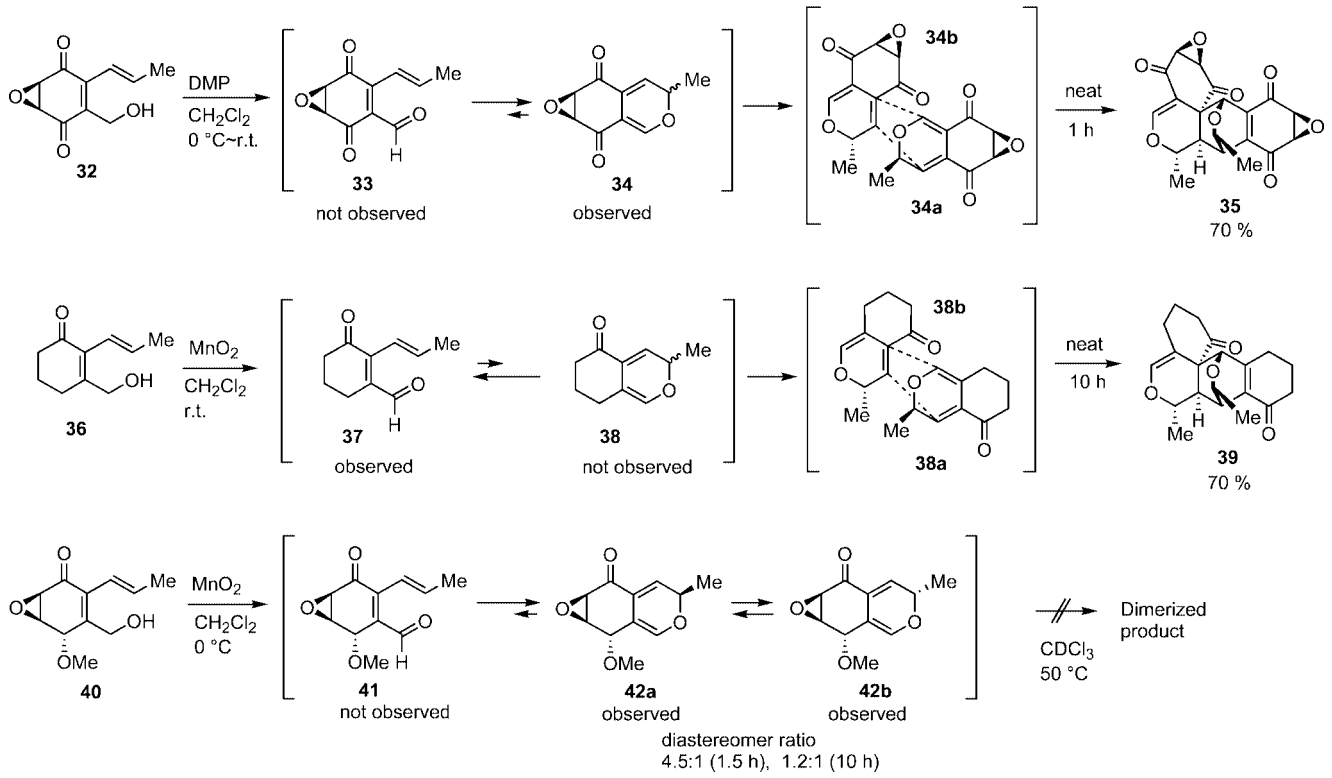
Scheme 5. Synthesis of epoxyquinols A, B, and C and epoxytwinol A.

was performed in toluene, which afforded the more potent dimer, epoxyquinol B (**2**) predominantly. Dimerization proceeded in 10 h at room temperature and the crude material was carefully purified by column chromatography, affording epoxyquinols A and B in 24 and 33% yields, respectively, along with epoxyquinol C in 1% yield and epoxytwinol A in 8% yield (Scheme 5). Epoxyquinol C, which is known to be formed from epoxyquinol A by microwave irradiation,[14] is a Diels–Alder adduct of 2*H*-pyran **16b**. As for epoxytwinol A, it is a product of a formal [4+4] cycloaddition of 2*H*-pyran **16a**, which gradually transformed into epoxyquinol B. In addition to the total synthesis of these four compounds, all of these compounds are isolated from the same soil fungus. The fact that **16a** and **16b** spontaneously dimerize to afford epoxyquinols A, B, and C and epoxytwinol A indicates that an enzyme such as Diels–Alderase would not be involved in this transformation.

3.4 Oxidative Dimerization of other Cyclohexenols

Next, we prepared a few derivatives of the monomer (+)-**18** and investigated their oxidative dimerization. The results of the oxidation/6π-electrocyclization/Diels–Alder reaction of the monomers **32**, **36**, and **40** are summarized in Scheme 6. Although the oxidation of alcohol **32** with MnO_2 did not proceed owing to the neighboring electron-withdrawing substituent, **32** was smoothly oxidized within 15 minutes by Dess–Martin periodinane (DMP) in $CDCl_3$. ^1H NMR (400 MHz) showed that 2*H*-pyran **34** was formed while the corresponding aldehyde **33** could not be detected, and that epoxyquinol A type product **35** was formed in 50% yield with some 2*H*-pyran **34** remaining. When the crude reaction mixture was left neat for 1 h, 2*H*-pyran **34** was completely converted into the epoxyquinol A type product **35** in 70% yield without the formation of any other diastereomers. These results indicate that the 6π-electrocyclization is fast and that aldehyde **33** is readily converted into 2*H*-pyran **34**. The Diels–Alder reaction is also a fast process, proceeding only to afford epoxyquinol A type adduct **35** in good yield. Although 2*H*-pyran **34** 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 **34** acts as a reactive dienophile in the Diels–Alder reaction.

