1. Introduction

The introduction of small ring systems as molecular building blocks has drawn increasing attention from preparative perspectives.1—3 Due to their inherent ring strains,4—11 interesting preparative aspects specific to these ring compounds have been developed.12 With regard to the preparative perspective, the synthesis of optically active cyclobutane ring systems is particularly important since many compounds with such ring systems not only occur in nature13,14 but are also key intermediates15—18 in the synthesis of naturally occurring or biologically important target molecules.19 On the other hand, benzocyclobutenes represent a unique class of reactive molecules because of the thermodynamic stability associated with the aromatic system and the kinetic reactivity of the strained cyclobutene ring. The o-quinodimethanes resulting from thermolysis of benzocyclobutenes have shown important applications in the synthesis of a wide range of polycyclic compounds via intermolecular and intramolecular Diels–Alder reactions.20—24 In this context, we have been studying the development of novel types of reactions including concerted ring opening reaction of chiral oxaspiropentanes to give chiral cyclobutanones, successive ring expansion–insertion reaction of olefinic vinylcyclobutanols, and pericyclic reaction of benzocyclobutenes as well as cyclohexane-fused cyclobutenes.

2. Synthesis of Chiral Cyclobutanone—Successive Asymmetric Epoxidation and Enantiospecific Ring Expansion of Cyclopropyldienes

Due to their increasing importance as chiral synths, considerable effort has been devoted to developing efficient routes to optically active cyclobutane ring systems. These include [2 + 2] cycloaddition reactions via photolytic25—32 and thermolytic33—42 processes, enantioselective alkylation,43 ring contraction of cyclic acetals,44 radical cyclization,45 and chemical46 and enzymatic47 resolution of racemates or prochiral precursors. In contrast to these well documented methods described above, there have been few studies on the asymmetric induction of the ring expansion reaction of cyclopropane rings to form cyclobutanes.48 Therefore we examined the possibility of using a catalytic process to create chiral cyclobutane rings. Our preliminary goal49 in this context involves the catalytic asymmetric epoxidation of cyclopropylidene alcohol 1 to form chiral hydroxyoxaspiropentane 2, followed by its enantiospecific rearrangement to chiral cyclobutanone 3 (Chart 1).

The preparation of substituted cyclopropyldiene alcohols 1a—i, which are substrates for asymmetric epoxidation, is straightforward. Readily available tert-butyldiphenylsilyl-(TBDDS)oxyethyl ketones 4a—i were subjected to a Wittig reaction with cyclopropyldienetriphenylphosphorane under McMurry conditions50 using tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as catalyst to give cyclopropyldieneethyl silyl...
ethers 5a—i, which upon deprotection gave cyclopropylidene alcohols 1a—i quantitatively (Chart 2). Asymmetric epoxidation of these alcohols 1a—i was then carried out at −50 °C using tert-butyl hydroperoxide (TBHP) in the presence of diethyl D-(-)- and L- (+)- tartrates [(-)-DIPT and (+)-DIPT], titanium tetraisopropoxide[Ti(OiPr)4], and 3-A molecular sieves. These results indicated that the presumed initial products 2a—i were rearranged directly to cyclobutanones 3a—i under these reaction conditions (Table 1). In all of the experiments (entries 1—12) in Chart 3 examined, this successive reaction proceeded in a highly enantioselective manner. Hence this successive asymmetric epoxidation and ring expansion proceeds with complete transfer of the chirality of the in situ generated epoxy alcohol 2, and the observed stereoselectivity can be interpreted to arise from the concerted anti 1,2-migration of the C—C bond of the cyclopropane ring to the epoxide moiety.

As typical examples of the application of this methodology, the syntheses of the following biologically important natural products are shown. The first example is the enantiocontrolled total synthesis51,52) of (+)-laurene 6, which was isolated from Laurencia species and the marine red algae Laurencia elate53) (Fig. 1). Despite the relatively simple substitution pattern on the cyclopentene ring of 6, the cis-1,2-relationship between the secondary methyl group and the p-tolyl group has made the stereoselective and enantioselective synthesis of this sesquiterpene difficult. The first enantioselective total synthesis of (+)-laurene is shown in Charts 3 and 4. Grignard reaction of (S)-2-methyl-2-(p-tolyl)cyclobutanone 7, prepared from (S)-3g, afforded the easily separable allyl alcohols 8 and 9 in yields of 59% and 24%, respectively. The diastereomeric mixture of epoxide 10, derived from 8, was treated with acid to effect ring expansion to give...

