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RECENT APPLICATION OF *ORTHO*-QUINODIMETHANE CHEMISTRY FOR SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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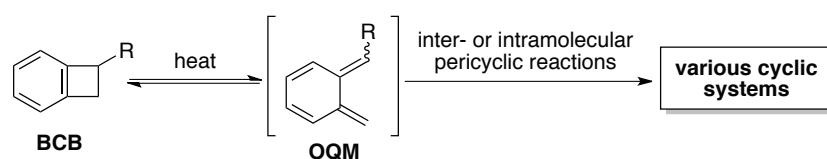
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This review is dedicated to the late Professor Emeritus Hideo Nemoto (University of Toyama).

Abstract – The *o*-quinodimethanes, generated by concerted 4π -electrocyclic ring-opening of benzocyclobutenes, have been widely utilized as a powerful intermediate for the construction of various fused-cyclic frameworks. In this review, recent applications for the construction of heterocycles as well as their biological aspects are surveyed.

INTRODUCTION

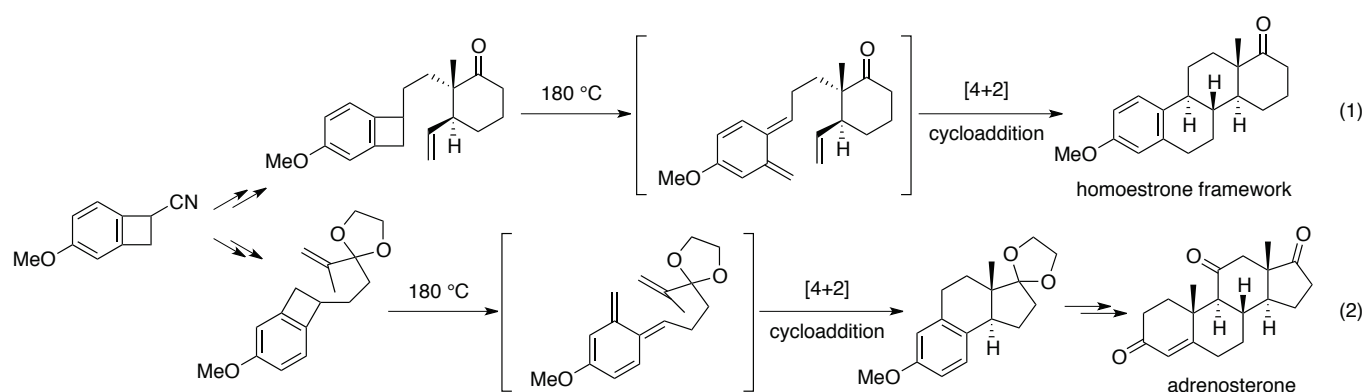
Thermal interconversion between benzocyclobutenes (BCBs) and *o*-quinodimethanes (OQMs) is one of the most popular 4π -electrocyclic reactions, and the OQMs thus generated have been regarded as a highly reactive and important intermediate for the construction of fused-cyclic systems via inter- or intramolecular pericyclic reactions such as cycloadditions and electrocyclizations (Scheme 1).¹ These ring-opening reactions are caused by heating or light irradiation according to the Woodward-Hoffmann rule, and ordinarily thermal conditions have been adopted in the synthetic chemistry field. Except for special cases, these ring fissions require over 100 °C heating.¹



Scheme 1. General Drawing of OQM Formation from BCB and Its Synthetic Application

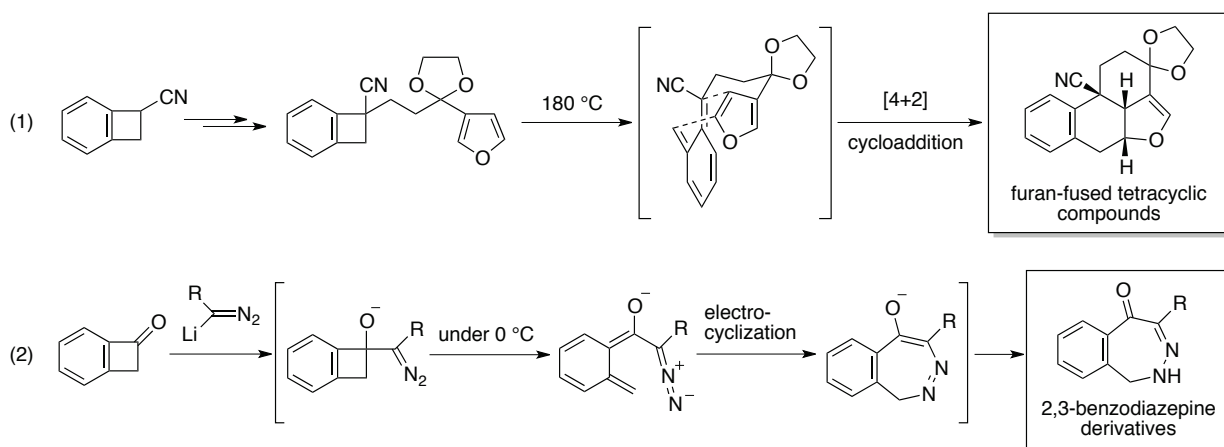
One of the most impressive synthetic applications of these OQM formations is exemplified by the construction of a steroidal framework, in which the substrate BCB has a suitably designed pendant