The reaction profile of cyclohexenone monomer **36** is rather different to that of epoxyquinone **32**. Unlike epoxyquinone **32**, the oxidation of **36** proceeds efficiently with MnO_2 and the ^1H NMR spectrum of the reaction suggests



Scheme 6. Oxidative dimerization of dienols **32**, **36**, and **40**.

the presence of aldehyde **37**, 2*H*-pyran **38** not being observed. Generation of the Diels–Alder adduct **39** was slow and aldehyde **37** was gradually converted into epoxyquinol A type product **39** without detection of the 2*H*-pyran intermediate **38**. Eventually epoxyquinol A type product **39** was gradually formed in 70% yield after standing aldehyde **37** neat for 10 h without the formation of the epoxyquinol B type product. These results indicate that the formation of the dimerized product is slow and that only epoxuquinol A type dimerization occurs. This phenomenon, namely that the observed intermediate (aldehyde or 2*H*-pyran) is completely different for the reactions of epoxyquinone **32** and cyclohexenone **36**, is quite puzzling (vide infra).

The methoxy derivative **40**, however, gave quite different results from epoxyquinol **18**. When **40** was oxidized with MnO_2, aldehyde **41**, which was not detected by ^{1}H NMR, was smoothly and completely converted into 2*H*-pyran derivatives **42** in a 4.5:1 diastereomeric ratio after 1.5 h, although which isomer predominates was not determined. As the Diels–Alder reaction of methoxy-2*H*-pyran **42** does not proceed even under more forcing reaction conditions, the single 6π-electrocyclization process can be monitored in this system. The diastereomeric ratio of **42** changed from 4.5:1 to 1.2:1 after 10 h. This result clearly indicates the existence of an equilibrium[23] between the *anti*- and *syn*-2*H*-pyrans **42**.

The present oxidative dimerization is composed of three successive 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-electrocyclization and Diels–Alder reactions were separately investigated using theoretical calculations.

3.5 Theoretical Study of the 6π-Electrocyclization

Theoretical calculations were carried out in order to understand the reaction profile of the 6π-electrocyclization and Diels–Alder dimerization reactions. The geometries of all the stationary points were fully optimized at the B3LYP/6-31G* level and the properties of the molecules were also calculated at the same level.[46] All points were characterized as minima or saddle points by calculation of the harmonic vibrational frequencies using analytical second derivatives.

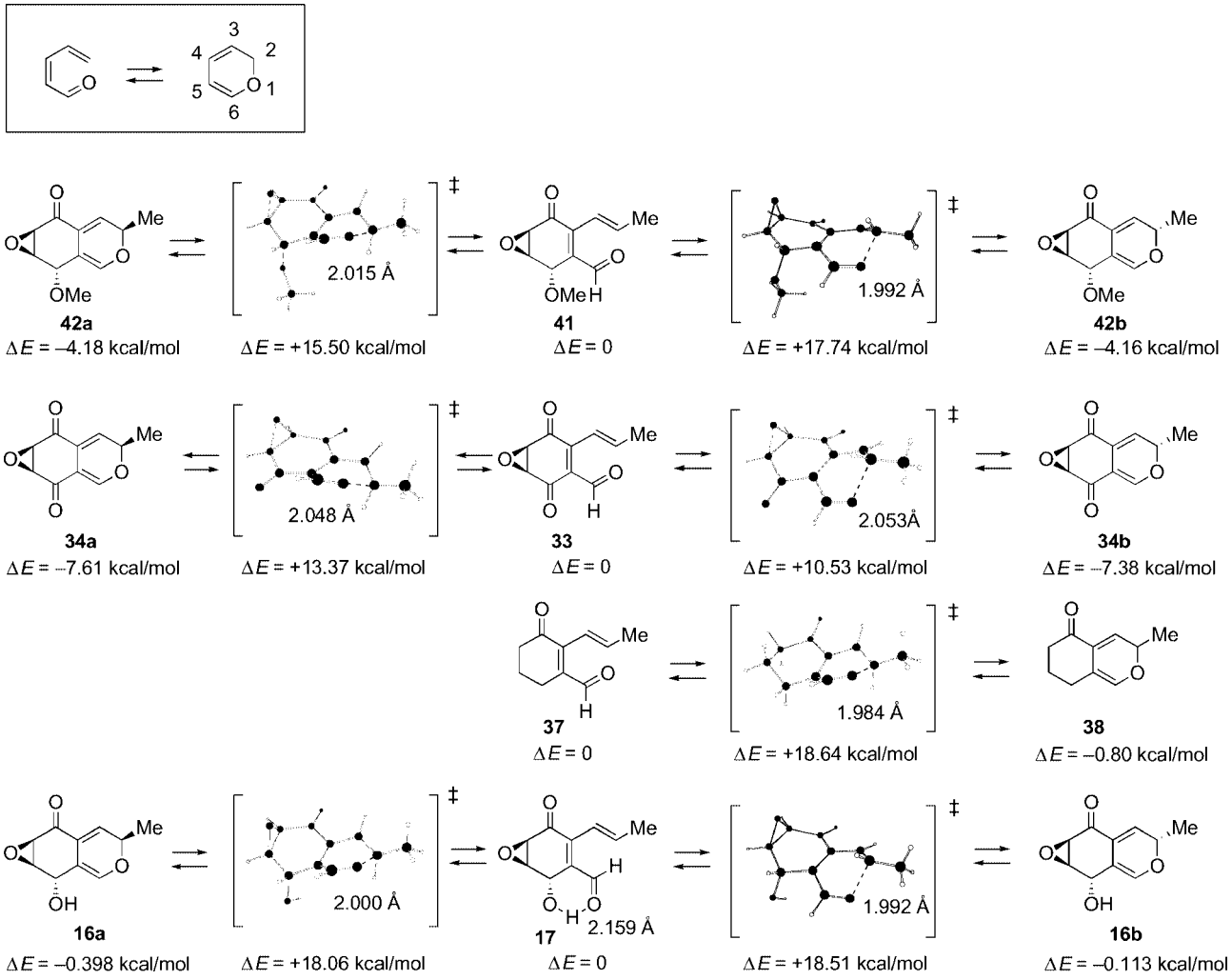
Rodríguez-Otero studied a series of 6π-electrocyclizations of (*Z*)-hexa-1,3,5-triene and its hetero-substituted analogues at various levels of theory and found that the reaction is slightly endothermic, the required TS energy for the 6π-electrocyclization of (2*Z*)-2,4-pentadienal being calculated as 21.52 kcal/mol at the B3LYP/6-31G**//B3LYP/6-31G** level.[47] Porco and co-workers 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.[19b] As there has been no systematic study of substituent effects on 6π-electrocyclizations,[23] the 6π-electrocyclizations of the methyl ether epoxyquinol derivative **41**, epoxyquinone **33**,

epoxyquinol **17**, and cyclohexenone **37** have been investigated in detail. Scheme 7 shows the transition-state structures leading to both the *syn*- and *anti*-2*H*-pyrans along with the TS energies and the lengths of the newly formed O1–C2 bond (2*H*-pyran numbering).