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**Table 1. Successive Asymmetric Epoxidation and Enantiospecific Ring Expansion of 1a—i**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate R</th>
<th>Tartrate</th>
<th>Yield (%)</th>
<th>(ee)</th>
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<tr>
<td>1</td>
<td>1a; Me</td>
<td>(-)-DET</td>
<td>(S) (53)</td>
<td>(89)</td>
</tr>
<tr>
<td>2</td>
<td>1a; Me</td>
<td>(+)-DIPT</td>
<td>(S) (38)</td>
<td>(93)</td>
</tr>
<tr>
<td>3</td>
<td>1a; Me</td>
<td>(+)-DIPT</td>
<td>(R) (54)</td>
<td>(92)</td>
</tr>
<tr>
<td>4</td>
<td>1b; Et</td>
<td>(-)-DIPT</td>
<td>(S) (80)</td>
<td>(96)</td>
</tr>
<tr>
<td>5</td>
<td>1c; Pr</td>
<td>(-)-DET</td>
<td>(S) (70)</td>
<td>(93)</td>
</tr>
<tr>
<td>6</td>
<td>1d; iPr</td>
<td>(-)-DET</td>
<td>(S) (73)</td>
<td>(89)</td>
</tr>
<tr>
<td>7</td>
<td>1e; Bu</td>
<td>(-)-DET</td>
<td>(S) (70)</td>
<td>(94)</td>
</tr>
<tr>
<td>8</td>
<td>1f; Bu</td>
<td>(-)-DET</td>
<td>(S) (96)</td>
<td>(91)</td>
</tr>
<tr>
<td>9</td>
<td>1g; Tol</td>
<td>(-)-DET</td>
<td>(R) (76)</td>
<td>(79)</td>
</tr>
<tr>
<td>10</td>
<td>1g; Tol</td>
<td>(+)-DET</td>
<td>(R) (75)</td>
<td>(78)</td>
</tr>
<tr>
<td>11</td>
<td>1h; Ph</td>
<td>(-)-DET</td>
<td>(R) (89)</td>
<td>(83)</td>
</tr>
<tr>
<td>12</td>
<td>1i; PMP</td>
<td>(-)-DET</td>
<td>(R) (82)</td>
<td>(73)</td>
</tr>
</tbody>
</table>

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cyclopentanone 11, which was dehydrated to give enone 12 (76% from 10). The conversion of 8 and 9 into 12 was achieved more effectively by palladium-catalyzed ring expansion.54,55) Thus silyl ethers 13 and 14 prepared from 8 and 9 in yields of 90% and 95%, respectively, were treated with PdCl$_2$(MeCN)$_2$ and $p$-benzoquinone to give enone 12 in yields of 86% and 70%, respectively (Chart 3). Since the direct hydrogenation of 12 to give the thermodynamically unstable keto 15 and its diastereoisomer 16 showed poor selectivity (89% yield, in the ratio 3:2), stereoselective conversion was achieved as follows. Reduction of enone 12 gave allyl alcohols 17 (72%) and 18 (19%). Benzoate 19, prepared by direct esterification (99%) of 18 and with inversion (98%) of chirality at the hydroxy group of 17 under Mitsunobu conditions, was converted stereoselectively into alcohol 20 (92%) by successive hydrogenation and hydrolysis. Careful oxidation (92%) of 20 followed by methylation (40%) of the resulting furnished (+)-laurene (6) (Chart 4).

This methodology for the synthesis of chiral cyclobutanone via successive asymmetric epoxidation and enantiospecific ring expansion of cyclopropylidene was further applied to the synthesis of (+)-α-cuparenone (21) and (−)-α-cuparenone (22),49) (+)-ipomeamarone (25), (+)-epipomeamarone (26), and (−)-ngaione (27).50) (−)-α-bisabolol, (28)51) (−)-alysin (29) and (−)-debroamoplysin (30),52) (−)-mesembrine (31),53) (−)-filiformin (32) and (−)-debroamoplysin (33),54) and (−)-4-deoxyverrucarol (34)61) (Fig. 2).

