Review

Synthetic Organic Chemistry Based on Small Ring Compounds

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Small ring systems are important topics in both organic and inorganic chemistry, and draw considerable attention from both theoretical and preparative perspectives. This review intends to summarize the studies, focusing on the preparative aspects, that have been carried out in our laboratory. Namely, synthesis of (+)- and (−)-α-cuparenone, (+)-ipomeamarone, (+)-epiipomeamarone, (−)-ngaione, (−)-α-bisabolol, (−)-aplysin, (−)-debromoaplysin, (−)-mesembrine, (−)-filiformin, (−)-debromofiliformin, and (−)-4-deoxyverrucarol *via* successive asymmetric epoxidation and enantiospecific ring expansion of cyclopropylidenes, (+)-equilenin *via* successive ring expansion–insertion reaction, estrone, estradiol, chenodeoxycholic acid, 19-norspironolactone, 19-nordeoxycorticosterone, cortisone, adrenosterone, 11-oxoprogesterone, and 1α,25-dihydroxyvitamin D3 *via* intramolecular cycloaddition reaction of *o*-quinodimethanes. Medicinal chemistry aiming at developing a new type of anti-influenza agent, novel reaction mode of electrocyclic reaction, and substituent effect on that reaction are also discussed.

Key words small ring compound; pericyclic reaction; medicinal chemistry; concerted reaction; ring expansion; anti-influenza agent

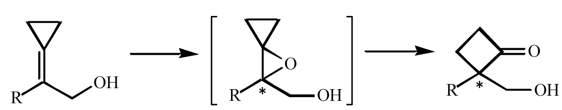
1. Introduction

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 nature[13,14] but are also key intermediates[15—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 Cyclopropylidenes

Due to their increasing importance as chiral synthons, considerable effort has been devoted to developing efficient routes to optically active cyclobutane ring systems. These include [2+2] cycloaddition reactions *via* photolytic[25—32] and thermolytic[33—42] processes, enantioselective alkylation,[43] ring contraction of cyclic acetals,[44] radical cyclization,[45] and chemical[46] and enzymatic[47] 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 goal[49] 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 cyclopropylidene alcohols **1a**—**i**, which are substrates for asymmetric epoxidation, is straightforward. Readily available *tert*-butyldiphenylsilyl-(TBDPS)oxymethyl ketones **4a**—**i** were subjected to a Wittig reaction with cyclopropylidenetriphenylphosphorane under McMurry conditions[50] using tris[2-(2-methoxyethoxy)ethyl-amine (TDA-1) as catalyst to give cyclopropylideneethyl silyl



1 **2** **3**

Chart 1. Chiral Cyclobutanone from Cyclopropylidene Alcohol

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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(O*i*Pr)$_4$], 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 synthesis[51,52] of (+)-laurene (**6**), which was isolated from *Laurencia* species and the marine red algae *Laurencia elate*[53] (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[49] from (*S*)-**3g**, afforded the easily separable allyl alcohols **8** and **9** in yields of 59% and 24%, respectively. The diastereoisomeric mixture of epoxide **10**, derived from **8**, was treated with acid to effect ring expansion to give

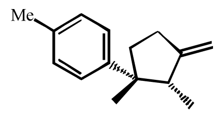

Fig. 1. (+)-Laurene

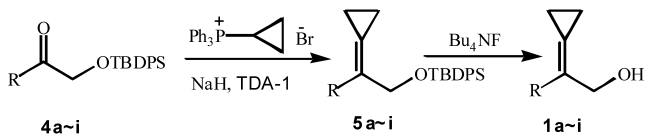

Chart 2. Synthesis of Cyclopropylidene Alcohol

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

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

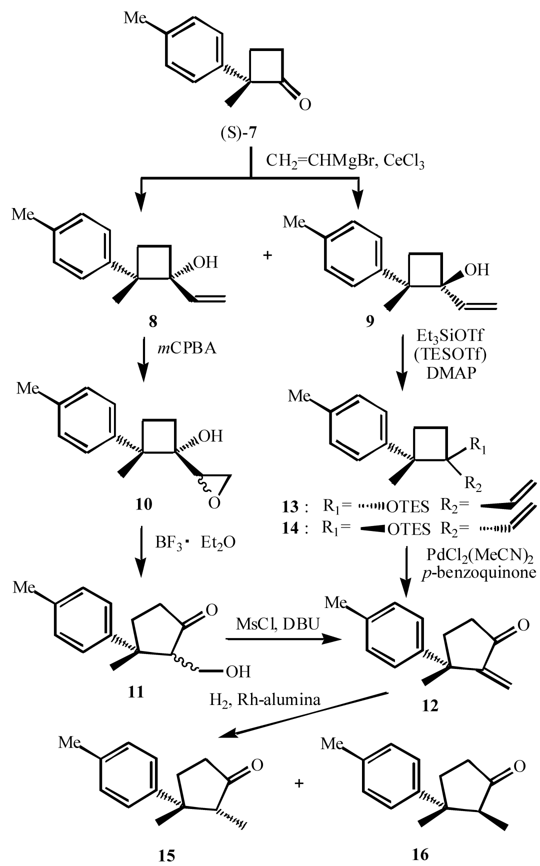

Chart 3. Synthesis of (+)-Laurene-1

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Hideo Nemoto

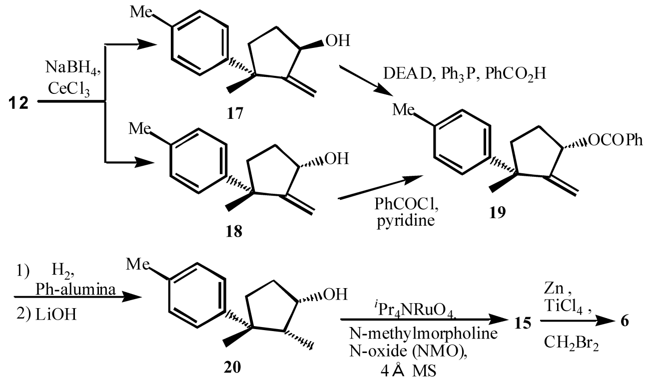


Chart 4. Synthesis of (+)-Laurene-2

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 a catalytic amount of $PdCl_2(MeCN)_2$ 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 ketone **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 methylenation (40%) of the resulting **15** 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**), (+)-epi-ipomeamarone (**26**), and (−)-ngaione (**27**),[56] (−)-α-bisabolol, (**28**)[57] (−)-aplysin (**29**) and (−)-debromoaplysin (**30**),[58] (−)-mesembrine (**31**),[59] (−)-filiformin (**32**) and (−)-debromofiliformin (**33**),[60] 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 carbopalladations[65—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

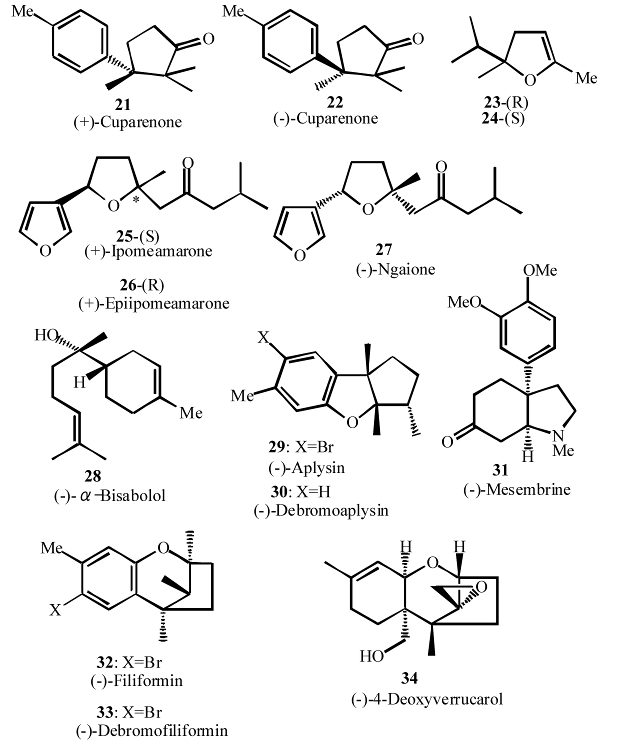


Fig. 2. Other Natural Products Synthesized *via* Successive Asymmetric Epoxidation and Ring Expansion Reaction