The methoxy derivative **41** is an ideal substrate as there is no subsequent Diels–Alder reaction in $CDCl_3$, and hence the electrocyclization itself can easily be monitored experimentally. Therefore the 6π-electrocyclization of this compound was examined first. 6π-Electrocyclization of **41** is exothermic, and both the *syn*- and *anti*-2*H*-pyrans **42** are calculated to be more stable than the parent aldehyde **41** by 4.18 and 4.16 kcal/mol, respectively. The energies of the TSs leading to the two diastereomers of the 2*H*-pyran are low (15.50 and 17.74 kcal/mol), and the TS energies of the 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 **42a** is lower than that leading to *anti*-isomer **42b**, while the *anti* and *syn* isomers have almost the same stability.

These calculations are in good agreement with experimental observations. 1) After oxidation, 2*H*-pyran **42** was observed without detection of intermediate aldehyde **41**. This is because on formation aldehyde **41** immediately converted into 2*H*-pyran **42** as the TS energy is low and the 6π-electrocyclization is exothermic. 2) Although the major isomer of **42** has not been determined, the diastereomeric ratio of 2*H*-pyrans **42a/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 the 2*H*-pyrans **42a/b** and aldehyde **41**, a result of the low TS energies of both the 6π-electrocyclization and its retro reaction.

As the calculated results for the methoxy derivative **41** proved to be in good agreement with experimental findings, the 6π-electrocyclizations of **17**, **33**, and **37** were also examined and the following noteworthy features were found by 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 of the dihedral angles of C2–O1–C6–C5 (2*H*-pyran numbering), and this is consistent with the calculations of Rodríguez-Otero on the parent 2,4-pentadienal.[47] 2) As the TS energies of both the 6π-electrocyclization and retro-6π-electrocyclization reactions are below 22 kcal/mol for all the substrates, there is an equilib-



Scheme 7. Theoretical calculations of the 6π-electrocyclization reactions.

rium between the *anti*- and *syn*-2*H*-pyrans and the aldehyde at room temp. 3) As the substituent becomes more electron-withdrawing, the TS energy becomes lower, indicating that 6π-electrocyclization becomes easier. 4) The length of the newly formed O1–C2 bond in the transition state decreases as follows: Epoxyquinone **33** > epoxyquinol **17** = methoxy derivative **41** > cyclohexenone **37**. As the substituent becomes more electron-withdrawing, the length of the O1–C2 bond in the TS becomes longer, indicating that the new bond has formed to a 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 relative to the aldehyde increases except in the case of epoxyquinol **17**. 6) The reaction of epoxyquinol **17** is a special case in which aldehyde **17** and 2*H*-pyrans **16a/b** are of almost the same energy, while for the corresponding methoxy derivative 2*H*-pyrans **42a/b** are more stable than aldehyde **41** by around 4 kcal/mol. This is because there is a hydrogen-bonding interaction between the hydroxy and the formyl group in **17** (2.159 Å), as shown in Scheme 7, and this stabilizes the aldehyde **17**. The hydrogen bond found in **17** puts the dienal in the wrong conformation and adds a rotational barrier to the electrocyclization process so more energy is required for the conversion of **17** into 2*H*-pyrans **16** than for the conversion of the corresponding methyl ether **41** into **42**.

3.6 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 8, according to frontier orbital theory.[12] For this regiochemistry, there are 16 possible reaction modes[22b] for the Diels–Alder reactions of epoxyquinone **32** and epoxyquinol **18**. Of these, only epoxyquinol A type dimer **35** is observed with epoxyquinone **32**, while both epoxyquinol A (**1**) and epoxyquinol B (**2**) are detected with epoxyquinol **18**. In the case of cyclohexenone **36**, of the eight possible reaction modes,[22b] only epoxyquinol A type dimer **39** was observed.

Scheme 8. Reaction modes of the 2*H*-pyrans.