substituent containing an olefin part and successive intramolecular [4+2] cycloaddition of the OQM is involved with a high stereoselectivity.^{1a} The pioneering work was reported by Nemoto and co-workers in 1976, and a homoeurone framework was elegantly constructed with a high efficiency (Scheme 2-(1)).² They also applied this OQM chemistry for the construction of the BCD ring of steroidal system (benzoperhydroindane), which was easily transformed into a full steroidal framework, such as adrenosterone (Scheme 2-(2)).³ Thus, the OQM chemistry has greatly been developed as the second-generation steroid synthesis to date.^{1a}



Scheme 2. Examples of Application for the Construction of Steroidal Framework

Beside such extensive researches for the construction of carbocyclic compounds,⁴ the OQM chemistry has also been expanded toward the heterocycles construction. In this review, I'd like to account for our recent studies on the synthesis of (1) furan-fused tetracyclic compounds and (2) 2,3-benzodiazepine derivatives (Scheme 3), including their biological activities.



Scheme 3. Application for the Construction of Some Heterocycles

(1) FURAN-FUSED TETRACYCLIC COMPOUNDS

A beginning of the plan for syntheses of the furan-fused tetracyclenic compounds was notice of intriguing antiviral natural products, halenaquinol and halenaquinone, possessing furan-fused pentacyclenic structures (Figure 1).⁵ These polyketides inspired us to design a simplified tetracyclenic core, which was envisioned to be accessible from OQMs containing a furan moiety as a dienophilic part (Figure 1). While an aromatic furan ring has frequently been utilized as a diene in the normal Diels-Alder cycloaddition, its electron-rich property enables the action as a dienophile in the inverse electron demand Diels-Alder cycloaddition. We regard the OQMs having a cyano substituent as an electron-poor diene in the Diels-Alder reaction.⁶

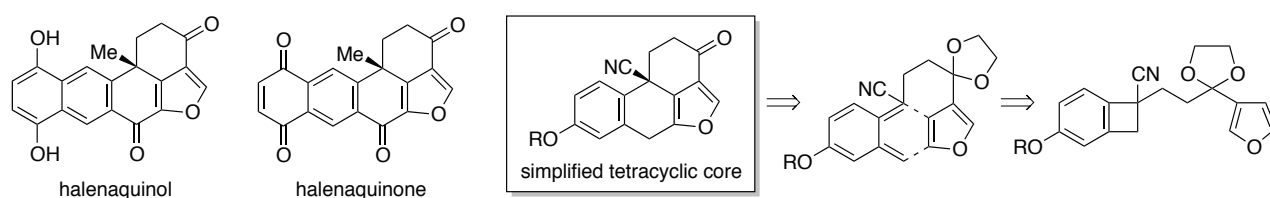
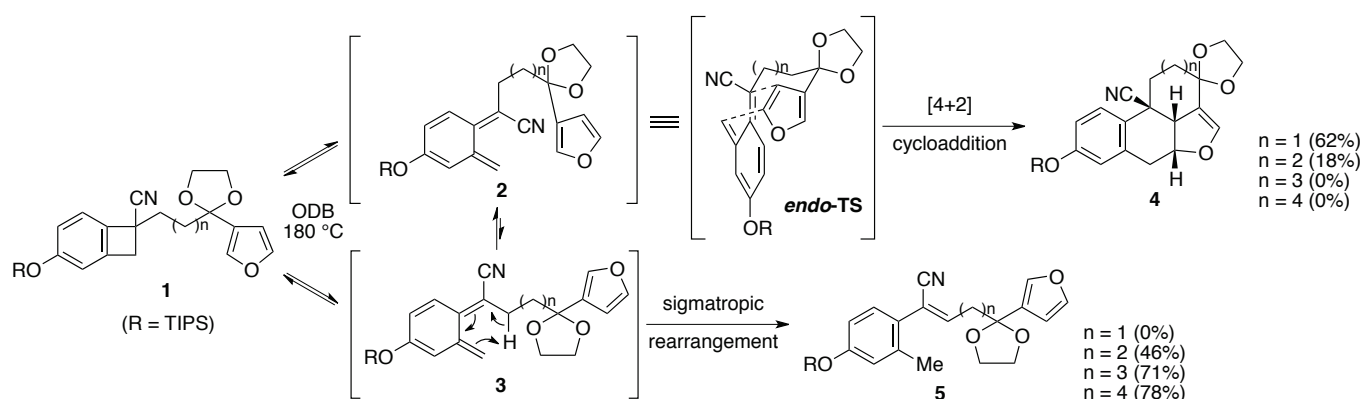