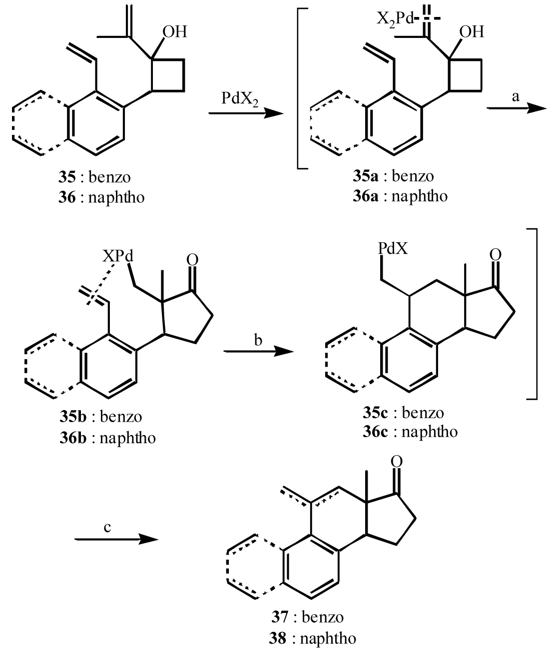


Chart 5. Successive Ring Expansion–Insertion Reaction

(+)-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 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

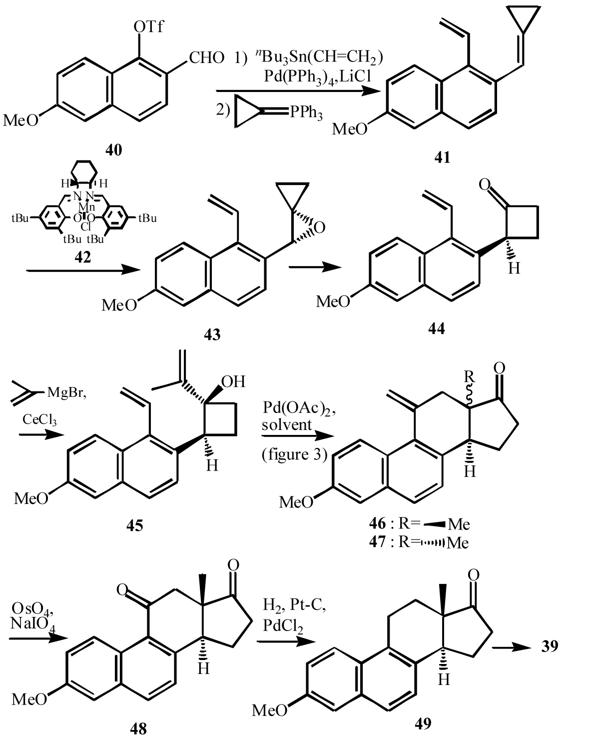


Chart 6. Synthesis of (+)-Equilenin (**39**)

Run	solvent	**46 : 47**	% yield
1	HMPA - THF (1 : 4)	73 : 27	60
2	CH_2ClCH_2Cl	0 : 100	63

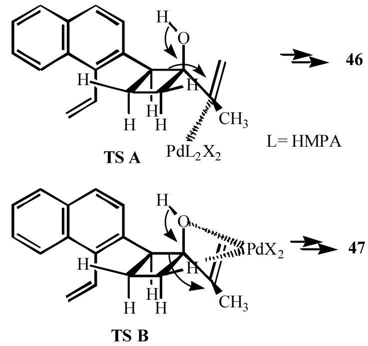


Fig. 3. Solvent Effect on the Ring Expansion Reaction

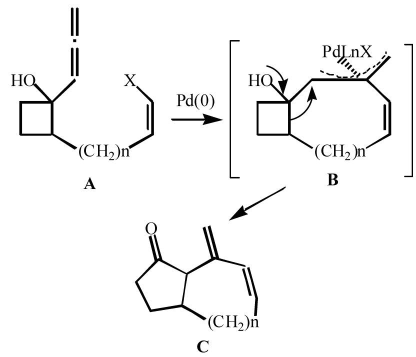


Chart 7. Sccessive Reaction of Allenylcyclobutanol

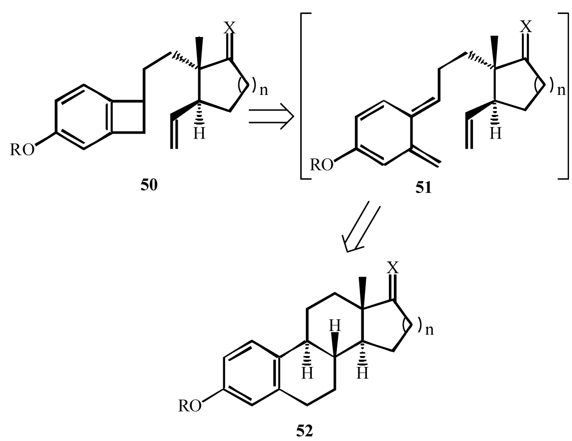


Chart 8. Synthesis of Estrane Type of Steroid

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 HMPA-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 HMPA, 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**,[70] 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 bicyclo[n+3.3.0]ring system **C** (Chart 7).[71] This sequential process provides a unique entry into the biologically impotant natural products having 5,7-[72] and 5,8-fused ring frameworks.[73]

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**,[74—76] the related approaches for other steroids have been developed extensively by several groups (Chart 8).[77—79] In connection with this approach, the first

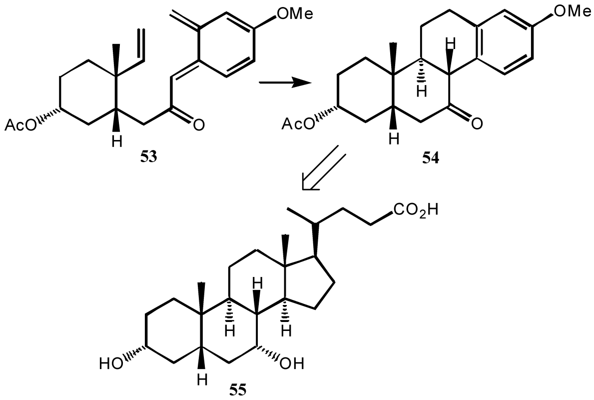


Chart 9. Synthesis of (+)-Chenodeoxycholic Acid (**55**)