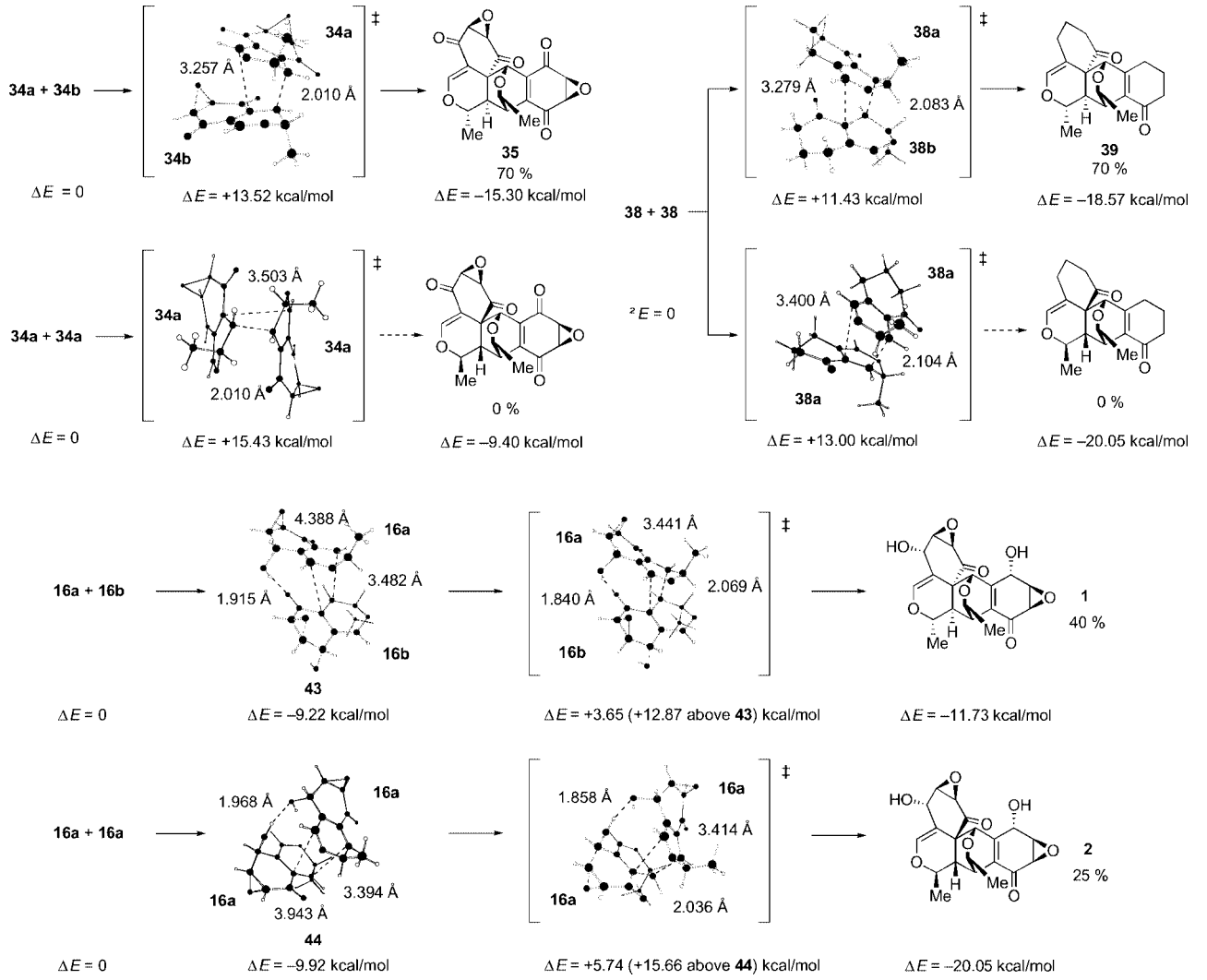
Calculations indicate that the orientation of the methyl groups is very important. The three reaction modes with the lowest TS energy form epoxyquinols A, B, and C; in each case the two methyl groups are oriented on opposite sides of the approaching dienophile and diene. That is, the steric hindrance caused by the methyl groups is so large that the methyl groups of the diene and dienophile monomers should be oriented *anti* to their reacting faces, otherwise the TS energies are over 16 kcal/mol.

Of the 16 reaction modes, the energy of the TS forming the epoxyquinol A type adduct is found to be the lowest, 13.52 kcal/mol, indicating that this reaction is a facile process. Scheme 9 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[22b] and also because of its secondary orbital interactions (*endo* rule). The next lowest reaction mode is the formation of the epoxyquinol B type product. As this second lowest TS energy is 15.43 kcal/mol, which is 1.91 kcal/mol higher than that of the lowest, the reaction should not proceed via this mode but via the epoxyquinol A type adduct alone, which is consistent with the experimental result that the epoxyquinol A type dimer **35** was selectively obtained.

In the case of cyclohexenone **36** (**38**), two reaction modes leading to epoxyquinol A and B type products were investigated (Scheme 9). The TS energy of the epoxyquinol A type mode (11.43 kcal/mol) is lower than that of the epoxyquinol B type mode (13.00 kcal/mol), which is consistent with the experimental result that the epoxyquinol A type dimer **39** was selectively formed.

As described previously, only 2*H*-pyran **34**, but not aldehyde **33**, was detected with epoxyquinone **32**, while only aldehyde **37**, but not 2*H*-pyran **38**, was observed with cyclohexenone **36**. These contrasting results can be reasonably explained by comparing the TS energies of the 6π-electrocyclization and the Diels–Alder reaction of epoxyquinone **32** and cyclohexenone **36** (Scheme 7 and Scheme 9). That is, the rate-determining step has been reversed: The rate-determining step for epoxyquinone **32** is the Diels–Alder reaction (6π: 10.53 and 13.37 kcal/mol; D.A.: 13.52 kcal/mol), while that for cyclohexenone **36** is the 6π-electrocyclization (6π: 18.64 kcal/mol; D.A.: 11.43 kcal/mol). For the 6π-electrocyclization, the TS energy for epoxyquinone **32** is lower than that for cyclohexenone **36** because the TS energy becomes lower as the substituent becomes more electron-withdrawing, and there are two electron-withdrawing groups in **32** compared with only one in **36**. On the other hand, the TS energy of the Diels–Alder reaction of epoxyquinone **32** is higher than that of cyclohexenone **36** because there is steric hindrance caused by the epoxide in **32** and also because the Diels–Alder reaction of **36** is orbitally favorable. As a result, the rate-determining step is reversed.

Compared with the above two substrates, the epoxyquinol **18** (**16a/b**) had a different profile: Although the two 2*H*-pyran monomers **34** and **38** react to afford the dimerized product, monomer **16** from epoxyquinol **18** was not directly transformed into the Diels–Alder products **1** and **2**. Calculations suggest that initially the two monomers **16a/b** preassociate to give intermediate complexes **43** and **44**, which are more stable than the parent **16a**+**16b** and **16a**+**16a** by 9.22 and 9.92 kcal/mol, respectively. This stabilization can be ascribed to a hydrogen-bonding interaction, as shown in Scheme 9. The hydroxy group of **16a** coordinates the carbonyl lone pair of **16b** in **43**, at a distance of 1.915 Å, while the OHs of two different molecules of **16a** interact with each other in **44** at a distance of 1.968 Å. From these intermediates **43** and **44**, the dimerization proceeds to afford Diels–Alder products **1** and **2**. As the TS energies for ep-