Figure 1. Example of Antiviral Polyketides and Model Core Structure

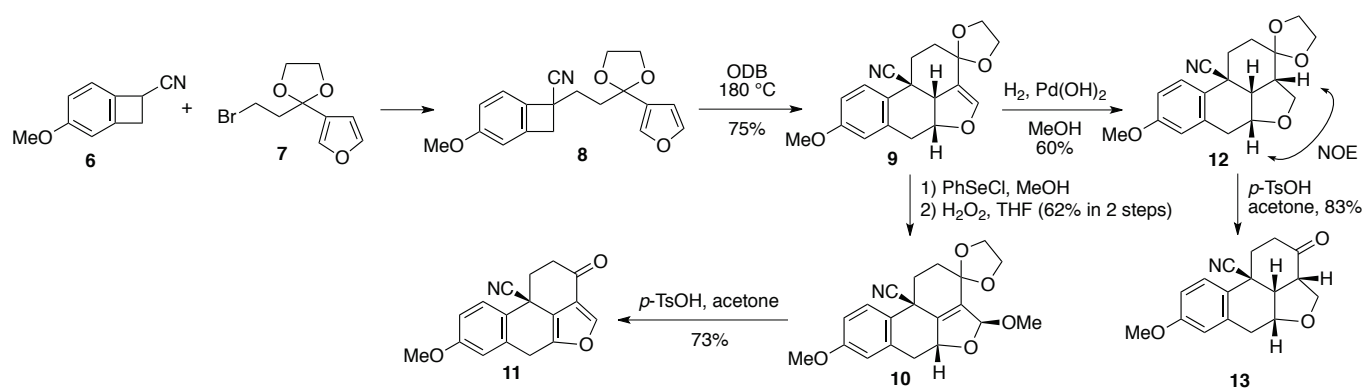
In fact, the furan-containing BCB (**1**, $n = 1$), prepared from cyano-BCB via alkylation, was subjected to thermal conditions (180 °C in *o*-dichlorobenzene (ODB)), and the desired cycloadduct **4** was obtained as a sole product with an exclusive stereoselectivity. This diastereomer obviously arises from (*Z*)-OQM intermediate **2** via *endo* transition state. On the other hand, elongation of the alkyl chain between the BCB and the furan moiety caused destabilization of the transition state for cycloaddition, and instead, the alkene products **5** were formed predominantly from (*E*)-OQM intermediate **3** via sigmatropic rearrangement (Scheme 4). Thus, intramolecular [4+2] cycloaddition accompanied by six-membered ring formation ($n = 1$) is a suitable approach for the construction of furan-fused tetracyclenic compounds. Actually, these transformations were found to have a high generality and an exclusive stereoselectivity.⁷



Scheme 4. Possible Reaction Course of the OQM from the Furan-Containing BCB (**1**)

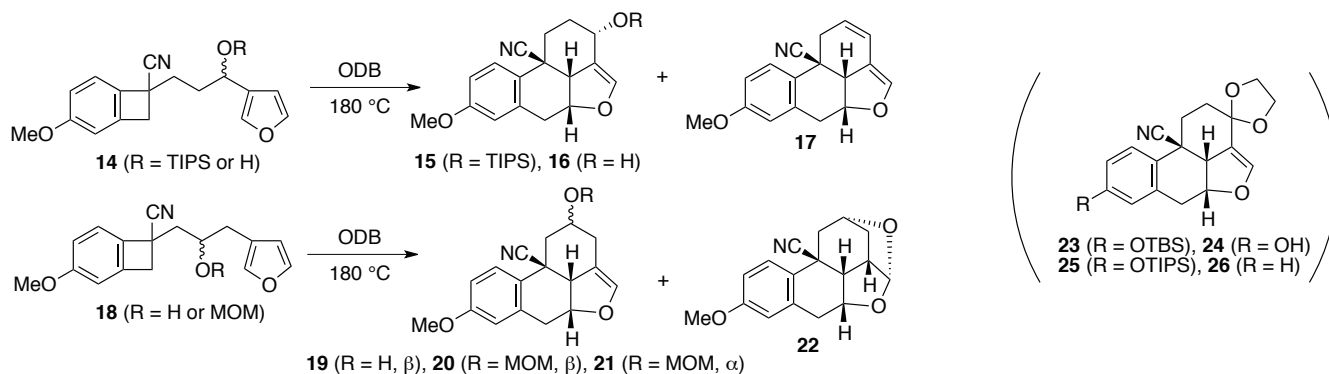
(1)-1. Exploration for novel antiviral compounds⁶⁻⁸

