

Award Accounts

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Total Synthesis of Epoxyquinonoid Natural Products

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Asymmetric total synthesis of epoxyquinonoid natural products, such as epoxyquinols A, B, and C, epoxytwinol A, and EI-1941-1, -2, and -3, are described. In the first-generation synthesis of epoxyquinols, the $HfCl_4$-mediated diastereoselective Diels–Alder reaction of furan with a chiral acrylate ester was developed. In the second-generation synthesis, a chromatography-free preparation of an iodolactone by using acryloyl chloride as the dienophile in the Diels–Alder reaction of furan, and the lipase-mediated kinetic resolution of a cyclohexenol derivative were developed. This second-generation synthesis is suitable for large-scale preparation. A biomimetic cascade reaction involving oxidation, 6π-electrocyclization, then Diels–Alder dimerization, is the key reaction in the formation of epoxyquinols A–C. Epoxytwinol A was synthesized by the cascade reaction composed of oxidation, 6π-electrocyclization, and formal [4 + 4] cycloaddition. 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. The asymmetric total synthesis of EI-1941s was accomplished, starting from a chiral epoxy iodoquinone, a key intermediate in the total synthesis of epoxyquinols. They were diastereoselectively synthesized via an intramolecular carboxypalladation in a 6-*endo* cyclization mode, followed by β-hydride elimination, as the key steps.

Epoxyquinonoid skeletons are widely found in many natural products, which have various interesting bioactivities. 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**) (Fig. 1),[5] from an unknown soil fungus. These small natural products have structures quite distinct from those of known angiogenesis inhibitors, making their mechanism of action a matter of considerable interest. ECH (**5**), the monomeric precursor of **1**–**4**, is an inhibitor of Fas-mediated apoptosis.[6] In addition, inhibitors of interleukin-1β converting enzyme (ICE) have been shown to prevent inflammation in several acute models,[7] suggesting that ICE inhibitors should be useful as anti-inflammatory drugs. Koizumi and co-workers have isolated EI-1941-1 (**6**), -2 (**7**), and -3 (**8**) from culture broths of *Farrowia* sp., the first two of which selectively inhibit human recombinant ICE activity with IC_{50} values of 0.086 and 0.006 mM (1 M = 1 mol dm^{-3}), respectively, whereas the last is inactive at concentrations up to 10 mM in an in vitro system.[8] EI-1941-2 has also weak antimicrobial activities against Gram-positive bacteria and moderate activity against *Proteus vulgaris*.[8] A sufficient quantity of the natural products is needed for biological investigations and for the study of structure–activity relationships requires derivatives. For these purposes an efficient and flexible total synthesis is highly desirable, and recently, we have accomplished the first total synthesis of epoxyquinols A and B,[9] and EI-1941-1, -2, and -3.[10]

Epoxyquinols A (**1**), B (**2**), and C (**3**) are novel pentaketide dimers, with complex, highly oxygenated, heptacyclic structures that contain 12 chiral centers, and they are postulated to be biosynthetically generated from ECH (**5**)[11] by a cascade reaction sequence of oxidation, 6π-electrocyclization[12] and Diels–Alder reaction.[2,3] That is, diol monomer **5** is oxidized to aldehyde **15**, from which 6π-electrocyclization proceeds, affording 2*H*-pyran derivative **14** (Scheme 1). Diels–Alder dimerization of 2*H*-pyran **14** proceeds to afford 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**) have 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, which is completely different structure from those of epoxyquinols A (**1**), B (**2**), and C (**3**). It is postulated that epoxytwinol A (**4**) is biosynthetically generated by a formal [4 + 4] cycloaddition reaction of the same key 2*H*-pyran intermediate **14**, which is used in the construction of epoxyquinols A, B, and C (vide infra). Since these compounds have important biological properties and synthetically challenging structures, several research groups, including ours,[9] have investigated the total synthesis of these compounds.

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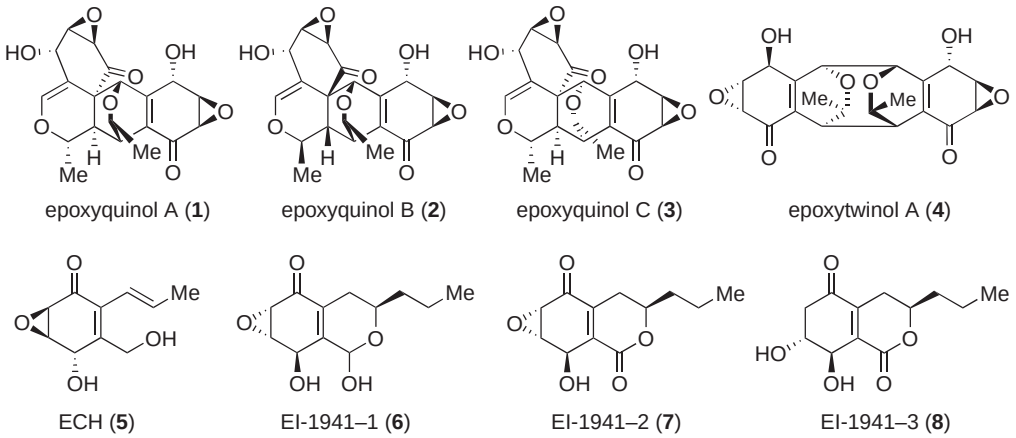
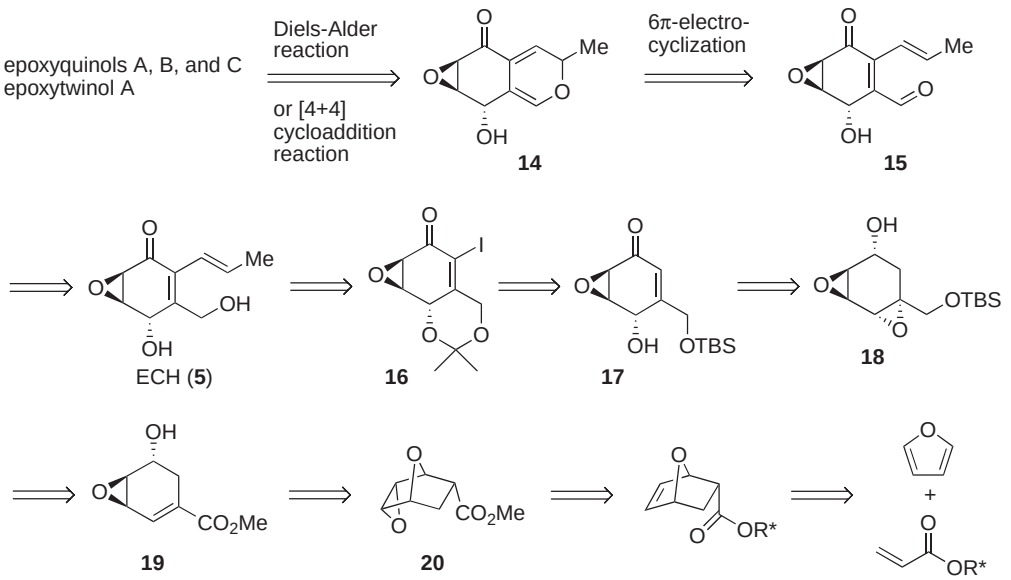


Fig. 1. Epoxyquinols A (**1**), B (**2**), and C (**3**), epoxytwinol A (**4**), ECH (**5**), EI-1941-1 (**6**), -2 (**7**), and -3 (**8**).



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

Our group has accomplished the first total synthesis of epoxyquinols A (**1**) and B (**2**), employing the biomimetic oxidative dimerization of the monomer **5** as a key step, and have determined their absolute configulations.[9] Other groups also employed the same biomimetic dimerization.[13] Starting from 2,5-dihydroxybenzaldehyde, Porco et al. have reported their elegant synthesis of the monomer **5** via diisopropyl tartrate-mediated asymmetric epoxidation of cyclohexenone derivative.[14] In order to obtain optically pure **5**, Mehta and Islam have used lipase-mediated kinetic resolution,[15] and Kuwahara and Imada have employed Evans' asymmetric aldol reaction, respectively.[16] All of these synthetic schemes provided the monomer with high enantioselectivities. Ours and Mehta's groups oxidized monomer **5** 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**). Porco and Li have reported the elegant, alkoxysilanol-facilitated total synthesis of epoxytwinol A (**4**).[17] The related epoxyquinonoid Diels–Alder dimer, (+)-torreyanic acid with selective cytotoxicity against human cancer cell lines,[18] was isolated by Lee and co-workers from fungus *Pestalotiopsis*, and has independently been synthesized by Porco's[19] and Mehta's[20] groups.

In our first asymmetric total synthesis of epoxyquinols A and B,[9a] 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 key reactions. We determined the importance of hydrogen-bonding in the Diels–Alder reaction forming epoxyquinol B by combining of synthetic organic chemistry and theoretical chemistry.[22] We also developed a practical total synthesis with a kinetic resolution using lipase as a key step.[9b] In a study on the large scale preparation of epoxyquinols A and B, we carefully investigated the minor isomers of the key oxidative dimerization, and we isolated and identified epoxyquinol C and epoxytwinol A from the crude reaction mixture.

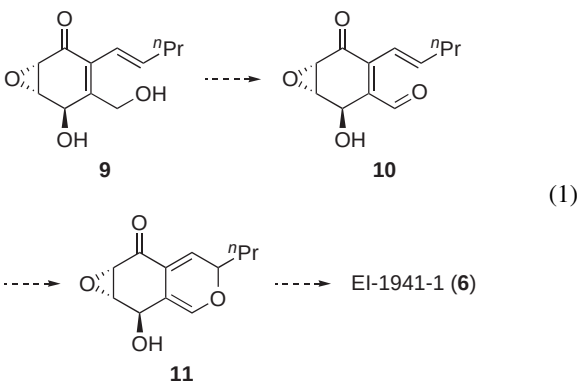
In the course of the oxidative dimerization of the monomer derivatives, such as **25** and **29**, epoxyquinol A-type dimers were obtained predominantly (vide infra, Scheme 5). To understand the difference in reaction modes between epoxyquinol **5** and epoxyquinone **25**, the oxidative dimerization of parent monomer **29**, without epoxide and hydroxy groups, was examined. The methoxycyclohexenone **33** was also investigat-

ed to shed light on the effect of the hydroxy group in **5**. In the key oxidative dimerization, oxidation of dienol **5** and subsequent 6π-electrocyclization affords 2*H*-pyran derivative **14**, which dimerizes to afford epoxyquinols A (**1**) and B (**2**). 2*H*-Pyran derivatives are seldom employed in organic synthesis and their reactivity has not been systematically investigated because of difficulty in generating them owing to their easy isomerization into dienals.[23] Since we found a simple method for generation of 2*H*-pyran intermediates by oxidation and 6π-electrocyclization during the synthesis of epoxyquinols A and B, we have investigated their reactivity as the diene component in the Diels–Alder reaction.