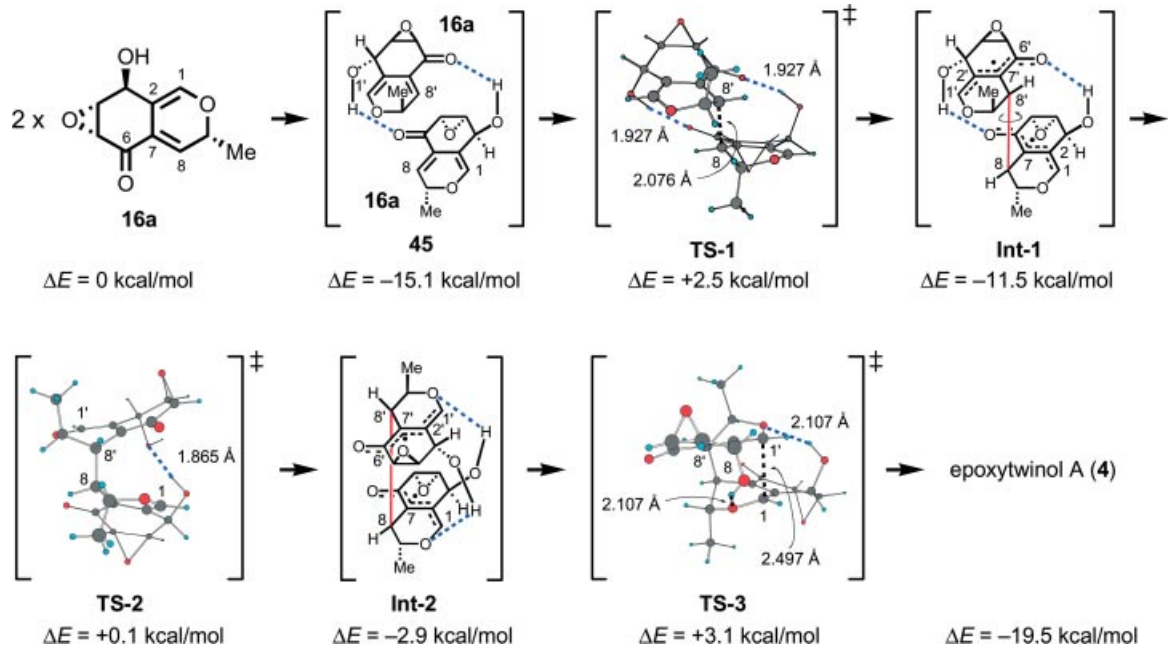


Scheme 9. Theoretical calculation of the Diels–Alder reactions.

oxyquinols A (**1**) and B (**2**) are 12.87 and 15.66 kcal/mol, respectively, the former would theoretically be more favorable than the latter and this is consistent with the experimental result that epoxyquinol A (**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 experimental results as epoxyquinol B (**2**) was also formed in 25% yield. This discrepancy could be the result of neglecting solvent effects in the calculations,[22b] 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 9, the hydrogen bond activates the ketone function in epoxyquinol A (**1**) formation, whereas there is hydrogen-bonding stabilization of the TS in epoxyquinol B (**2**) formation.

As mentioned above, epoxytwinol A (**4**), a formal [4+4] cycloadduct, is generated even in the dark, which means epoxytwinol A (**4**) is a thermal [4+4] cycloadduct. In view of the Woodward–Hoffmann rules,[48] a stepwise rather than concerted mechanism is expected for a thermal [4+4] cycloaddition reaction. Indeed, stepwise biradical mechanisms have been proposed for the [4+4] dimerization of *o*-quinodimethane and its derivatives.[49] Density functional B3LYP treatment with unrestricted formalism (UB3LYP)[50] provides relatively reasonable results for the energy of biradical or biradicaloid species, and the UB3LYP method[51] has been successfully employed to investigate reaction paths involving biradical species or to compare the energetics of stepwise, biradical reaction paths with those of concerted, closed-shell paths.[52] We therefore employed this method in conjunction with the 6-31G(d) basis set to locate the stationary points along the reaction coordinate for the [4+4] cycloaddition reaction.[53]

The first process is the formation of the C8–C8′ bond. Two monomers **16a** preassociate to give complex **45**, which is more stable than two molecules of **16a** by 15.1 and 7.9 kcal/mol at the B3LYP/6-31G(d) and B3LYP/6-31+G(d,p) levels, respectively.[54] Counterpoise calculations[55] at these computational levels afforded BSSEs of 7.7 and 2.0 kcal/mol and hence the BSSE-corrected stabilization energies for complex **45** are 7.4 and 5.9 kcal/mol. This



Scheme 10. Reaction intermediates and transition states for the thermal [4+4] cycloaddition of **16a** in the synthesis of epoxytwinol A (**4**).

stabilization can be ascribed to the two hydrogen-bonding interactions shown in Scheme 10. From this complex **45**, the C8–C8′ bond is formed with breaking of the C7–C8 and C7′–C8′ double bonds, affording a biradical intermediate **Int-1** via transition state (**TS-1**) in which there are two hydrogen-bonding interactions and the bond lengths of O···H and the forming C8–C8′ bond are 1.927 and 2.076 Å, respectively. Each hydroxy group coordinates to a carbonyl oxygen, acting as a Brønsted acid. In **Int-1**, the dihedral angle Ha–C8–C8′–Ha′ is –171.3°. The barrier height for the first step is 17.6 kcal/mol and the radical is stabilized by the hydrogen-bonding interactions.

The second step is rotation about the C8–C8′ bond to afford **Int-2** in which the dihedral angle Ha–C8–C8′–Ha′ is +26.3°. The transition state (**TS-2**) is shown in Scheme 10, and the activation energy for this second step is 11.6 kcal/mol.[54]

In the third step, an intramolecular radical coupling of **Int-2** generates epoxytwinol A (**4**) through the formation of the C1–C1′ bond, the barrier height for this third step being 6.0 kcal/mol. There are also two hydrogen-bonding interactions in the transition state **TS-3**, the alcohol protons coordinating to a lone pair of the oxygen atoms of the pyran rings with O···H bond lengths of 2.107 Å.