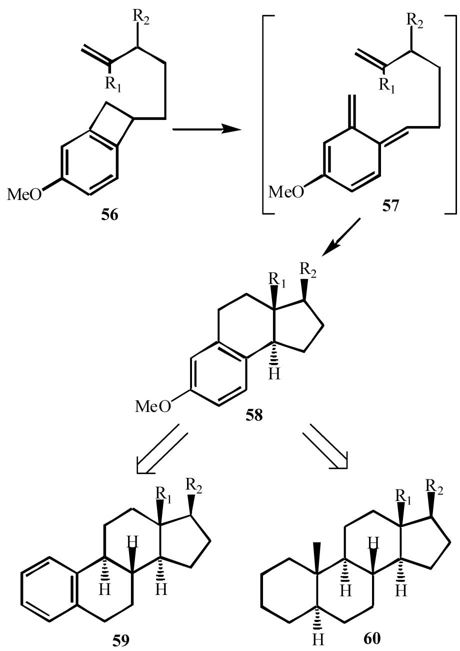


Chart 10. Synthesis of Steroid *via trans*-Benzoperhydroindane

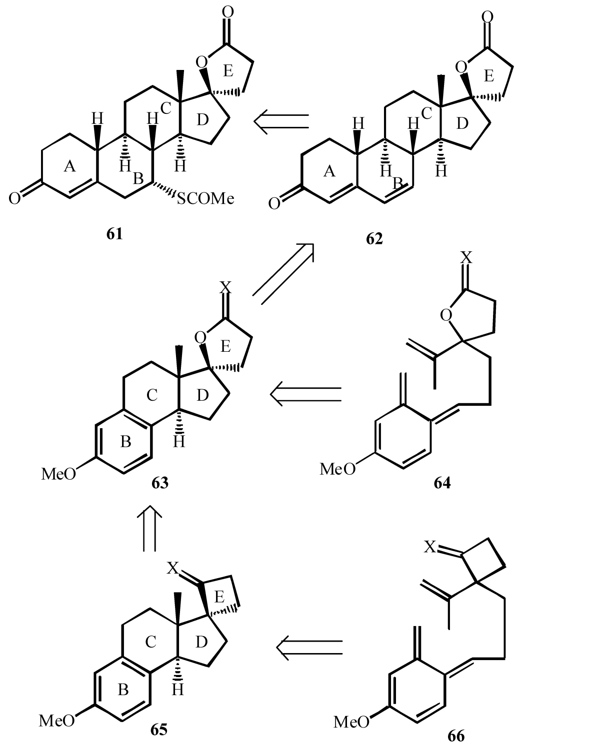


Chart 11. Synthetic Strategy for 19-Norspironolactone (**61**)

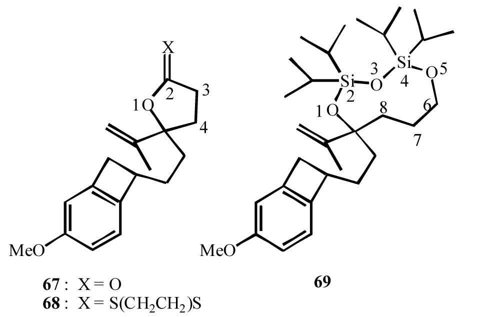
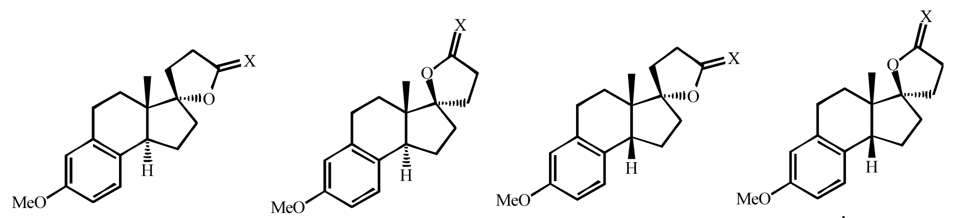


Fig. 4. Substrates for Preliminary Study of Thermolysis

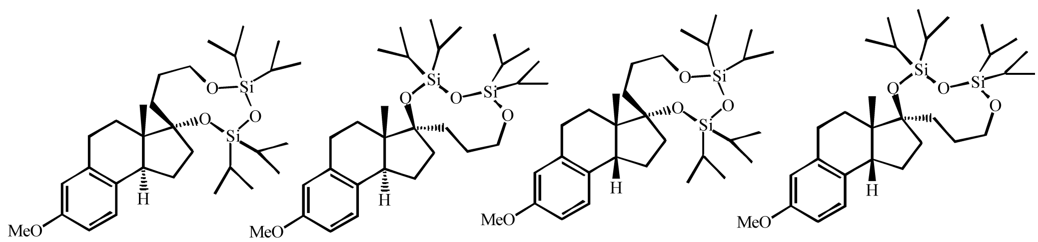
asymmetric total synthesis of (+)-chenodeoxycholic acid (**55**) was achieved *via* D-trienic steroid **54** by the intramolecular cycloaddition of the *o*-quinodimethane **53** as a key step (Chart 9).[80] Then, we have been involved in developing more flexible and efficient routes to both aromatic 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**[81] 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[82—84] where in the spirolactone 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**, **74**, and **78** 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

Table 2. Product Ratio of Thermolysis of **67**, **68**, and **69**



	trans - anti	trans - syn	cis - anti	cis - syn
X=O	**70** (94)	**71** (6)	**72** (0)	**73** (0)
X=S$(CH_2)_2$S	**74** (93)	**75** (7)	**76** (0)	**77** (0)



	trans - anti	trans - syn	cis - anti	cis - syn
	78 (96)	**79** (4)	**80** (0)	**81** (0)

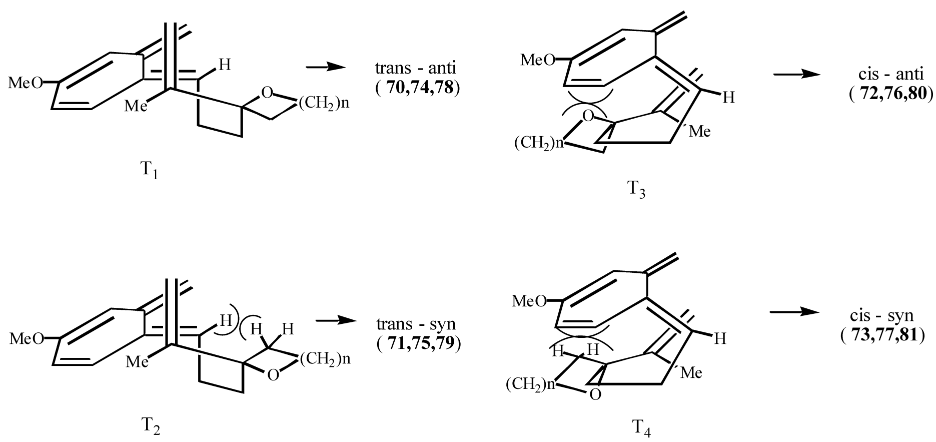


Fig. 5. Transition States for [4+2] Cycloaddition Reaction

about the stereochemical course of the cycloaddition reactions of the olefinic *o*-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 *o*-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 *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**—**i** (Fig. 6) were conducted in refluxing *o*-dichlorobenzene. Table 3 summarizes the distribution of the products for each substrate.