3. Successive Ring Expansion–Insertion Reaction

Palladium-mediated cyclization of substrates containing various unsaturated systems has provided general and versatile methods for the synthesis of both simple and complex compounds.62—64) Of these, cyclic cascade carbopalladations65—68) have gained wide acceptance and have become a rapidly growing area in synthetic organic chemistry because of their increasing synthetic efficiency. In this context, we developed a novel palladium-mediated successive reaction providing a new general route to benzo- and naphthohydrindans 37 and 38, respectively.69) The goal of this successive reaction was initiated by complexation (35a, 36a) of palladium followed by ring expansion (a) of the cyclobutanol ring to a cyclopentanone palladium complex (35b, 36b), insertion (b) of olefins (35c, 36c), and elimination (c) of palladium to give 37 and 38 (Chart 5). Thus an asymmetric total synthesis of (+)-equilenin (39) was achieved through the combination of two types of successive reactions, namely this successive ring expansion–insertion reaction and previous successive asymmetric epoxidation-enantiospecific ring expansion reaction of cyclopropylidene (Chart 6). The cyclopropylidene 41 was subjected to the first successive asymmetric epoxidation-enantiospecific ring expansion reaction using 5 mol% of (R,R)-(salen)Mn(III)complex 42 to give the chiral cyclobutanone 44 (78% ee, 55%) in one step via oxaspiropentane 43. The
chiral cyclobutanone 44 was then converted stereoselectively to the isopropenylcyclobutanol 45 by Grignard reaction with isopropenylmagnesium bromide in the presence of cerium trichloride (82%). Next, we examined various conditions to construct diastereoselectively the trans-naphthohydrindan from 45 and found that the trans-fused product 46 was selectively produced utilizing Pd(OAc)$_2$ in HMP A-THF (entry 1). Interestingly, when the solvent was changed to 1,2-dichloroethane, the cis-fused product 47 was obtained as a sole product (entry 2). These remarkable effects indicate that solvent polarity is an important factor to control the diastereoselectivity of products. Thus in polar solvent such as HMP A, the ring expansion reaction has been suggested to proceed via intermediate TS A to give 46, in which palladium was associated with only olefin because solvent itself associated to palladium as a ligand. In contrast, in non-polar solvent such as 1,2-dichloroethane, the reaction seems to proceed via TS B to give 47 (Fig. 3). To complete the synthesis of equilenin, the mixture of 46 and 47 was treated with osmium tetroxide and sodium periodate to furnish diketone 48 after the separation of its diastereomer (59% from 46 prepared by entry 1). Finally, the selective reduction of the benzylic ketone of 48 was carried out to give 49, which could be obtained in optically pure form after recrystallization. Since 49 has been converted to 39, our asymmetric synthesis of (+)-equilenin (39) was achieved.

This type of palladium-mediated successive reaction was extended to the insertion–ring expansion reaction of allenylcyclobutanol having halogenoalkene. Thus we found a novel unprecedented type of intramolecular carbopalladation of allenes, in which the ring tranformation of the π-allylpalladium B in situ generated by the intramolecular carbopalladation of A is accompanied by the strain release of the cyclobutane ring to give directly the fused bicyclic[\(n+3.3.0\)]ring system C (Chart 7). This sequential process provides a unique entry into the biologically impotant natural products having 5,7- and 5,8-fused ring frameworks.

4. Pericyclic Reaction

4.1. Total Synthesis of Steroid

Since our first introduction of intramolecular cycloadditions of o-quinodimethane 51, generated in situ by thermolysis of the corresponding benzocyclobutene 50, for the total synthesis of estrane type of steroid 52, the related approaches for other steroids have been developed extensively by several groups (Chart 8). In connection with this approach, the first
asymmetric total synthesis of (+)-chenodeoxycholic acid (55) was achieved via D-trienic steroid 54 by the intramolecular cycloaddition of the o-quinodimethane 53 as a key step (Chart 9). Then, we have been involved in developing more flexible and efficient routes to both aromatic and non-aromatic steroids than those of Charts 8 and 9. Thus the route was planned on the basis of the reaction sequence outlined in Chart 10. In this route, the trans-benzoperhydroindane 58 was set as a key compound for preparing either A-trienic or non-aromatic steroids (59 or 60, respectively) by easy manipulation of its benzene ring. In turn, 58 could be accessed by intramolecular cycloaddition of the o-quinodimethane 57, generated in situ by thermolysis of benzocyclobutene 56 (Chart 10).