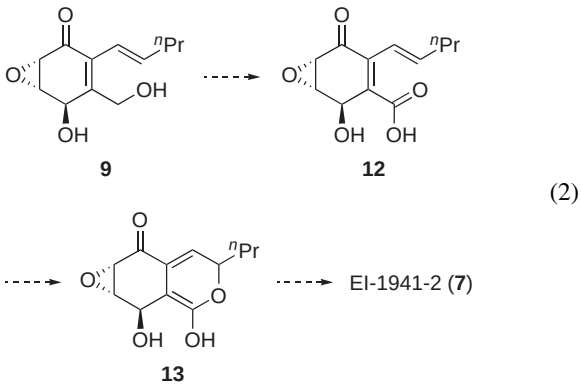
EI-1941-1 (**6**) and -2 (**7**) also have an epoxyquinone core, such as epoxyquinols A, B, and C, epoxytwinol A, and their monomer, ECH (**5**). At the time we started this project, the relative and absolute stereochemistries of EI-1941-1 (**6**), -2 (**7**), and -3 (**8**) were not known.[8] As most of the epoxyquinol natural products have a *trans* relationship between the epoxide and the 4-hydroxy group on the cyclohexenone,[24] work on a synthetic route by which the two diastereomers (EI-1941-2 and epi-EI-1941-2) can be generated with high optical purity was undertaken in order to determine the relative stereochemistries. In order to determine the absolute stereochemistry, with the structural similarity between EI-1941s and ECH, we tried to synthesize (4*S*,5*R*,6*R*)-5,6-epoxy-4-hydroxycyclohexenone derivative, as our first target.

When we had nearly finished the synthesis of the targeted isomer of EI-1941-2 and its epimer, the absolute and relative stereochemistries of EI-1941-1 and -2 were reported,[25] while those of EI-1941-3 were not determined, because of its low availability from fermentation broth. Those determinations are based on the crystallographic analysis of the *p*-bromobenzoyl ester of EI-1941-2 and the chemical correlation between EI-1941-1 and -2. These results indicate that the compounds that we have synthesized are opposite enantiomers of the natural EI-1941-2 and its epimer.[10a]

As for the biosynthesis, we postulated the following path: oxidation of alcohol **9** affords aldehyde **10**, from which 6π-electrocyclization[23] proceeds to generate 2*H*-pyran **11**; hydration of **11** and subsequent isomerization would afford EI-1941-1, the oxidation of which would provide EI-1941-2 (Eq. 1). Another possible path involves the oxidation of alcohol **9** to carboxylic acid **12**, from which 6π-electrocyclization proceeds to generate hydroxy-2*H*-pyran **13** (Eq. 2). Isomerization affords EI-1941-2, the reduction of which gives EI-1941-1.



(1)



(2)

Based on this hypothesis, we have attempted the synthesis of EI-1941-1 (**6**) and -2 (**7**); however, the δ-lactone could not be constructed. Therefore, we found an alternative cyclization method, carboxypalladation, and accomplished the first total synthesis of **6** and **7**.[10b] After our total synthesis, Mehta's[26] and Porco's[27] groups have independently reported the total synthesis of EI-1941-2 (**7**) via oxidative formation of the α-pyron from corresponding dienol.

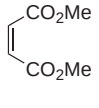
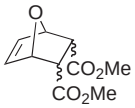
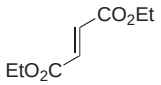
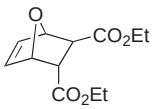
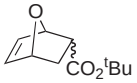
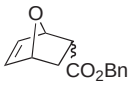
1. Epoxyquinols A, B, and C, and Epoxytwinol A

1.1 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 are synthesized from monomer **5** by using a postulated biosynthetic pathway that involves 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. Monomer **5** can be synthesized from iodocyclohexenone **16** by the Suzuki coupling reaction. Iodocyclohexenone **16** would be prepared by the α-iodination of cyclohexenone **17**, which should be available from bisepoxycyclohexenol **18**. Chiral cyclohexenol **18** 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 that should be pointed out: (1) synthesis of 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; (2) all carbon atoms except 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; and (3) chirality is introduced at the stage of the initial Diels–Alder reaction, and highly diastereoselective synthesis of the monomer would be possible by exploiting neighboring-group participation.

1.2 $HfCl_4$-Mediated Diels–Alder Reaction of Furan. Based on the above retrosynthetic analysis, the Diels–Alder reaction of furan,[28] which is a difficult cycloaddition owing to the facile retro-Diels–Alder reaction and low reactivity of furan as a diene due to its aromatic character, is the first step of our total synthesis. In addition to the use of highly reactive dienophiles in the Diels–Alder reaction,[29] several methods have been developed to overcome these difficulties, such as

Table 1. Diels–Alder Reaction of Furan[a)]

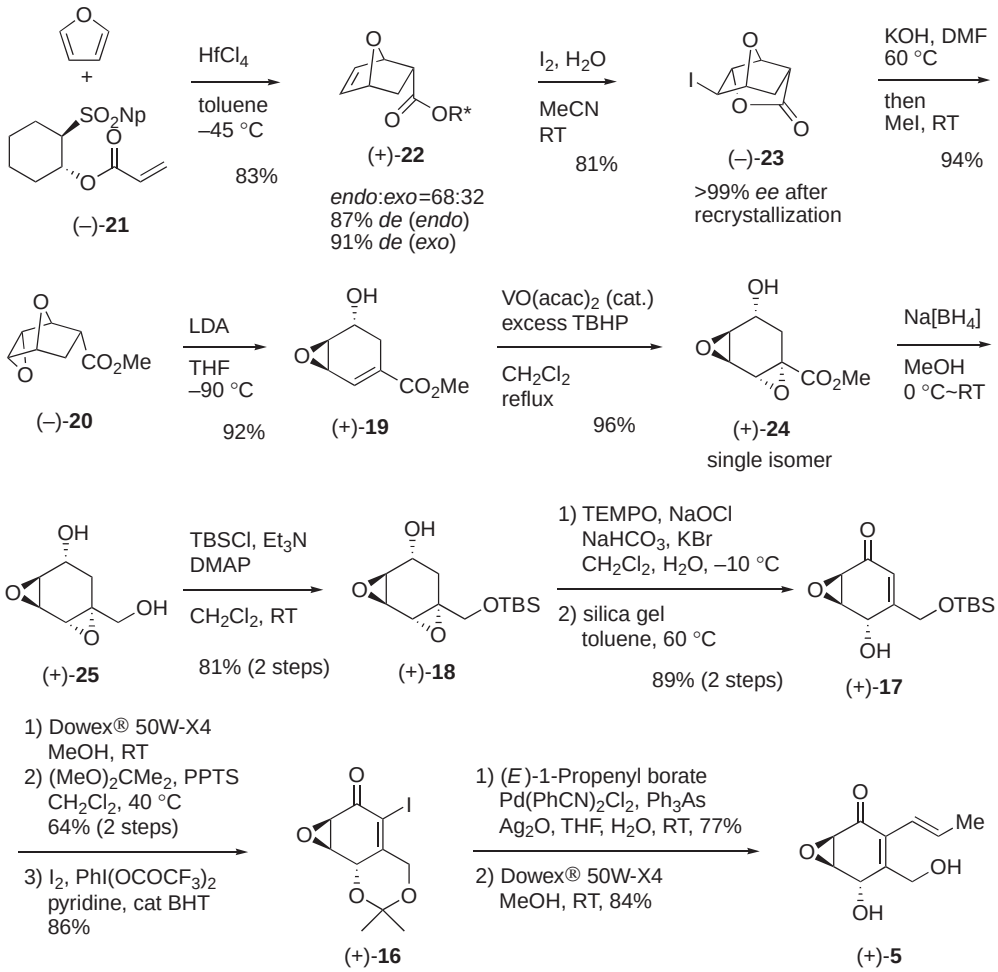
Entry	Dienophile	Product	Mol. amt. of $HfCl_4$	Temp/°C	Time/h	Yield/%[b)]	*endo*/*exo*[c)]
1			1.1	0	4	88	72/28
2			1.1	−20	5	91	93/7
3			1.1	−50	66	91	98/2
4			0.2	0	20	88	89/11
5			1.1	−20	7	84	—
6			1.1	−50	17	82	—
7			0.2	0	26	39	—
8			1.1	−50	25	84	69/31
9			1.1	−50	8	98	78/22
10			0.2	0	20	56	76/24
11			0.2	0	40	73	60/40
12			0.2	0	51	88	50/50

a) Furan/dienophile = 20/1. b) Isolated yield. c) The ratio was determined by ^{1}H NMR analysis (400 MHz).

the use of high pressure[30] or Lewis acid mediated reactions.[31] Although several Lewis acids have been reported to promote the reaction efficiently, there are problems in terms of generality. For example, $BF_3 \cdot OEt_2$ is a good catalyst for methyl acrylate but a poor promoter for other dienophiles,[31c] ZnI_2 is suitable for acrylonitrile but not for α,β-unsaturated esters,[31a] while methyl vinyl ketone and acrylonitrile are activated by $BiCl_3$.[31l] Some Lewis acids supported on silica gel have also been utilized for the promotion of Diels–Alder reactions of particular dienophiles with furan.[31e,g,i,j] However, low *endo*/*exo* selectivity is generally obtained, because of the facile retro-Diels–Alder reaction.