These calculations suggest that the hydroxy group of **16a** plays an essential role in this thermal [4+4] cycloaddition reaction by forming hydrogen bonds throughout the course of the reaction, from initiation until the formation of the final product. The importance of this hydroxy group is supported experimentally by the observations that only Diels–Alder adducts were obtained in the reaction of **38**, having no hydroxy or epoxy groups,[22b] and in the reaction of **42a**, containing a methoxy group in place of the hydroxy group. C_2 symmetry is preserved throughout the reaction except in **TS-2** in which the hydrogen bonds recombine. It should be noted that the intermediate radical is rather stable owing to the delocalization of spin density through O1–C1–C2–C7–C6–O2. Calculations indicate that the transformation of epoxytwinol A (**4**) into epoxyquinol B (**2**) also involves three steps. Homolytic cleavage of the C1–C1′ bond affords biradical intermediate **Int-2**. Rotation around the C8–C8′ bond generates **Int-3** (Figure 2) in which the dihedral angle of Ha–C8–C8′–Ha′ is +58.7°. Epoxyquinol B (**2**) is generated by a coupling reaction between C1 and C7′. The transition-state energy going from epoxytwinol A (**4**) to epoxyquinol B (**2**) is 22.6 kcal/mol, and the latter is thermodynamically more stable than the former by 0.6 kcal/mol, which explains the facile transformation of the former to the latter.

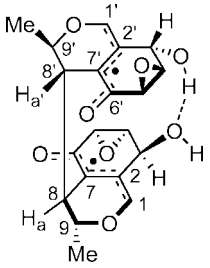


Figure 2. Structure of **Int-3**.

3.7 Reactivity of a 2*H*-Pyran Derivative

In the biomimetic oxidative dimerization of monomer (+)-**18**, the reactive intermediate 2*H*-pyran (+)-**16** is gener-

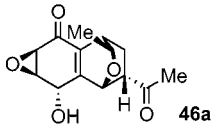
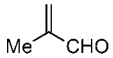
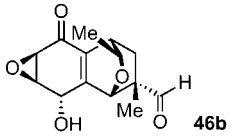
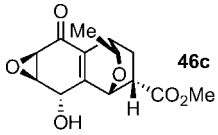
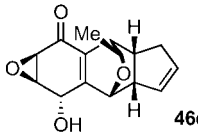
ated, which acts both as a diene and a dienophile.[2,8a] The oxidation/6π-electrocyclyzation cascade reaction is a useful synthetic method for the formation of 2*H*-pyran derivatives, but no systematic study has been made of the reactivity of this reactive intermediate. Moreover, if the 2*H*-pyran derivative was to react with another diene or dienophile instead of dimerizing, an efficient method for the synthesis of polycyclic compounds would be realized.

With this in mind, we examined the Diels–Alder reaction of a 2*H*-pyran derivative with several dienophiles and dienes. We chose epoxycyclohexenone (+)-**18** to investigate the reactivity of 2*H*-pyrans. The reactions using (+)-**18** were performed as follows. Alcohol (+)-**18** was oxidized with MnO_2 in CH_2Cl_2 at 0 °C and room temperature each for 1 h. After removal of inorganic material by filtration, the solvent was carefully evaporated under reduced pressure at 0 °C to suppress self-dimerization. Immediately after removal of the solvent, an excess of dienophile or diene was added to the reaction mixture, which was then stirred at room temperature.

The 2*H*-pyran **16**, acting as a diene, reacted with reactive dienophiles such as methyl vinyl ketone, methacrolein, and methyl acrylate, affording polycyclic compounds in moderate yields (56–69%) along with the self-dimerized products in 10–20% yields, the results of which are summarized in Table 1.[8c] Only the *endo* Diels–Alder adducts were obtained stereoselectively in every reaction examined, and the stereochemistry of the methyl group was regulated to reduce steric repulsion of the dienophiles. Although 2*H*-pyran **16** also reacted with maleic anhydride, acryloyl chloride, and fumaryl chloride to provide Diels–Alder adducts quantitatively as single isomers, as judged by ^{1}H NMR, attempts to isolate and characterize the products after conversion into the corresponding methyl esters were not successful.

Next the reaction with dienes was examined. Cyclopentadiene, known to be a reactive diene, reacted with 2*H*-pyran **16** as a dienophile, affording a tetracyclic compound in moderate yield. Other dienes such as isoprene gave complex mixtures. The fact that cyclopentadiene reacted as a dienophile instead of a diene demonstrates the high reactivity of 2*H*-pyran **16** as a diene (Scheme 11).

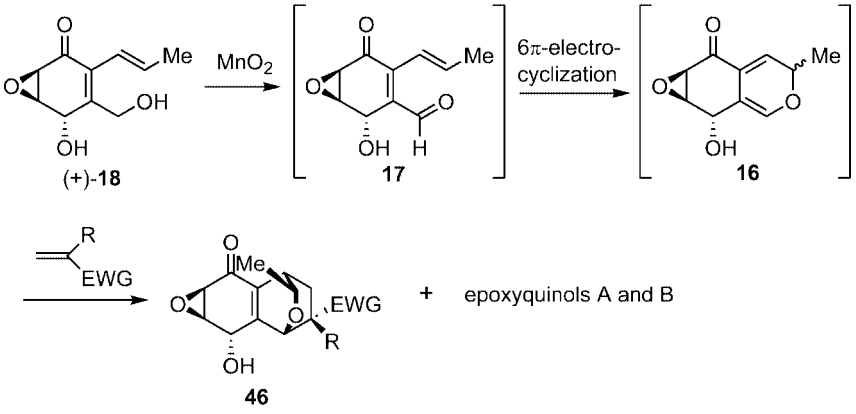
Table 1. Cascade reaction of (+)-**18** with several dienophiles.

Entry	Dienophile	Product	Yield[a]
1		 **46a**	64 %
2		 **46b**	69 %
3		 **46c**	56 %
4		 **46d**	45 %

[a] Isolated yield.