The total synthesis of 19-norspironolactone (**61**) was completed as follows. The tetracyclic cyclobutanone **65a** was prepared in stereoselective manner by thermolysis of the

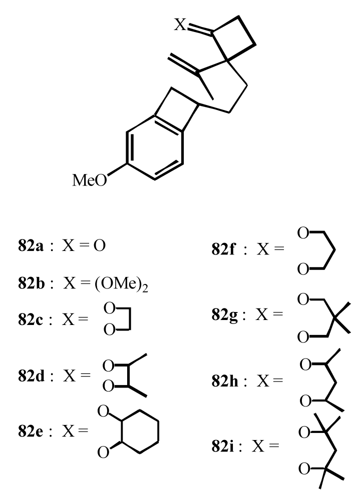
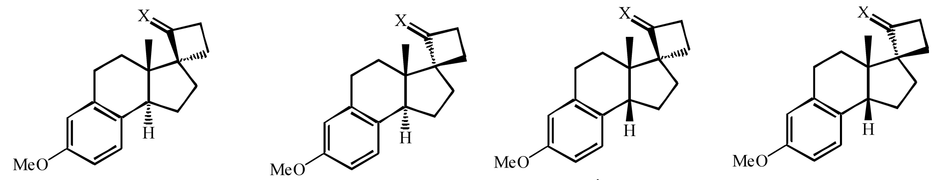
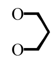
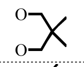
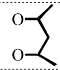
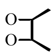
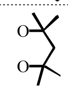
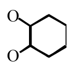


Fig. 6. Substrates for Study of Thermolysis

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



	Product ratio **65** : **83** : **84** : **85**	Yield (%)		Product ratio **65** : **83** : **84** : **85**	Yield (%)
a: X=O	28 : 60 : 12 : 0	97	**f**: X= 	65 : 15 : 20 : 0	82
b: X=$(OMe)_2$	88 : 3 : 9 : 0	56	**g**: X= 	62 : 13 : 25 : 0	75
c: X= 	60 : 21 : 19 : 0	73	**h**: X= 	66 : 15 : 19 : 0	99
d: X= 	59 : 22 : 19 : 0	97	**i**: X= 	61 : 20 : 19 : 0	90
e: X= 	59 : 23 : 18 : 0	97			

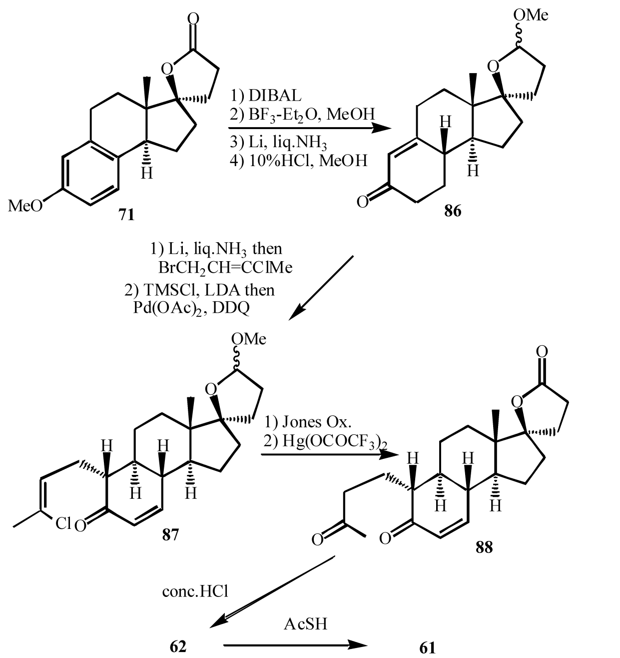


Chart 12. Synthesis of 19-Norspironolactone (**61**)

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[83] 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).

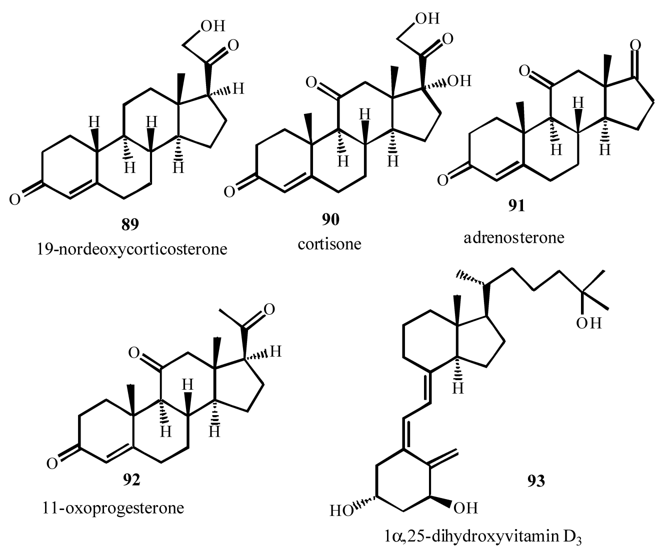


Fig. 7. Other Steroids Synthesized *via* A-Nor, B-Trienic Steroids

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-

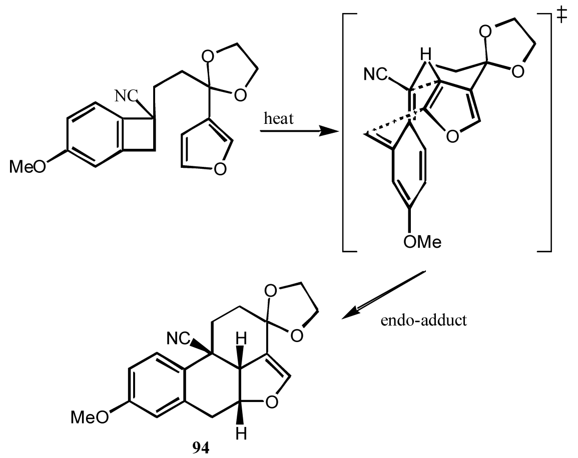


Chart 13. Concise Synthesis of Furan-Fused Tetracyclic Compound

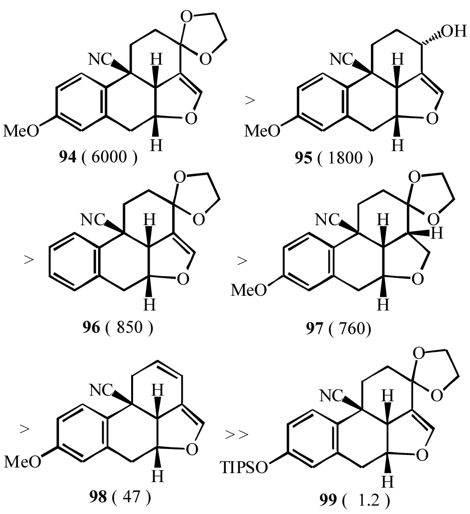


Fig. 8. Minimum Inhibit ory Concentration (MIC) (nmol/ml)

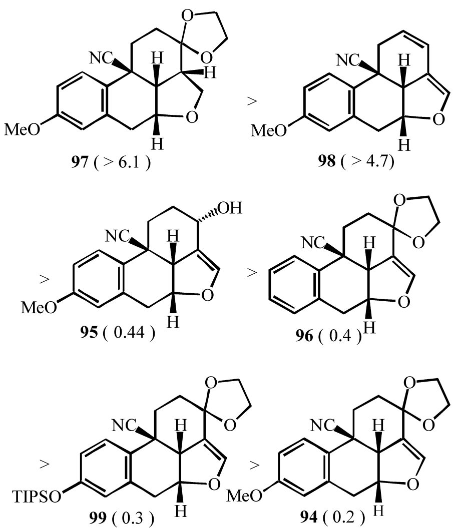


Fig. 9. Maximum Cytotoxic Concentration (MCC) (nmol/ml)

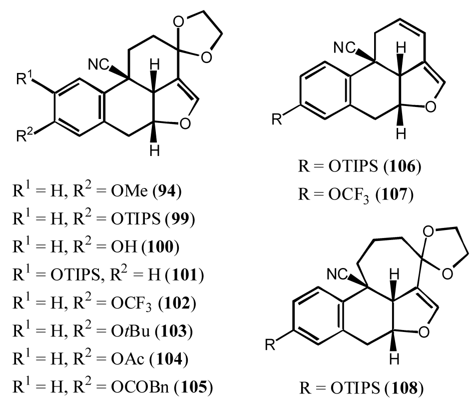


Fig. 10. Test Compounds for Anti-influenza Activity

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.[94] 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[95] 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,[92] and the OD (optical density) values for 24-h cultured MDCK

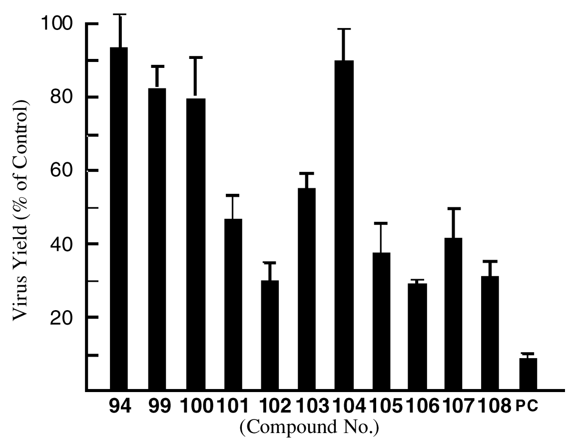


Fig. 11. Inhibitory Effect of **94**, **99**—**108** on the Growth of Influenza A/Aichi/2/68 Virus in MDCK Cells at 10 μM Drug Concentration

Amantadine was used as a positive control (PC).