First, we looked for an appropriate Lewis acid using the reaction of furan and dimethyl maleate as a model and employing furan as the solvent (40 molar amounts). The reaction was performed in the presence of an equimolar amount of Lewis acid at room temperature for 15 h. Of the several Lewis acids screened,[32] $HfCl_4$ was found to have suitable Lewis acidity to promote the Diels–Alder reaction in moderate yield (60%).[33] Although most of the reported Lewis acids lose their Lewis acidity by coordination with furan, which acts as a Lewis base, $HfCl_4$ still activates α,β-unsaturated esters efficiently even in the presence of an excess amount of furan. Next, the use of a solvent was examined, and CH_2Cl_2 was found to be the best with respect to both yield and *endo*/*exo* selectivity.[34] For example, the Diels–Alder reaction of dimethyl maleate and furan proceeds in CH_2Cl_2 at −20 °C within 5 h to afford the cycloadduct in good yield (91%) and high diastereoselectivity (*endo*/*exo* = 93/7; Table 1, Entry 2). The effect of temperature on the yield and diastereoselectivity of the reaction is shown in Entries 1–3. As the temperature is lowered, the diastereoselectivity increases, and very high *endo* selectivity (98/2) was attained when the reaction was conducted at −50 °C. This is the second highest *endo*-selectivity so far reported for the Diels–Alder reactions of furan with maleic acid derivatives, the first being a reaction performed under high-pressure conditions,[30a] and the present reaction is complimentary to the thermal Diels–Alder reaction of maleic anhydride and furan, which affords predominantly the thermodynamically stable *exo* isomer.[29c]

The generality of this $HfCl_4$-mediated Diels–Alder reaction of furan with respect to dienophiles was investigated (Table 1). The reaction of diethyl fumarate proceeds smoothly at −20 °C to afford the Diels–Alder adduct in good yield (Entry 5). The ester group has a large effect both on the yield and selectivity in the reaction of acrylate derivatives; the reaction of the benzyl ester is faster (8 h) and more selective (*endo*/*exo* = 78/22, Entry 9) than that of the *tert*-butyl ester (25 h, *endo*/*exo* = 69/31, Entry 8). When the reaction of furan and dimethyl maleate was performed in the presence of only a catalytic molar amount (20%) of $HfCl_4$, the reaction proceeds at 0 °C to afford the Diels–Alder adducts in good yield with high *endo*/*exo* selectivity (Entry 4). On the other hand, fumarate ester is not a suitable substrate for the present reaction, because Diels–Alder adducts were formed in low yield, when the amount of $HfCl_4$ was reduced to 0.20 molar amount (Entry 7). The yield

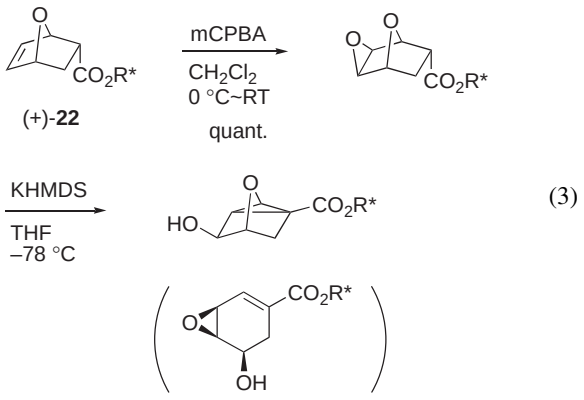


Scheme 2. Synthesis of (+)-**5**.

for the catalytic reaction using benzyl acrylate as the dienophile increased with an increase in the reaction time, whereas the diastereoselectivity decreased (Entries 10–12). This observation can be attributed to thermodynamic equilibration in the presence of $HfCl_4$ at 0 °C in favor of the *exo* isomer. High *endo* selectivity in the reaction using an equimolar amount of $HfCl_4$ at low temperature can be achieved under kinetic control (Table 1, Entry 9).

1.3 First-Generation Monomer Synthesis. Although there are a number of methods for the diastereoselective Diels–Alder reaction of a chiral acrylate ester with furan,[35] few of these are synthetically useful with high *endo*/*exo*- and/or diastereoselectivities. We found that $HfCl_4$ was 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. The $HfCl_4$-mediated Diels–Alder reaction of furan was applied to chiral acrylate esters, and the choice of the chiral auxiliary was found to be important. Although a chiral Evans' acrylate derivative, 3-acryloyl-4-benzyl-1,3-oxazolidin-2-one,[36] gave poor diastereoselectivity, high selectivity was obtained with the acrylate ester derived from Corey's chiral auxiliary ((−)-(1*R*,2*R*)-2-(2-naphthylsulfonyl)cyclohexanol).[21b] That is, in the presence of 1.1 molar amount of $HfCl_4$, the acrylate ester (−)-**21** reacts with furan in toluene at low temperature (−45 °C) for 34 h, giving the cycloadducts (+)-**22** in good yield with moderate *endo*/*exo*- and high diastereoselectivities (Scheme 2).

Direct epoxidation of (+)-**22** with mCPBA gave stereoselectively the *exo* epoxide,[37] which when reacted with KHMDS afforded an undesired cyclopropane derivative (Eq. 3).[38] 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 (−)-**23**. Treatment of *endo* Diels–Alder adduct (+)-**22** with I_2 in aqueous MeCN afforded iodolactone (−)-**23** in 81% yield with recovery of the chiral auxiliary in 94% yield. After recrystallization, optically pure lactone (−)-**23** was obtained, and its absolute stereochemistry was determined by comparing its optical rotation with that reported in the literature.[39] Though the direct transformation of iodolactone (−)-**23** to epoxy methyl ester (−)-**20** 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 (−)-**23** with KOH in DMF at 60 °C for 10 h, followed by esterification with MeI under sonication conditions for 1 h furnished epoxyester (−)-**20** in one pot and high yield (94%).



(3)

Exposure of (−)-**20** to LDA at −90 °C for 30 min led to β-elimination, affording hydroxy ester (+)-**19**. Low temperature and an exact equivalent of LDA are both essential for high yield in this step; otherwise, Michael addition of diisopropylamine to (+)-**19** occurs, generating a β-amino ester as a side product. Hydroxy-directed epoxidation of homoallylic alcohol (+)-**19** using a catalytic amount of $VO(acac)_2$ and excess *tert*-butylhydroperoxide (TBHP) under reflux in CH_2Cl_2[40] proceeded to give diepoxide (+)-**24** as a single isomer in high yield. Although reduction of ester (+)-**24** with DIBAL proceeded smoothly, the recovered yield of the diol (+)-**25** was quite low owing to its water solubility. Thus, a nonaqueous workup was examined: reduction with $Na[BH_4]$ in MeOH at room temperature for 15 min, removal of solvent in vacuo, and flash column chromatography afforded the diol (+)-**25**. The primary hydroxy group of (+)-**25** was selectively protected with TBSCl, affording (+)-**18** in 81% yield over two steps. Though the oxidation of (+)-**18** with SO_3·pyridine[41] afforded 2-(*tert*-butyldimethylsiloxymethyl)-5,6-epoxy-2-cyclohexene-1,4-dione from over-oxidation of (+)-**17**, TEMPO oxidation[42] 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,[43] affording α,β-unsaturated ketone (+)-**17** in 89% yield over two steps.

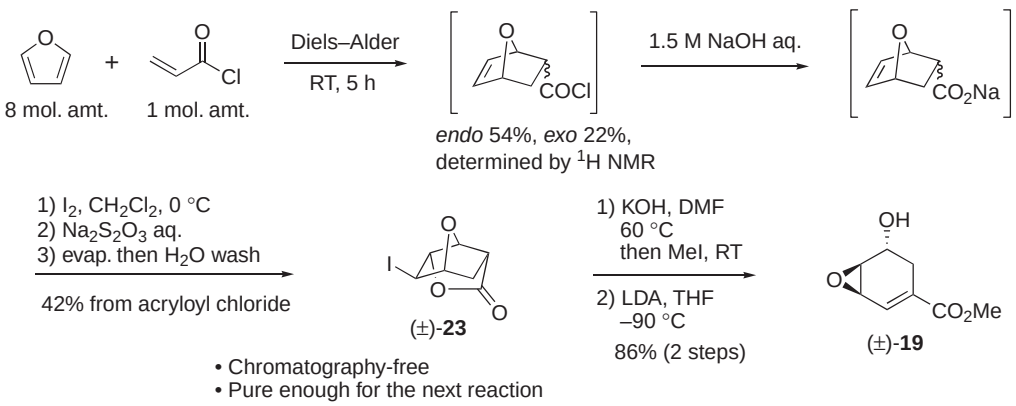
α-Iodination of cyclohexenone (+)-**17** was problematic, and the choice of diol protecting group and iodination reagent was found to be important for the success of this reaction. None of the desired product was obtained on treatment of hydroxy ketone (+)-**17** with I_2/DMAP,[44] I_2/$TMSN_3$,[45] or NaN_3/ICl,[46] whereas the secondary alcohol was oxidized, affording epoxyquinone in the reaction using I_2/$PhI(OCOCF_3)_2$/pyridine.[47]

The low reactivity and side reaction of (+)-**17** can be attributed to steric hindrance caused by the *tert*-butyldimethylsiloxymethyl group at the C3 position and nonprotected hydroxy group at the C4 position, respectively, and so the sterically smaller protecting group had to be employed. An acetonide derivative was prepared in 64% yield from (+)-**17** over two steps by removal of TBS group with Dowex® 50W-X4 in MeOH and protection of the resulting 1,3-diol with 2,2-dimethoxypropane. Unlike the result obtained with (+)-**17**, the reaction of the acetonide proceeded in the presence of I_2/$PhI(OCOCF_3)_2$/pyridine, affording (+)-**16**, but not reproducibly. After careful examination, it was found that the iodination proceeded only after a certain induction period, and that once generated, (+)-**16** 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, conditions which gave reproducible results, providing (+)-**16** in 86% yield.

As iodinated cyclohexenone (+)-**16** was labile, it was immediately subjected to the Suzuki coupling reaction with (*E*)-1-propenyl borate[48] under Johnson's conditions,[49] affording the corresponding dienone in 77% yield. Cleavage of the acetonide under acidic conditions provided monomer (+)-**5** in 84% yield.