As a typical example of the application of this methodology, the synthesis of (+)-19-norspironolactone 61 is shown as follows. Our synthetic strategy for 61 is characterized by the one step creation of B, C, D, and E rings (63 or its precursor 65) in a stereoselective manner via intramolecular [4+2] cycloaddition of the o-quinodimethanes 64 or 66, and then A-ring formation (63→62) followed by functionalization of the C-7 position (62→61) (Chart 11). This is in contrast to the traditional methods where in the spiranolactone ring is created by manipulation of the preformed C-17 keto steroids. As a preliminary investigation, the thermolysis of olefinic γ-lactone 67, its thioacetal 68, and disiloxane 69 (Fig. 4), all of which had ring E of 61 or its equivalent, was carried out and the results are summarized in Table 2. These results show that all of these reactions proceed with high stereoselectivity, leading to the preferred formation of the trans-anti isomers 70, 73, and 76 rather than the trans-syn isomers 71, 75, and 79. None of the cis-anti isomers 72, 76, and 80 and cis-syn isomers 73, 77, and 80 was detected. Thus it seems possible that the high stereoselectivity for trans-anti isomers might reflect the severe steric interactions present in the endo transition states T3 and T4 and the exo transition state T2 relative to the exo transition state T1 (Fig. 5). The syn or anti selectivity is strictly controlled by the bulk of position 1 or 4 (for 67 and 68) and position 1 or 8 (for 69) and not affected by the bulk at position 2 to a detectable degree, despite large steric bulk (1,2-dithiane ring for 68 and diisopropylsilyl group for 69) (Fig. 4). Thus we could obtain information

Chart 9. Synthesis of (+)-Chenodeoxycholic Acid (55)

Chart 10. Synthesis of Steroid via trans-Benzoperhydroindane

Chart 11. Synthetic Strategy for 19-Norspironolactone (61)

Fig. 4. Substrates for Preliminary Study of Thermolysis
about the stereochemical course of the cycloaddition reactions of the olefinic \( \alpha \)-quinodimethanes \( 63 \) that have unsymmetrically substituted tertiary chiral centers. On the basis of these results, our efforts were then directed toward the cycloaddition reaction of the olefinic \( \alpha \)-quinodimethanes \( 66 \) that have a cyclobutane ring with various substituents (X). It was expected that the bond having a bulky substituent (X) on the cyclobutane ring in the product \( 65 \) would be \( \text{syn} \). Thus the cyclobutanone acetals were suitable candidates for this steric demand. Furthermore, the functional group is versatile and suitable for further synthetic transformation to spirolactones. Thermolyses of these cyclobutanone derivatives \( 82a\text{---}i \) (Fig. 6) were conducted in refluxing \( \alpha \)-dichlorobenzene. Table 3 summarizes the distribution of the products for each substrate.

The total synthesis of 19-norspirotonolactone (61) was completed as follows. The tetracyclic cyclobutanone \( 65a \) was prepared in stereoselective manner by thermolysis of the
olefinic cyclobutanone acetals (the best yield for trans-syn isomer is shown in entry 8) followed by acid treatment. This cyclobutanone was subjected to Baeyer–Villiger oxidation to give the lactone 71. The lactone 71 thus obtained was converted into the enone 86 (65%) whose reductive alkylation followed by dehydrogenation gave the enone 87 (45%). Acid treatment of 88, which was prepared from 87 in two steps (82%), furnished the pentacyclic dienone, 19-norcanrenone (62) (54%). Since 19-norcanrenone (62) has already been converted into 19-norspironolactone (61), this work constitutes a formal total synthesis of 19-norspironolactone (61) (Chart 12). This methodology was further applied to the syntheses of 19-nordeoxycorticosterone (89),85) cortisone (90),86) adrenosterone (91),87) 11-oxoprogesterone (92),88) and 1α,25-dihydroxyvitamin D3 (93)89) (Fig. 7).