The OQM precursor **8**, assembled from cyano-BCB **6** and bromoalkylated furan **7**, was clearly converted into the furan-fused tetracyclic system **9** with all *cis* configurations under thermal conditions. To arrange the same oxidation state of the furan ring as those of halenaquinol and halenaquinone, the compound **9** was transformed into the aromatic furan compound **11** through a three-step sequence. In addition, catalytic hydrogenation of the furan moiety of **9** was also examined to afford the tetrahydro derivatives **12** and **13** in good yields. The addition of hydrogen occurred from a convex side exclusively (Scheme 5).^{6,8}



Scheme 5. Syntheses of Different Oxidation States of Furan Moiety

The generality of these thermal reactions involving intramolecular Diels-Alder cycloaddition of the furan moiety was demonstrated using **14** and **18** with different position of oxygen substituents (Scheme 6). The substrates **14** gave α -oxy derivative (**15** or **16**) and elimination product **17** (from β -oxy derivatives), and the substrates **18** afforded the cycloadducts **19–21**, depending on the substituents R. Interestingly, α -hydroxy product (diastereomer of **19**) was converted to the highly rigid cage-type acetal product **22**. Moreover, modifications of the substituents on the benzene ring were also possible through the similar OQM chemistry strategy to get the derivatives **23–26**.⁸



Scheme 6. Syntheses of Various Types of Furan-Fused Derivatives

Evaluation of antiviral activity of the synthesized compounds was performed against HVJ in LLC-MK2 cells using hemagglutinin (HA) titers assay method (Table 1). The compound **25** was found to exert the most potent activity with 0.6 $\mu\text{g/mL}$ of minimum inhibitory concentration (MIC) and good therapeutic index (0.0048).⁸

Table 1. Effects of the Furan-Fused Tetracyclic Compounds on the Growth of HVJ in LLC-MK2 Cells^a

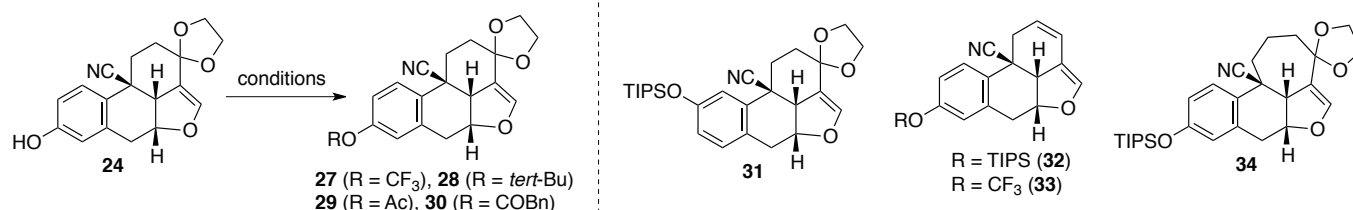
Compound No.	HA titers in culture supernatants in the presence of the indicated sample concentrations ($\mu\text{g/mL}$) ^b						MIC (α) ^c ($\mu\text{g/mL}$)	MCC (β) ^d ($\mu\text{g/mL}$)	Therapeutic Index (α/β)
	2,000	1,000	500	250	125	62.5			
9	16	32	32	32	32	64	2,000	62.5	32
15	64	64	64	64	64	64	-	-	-
16	4	4	4	32	64	64	500	125	4
17	-	-	-	< 4	< 4	< 4	12.5	-	-
19	-	< 4	4	4	16	64	125	-	-
22	-	64	64	128	128	128	-	-	-
20	-	< 4	4	4	4	8	62.5	-	-
21	-	< 4	< 4	4	4	4	62.5	-	-
12	4	4	4	16	64	64	250	> 2,000	< 0.125
13	128	256	512	512	-	-	-	-	-
11	-	-	-	-	256	256	-	-	-
23	< 4	8	32	64	64	64	1,000	> 2,000	< 0.5
24	-	-	-	32	32	-	-	-	-
25	-	-	-	-	-	< 4	-	-	-
26	< 4	< 4	< 4	< 4	32	32	250	125	2
Sample concentrations ($\mu\text{g/mL}$)									
	5	2.5	1.25	0.6	0.3	0.15			
25	< 4	< 4	4	8	32	128	0.6	125	0.0048

^a The virus was adsorbed on the medium one hour before the sample was added and cultured for 24 h at 37 °C.

^b In the absence of the sample (control experiment), the HA titers were 128. ^c The minimum inhibitory concentrations (MIC) of more active compounds than **9** are shown. ^d The maximum cytotoxic concentrations (MCC) of the compounds having less toxicity than **9** are shown.