The first total synthesis of epoxyquinols A (**1**) and B (**2**) was accomplished using (+)-**19** (vide infra). Though 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 (+)-**19** for epoxyquinols A (**1**), B (**2**), and C (**3**), and epoxytwinol A (**4**).

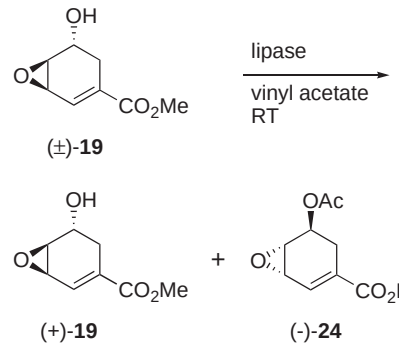
1.4 Second-Generation Monomer Synthesis. We chose as the key reaction of our new strategy the lipase-mediated kinetic resolution[50] of racemic cyclohexenol (±)-**19**, as such reactions are known to be readily scaleable. However, preparation of this intermediate itself proved to be difficult, because



Scheme 3. Large-scale preparation of (±)-**19**.

although the Diels–Alder reaction of furan and acrylate derivatives is a powerful means of synthesizing this class of compounds,[28,51] no method suitable for 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. Under these conditions the thermodynamically stable, *exo*-isomer predominates (*endo*:*exo* = 3:7).[51] 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 molar amounts) proceeds in 5 h at room temperature, providing the *endo* and *exo* cycloadducts in 54 and 22% yield, respectively (^{1}H NMR yield, Scheme 3). Though 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 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, (±)-**23** was precipitated from the reaction mixture in 42% yield as a white solid, which is pure enough to be used in the next experiment. Unreacted acryloyl chloride, and the *exo*-Diels–Alder adduct could be easily separated from iodolactone (±)-**23** as they both remained in the aqueous phase as the sodium salts of the corresponding acids. Though the yield was moderate, an efficient, chromatography-free procedure without extraction for the synthesis of iodolactone (±)-**23** has been developed,[52] and the reaction could easily be scaled up to 110 g.

After conversion of iodolactone (±)-**23** to cyclohexenol (±)-**19** by the same procedure described in Scheme 2, the kinetic resolution of (±)-**19** was examined (Eq. 4)



(4)

with the results summarized in Table 2. The reaction was performed at room temperature in the presence of several lipases (40–100 wt %) using vinyl acetate as solvent. Among the lipases examined, *Pseudomonas stutzeri* lipase (Meito TL) was found to be the most efficient. When (±)-**19** was treated with a catalytic amount of lipase TL (40 wt %) in vinyl acetate at room temperature for 18 h, acetate (−)-**24** was obtained in 50% yield with 97% ee, and the desired alcohol (+)-**19** was recovered in 50% yield with 96% ee, indicating a very high selectivity ($k_{fast}/k_{slow} = 215$).

Next, large scale kinetic resolution was examined using recovered lipase TL, and the results are summarized in Table 3. The reaction proceeded efficiently even with 10 wt % of the lipase TL, with a very high value of k_{fast}/k_{slow}, though a longer reaction time was necessary. The activity of recovered lipase did not decrease, and it worked as efficiently as fresh batches.

Table 2. Kinetic Resolution of Cyclohexenol (±)-**19** Using Various Lipases[a)]

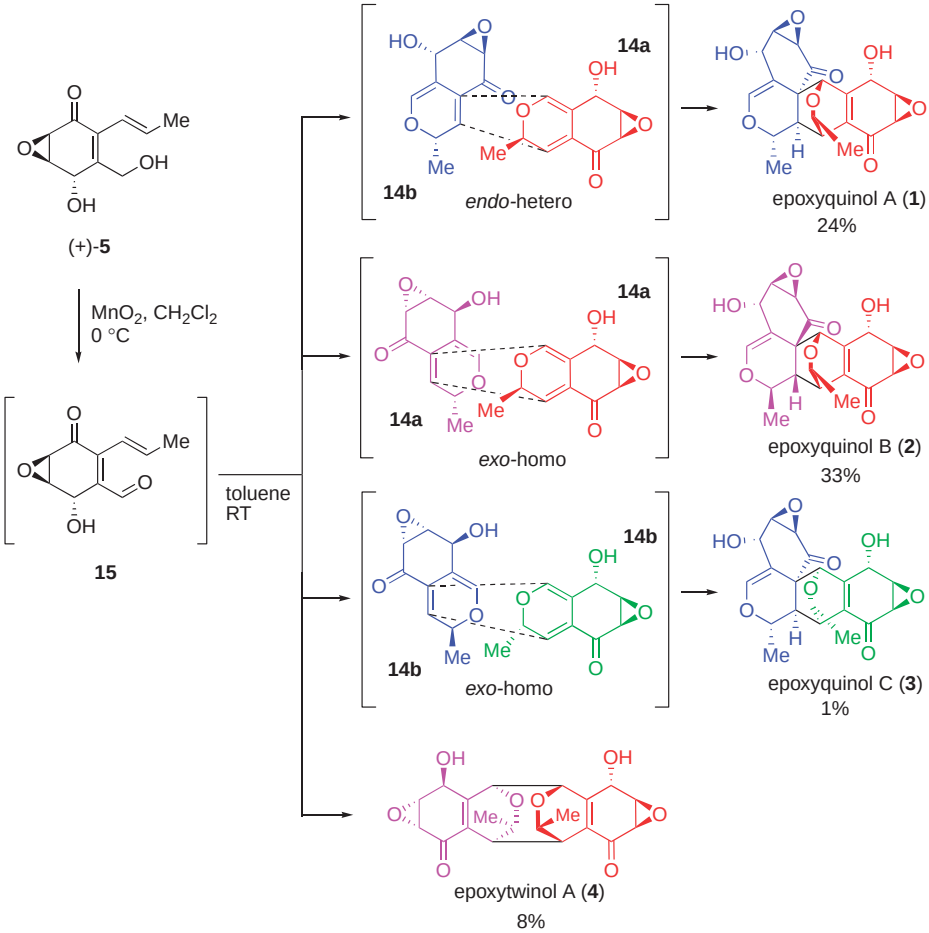
Entry	Lipase	wt %	Ratio **19**:**24**[b)]	**19**/%ee[c)]	**24**/%ee[c)]	k_{fast}/k_{slow}
1	Lipase TL	40	50:50	96	97	215
2	Lipase QL	50	53:47	85	98	128
3	Lipase QLM	50	47:53	99	95	80
4	Lipase PL	90	55:45	75	94	52
5	Lipase PS	50	83:17	19	97	32
6	Lipase SL	100	82:18	19	98	17
7	Chirazyme L-2	40	42:58	70	60	6.1

a) The reaction was performed using 0.12 mmol of (±)-**19** for 18 h at room temperature. b) The ratio was determined by ^{1}H NMR. c) Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column.

Table 3. Large Scale Kinetic Resolution Using Recovered Lipase TL[a)]

Entry	Scale/g	Time/h	Ratio **19**:**24**[b)]	**19**/%ee[c)]	**24**/%ee[c)]	k_{fast}/k_{slow}
1	8	36	49:51	99	96	211
2[d)]	14	40	49:51	99	93	201
3[e)]	21	36	49:51	99	94	195

a) The reaction was performed with 10 wt % of lipase TL. b) Determined by ^{1}H NMR. c) Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column. d) Once-recycled lipase TL was employed. e) Twice-recycled lipase TL was employed.

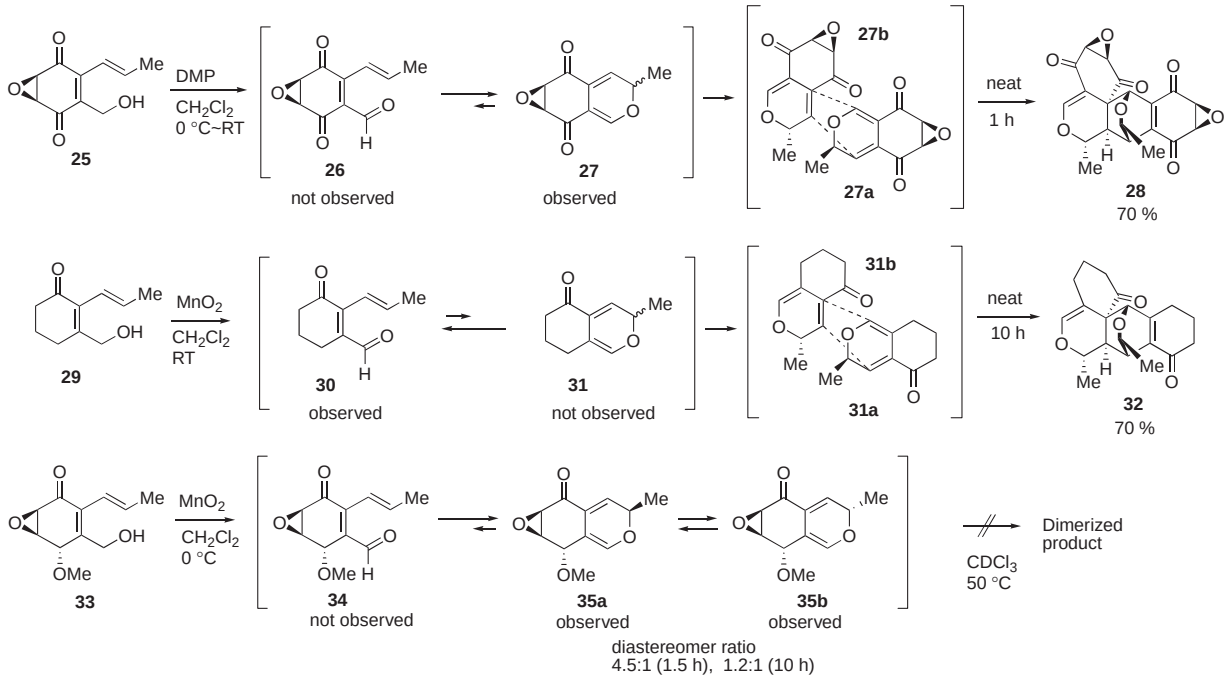


Scheme 4. Synthesis of epoxyquinols A (**1**), B (**2**), and C (**3**), and epoxytwinol A (**4**).