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

Table 4. MTT Assay for Evaluation of the Direct Cytotoxicity

Compound	OD value	
	100 μM	200 μM
102	1.018±0.044	1.062±0.029
106	1.035±0.054	1.085±0.065
108	1.010±0.066	0.722±0.018
Control	1.071±0.050	

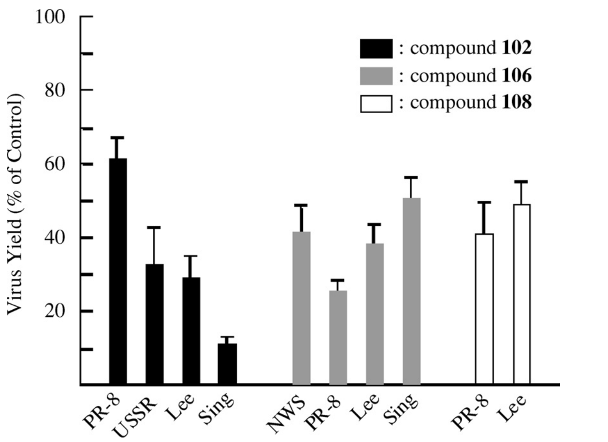


Fig. 12. Anti-viral Activity against Various Strains of Influenza A and B Viruses

Data are expressed as mean±S.D. of three experiments (percent of control) at 100 μM drug concentration. Viruses used are A/PR/8/34 (PR-8), A/USSR/92/77 (USSR), A/NWS/33 (NWS), B/Lee (Lee), and B/Singapore/222/79 (Sing).

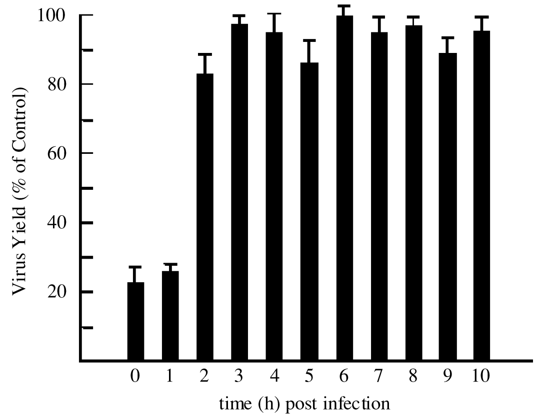


Fig. 13. Time-Related Effect of the Compound **102** on the Growth of Influenza A/Aichi/2/68 Virus in MDCK Cells at 100 μM Drug Concentration

After infection under drug-free condition, the cells were treated after various delays of 0—10 h at 37 °C. After a total of 24 h incubation, data are expressed as mean (% of control)±S.D. of three experiments.

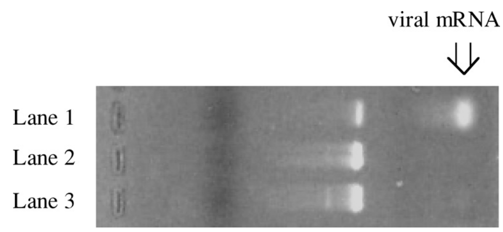


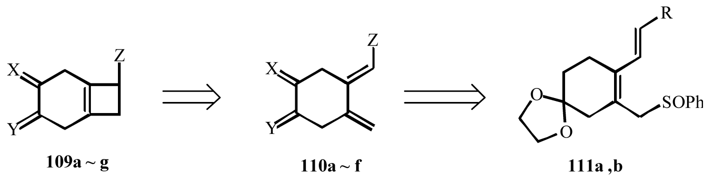
Fig. 14. Electrophoresis of RNA Derived from MDCK Cells Infected with Influenza A/Aichi/2/68 Virus (Lane 1: No Drug Treatment, Lane 2: 100 μM Drug **102** Treatment) or without Infection (Lane 3)

After isolation of total RNA, reverse transcription, and PCR, the mRNA preparations were electrophoresed in 1.6% agarose gel.

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.[96] 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.[91] 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.[97] 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.

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

Table 5. Substituent Effect on Ring-Opening Reaction of Cyclobutene (1)



Entry	Substrate	X	Y	Z	Product			
					110a—f	Yield (%)	**111a, b**	Yield (%)
1	**109a**	OCH_2CH_2O	H_2	CH_2SO_2p-Tol	**110a**	(58)		—
2	**109b**	H_2	OCH_2CH_2O	CH_2SO_2p-Tol	**110b**	(90)		—
3	**109c**	H_2	OCH_2CH_2O	CH_2SO_2Ph	**110c**	(92)		—
4	**109d**	OCH_2CH_2O	H_2	CH_2POPh_2	**110d**	(76)		—
5	**109e**	H_2	OCH_2CH_2O	CH_2SOPh	**110e**	(47)	**111a**	R=H (50)
6	**109f**	H_2	OCH_2CH_2O	$CH(CH_3)SO_2Ph$	**110f**	(31)		—
7	**109g**	H_2	OCH_2CH_2O	$CH(CH_3)SOPh$	—		**111b**	$R=CH_3$ (70)

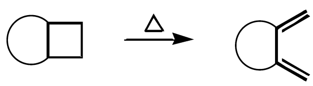


Chart 14. 4π-Electrocyclic Reaction

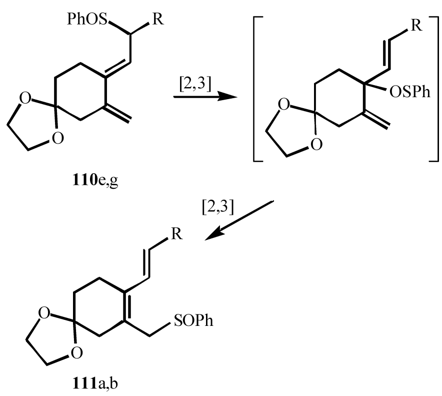


Chart 15. Double [2,3] Sigmapropic Rearrangement

ring (Chart 14).[98—100] 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.[101,102] The systems chosen for study were the (arylsulfinyl), (arylsulfonyl), and (diphenylphosphinyl)methylcyclobutenes, dienes generated from them constituting an essential part of the skeleton of the vitamin D series.[103,104] All the reactions were carried out in THF at $-30\,°C$ for 10 min using *n*-butyllithium as base and were found to proceed in moderate to high yields to give the initial products **110a**—**f** together with the double [2,3] sigmatropic rearrangement products **111a** and **111b** 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 **109c** and **109e**, 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 **109f** and **109g** 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,[90,91,105] we focused our interest on the substituent effect for the thermal cleavage of benzocyclobutenes, especially on the silyl substituents[106] in conjunction with recent reports on their rate enhancement effects for that of monocyclic cyclobutenes.[107,108] The compounds **112a**—**c** and **113a**—**c** 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 **112a** was subjected to condition A (toluene, reflux, 24 h), only a small amount of adduct **114a** was formed (9% yield). Likewise, compound **112b** afforded **114b** in only 30% yield. On the other hand, a notable acceleration of the reaction was observed for the β-silylated benzocyclobutene **112c**, which gave adduct **114c** 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 **112c** gave a nearly quantitative yield of **114c** as compared with **112a** and **112b** 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 **114**, although a slight difference was observed among the yields. The products **114a**—**c** 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-