(1)-2. Exploration for anti-influenza drug candidates⁹

Previous section revealed that the tetracyclic compounds having a dihydrofuran structure would be a potential antiviral agent, especially TIPS derivative **25** exhibited potent activity. With these findings in mind, novel anti-influenza agents are explored among the dihydrofuran-fused tetracyclic compounds obtained through the OQM chemistry.⁹

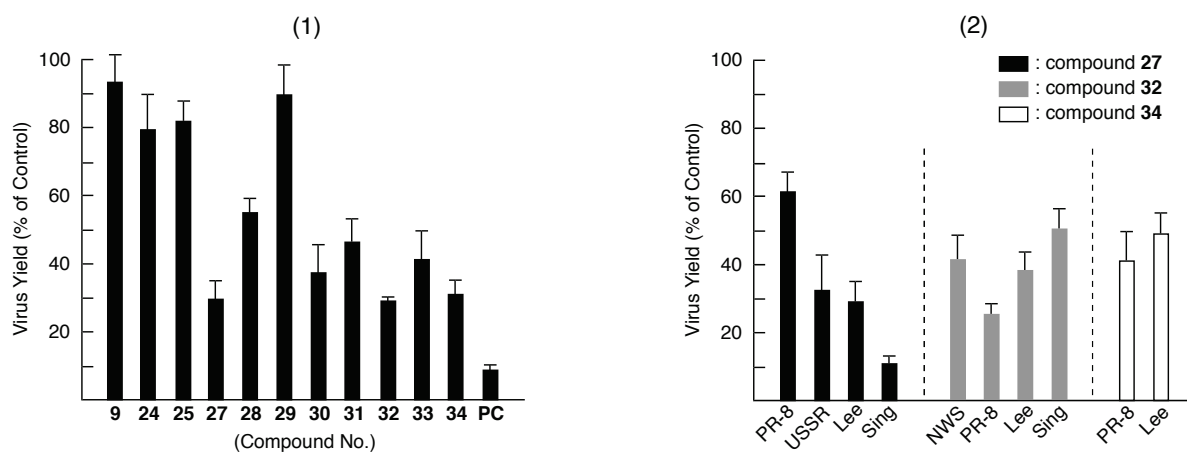


Conditions: *S*-(trifluoromethyl)dibenzothiofenium triflate, K₂CO₃ (**27**, 54%); *tert*-BuOC(=NH)CCl₃, BF₃·OEt₂ (**28**, 47%); Ac₂O, pyridine (**29**, 79%); PhCH₂COCl, Et₃N, DMAP (**30**, 61%)

Figure 2. Potential Candidates of New Anti-Influenza Agents

Because the TIPS substituent was characterized as lipophilic and sterically congested nature, several derivatives **27–30** were prepared from the phenolic compound **24**. Further derivatives **31–34** possessing TIPS or CF₃ substituents were also synthesized according to the general synthetic scheme for the furan-fused tetracyclic compounds (Figure 2).^{9a}

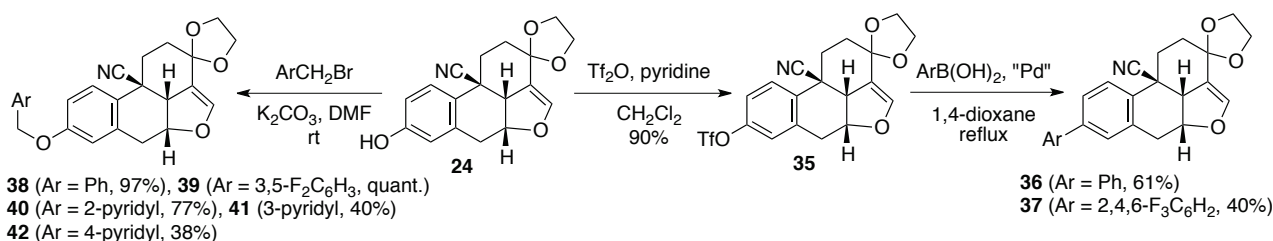
Inhibitory effects of the synthesized compounds on the growth of influenza A/Aichi/2/68 virus in MDCK cells were surveyed (Figure 3-(1)). Several derivatives having TIPS or CF₃ substituents exhibited notable activities against influenza viral growth at 10 μM drug concentration. Additionally, it was found that relatively potent derivatives **27** (CF₃), **32** (TIPS), **34** (TIPS) were all effective for wide range of virus strains including influenza A and B (Figure 3-(2)).^{9a}



(1) Inhibition on the growth of influenza A/Aichi/2/68 virus in MDCK cells at 10 μM drug concentration. PC = amantadine
 (2) Inhibition on the growth of various strains of influenza A and B viruses at 100 μM drug concentration. A/PR/8/34 (PR-8), A/USSR/92/77 (USSR), A/NWS/33 (NWS), B/Lee (Lee), B/Singapore/222/79 (Sing).