4.2. Synthesis and Medicinal Chemistry In our ongoing efforts on the short-step synthesis of a model core structure associated with halenaquinone and related natural compounds,90) we revealed that the furan-fused tetracyclic compound 94, which was concisely synthesized on the basis of o-quinodimethane chemistry (Chart 13), possesses a notable antiviral activity. This new finding inspired us to examine the structure–activity relationships of its congeners, aiming at the discovery of new candidates for antiviral drugs.91) As a preliminary study, the antiviral activity was surveyed using the assay method of hemagglutinin (HA) titers.92) HVJ in LLC-MK2 cells was used for the assay, and the inhibitory activity on the virus growth was assessed as minimum inhibitory concentrations (MIC), which are summarized in Fig. 8. Cytotoxic assay of several compounds was performed by MTT method,93) and the results are summarized as the maxi-

### Table 3. Product Ratio and Yield of Thermolysis of 82a—i

<table>
<thead>
<tr>
<th>Product ratio</th>
<th>Yield (%)</th>
<th>Product ratio</th>
<th>Yield (%)</th>
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<tr>
<td>65 : 83 : 84 : 85</td>
<td>97</td>
<td>65 : 15 : 20 : 0</td>
<td>82</td>
</tr>
<tr>
<td>60 : 21 : 19 : 0</td>
<td>73</td>
<td>62 : 13 : 25 : 0</td>
<td>75</td>
</tr>
<tr>
<td>59 : 23 : 18 : 0</td>
<td>97</td>
<td>61 : 20 : 19 : 0</td>
<td>90</td>
</tr>
</tbody>
</table>

Fig. 7. Other Steroids Synthesized via A-Nor, B-Trienic Steroids

Chart 12. Synthesis of 19-Norspironolactone (61)
mum cytotoxic concentrations (MCC) as shown in Fig. 9. Thus we could find several derivatives having more potent anti-viral activity than the lead compound 94, and especially, the TIPS derivative 99 was revealed to have the lowest MIC value and good therapeutic index. These results prompted us to investigate the possibility of revealing dihydrofuran-fused compounds as a new class of anti-influenza agents possessing a novel structural characteristic. Initially, we examined the inhibitory activity of the test compounds (94, 99–108, Fig. 10) against viral growth in Madin–Darby canine kidney (MDCK) cells using influenza A/Aichi/2/68 (H3N2 subtype) virus strain at 10 mM drug concentration. The virus yields as a percent of control were estimated by a plaque titration method and the results are shown in Fig. 11, including amantadine as positive control (PC). This survey disclosed that several compounds inhibited the virus growth and could have potential as new anti-influenza agents. In particular, compounds 102, 106, and 108 exhibited potent activity, suppressing the virus proliferation up to ca. 30% of control, and consequently these three compounds were subjected to examinations of cytotoxicity. Thus the cytotoxic activity was evaluated by the standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay method, and the OD (optical density) values for 24-h cultured MDCK cells after treatment with 100 mM or 200 mM of the test compounds are summarized in Table 4. These results indicate that these compounds do not exhibit any direct cytotoxicity, at least at 100 mM drug concentration, and are expected to have good safety indexes. The scope of applicability of the compounds was investigated using a variety of influenza...
virus strains, including A/PR/8/34 (H1N1), A/USSR/92/77 (H1N1), A/NWS/33 (H1N1), B/Lee, and B/Singapore/222/79. As shown in Fig. 12, it was found that these compounds were effective for both influenza A and B type viruses, implying that the mechanism of action differs from that of amantadine. These data suggest that the series of dihydrofuran-fused perhydrophenanthrenes investigated in this study are likely to have a broad spectrum of anti-influenza activity and may be useful for the management of outbreaks with pandemic potential. To investigate the mode of action, several experiments were performed using compound 102 as representative. At first, the time-related effect of the test compound was investigated, including a comparison among the drug treatments initiated at various times post-infection. The results, shown in Fig. 13, indicate that anti-influenza effect was observed only when drug treatment was initiated within 1 h post-infection, and the virus yields were comparable to that of control culture in the cases of 2 h or later after virus infection. These observations suggest that the drug affects influenza virus growth at a relatively early stage in the replication process. In the light of the time-related effect above described, we investigated whether mRNA synthesis occurred after drug treatment. The experiments were performed by isolation of RNA from MDCK cells infected with influenza A/Aichi/2/68 virus, reverse transcription, followed by PCR and electrophoresis, and the results are shown in Fig. 14. Low pH environments in endosomes and lysosomes are known to play an important role in the uncoating process of viral RNA during influenza infection. For example, bafilomycin A1 has been reported to exert inhibitory effects on influenza virus growth through specific inhibition of vacuolar-type proton pump to raise the pH in endosomes and lysosomes. To examine whether drug 10 could exert a similar effect, acidification of intracellular compartments under influence of the drug was monitored by vital fluorescence microscopy with acridine orange. This examination revealed that the amount and intensity of fluorescence in the drug-treated cells were almost identical with the control cells, implying that the drug did not affect the acidic environment of intracellular compartments, which causes the uncoating process. Although further studies may be necessary to elucidate a conclusive mechanism of action, we overall consider that the dihydrofuran-fused perhydrophenanthrenes investigated in this study exhibit anti-influenza activity by affecting a process of mRNA synthesis. Thus we disclosed that dihydrofuran-fused perhydrophenanthrenes could have potential for a new type of anti-influenza agent. Novel structural features of these compounds may serve for a new therapeutic option against influenza infections. Broad generality of the synthetic method to the core structure by means of the o-quinodimethane chemistry will facilitate preparation of a wide variety of analogous derivatives, which can contribute further in-depth SAR considerations.