The absolute configuration of (+)-**19** was determined by comparison of its optical rotation with that of previously synthesized (+)-**19**, as well as by using the advanced Mosher's MTPA method.[53] Since acetate (−)-**24** was easily converted to alcohol (−)-**19** on treatment with K_2CO_3 in MeOH, affording (−)-**19** in 97% yield, both enantiomers of alcohol **19** could be synthesized in large quantities and with high optical purity. This kinetic resolution is suitable for producing both optically active cyclohexenols (+)-**19** and (−)-**19** 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.

1.5 The Biomimetic, Oxidative Dimerization of the Monomer. Because monomer (+)-**5** was available, we examined its oxidative dimerization. In order to accomplish the reaction, it is necessary to distinguish the two allylic alcohols. After several experiments, it was found that (+)-**5** could be directly oxidized without protection of the secondary hydroxy group. That is, the oxidation proceeded on treatment of 0.03 mmol of (+)-**5** with excess MnO_2 in CH_2Cl_2 at 0 °C, affording hydroxyaldehyde **15** and 2*H*-pyran derivatives **14a**/**14b**, which may be formed by 6π-electrocyclization reaction of **15** (Scheme 4). 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.[9a] Epoxyquinol A (**1**) is a heterodimer of **14a** and **14b**, which is probably generated by an *endo* intermolecular Diels–Alder reaction with the *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 **14a**, 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 jesterone dimer (unnatural product),[54] Porco, Jr. et al. have demonstrated the oxidative dimerization of epoxyquinones, in which only heterodimers form. As shown in the dimerization of (+)-**5**, not only epoxyquinones, but also epoxycyclohexenones can be oxidatively dimerized to form highly functionalized heptacyclic ring systems, in which both hetero- and homo-dimerization occur.

In order to search for other diastereomers in the crude reaction mixture, we scaled up the reaction on a 0.4 mmol scale. Since there is a large solvent effect in this oxidative Diels–Alder reaction,[22b] the investigation was performed in toluene, which predominantly afforded the more potent dimer, epoxyquinol B (**2**) (vide infra, Table 4). Dimerization proceeded in 10 h at room temperature, and the crude material was carefully purified by column chromatography, affording epoxyquinols A (**1**) and B (**2**) in 24 and 33% yields, respectively, along with epoxyquinol C (**3**) in 1% yield and epoxytwinol A (**4**) in 8% yield. Epoxyquinol C (**3**), which is known to be formed from



Scheme 5. Oxidative dimerization of dienols **25**, **29**, and **33**.

epoxyquinol A (**1**) by microwave irradiation,[14a] is a Diels–Alder adduct of 2*H*-pyran **14b**. As for epoxytwinol A (**4**), it is a formal [4 + 4] cycloaddition product of 2*H*-pyran **14a**, which gradually transformed into epoxyquinol B. In addition to the total synthesis of these four compounds, all of these compounds can be isolated from the same soil fungus. The fact that **14a** and **14b** 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.

1.6 Oxidative Dimerization of Other Dienols. Next, we prepared a few derivatives of the monomer (+)-**5** and investigated the oxidative dimerization of them. The results for the oxidation/6π-electrocyclization/Diels–Alder reaction of the monomers **25**, **29**, and **33** are summarized in Scheme 5. Though oxidation of alcohol **25** with MnO_2 did not proceed owing to the neighboring electron-withdrawing substituent, **25** was smoothly oxidized within 15 min by Dess–Martin periodinane (DMP) in $CDCl_3$. ^{1}H NMR (400 MHz) showed that 2*H*-pyran **27** formed, whereas the corresponding aldehyde **26** could not be detected, and that epoxyquinol A-type product **28** had been formed in 50% yield with some 2*H*-pyran **27** remaining. When the crude reaction mixture was left neat for 1 h, 2*H*-pyran **27** completely converted to the epoxyquinol A-type product **28** in 70% yield without formation of any other diastereomers. These results indicate that the 6π-electrocyclization is fast and that aldehyde **26** is readily converted to 2*H*-pyran **27**. The Diels–Alder reaction is also a fast process, affording epoxyquinol A-type adduct **28** in good yield. Although 2*H*-pyran **27** 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 **27** acts as a reactive dienophile in the Diels–Alder reaction.

The reaction profile of cyclohexenone monomer **29** was rather different from that of epoxyquinone **25**. Unlike epoxyquinone **25**, the oxidation of **29** proceeded efficiently with MnO_2, and the ^{1}H NMR spectrum of the reaction suggests the presence of aldehyde **30**, 2*H*-pyran **31** not being observed. Generation of the Diels–Alder adduct **32** was slow, and aldehyde **30** slowly converted into epoxyquinol A-type product **32** without detection of the 2*H*-pyran intermediate **31**. Eventually epoxyquinol A-type product **32** gradually formed in 70% yield without formation of epoxyquinol B-type product after standing aldehyde **30** neat for 10 h. These results indicate that 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 **25** and cyclohexenone **29**, is quite puzzling.

Methoxy derivative **33**, however, gave quite different results to epoxyquinol **5**. When **33** was oxidized with MnO_2, aldehyde **34**, which was not detected by ^{1}H NMR, smoothly and completely converted into 2*H*-pyran derivatives **35** in 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 **35** did not proceed even under more forcing reaction conditions, the single process of 6π-electrocyclization can be monitored in this system. The diastereomer ratio of **35** changed from 4.5:1 into 1.2:1 after 10 h. This result clearly indicates the existence of an equilibrium[23] between *anti*- and *syn*-2*H*-pyrans **35**.

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, whereas the next two reactions are dependent on the substituents. 6π-Electrocyclization and Diels–Alder reactions were separately investigated using theoretical calculations.[22b]

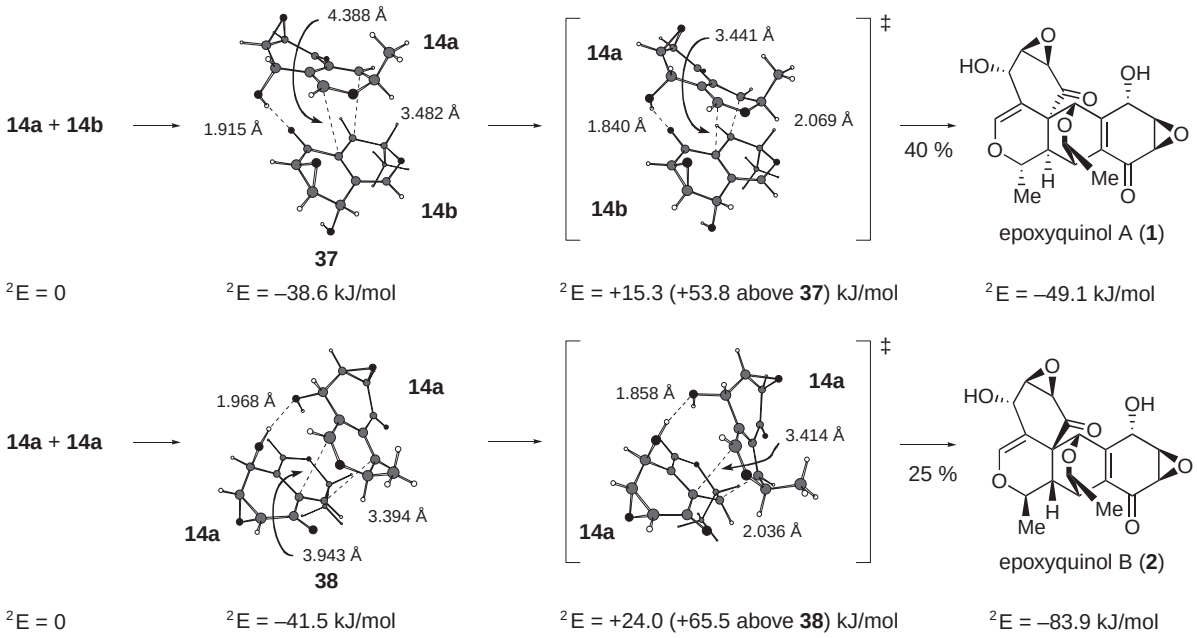
1.7 Theoretical Study of the Diels–Alder Dimerization. Theoretical calculations on the homo-Diels–Alder reaction of 2*H*-pyran indicate the regiochemistry should be one of those shown in Scheme 6 according to the frontier orbital theory.[12] For this regiochemistry, there are 16 possible reaction modes[22b] of the Diels–Alder reaction of both epoxyquinone **25** and epoxyquinol **5**. Of these, only epoxyquinol A-type dimer **28** was observed with epoxyquinone **25**, whereas both epoxyquinol A (**1**) and epoxyquinol B (**2**) were detected with epoxyquinol **5**. In the case of cyclohexenone **29**, of the eight possible reaction modes[22b] only epoxyquinol A-type dimer **32** was observed.

Calculations indicate that the orientation of the methyl groups is very important.[55] That is, the three reaction modes with the lowest TS energy form epoxyquinols A, B, and C, in which the two methyl groups are oriented on opposite sides of the approaching dienophile and diene.[22b] In other words, 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 67 kJ mol^{-1}.