Figure 3. The First Survey of Furan-Fused Tetracyclic Compounds for Anti-Influenza Activities

Since the CF₃ derivative **27** was found to exert potent anti-influenza activity, further derivatization was performed starting from the phenolic compound **24**, aiming at introduction of various fluoro-containing substituents. Triflate **35**, prepared from **24**, was a good substrate for subsequent Suzuki-coupling reactions, and also **24** could be transformed into various benzylic ether derivatives **38–42** via simple etherification (Scheme 7).^{9b}



Scheme 7. Preparation of Various Fluoro-Containing Furan-Fused Tetracyclic Compounds

Evaluation of these derivatives as anti-influenza agent revealed that the benzyl ethers **38–42** were promising candidates for a new lead compound comparable with **27**, whereas the triflate **35** and C–C coupling derivatives **36** and **37** significantly decreased the activity (Figure 4).^{9b}

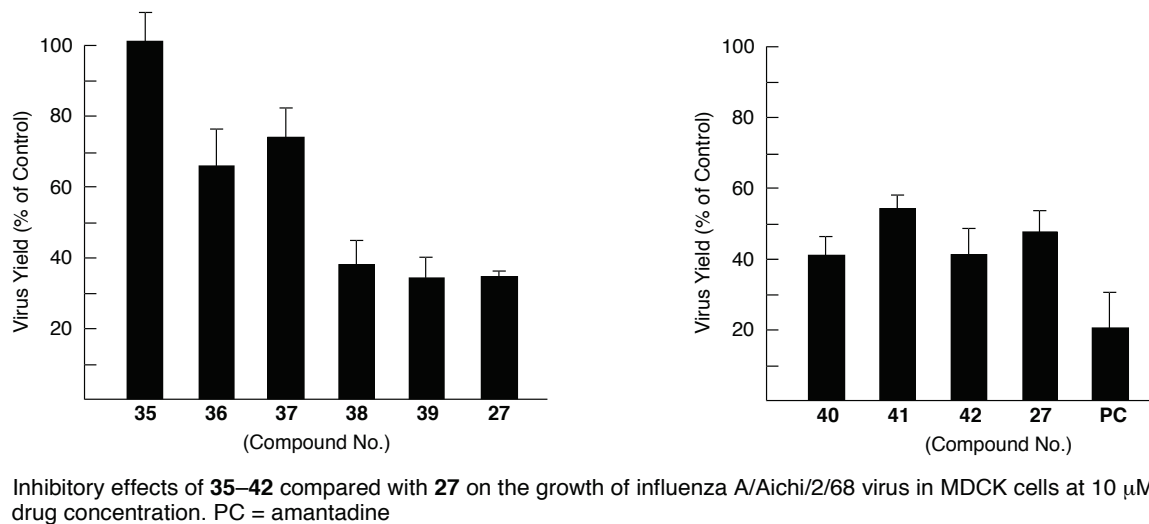


Figure 4. The Second Survey of Furan-Fused Tetracyclic Compounds for Anti-Influenza Activities

(1)-3. Exploration for novel anti-Alzheimer's disease agents^{10,11}

The furan-fused tetracyclic compounds showing antiviral (anti-influenza) activities necessarily possess a carbon or silyl substituent on the aromatic ring, and phenolic derivative **24** exhibited only limited antiviral activity. On the other hand, screening experiments seeking for new anti-Alzheimer's disease agents disclosed that the phenolic derivative **24** showed potent activity for the dendritic extension in $A\beta$ -damaged neurons.^{10a} Conversely, anti-influenza derivatives having a hydrophobic substituent did not exhibit such activities, suggesting that the free phenolic hydroxy group played an important role for the bioactivity. Several phenolic derivatives **24** and **43–45** were the first targets in this study (Figure 5).^{10a}