### Table 4. MTT Assay for Evaluation of the Direct Cytotoxicity

<table>
<thead>
<tr>
<th>Compound</th>
<th>OD value</th>
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<tr>
<td></td>
<td>100 µM</td>
</tr>
<tr>
<td>102</td>
<td>1.018±0.044</td>
</tr>
<tr>
<td>106</td>
<td>1.035±0.054</td>
</tr>
<tr>
<td>108</td>
<td>1.010±0.066</td>
</tr>
<tr>
<td>Control</td>
<td>1.071±0.050</td>
</tr>
</tbody>
</table>

### 4.3. Novel Reaction Mode and Substituent Effect

The facility of the thermally allowed conrotatory 4π-electrocyclic ring opening of cyclobutenes is known to depend on the electronic nature of the substituents on the cyclobutene...
In the course of our study of the substituent effect on this reaction, we disclosed the exceptionally facile ring opening reaction of cyclobutenes, facilitated by arylsulfinyl, arylsulfonyl, and diphenylphosphinyl carbanion. The systems chosen for study were the (aryl-sulfinyl), (arylsulfonyl), and (diphenylphosphinyl)methylcyclobutenes, dienes generated from them constituting an essential part of the skeleton of the vitamin D series. All the reactions were carried out in THF at 78 °C for 10 min using n-butyllithium as base and were found to proceed in moderate to high yields to give the initial products together with the double [2,3] sigmatropic rearrangement products in case of entries 5 and 7, respectively (Table 5, Chart 15). A very attractive feature of this method of diene generation is that alkylation of involving essentially the same conditions as above, n-BuLi/THF, can be carried out at −78 °C, at which temperature the butene ring remains intact. Thus compounds and were obtained in almost quantitative yields by using 1.2 eq of n-butyllithium and 1.2 eq of methyl iodide.