Though the two 2*H*-pyran monomers **27** and **31** reacted to afford dimerized product, monomer **14** from epoxyquinol **5** was not directly transformed into the Diels–Alder products **1** and **2**. Calculations suggest that initially the two monomers **14a**/**14b** preassociate to give intermediate complexes **37** and **38**, which are more stable than the parent **14a** + **14b** and **14a** + **14a** by 38.6 and 41.5 kJ mol^{-1}, respectively. This stabilization can be ascribed to a hydrogen-bond interaction as shown in Scheme 7. The hydroxy group of **14a** coordinates the carbonyl lone pair of **14b** in **37**, at a distance of 1.915 Å, and two OHs of two different **14a**s interact with each other in **38**, at a distance of 1.968 Å. From these intermediates **37** and **38**, the dimerization proceeds to afford Diels–Alder products **1** and **2**. As the TS energies for epoxyquinols A (**1**) and B (**2**) are 53.8 and 65.5 kJ mol^{-1}, respectively, the former would be theoretically more favorable than the latter, and this is consistent with the experimental result that epoxyquinol A (**1**) predominantly formed. However, the large difference between the TS energies of the two modes (11.7 kJ mol^{-1}) is not in agreement with the experimental results, in which epoxyquinol B (**2**) also formed in 25% yield. This discrepancy could be the result of solvent effects neglected in the calculation, which would be detrimental owing to the existence of the hydrogen-bonding. The hydrogen-bonding effect occurs not only in the ground state, but also in the transition state. As shown in Scheme 7, hydrogen-bonding activates the ketone function in epoxyquinol A (**1**) formation, whereas there is hydrogen-bonding stabilization of the TS in epoxyquinol B (**2**) formation.[22b]

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 hydroxy groups has in fact been observed.[56] 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 4, epoxyquinol A (**1**) predominantly formed in neat conditions or in benzene solution, while epoxyquinol B (**2**) was the major product in toluene and CH_2Cl_2. Lewis acids, such as $LiClO_4$,[31h] 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 **29**, in which the product distribution is not affected at all by the solvent (Table 5). That is, epoxyquinol A-type product **32** was selectively obtained as the sole product, irrespective

Scheme 6. Reaction modes of 2*H*-pyran.



Scheme 7. The theoretical calculation of Diels–Alder reaction.

Table 4. Solvent Effect on the Oxidative Dimerization of **5**

Entry	Solvent[a)]	Time/h	Yield/%[b)]	
			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	MeCN	140	14	21

a) 0.05 M. b) Isolated yield.

Table 5. Solvent Effect on the Oxidative Dimerization of **29**

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 **32**.

of the solvent. Another interesting observation is that the reaction of **29** in MeOH was much faster than that in benzene, toluene, and CH_2Cl_2, while the reaction of epoxyquinol **5** was slower in MeOH than that in benzene and toluene. Hydrogen-bonding activation by MeOH, which has been observed in the reaction of **29**, cannot occur in the reaction of **5**, due to the strong intermolecular hydrogen-bonding. This is further evidence for the importance of hydrogen-bonding in the oxidative dimerization of **5**.

Moreover, the predominant formation of epoxyquinol B (**2**) in toluene is synthetically useful, because epoxyquinol B (**2**) is a more potent angiogenesis inhibitor than epoxyquinol A (**1**).[2]

The importance of the hydroxy group is also demonstrated by the Diels–Alder dimerization of the methyl ether **33**, in which there is no hydrogen-bonding interaction. It did not proceed, though the 6π-electrocyclization did (vide supra, Scheme 5). This is another piece of evidence, which supports the importance of the hydroxy group in the dimerization of epoxyquinol **5**. The steric hindrance caused by the methoxy groups of **33** would prevent the Diels–Alder reaction.

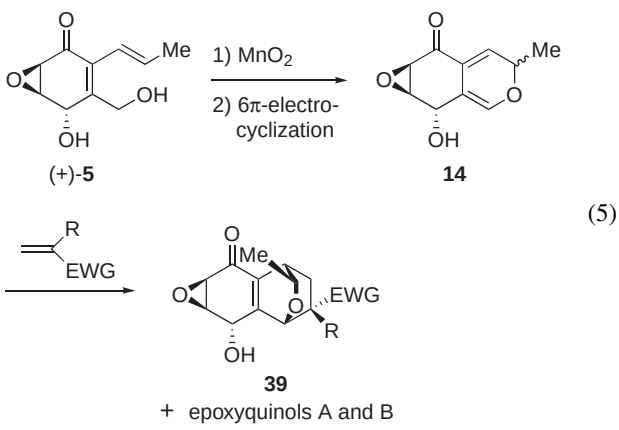
There are literature precedents, in which intermolecular hydrogen-bonding can be successfully utilized for the control of the stereochemistry of a Diels–Alder reaction.[57] In this oxidative dimerization, nature has also successfully employed hydrogen-bonding in the Diels–Alder reaction for the formation of epoxyquinol B.

1.8 The Reactivity of a 2*H*-Pyran Derivative. In the biomimetic oxidative dimerization of monomer (+)-**5**, the reactive intermediate, 2*H*-pyran **14**, is generated, which acts both as a diene and a dienophile.[2,9a] The cascade reaction of oxidation/6π-electrocyclization 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 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 (+)-**5** and cyclohexenone **29**, with and without the epoxide and a secondary hydroxy group as the monomers to investigate the reactivity of 2*H*-pyrans. The reactions using (+)-**5** and **29** were performed as follows. Alcohols (+)-**5** and **29** were oxidized with MnO_2 in CH_2Cl_2 at 0 °C and room temperature respectively for 1 h. After removal of inorganic materials by filtration, the solvent was carefully removed under reduced pressure at 0 °C to suppress the self-dimerization. Immediately after removal of the solvent, an excess of a dienophile or a diene was added to the reaction mixture, which was then stirred at room temperature.

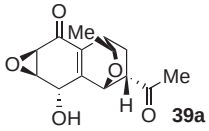
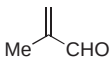
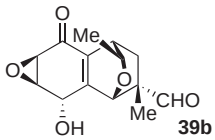
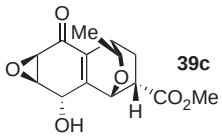
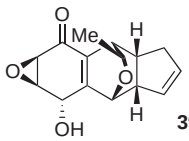
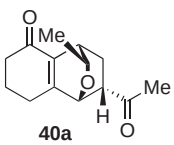
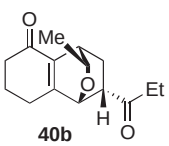
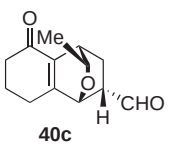
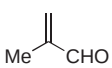
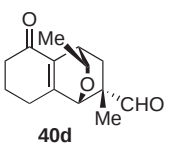
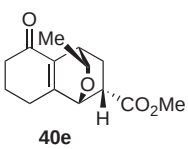
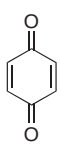
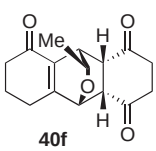
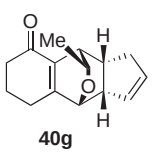
The 2*H*-pyrans **14** and **31**, acting as a diene, reacted with reactive dienophiles, such as methyl vinyl ketone, ethyl vinyl ketone, acrylaldehyde, methacrylaldehyde, methyl acrylate, and benzoquinone, affording polycyclic compounds in moderate to good yield (52–76%) along with the self-dimerized product in 10–20% yield. The results of which are summarized in Table 6.[9c] In the case of benzoquinone, isolation and characterization were performed after hydrogenolysis of the Diels–Alder adduct owing to the latter's instability. Only the *endo* Diels–Alder adducts were obtained stereoselectively in every reaction examined, and the stereochemistry of the methyl group was regulated to reduce the steric repulsion to dienophiles. Though 2*H*-pyrans **14** and **31** also reacted with maleic anhydride, acryloyl chloride, and fumaryl chloride, to provide Diels–Alder adducts quantitatively as single isomers as judged from ^{1}H NMR, attempts to isolate and characterize the products after conversion into the corresponding methyl esters were not successful. Less reactive dienophiles, such as 2-cyclohexen-1-one and 2-cyclopenten-1-one, did not react with 2*H*-pyran **31**, which instead generated the self-dimerization product **32**.[22b]

Next, the reaction with dienes was examined. Cyclopentadiene, known to be a reactive diene, reacted with 2*H*-pyrans **14** and **31** 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 diene, demonstrates the high reactivity of 2*H*-pyrans **14** and **31** as diene components.

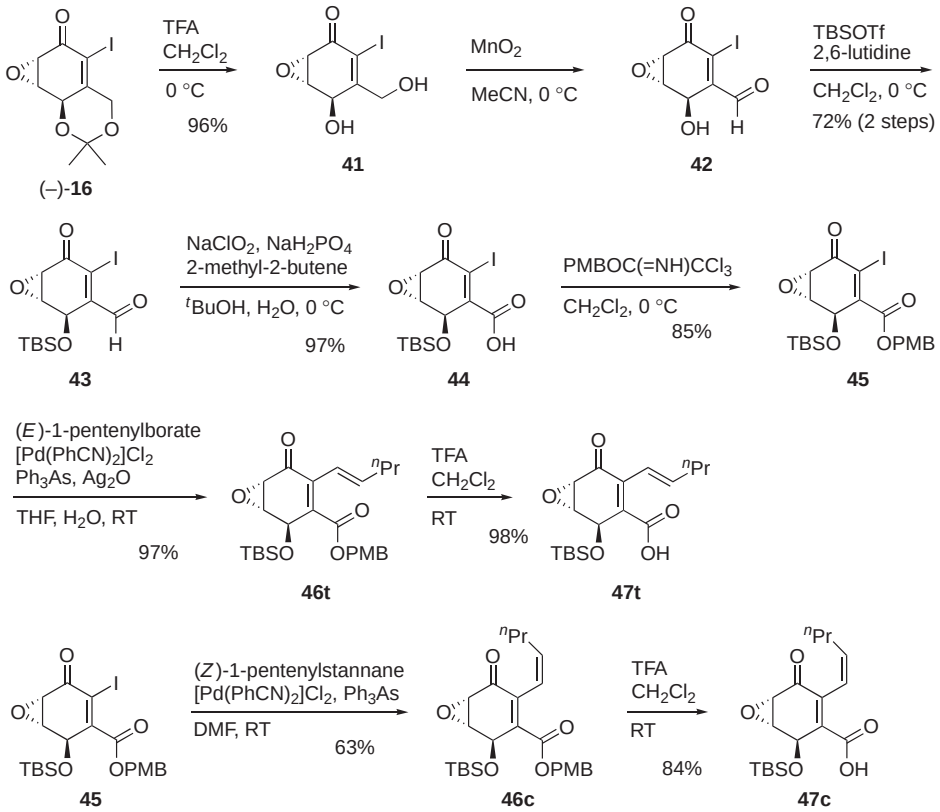


(5)

Table 6. Cascade Reaction of (+)-**5** and **29** with Several Dienophiles

Entry	Cyclohexenone	Dienophile	Product	Yield/%[a)]
1	(+)-**5**		 **39a**	64
2	(+)-**5**		 **39b**	69
3	(+)-**5**		 **39c**	56
4	(+)-**5**		 **39d**	45
5	**29**		 **40a**	76
6	**29**		 **40b**	70
7	**29**		 **40c**	52
8	**29**		 **40d**	63
9	**29**		 **40e**	66
10	**29**		 **40f**	55[b)]
11	**29**		 **40g**	49

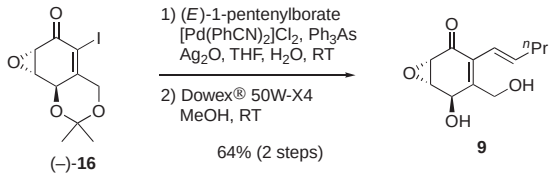
a) Isolated yield. b) **40f** was isolated after hydrogenolysis of the Diels–Alder adduct.