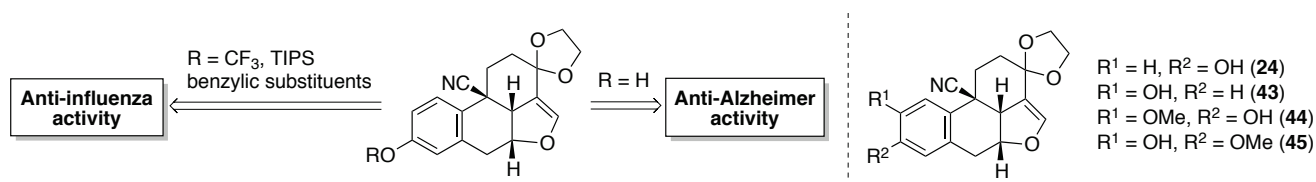
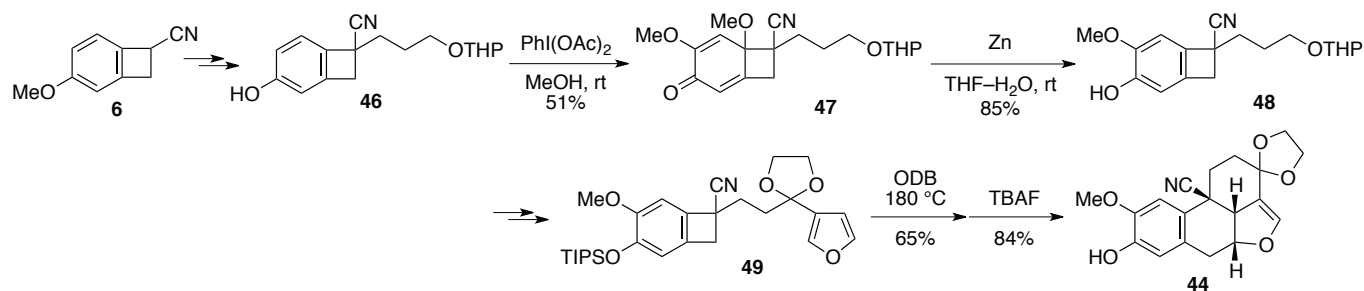


Figure 5. Discovery of Phenolic Furan-Fused Tetracyclic Compounds with Anti-Alzheimer Activity

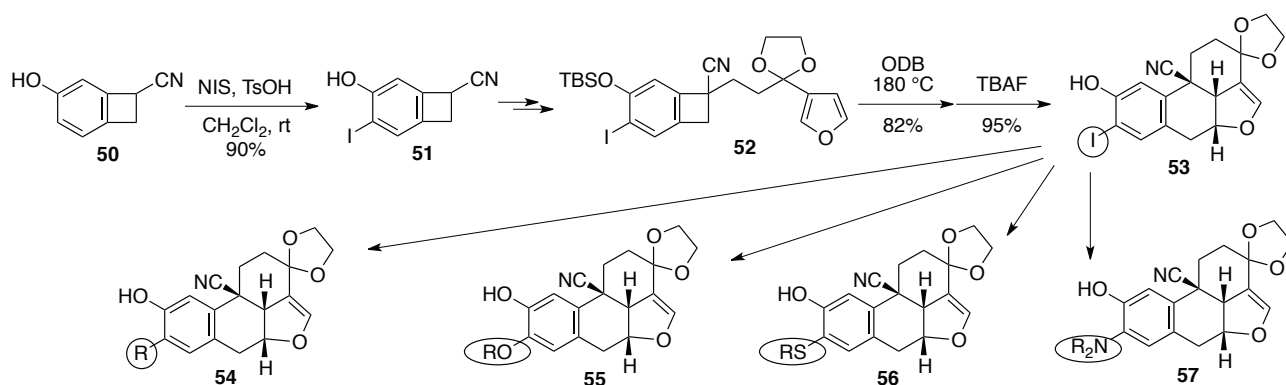
Hypervalent iodine oxidation of BCB was adopted for the synthesis of dioxy-substituted derivatives **44** and **45** (Scheme 8). The alkylated BCB **46** derived from **6** was subjected to $\text{PhI}(\text{OAc})_2$ oxidation conditions in MeOH to furnish the dimethoxy product **47**, which was immediately exposed to zinc reduction to afford the required dioxy-BCB **48** in moderate yields. This compound was successfully

converted to the tetracyclic system **44** through the thermal reaction of the intermediate **49**. Another dioxy-substituted derivative **45** was also synthesized from the corresponding isomer of **6** in a similar way. Biological evaluation of these derivatives revealed that the derivative **45** was the most potent and promising compound for a new anti-Alzheimer's disease candidate.^{10a}



Scheme 8. Synthesis of Dioxy-Substituted Derivatives via Hypervalent Iodine Oxidation of BCB

Taking the substitution pattern of **45** into consideration, divergent derivatization of the iodide **53** was undertaken utilizing various cross-coupling reactions (Scheme 9).^{10b} The substrate tetracyclic compound **53** was synthesized from BCB **50** via regioselective iodination and thermal cycloaddition. Sonogashira, Heck, and Suzuki coupling reactions of **53** proceeded to give **54** with a variety of carbon side-chain. Copper-catalyzed coupling reactions with various alcohols or thiols afforded corresponding ether and sulfide derivatives (**55** and **56**) in moderate to good yields.^{10b} Copper-mediated amination of **53** also successfully provided the amino derivatives **57**.¹¹