3.8 Total Syntheses of Panepophenanthrin and Hexacyclinol

Panepophenanthrin (**47**) is the first natural product to inhibit ubiquitin-activating enzyme (E1), isolated by Sekizawa et al. in 2002 from the mushroom strain *Panus rudis* Fr. IFO8994.[56] As E1 plays an important role in the ubiquitin-proteasome pathway (UPP), which regulates a variety of important cellular processes via degradation or processing of target proteins, the inhibitor of E1 would be a promising drug candidate for cancers, inflammation, and neurodegenerative disease.[57] Structurally, panepophenanthrin has a complex architecture with a highly substituted tetracyclic skeleton containing 11 contiguous stereocenters. Panepophenanthrin is a member of the so-called epoxyquinoid natural product family which are synthesized by Diels–Alder dimerization of much simpler epoxyquinol monomers.[11] Its synthetically challenging structure along with



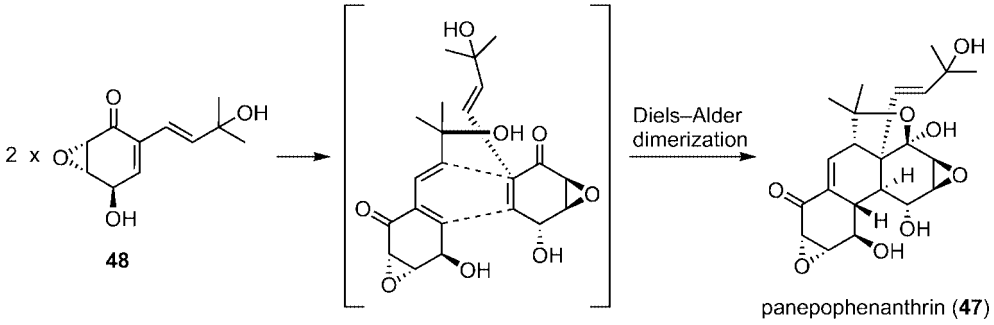
Scheme 11. Synthesis of various polycyclic compounds **46**.

its important biological activity makes panepophenanthrin an attractive synthetic target. In fact, since its isolation in 2002, four groups, including ours, have accomplished its total synthesis. All of them employed spontaneous Diels–Alder dimerization of the monomer **48** to produce panepophenanthrin (**47**) (Scheme 12).

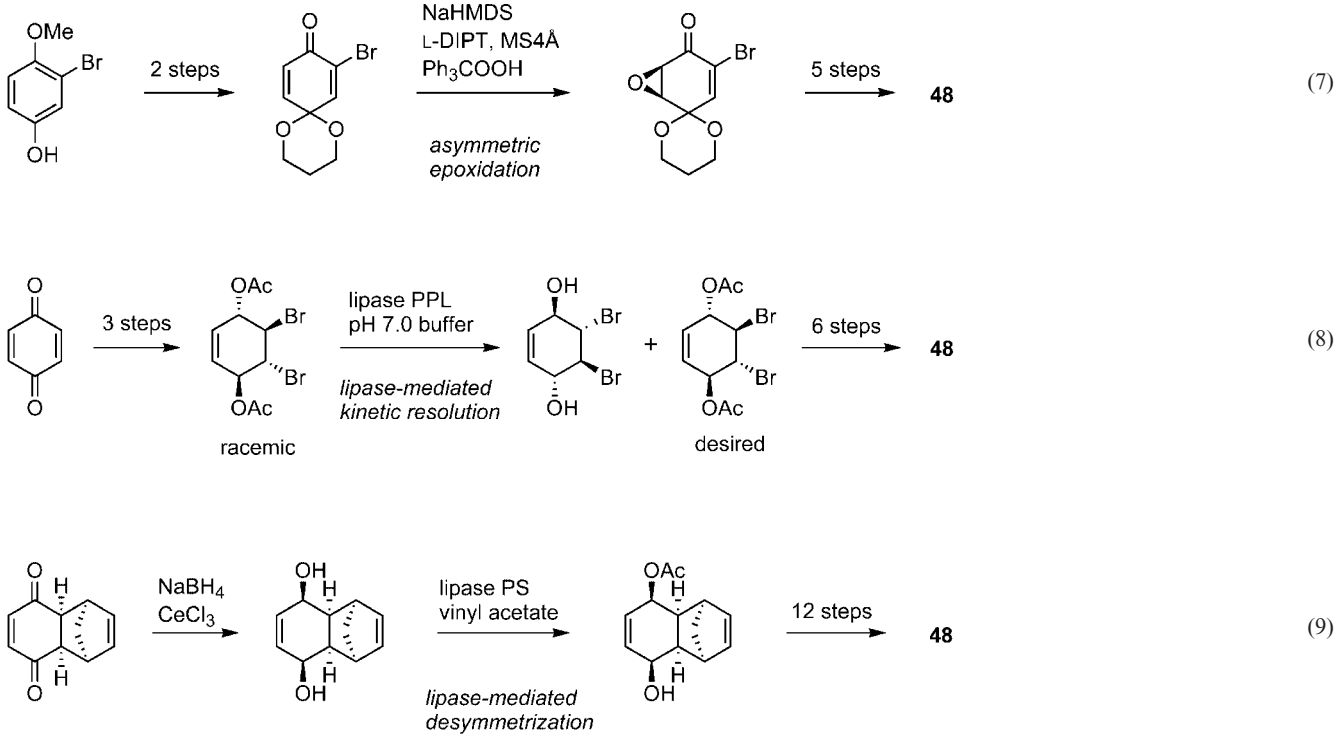
The first asymmetric total synthesis was reported by Porco and co-workers in which the monomer **48** was synthesized by diisopropyl tartrate mediated asymmetric epoxidation using excess amounts (1.6 equiv.) of a chiral controller [Equation (7)].[58] They explained the reaction mechanism of the Diels–Alder dimerization clearly. Baldwin and Moses and co-workers prepared the monomer in its racemic form from known (±)-bromoxone, while (–)-bromoxone is a known compound [Equation (8)].[59] Mehta and co-workers synthesized the monomer using lipase-mediated desymmetrization as a key step [Equation (9)],[60a] while an enantiomer of the natural panepophenanthrin was synthesized via lipase-mediated enzymatic resolution by the same group.[60b] On the other hand, our group developed the proline-mediated asymmetric catalytic α-aminoxylation of carbonyl compounds,[61] which is a powerful method for the synthesis of α-hydroxy carbonyl derivatives. By employing this reaction as a key step and via several diastereoselective transformations, we accomplished the asymmetric total synthesis of panepophenanthrin [Equation (10)].[62]