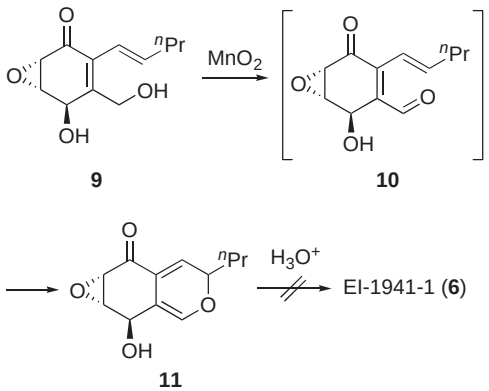
Scheme 8. Synthesis of **47t** and **47c**.

2. EI-1941-1, -2, and -3

2.1 Synthetic Study Based on Our Postulated Biosynthetic Pathway. As described in the introduction, we postulated the biosynthesis of EI-1941-1 (**6**) by the hydration and isomerization of 2*H*-pyran **11**, and we had already found that similar 2*H*-pyran **14**, generated by the oxidation of ECH (**5**), dimerized gradually under neat condition or in a rather condensed solution (Scheme 4).[9a,c,22b] We thought the vinyl ether moiety of **11** reacted with H_2O before it dimerized when 2*H*-pyran **11** was treated with acid in a dilute solution. Epoxycyclohexenol **9**, the starting material, was synthesized from the chiral iodocyclohexenone (−)-**16**,[9] an enantiomer of the intermediate of our total synthesis of epoxyquinols, by Suzuki coupling reaction with (*E*)-1-pentenylborate[58] and Ag_2O in the presence of a catalytic amount of $Pd(PhCN)_2Cl_2$ and Ph_3As,[49] followed by cleavage of the acetonide on acid treatment (Eq. 6). 2*H*-Pyran derivative **11** was isolated after oxidation of alcohol **9** with MnO_2, followed by 6π-electrocyclization. Though 2*H*-pyran **11** was treated with several acids, such as PPTS, $TsOH\cdot H_2O$, CF_3CO_2H, in several dilute aqueous solutions, a complex mixture was obtained without isolation of the desired product (Eq. 7), which prompted us to examine 6π-electrocyclization of a diene carboxylic acid derivative.



(6)



(7)

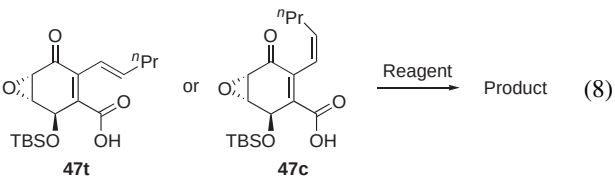
2.2 Synthesis of Carboxylic Acid Derivatives. The synthesis of carboxylic acid **47t** was started with iodocyclohexenone (−)-**16**, which is the enantiomer of the key intermediate of the total synthesis of epoxyquinols (Scheme 8).[9] Cleavage of acetonide of (−)-**16** with acid treatment gave diol **41**. Selective oxidation of the primary alcohol with excess MnO_2 in MeCN gave aldehyde **42**, the secondary alcohol of which was protected using TBSOTf and 2,6-lutidine, affording **43** in 72% yield over two steps. Oxidation of this aldehyde to the carboxylic acid was successfully performed under Kraus' conditions.[59] The carboxylic acid was protected as its *p*-methoxybenzyl ester **45** by the reaction with *p*-methoxybenzyl trichloroacetimidate[60] in 85% yield. Introduction of a side chain by Suzuki coupling reaction with (*E*)-1-pentenylborate and Ag_2O in the presence of a catalytic amount of $Pd(PhCN)_2Cl_2$ and Ph_3As afforded **46t** in 97% yield. Acid treatment then gave carboxylic

acid **47t** in excellent yield. The isomer with the (*Z*)-side chain **47c** was prepared in good yield by Stille coupling reaction using (*Z*)-tributyl-1-pentenylstannane in the presence of a catalytic amount of $Pd(PhCN)_2Cl_2$ and Ph_3As, followed by the acid treatment.

With the starting materials in hand, we investigated the 6π-electrocyclization of dienecarboxylic acid. No reaction proceeded even at reflux in toluene, the starting materials in the cases of carboxylic acid **47t** and ester **46t** were recovered. When the acid chloride, generated from carboxylic acid **47t** with oxalyl chloride and a catalytic amount of DMF, was gently heated up to 60 °C in $CDCl_3$, a complex mixture was obtained. Only decomposition occurred when the acid chloride was treated with $AlCl_3$ to generate the acylium ion.

Since all our trials via 6π-electrocyclization as a key step were unsuccessful, we pursued another synthetic route using intramolecular carboxymetallation.

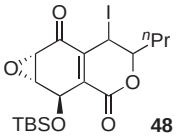
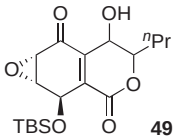
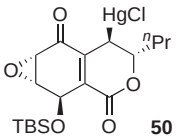
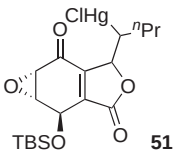
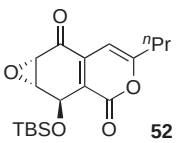
2.3 Intramolecular Carboxymetallation. Intramolecular addition of the carboxylic acid onto the alkene activated with iodine or metal salts was examined, though diastereoselectivity and alternate reaction modes, such as 6-*endo* or 5-*exo*, are possible problems with this approach (Table 7). In fact, iodolactonization proceeded in the 6-*endo* mode in low yield (Entry 1), whereas in the case of carboxymercuration using $Hg(OTf)_2$,[61] the 6-*endo* cyclized product was obtained in excellent yield as a single isomer, albeit with the incorrect relative side-chain stereochemistry at C7 in the reaction of (*E*)-isomer **47t** (Entry 2). Undesired 5-*exo* cyclization was observed in that of the (*Z*)-isomer **47c** (Entry 3). On the other hand, 7,8-dihydro-6*H*-isochromene-1,5-dione structure **52** formed when palladium(II) was used as a catalyst. That is, when **47t** was treated with *p*-benzoquinone and a catalytic amount of $[Pd(PhCN)_2]Cl_2$,[62] carboxypalladation proceeded, followed by the β-hydride elimination, affording **52** in 70% yield (Entry 4).



(8)

The remaining steps are reduction of the double bond and deprotection. Hydrogenation of **52** under an H_2 atmosphere in the presence of Pd/C or $Pd(OH)_2$ did not afford the desired lactone. As the keto group might be the cause of this reluctance to undergo hydrogenation, it was reduced with $Na[BH_4]$ in MeOH to afford alcohols **53** and **54** in 98% yield and equal amounts, which were separated by column chromatography (Scheme 9). The relative stereochemistry was determined by using the advanced Mosher's method[53] of **53**. Hydrogenation of β-alcohol **53** proceeded smoothly and stereoselectively, affording an inseparable mixture of **55** and **56** in excellent yield (95%) and with high diastereoselectivity (95:5). It should be noted that the concentration is important for the diastereoselectivity. While excellent diastereoselectivity (95:5) was obtained at 0.01 M concentration, lower selectivity (87:13) was observed at higher concentration (0.1 M).[10a,63] The mixture of **55** and **56** was oxidized with MnO_2, affording ketones **57** and **58** in 92% yield (95:5), which were easily separated by thin-layer chromatography (TLC). Though hydrogenation of α-alcohol **54** proceeded slowly, the reduced products **59** and **60** were obtained in 96% yield with the desired isomer stereoselectively (97:3). In this hydrogenation, the concentration was also crucial. Excellent diastereoselectivity (97:3) was observed at low concentration (0.01 M), in contrast to the lower selectivity (83:17) at higher concentration (0.1 M).[10a] Oxidation of alcohols **59** and **60** with MnO_2 gave **57** and **58** in 91% yield in a 97:3 ratio, and these were separated by TLC.