In the course of our continuous research on o-quinodimethane chemistry, we focused our interest on the substituent effect for the thermal cleavage of benzocyclobutenes, especially on the silyl substituents in conjunction with recent reports on their rate enhancement effects for that of monocyclic cyclobutenes. The compounds and were conducted to thermal electrocyclic reaction involving concurrent [4+2] cycloaddition with maleic anhydride. Three different conditions were applied to each compound, to estimate and compare the reaction efficiencies, in the presence of an excess amount of the dienophile (Chart 16). As shown in Fig. 15, when compound was subjected to condition A (toluene, reflux, 24 h), only a small amount of adduct was formed (9% yield). Likewise, compound afforded in only 30% yield. On the other hand, a notable acceleration of the reaction was observed for the b-silylated benzocyclobutene , which gave adduct in 68% yield under the same conditions. A similar effect of the silyl group was also noticed under condition B (xylene, reflux, 3 h), in which compound gave a nearly quantitative yield of as compared with resulting in low-to-moderate yields. Under the more drastic condition C (o-dichlorobenzene, reflux, 2 h), all three substrates were almost transformed into adduct, although a slight difference was observed among the yields. The products were formed as a purely single stereoisomer, depicted in Chart 16. This result showed that the reaction proceeded through the formation of the o-quinodimethane having the indicated geometry followed by endo cycloaddi-
tion with the dienophile (Chart 16), in consideration of a strong preference of maleic anhydride for endo addition and reported torquoselectivity of benzocyclobutenes. The same experiments were repeated using compounds 113a—c as substrate, and a similar acceleration effect of the β-silyl group was confirmed as shown in Fig. 15. The stereochemical outcome of the adducts 115a—c was again dictated by the outward torquoselectivity of the substituent R, affording the same stereoisomer as 114a—c, as a major product, concomitant with a small amount of the diastereomer (R=β-configuration, ratio 1/10 to 1/15). In every case, no side-reactions were involved and the starting benzocyclobutenes remained unchanged when the reactions were incomplete. In addition, 1,5-sigmatropic rearrangement of the o-quinodimethane to give a toluene derivative, which often competes with the Diels–Alder reaction, could not be observed at all. These observations indicate that the Diels–Alder trap was so suffciently rapid that the yields shown in Fig. 15 could reflect the efficiency of the electrocyclic ring opening of the benzocyclobutene derivatives. It is an important note that the structural difference between 112b (113b) and 112c (113c) is only the kind of β-element, carbon or silicon, minimizing a steric factor on the reaction. Thus we can consider that the β-silyl substituent on the benzocyclobutene ring causes a significant acceleration effect on the electrocyclic reaction. A rationale of the acceleration effect of the β-silyl substituent on the electrocyclic reaction yet remains unclear, but we assume that the present acceleration effect can be attributed to the s-donating ability of the C(α)–Si(β) bond, which is associated with the so-called β-effect of a silicon atom. Next, we performed an analogous examination utilizing simple, nonbenzo-type cyclobutene derivatives 116a and 116b. As shown in Chart 17, the substrate 116a gave a ring-opened diene product 117a only in 19% yield after 1 h in refluxing toluene, whereas the corresponding β-silyl substrate 116b afforded a diene 117b in 61% yield under the same condition. These results clearly indicate that the accelerating effect of a β-silyl element can have wide generality for the electrocyclic ring cleavage reaction of various cyclobutene derivatives.

Along with this substituent effect on 4π-electrocyclic ring opening of cyclobutenes, we disclosed notably facile and mild transformation of benzocyclobutenones to 2,3-benzodiazepines, which is a biologically important heterocyclic core structure, through nucleophilic addition of a diazomethylene anion followed by a cascade electrocyclic reaction sequence involving a formal and net diazomethylene insertion into the cyclobutene ring. Our strategic outline is illustrated in Chart 18, representing stepwise transformations with three running reactions. The initial nucleophilic addition of diazomethylene anion to benzocyclobutenone 118 provides an alkoxide 119, which may easily undergo oxygen-accelerated electrocyclic ring-opening reaction at low temperature to generate o-quinodimethane 120. Strong preference for outward rotation of the oxide group can dictate the geometry of 120, in which the diazo function lies at a favorable position for the next electrocyclization. Formal 8π-electrocyclization of 120 will be promoted by the reconstruction of the stable benzene ring to furnish the 2,3-benzodiazepine derivative 122 via its enolate form 121 (Chart 18).

Initially, lithiated (trimethylsilyl)diazomethane was examined as a nucleophile, and several substituted benzocyclobutenones (118a—d) were subjected for the reaction (Chart 19). (Trimethylsilyl)diazomethane was treated with n-BuLi in THF at −78 °C, and to the resulting solution, the benzocyclobutenone (118) was added at the same temperature. After that, the cooling bath was immediately removed to allow the reaction to warm up to ambient temperature for 1 h. Gratifyingly, in all cases (substrates 118a—d), clean conversion was observed to result in the formation of 2,3-benzodiazepine-5-ones (122a—d) in high isolated yields (Table 6, entries 1—4). We consider that the present reaction proceeded through the tandem electrocyclic reactions depicted in Chart 18.

Although there have been several reports on 1,2-diazepine synthesis, including benzodiazepines, via an analogous 1,7-electrocyclization of diazo compounds, all of these require thermal activation and often suffer from predominant pyrazole formation via 1,5-cyclization. In our reaction system, on the other hand, high reactivity and geometrical fixation of the quinodimethane intermediate are responsible for the efficient transformation under the extraordinarily mild conditions, which have not been reported in the similar diazepine synthesis, to the best of our knowledge.

The other diazomethylene anion such as lithiated diazoacetate was demonstrated to work well for the diazepine-form-
The usefulness of small ring compounds for the syntheses of various pharmacologically important compounds and the novel reaction modes specific to these ring systems have been demonstrated. These findings may further serve as a means for the development of new reactions and synthetic methodologies.

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**References**