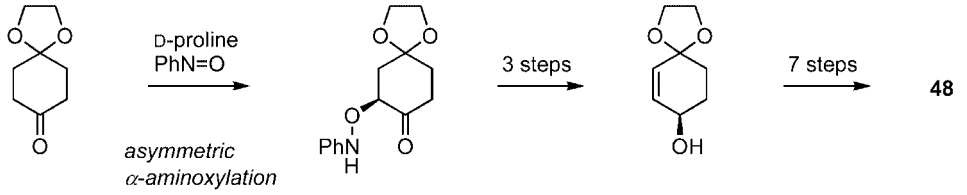
Hexacyclinol was isolated by Gräfe and co-workers from the *Panus rudis* strain HKI 0254 in 2002,[63] and its proposed structure **49** is shown in Figure 3. Although La Clair recently reported a total synthesis of **49**,[64] Rychnovsky proposed another structure for hexacyclinol **50** based on a calculation of the ^{13}C NMR chemical shift correlation which would be formed by a Diels–Alder dimerization of epoxyquinol derivative followed by S_N2' substitution reactions.[65]

Just recently, Porco et al. completed a synthesis of the structure proposed by Rychnovsky by Diels–Alder dimerization of the monomer **51**, which was similar to that of

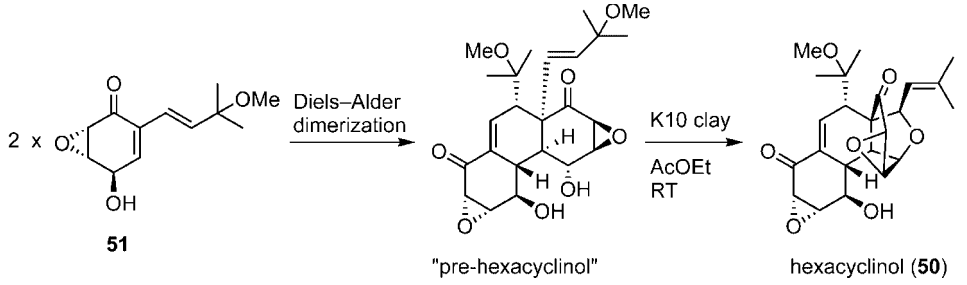


Scheme 12. Oxidative dimerization of **48** to form panepophenanthrin (**47**).





(10)



(11)

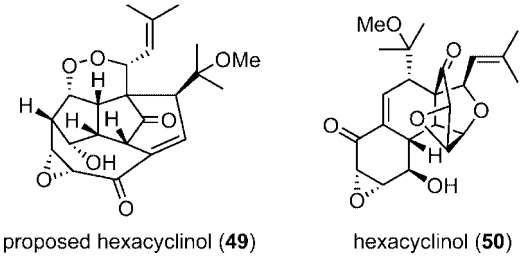


Figure 3. Proposed (**49**) and revised (**50**) structures of hexacyclinol.

panepophenanthrin, followed by acidic treatment [Equation (11)].[66] ^{1}H and ^{13}C NMR spectroscopic data for synthetic **50** was confirmed to be identical to those reported by Gräfe and co-workers. Moreover, the structural framework of synthetic **50** was confirmed by X-ray crystal structure analysis. Thus, the structure of hexacyclinol was revised to be that of **50**.

4. Conclusions

The total synthesis of epoxyquinols A, B, and C and epoxytwinol A has been accomplished by biomimetic cascade reactions. Epoxyquinols A, B, and C were synthesized by a cascade reaction consisting of oxidation/6π-electrocyclization/Diels–Alder dimerization of the monomer **18**, whereas epoxytwinol A was generated by a cascade reaction of oxidation/6π-electrocyclization/formal [4+4] cycloaddition reaction of the monomer **18**. The monomer **18** has been synthesized by two different routes. In the first, $HfCl_4$-mediated diastereoselective Diels–Alder reaction of furan with Corey's chiral auxiliary was employed, whereas chromatography-free preparation of an iodolactone and lipase-mediated kinetic resolution were key reactions in the second route. The present method is practical not only for synthesizing epoxyquinols in large quantities, but also for preparing various derivatives with different side-chains by the Suzuki coupling of (+)-**19** and alkenyl borates. In fact, we synthesized several monomers, the biological activities of which are under investigation.[67]

In the oxidative dimerization of epoxyquinone **32** and cyclohexenone **36**, epoxyquinol A type reaction modes are preferred, whereas both epoxyquinols A and B are formed in the dimerization of epoxyquinol **18** because of intermolecular hydrogen bonding which has been proved to exist experimentally and by theoretical calculations. 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 **40**. In the dimerization of epoxyquinol **18**, monomer 2*H*-pyrans **16** preassociate to afford complexes **43** and **44** which undergo Diels–Alder reactions. Theoretical calculations have also clarified the differences between the reaction profiles of epoxyquinone **32** and cyclohexenone **36**. Namely, the rate-determining step of the former is the Diels–Alder reaction, whereas that of the latter is the 6π-electrocyclization process.

We have also shown that the [4+4] cycloaddition of 2*H*-pyran **16a** consists of three consecutive steps involving biradical intermediates. The first step is the formation of the C8–C8′ bond with generation of a biradical intermediate (**Int-1**), the next is rotation about the C8–C8′ bond, and the last is radical coupling to form the C1–C1′ bond. The biradicals are stabilized by delocalization and two hydrogen-bonding interactions are essential for the realization of this exceptionally rare thermal [4+4] cycloaddition reaction. Biradicals are also involved in the transformation of epoxytwinol A (**4**) into epoxyquinol B (**2**). Another noteworthy feature described in this paper is the high reactivity of 2*H*-pyrans **16** as dienes, used to prepare several polycyclic compounds by the Diels–Alder reaction.

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