Table 7. Intramolecular Cyclization of **47t** and **47c**

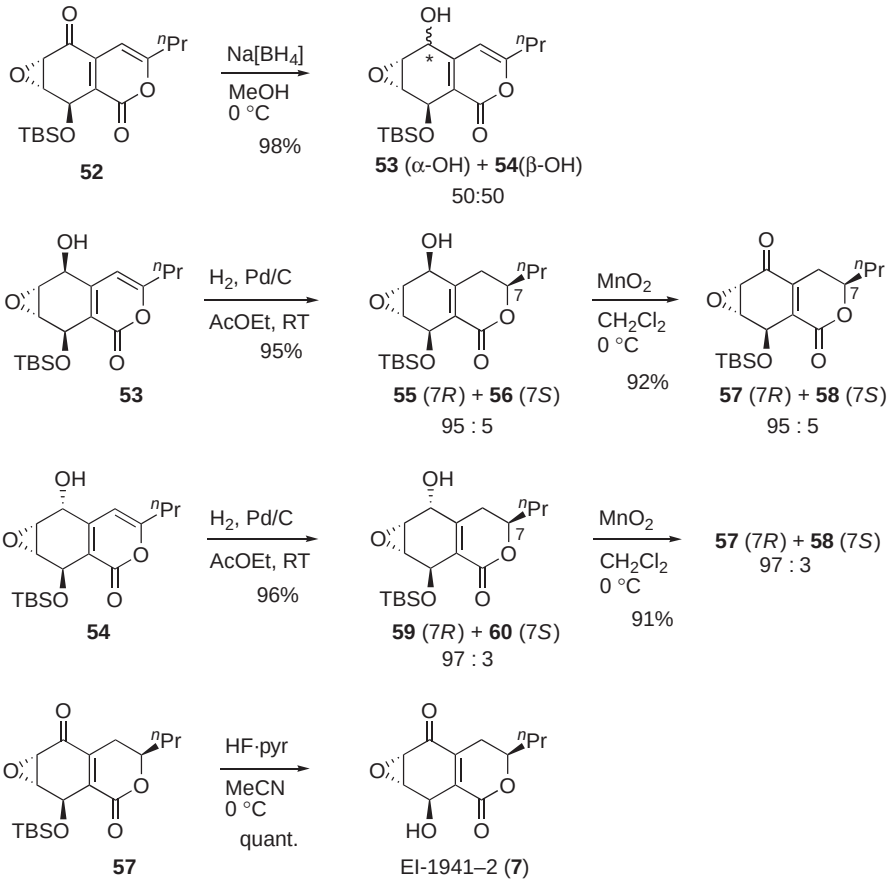
Entry	Reagent	SM[a)]	Products
1	NIS, $NaHCO_3$	**47t**	 **48** 35%
	THF/H_2O, rt, 1 h		 **49** 10%
2	1) $Hg(OTf)_2$, MS4A	**47t**	 **50** 99%
	EtCN/MeCN		
	–78 °C, 3 min		
	2) aq. NaCl		
3	1) $Hg(OTf)_2$, MS4A	**47c**	 **51** 99%
	EtCN/MeCN		
	–78 °C, 3 min		
	2) aq. NaCl		
4	$[Pd(PhCN)_2]Cl_2$[b)]	**47t**	 **52** 70%
	p-benzoquinone		
	THF, rt, 24 h		

a) Starting material. b) 0.10 molar amount was employed.

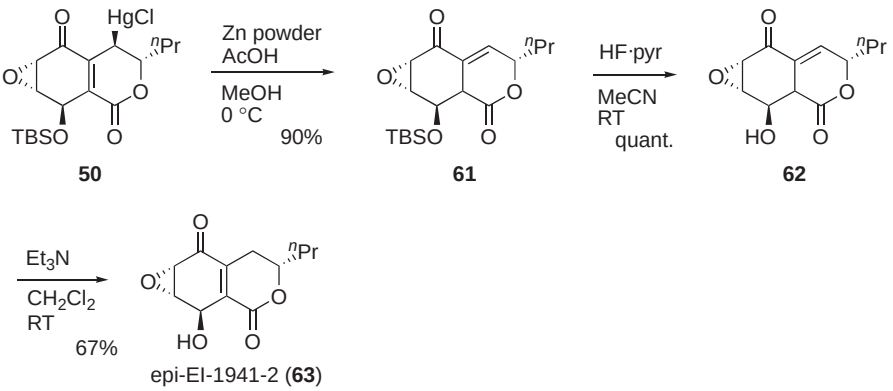
Removal of the TBS group of **57** afforded EI-1941-2 (**7**) in 86% yield. Synthetic EI-1941-2 (**7**) exhibited properties identical to those of the natural product[8b,25] including the optical rotation.

epi-EI-1941-2 (**63**) was also prepared stereoselectively from carboxymercurated derivative **50**. Though conventional demercuration using $^nBu_3SnH$ in the presence of AIBN[64] did not work, affording **47t**, we found that treatment of **50** with Zn powder in MeOH and AcOH[65] gave β,γ-unsaturated lactone **61** (Scheme 10). After removal of the TBS group, treatment with a catalytic amount of amine caused isomerization of the double bond to give epi-EI-1941-2 (**63**) in 67% yield.

2.4 Synthesis of EI-1941-1 and -3. EI-1941-1 (**6**) was synthesized from β-alcohol **55** and α-alcohol **59**, the intermediates of EI-1941-2 (**7**) (Scheme 11). When β-alcohols **55** and **56** (**55**:**56** = 95:5) were treated with DIBAL-H in CH_2Cl_2 at



Scheme 9. Synthesis of EI-1941-2 (**7**).



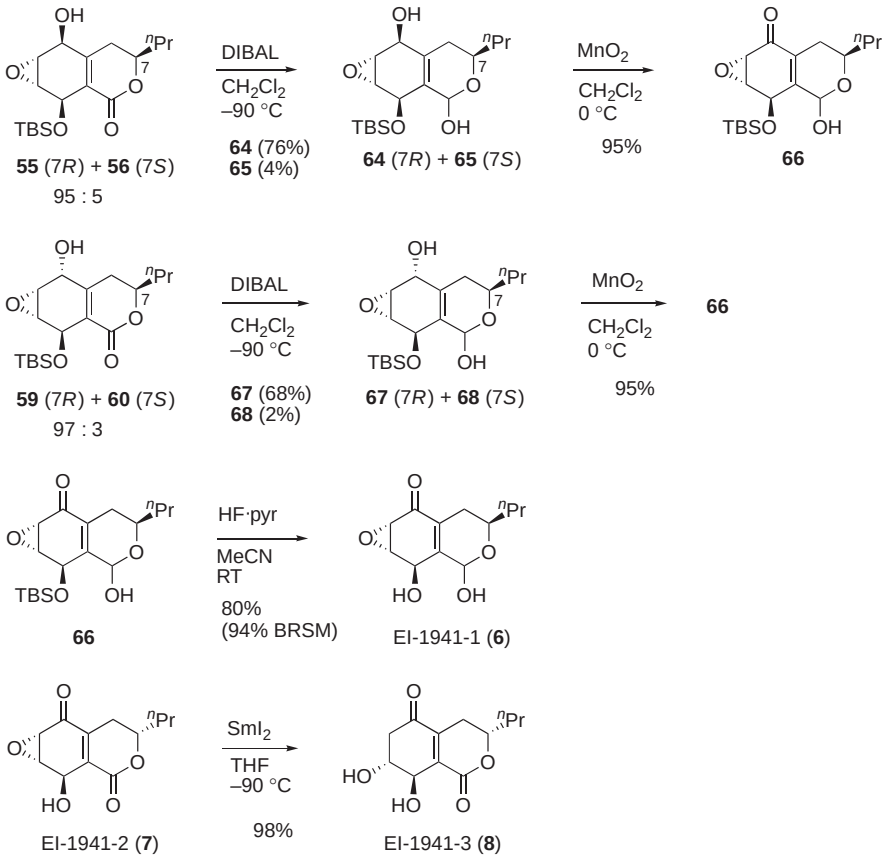
Scheme 10. Synthesis of epi-EI-1941-2 (**63**).

low temperature (−90 °C), the lactone was reduced to lactols **64** and **65** stereoselectively, which were separated by TLC (**64** 76%, **65** 4%). Oxidation of **64** with MnO_2 gave ketone **66** in excellent yield (95%). α-Alcohols **59** and **60** were also reduced with DIBAL-H to afford lactols **67** and **68**, which were separated by TLC (**67** 68%, **68** 2%). Oxidation of **67** gave the same ketone **66** in 95% yield. Deprotection with HF·pyridine afforded EI-1941-1 (**6**) in good yield.

Reduction of epoxide with SmI_2[66] at low temperature (−90 °C) cleanly converted EI-1941-2 (**7**) into EI-1941-3 (**8**) nearly quantitatively. Synthetic EI-1941-1, -2, and -3 exhibited properties identical to those of the natural products including the optical rotation, which indicate that natural enantiomers were successfully synthesized. Comparison of the optical rotation of EI-1941-3 determined its absolute stereochemistry.[10b]

3. Conclusion

The total synthesis of epoxyquinols A, B, and C and epoxytwinol A has been accomplished by a biomimetic cascade reaction. Epoxyquinols A, B, and C were synthesized by the cascade reaction consisting of oxidation/6π-electrocyclization/Diels–Alder dimerization of the monomer **5** as a key step, whereas epoxytwinol A was generated by the cascade reaction of oxidation/6π-electrocyclization/formal [4 + 4] cycloaddition reaction of monomer **5**. Monomer **5** was synthesized by two different routes. In the first, the $HfCl_4$-mediated diastereo-



Scheme 11. Synthesis of EI-1941-1 (**6**) and -3 (**8**).

selective Diels–Alder reaction of furan with an acrylate ester bering Corey's chiral auxiliary was developed, and a 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 to synthesize epoxyquinols in a large quantity but also to prepare various derivatives with different side chains via Suzuki coupling of (+)-**16** and alkenyl borates. In fact, we synthesized several monomers, the biological activity of which are under investigation.[67]

In the oxidative dimerization of epoxyquinone **25** and cyclohexenone **29**, the preferred reaction modes are epoxyquinol A-type, while both epoxyquinols A and B form in the dimerization of epoxyquinol **5**, because of intermolecular hydrogen-bonding, which has been shown to exist by theoretical calculations and several experimental results. Another noteworthy feature is that, in the dimerization of epoxyquinol **5**, monomer 2*H*-pyrans **14** preassociate to afford complexes **37** and **38**, from which the Diels–Alder reaction proceeds.

In addition, 2*H*-pyrans **14** and **31** were found to be highly reactive as dienes, and they could be used to prepare several polycyclic compounds via a Diels–Alder reaction.

We accomplished the first asymmetric total synthesis of EI-1941-1, -2, and -3, starting from the chiral epoxy iodoquinone (−)-**16**, a key intermediate in our total synthesis of epoxyquinols A, B, and C, and epoxytwinol A. A key step is the intramolecular, metal-mediated carboxylation of an alkene via 6-*endo* cyclization, in which Pd^{II} gave 2*H*-pyran-2-one via β-hydride elimination, affording EI-1941-2 after stereoselective hydrogenation, whereas $Hg(OTf)_2$ afforded a carboxymercurated product of a side-chain relative stereochemistry opposite to that of the natural product, leading eventually to epi-EI-1941-2 with high diastereoselectivity. EI-1941-1 was synthesized stereoselectively from the intermediate of EI-1941-2, and EI-1941-3 was synthesized in one step from EI-1941-2. From this asymmetric total synthesis, the absolute stereochemistry of EI-1941-3 was determined.

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