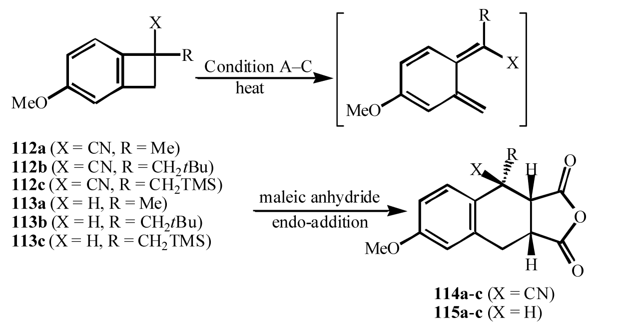


Chart 16. Thermal Electrocyclic Reaction–[4+2] Cycloaddition Reaction

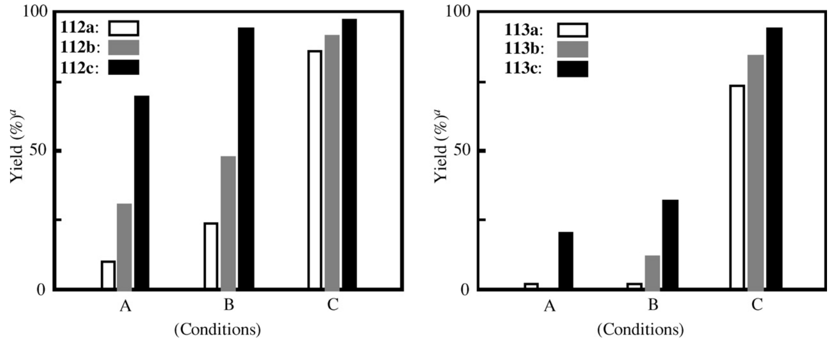
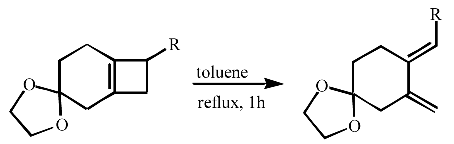


Fig. 15. Comparison of the *o*-Quinodimethane Formation Efficiency among **112a**—**c** and **113a**—**c**

tion with the dienophile (Chart 16), in consideration of a strong preference of maleic anhydride for endo addition and reported torquoselectivity of benzocyclobutenes.[100] 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 sufficiently 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, non-benzo-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[109] of benzocyclobutenones to 2,3-benzodiazepines, which is a biologically important heterocyclic core structure,[110,111] 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 il-



116a (R = CH_2tBu)
116b (R = CH_2TMS)

117a (19% yield)
117b (61% yield)

Chart 17. Thermal Electrocyclic Reaction

lustrated 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 oxy-anion-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-benzodiazepin-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,[112—115] all of these require thermal activation and often suffer from predominant pyrazole formation *via* 1,5-cyclization.[116,117] 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-

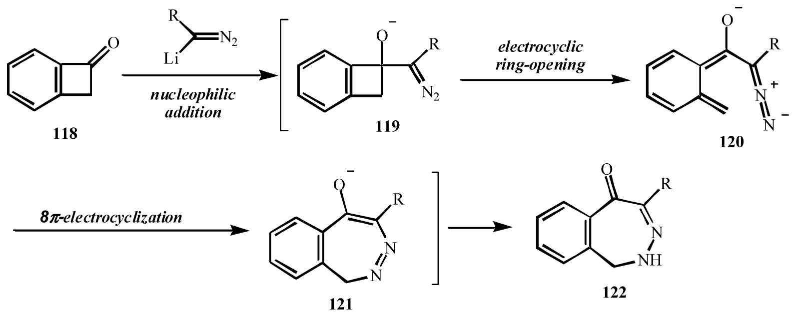


Chart 18. Strategic Outline for Synthesis of 2,3-Benzodiazepine

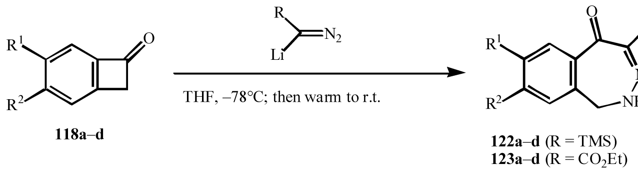


Chart 19. Reaction of Benzocyclobutenone and Lithiated Diazocompounds

Table 6. Transformation of Benzocyclobutenones into 2,3-Benzodiazepines

Entry	Benzocyclobutenone	Reagent	Product	Yield (%)[a]
1	**118a** (R^1=R^2=H)	R=TMS	**122a**	70
2	**118b** (R^1=H, R^2=OMe)	R=TMS	**122b**	79
3	**118c** (R^1=OMe, R^2=H)	R=TMS	**122c**	72
4	**118d** (R^1=R^2=OMe)	R=TMS	**122d**	82
5	**118a**	R=CO_2Et	**123a**	67
6	**118b**	R=CO_2Et	**123b**	79
7	**118c**	R=CO_2Et	**123c**	78
8	**118d**	R=CO_2Et	**123d**	69

ing reaction as shown in Chart 19 and Table 6 (entries 5—8). In every case, efficient transformation was achieved to afford 2,3-benzodiazepin-5-ones possessing a carboxylate functionality at the 4-positions. These results imply that a wide variety of a-diazocarbonyl compounds, which can generate a corresponding diazomethylene anion, may be applicable for the synthesis of functionalized 2,3-benzodiazepine derivatives. This reaction has the following advantages: (1) the oxy-anion formed by the nucleophilic addition extremely facilitates the first electrocyclic ring-opening; (2) the exclusive outward torquoselectivity of the oxide group dictates the geometry of the *o*-quinodimethane as required for the next electrocyclization; and (3) reconstruction of the stable 6π aromatic system facilitates the second 8π electrocyclization, involving a diazo group, which usually requires thermal activation.

5. Summary

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.

Acknowledgements I would like to express sincere appreciation to my numerous coworkers whose efforts, persistence, and ability made possible the performance of the described research. Names of collaborators in the present study are mentioned in the References.

References

1) Trost B. M., "Small Ring Compounds in Organic Synthesis I," ed. by de Meijere A., Springer-Verlag, Berlin, 1986, pp. 3—82.
2) Wong H. N. C., Lau K.-L., Tam K.-F., "Small Ring Compounds in Organic Synthesis I," ed. by de Meijere A., Springer-Verlag, Berlin, 1986, pp. 83—157.
3) Bellus D., Ernst B., *Angew. Chem. Int. Ed.*, **27**, 797—827 (1988).
4) Huisgen R., *Angew. Chem. Int. Ed.*, **25**, 297—311 (1986).
5) Wiberg K. B., *Angew. Chem. Int. Ed.*, **25**, 312—322 (1986).
6) Engler E. M., Andose J. D., Schleyer P. von R., *J. Am. Chem. Soc.*, **95**, 8005—8025 (1973).
7) Allinger N. L., *J. Am. Chem. Soc.*, **99**, 8127—8134 (1977).
8) Bauld N. L., Cessac J., *J. Am. Chem. Soc.*, **99**, 942—943 (1977).
9) Allinger N. L., Yuh Y., Sprague J. J., *J. Compt. Chem.*, **1**, 30—35 (1980).
10) Beekhaus H.-D., Ruchardt C., Kozhushkov S. I., Belov V. N., Verevkin S. P., de Meijere A., *J. Am. Chem. Soc.*, **117**, 11854—11860 (1995).
11) Sella A., Basch H., Hoz S., *J. Am. Chem. Soc.*, **118**, 416—420 (1996).
12) Namyslo J. C., Kaufmann D. E., *Chem. Rev.*, **103**, 1485—1537 (2003).
13) Devon T. K., Scott A. I., "Handbook of Naturally Occurring Compounds," Vol. II, Academic Press, New York, 1972.
14) Thomas A. F., Bassiere Y., "The Total Synthesis of Natural Products," Vol. 7, Wiley, New York, 1988, pp. 275—454.
15) Krief A., "Small Ring Compounds in Organic Synthesis II," ed. by de Meijere A., Springer-Verlag, Berlin, 1987, pp. 1—76.
16) Salaun J. R. Y., "Small Ring Compounds in Organic Synthesis III," ed. by de Meijere A., Springer-Verlag, Berlin, 1988, pp. 1—71.
17) Vidal J., Huet F., *J. Org. Chem.*, **53**, 611—616 (1988).
18) Cohen T., Brockunier L., *Tetrahedron*, **45**, 2917—2924 (1989).
19) Nemoto H., Fukumoto K., *Synlett*, **1997**, 863—875 (1997).
20) Vollhardt K. P. C., *Acc. Chem. Res.*, **10**, 1—8 (1977).
21) Oppolzer W., *Synthesis*, **1978**, 793—802 (1978).
22) Funk R. L., Vollhardt K. P. C., *Chem. Soc. Rev.*, **9**, 41—61 (1980).
23) Kametani T., Nemoto H., *Tetrahedron*, **37**, 3—16 (1981).
24) Nemoto H., Fukumoto K., *Tetrahedron*, **54**, 5425—5464 (1998).
25) Pasto D. J., Sugi K. D., Alonso D. E., *J. Org. Chem.*, **57**, 1146—1150 (1992).
26) Hansson T., Wickberg B., *J. Org. Chem.*, **57**, 5370—5376 (1992).
27) Tanaka M., Tomioka K., Koga K., *Tetrahedron*, **50**, 12829—12842 (1994).
28) Langer K., Mattay J., *J. Org. Chem.*, **60**, 7256—7266 (1995).
29) Alibes R., Boudelande J. L., Font J., Gregori A., Parella T., *Tetrahedron*, **52**, 1267—1278 (1996).
30) Soderberg B. C., Hegedus L. S., Sierra M. A., *J. Am. Chem. Soc.*, **112**, 4364—4374 (1990).
31) Wagner P. J., McMahon K., *J. Am. Chem. Soc.*, **116**, 10827—10828 (1994).
32) Vaida M., Shimon L. T. W., van Mil J., Ernst-Cbrera K., Addadi L., Leiserowitz L., Kahav M., *J. Am. Chem. Soc.*, **111**, 1029—1034 (1989).
33) Greene A. E., Charbonnier F., Luche M. J., Moyano A., *J. Am. Chem. Soc.*, **109**, 4752—4753 (1987).
34) Marino J. P., Laborde E., Paley R. S., *J. Am. Chem. Soc.*, **110**, 966—

968 (1988).
35) Collington E. W., Finch H., Montana J. G., Taylor R. J. K., *J. Chem. Soc. Perkin Trans. 1*, **1990**, 1839—1846 (1990).
36) Blaszczyk K., Tykarska E., Paryzek Z., *J. Chem. Soc. Perkin Trans. 2*, **1991**, 257—261 (1991).
37) Danheiser R. L., Casebier D. S., Loebach J. L., *Tetrahedron Lett.*, **33**, 1149—1152 (1992).
38) Pittol C. A., Roberts S. M., Sutton P. W., William J. O., *J. Chem. Soc. Chem. Commun.*, **1994**, 803—804 (1994).
39) de Azevedo M. B. M., Greene A. E., *J. Org. Chem.*, **60**, 4940—4942 (1995).
40) Danheiser R. L., Carini D. J., Fink D. M., Basak A., *Tetrahedron*, **39**, 935—947 (1983).
41) Narasaka K., Hayashi Y., Shimadzu H., Niihata S., *J. Am. Chem. Soc.*, **114**, 8869—8885 (1992).
42) Seebach D., Dahinden R., Marti R. E., Beck A. K., Plattner D. A., Kuhnle F. N. M., *J. Org. Chem.*, **60**, 1788—1799 (1995).
43) Misumi A., Iwanaga K., Furuta K., Yamamoto H., *J. Am. Chem. Soc.*, **107**, 3343—3345 (1985).
44) Ito H., Taguchi T., Hanzawa Y., *Tetrahedron Lett.*, **34**, 7639—7640 (1993).
45) Kocovsky P., Srogl J., Pour M., Gogoll A., *J. Am. Chem. Soc.*, **116**, 186—197 (1994).
46) Lemieux R. P., Schuster G. B., *J. Org. Chem.*, **58**, 100—110 (1993).
47) Jung M. E., Sledeski A. W., *J. Chem. Soc. Chem. Commun.*, **1993**, 589—591 (1993).
48) Hiroi K., Nakamura H., Anzai T., *J. Am. Chem. Soc.*, **109**, 1249—1250 (1987).
49) Nemoto H., Ishibashi H., Nagamochi M., Fukumoto K., *J. Org. Chem.*, **57**, 1707—1712 (1992).
50) Stafford J. A., McMurry J. E., *Tetrahedron Lett.*, **29**, 2531—2534 (1988).
51) Nemoto H., Nagamochi M., Fukumoto K., *J. Chem. Soc. Chem. Commun.*, **1992**, 1695—1697 (1992).
52) Nemoto H., Nagamochi M., Fukumoto K., *J. Chem. Soc. Perkin Trans. 1*, **1993**, 2329—2332 (1993).
53) Irie T., Suzuki T., Yasunari Y., Kurosawa E., Masamune T., *Tetrahedron*, **25**, 459—468 (1969).
54) Liebeskind L. S., Mitchell D., Foster B. S., *J. Am. Chem. Soc.*, **109**, 7908—7910 (1987).
55) Ollivier J., Legros J.-Y., Fiaud J.-C., de Meijere A., Salaun J., *Tetrahedron Lett.*, **31**, 4139—4142 (1990).
56) Nemoto H., Tanabe T., Nagamochi M., Fukumoto K., *Heterocycles*, **35**, 707—710 (1993).
57) Nemoto H., Shiraki M., Nagamochi M., Fukumoto K., *Tetrahedron Lett.*, **34**, 4939—4942 (1993).
58) Nemoto H., Nagamochi M., Ishibashi H., Fukumoto K., *J. Org. Chem.*, **59**, 74—79 (1992).
59) Nemoto H., Tanabe T., Fukumoto K., *J. Org. Chem.*, **60**, 6785—6790 (1992).
60) Nemoto H., Miyata J., Hakamata H., Nagamochi M., Fukumoto K., *Tetrahedron*, **51**, 5511—5522 (1995).
61) Miyata J., Nemoto H., Ihara M., *J. Org. Chem.*, **65**, 504—512 (2000).
62) de Meijere A., Meyer F. E., *Angew. Chem. Int. Ed.*, **33**, 2379—2411 (1994).
63) Tietze L. F., *Chem. Rev.*, **96**, 115—136 (1996).
64) Malacria M., *Chem. Rev.*, **96**, 289—306 (1996).
65) Ryu I., Sonoda N., Curran D. P., *Chem. Rev.*, **96**, 177—194 (1996).
66) Molander G. A., Harris C. R., *Chem. Rev.*, **96**, 307—338 (1996).
67) Snider B. B., *Chem. Rev.*, **96**, 339—363 (1996).
68) Sugihara T., Coperet C., Owczarczyk Z., Harring L. S., Negishi E., *J. Am. Chem. Soc.*, **116**, 7923—7924 (1994).
69) Nemoto H., Miyata J., Yoshida M., Raku N., Fukumoto K., *J. Org. Chem.*, **62**, 7850—7857 (1997).
70) Takano S., Inomata K., Ogasawara K., *J. Chem. Soc. Chem. Commun.*, **1990**, 1544—1546 (1990).
71) Nemoto H., Yoshida M., Fukumoto K., *J. Org. Chem.*, **62**, 6450—6451 (1997).
72) Lautens M., Kumanovic S., *J. Am. Chem. Soc.*, **117**, 1954—1964 (1995).
73) Myers A. G., Condroski K. R., *J. Am. Chem. Soc.*, **117**, 3057—3083 (1995).
74) Kametani T., Nemoto H., Ishikawa H., Shiroyama K., Fukumoto K., *J. Am. Chem. Soc.*, **98**, 3378—3379 (1976).
75) Kametani T., Nemoto H., Ishikawa H., Shiroyama K., Matsumoto H., Fukumoto K., *J. Am. Chem. Soc.*, **99**, 3461—3466 (1977).
76) Kametani T., Matsumoto H., Nemoto H., Fukumoto K., *J. Am. Chem. Soc.*, **100**, 6218—6220 (1978).
77) Oppolzer W., Roberts D. A., *Helv. Chim. Acta*, **63**, 1703—1705 (1980).
78) Quinkert G., *Chimia*, **31**, 225—228 (1977).
79) Funk R. L., Vollhardt K. P. C., *J. Am. Chem. Soc.*, **101**, 215—217 (1979).
80) Kametani T., Suzuki K., Nemoto H., *J. Am. Chem. Soc.*, **103**, 2890—2891 (1981).
81) Nemoto H., Fujita S., Nagai M., Fukumoto K., Kametani T., *J. Am. Chem. Soc.*, **110**, 2931—2938 (1988).
82) Kagawa C. M., Cella J. A., Van Arman C. G., *Science*, **126**, 1015—1016 (1957).
83) Johnson W. S., Dumas D. J., Brner D. J., *J. Am. Chem. Soc.*, **104**, 3510—3511 (1982).
84) Nickisch K., Bittler D., Casals-Stenzel J., Laurent H., Nickolson R., Nishino Y., Petzoldt K., Wiechert R. J., *J. Med. Chem.*, **28**, 546—550 (1985).
85) Nemoto H., Satoh A., Ando M., Fukumoto K., *J. Chem. Soc. Chem. Commun.*, **1990**, 1001—1002 (1990).
86) Nemoto H., Matsuhashi N., Imaizumi M., Nagai M., Fukumoto K., *J. Org. Chem.*, **55**, 5625—5631 (1990).
87) Nemoto H., Nagai M., Moizumi M., Kohzuki K., Fukumoto K., Kametani T., *J. Chem. Soc. Perkin Trans. 1*, **1989**, 1639—1645 (1989).
88) Nemoto H., Nagai Fukumoto K., Kametani T., *Tetrahedron Lett.*, **26**, 4613—4616 (1985).
89) Nemoto H., Ando M., Fukumoto K., *Tetrahedron Lett.*, **31**, 6205—6208 (1990).
90) Matsuya Y., Qin H., Nagaoka M., Nemoto H., *Heterocycles*, **62**, 207—211 (2004).
91) Matsuya Y., Sasaki K., Nagaoka M., Kakuda H., Toyooka N., Imanishi N., Ochiai H., Nemoto H., *J. Org. Chem.*, **69**, 7989—7993 (2004),
92) Ochiai H., Sakai S., Hirabayashi T., Shimizu Y., Terasawa K., *Antivir. Res.*, **27**, 425—430 (1995).
93) Mosmann T., *J. Immunol. Methods*, **65**, 55—63 (1983).
94) Matsuya Y., Sasaki K., Ochiai H., Nemoto H., *Bioorg. Med. Chem.*, **15**, 424—432 (2007).
95) Tobita K., *Med. Microbiol. Immunol.*, **62**, 23—27 (1975).
96) White J., Kielian M., Helenius A., *Rev. Biophys.*, **16**, 151—195 (1983).
97) Mantani N., Imanishi N., Kawamata H., Terasawa K., Ochiai H., *Planta Med.*, **67**, 240—243 (2001).
98) Oppolzer W., *Synthesis*, **1978**, 793—802 (1978).
99) Comber R. N., Swentn J. S., Wexler A. J., *J. Am. Chem. Soc.*, **101**, 5411— 5412 (1979).
100) Jefford C. W., Bernardinelli G., Wang Y., Spellmeyer D. C., Buda A., Houk K. N., *J. Am. Chem. Soc.*, **114**, 1157—1165 (1992).
101) Kametani T., Tsubuki M., Nemoto H., Suzuki K., *J. Am. Chem. Soc.*, **103**, 1256—1258 (1981).
102) Nemoto H., Suzuki K., Tsubuki M., Minemura K., Fukumoto K., Kametani T., Furuyama H., *Tetrahedron*, **39**, 1123—1132 (1983).
103) Lythgoe B., Nambudiry M. E. N., Tideswell J., *Tetrahedron Lett.*, **18**, 3685—3688 (1977).
104) Lythgoe B., Manwaring R., Milner J. R., Moran T. A., Nambudiry M. E. N., Tideswell J., *J. Chem. Soc. Perkin Trans. 1*, **1978**, 387—395 (1978).
105) Nemoto H., Fukumoto K., *Tetrahedron*, **54**, 5425—5464 (1998).
106) Matsuya Y., Ohsawa N., Nemoto H., *J. Am. Chem. Soc.*, **128**, 412—413 (2006).
107) Murakami M., Miyamoto Y., Ito Y., *Angew. Chem. Int. Ed.*, **40**, 189—190 (2001).
108) Ikeda H., Kato T., Inagaki S., *Chem. Lett.*, **2001**, 270—271 (2001).
109) Matsuya Y., Ohsawa N., Nemoto H., *J. Am. Chem. Soc.*, **128**, 13072—13073 (2006).
110) Zappala M., Postorino G., Micale N., Caccamese S., Parrinello N., Grazioso G., Roda G., Menniti F. S., De Sarro G., Grasso S., *J. Med. Chem.*, **49**, 575—581 (2006).
111) Elger B., Huth A., Neuhaus R., Ottow E., Schneider H., Seilheimer B., Turski L., *J. Med. Chem.*, **48**, 4618—4627 (2005).
112) Reid A. A., Sharp J. T., Sood H. R., Thorogood P. B., *J. Chem. Soc.*,

Perkin Trans. 1, **1973**, 2543—2551 (1973).
113) Munro D. P., Sharp J. T., *Tetrahedron Lett.*, **21**, 4109—4110 (1980).
114) Ohno M., Noda M., Yamamoto Y., Eguchi S., *J. Org. Chem.*, **64**, 707—712 (1999).
115) O'Leary M. A., Wege D., *Tetrahedron*, **37**, 801—811 (1981).
116) Sharp J. T., Findlay R. H., Thorogood P. B., *J. Chem. Soc.*, *Perkin Trans. 1*, **1975**, 102—113 (1975).
117) Stanley K. L. M., Dingwall J., Sharp J. T., Naisby T. W., *J. Chem. Soc.*, *Perkin Trans. 1*, **1979**, 1433—1441 (1979).