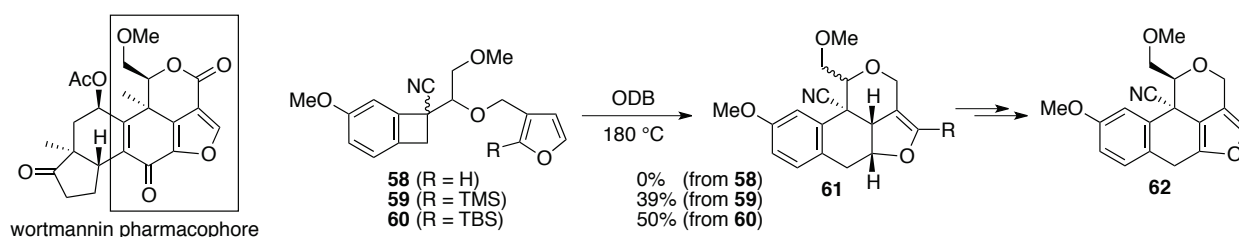


Scheme 9. Divergent Derivatization Using Cross-Coupling Reactions

Comprehensive structure-activity relationship studies revealed that introduction of the carbon side-chain (**54**) caused significant cytotoxicity on rat cortical neurons, and that ethereal (**55**) and sulfide (**56**) linkage gave rise to improved anti-Alzheimer's activity, especially in the case of EtO- and PhS- derivatives.^{10b}

(1)-4. Others¹³⁻¹⁵

Furano-steroidal natural products have been known to exhibit significant biological activities such as PI3-kinase inhibitor wortmannin.¹² For the construction of simplified pharmacophore structure of wortmannin, the OQM strategy was examined to find it was an effective approach (Scheme 10).¹³ Although the thermal reaction using simple substrate **58** did not give desired product unexpectedly, the silyl-containing substrates **59** and **60** afforded the cycloadduct **61** in a moderate yield. In the case of **58**, undesired cycloaddition reaction occurred involving the 2,3-double bond of the furan ring (instead of the 4,5-double bond to form desired **61**). It was remarkable that this cycloaddition proceeded via *exo* TS, probably due to the steric repulsion between the silyl substituents and the aromatic moiety in *endo* TS (Figure 6), which was consistently preferable TS in the forementioned cycloaddition reactions of the OQM and the furan moiety. The compound **61** thus obtained was transformed into **62**, which would be an important precursor for the wortmannin pharmacophore.¹³



Scheme 10. Synthetic Study toward Wortmannin Pharmacophore Structure

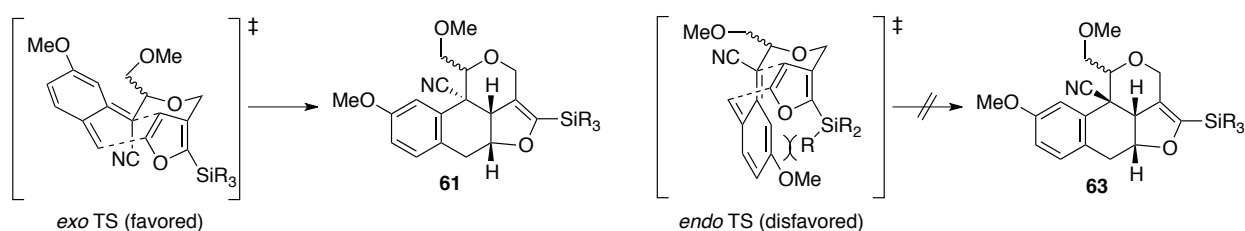
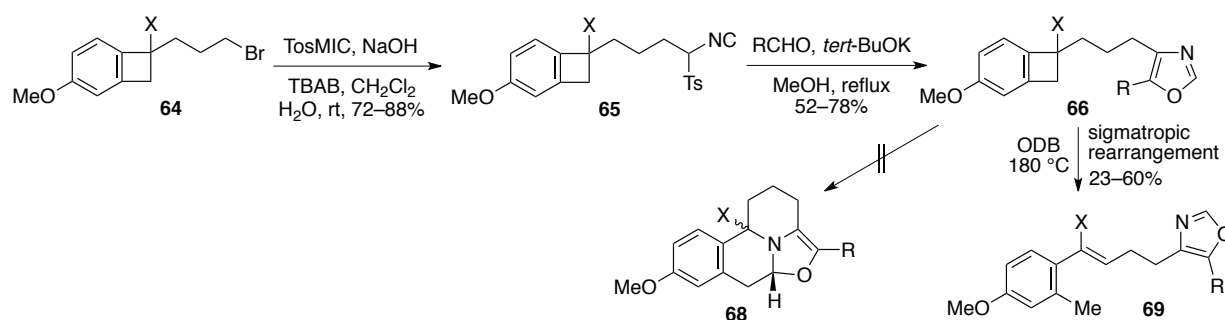


Figure 6. Possible Transition States for *exo*-Adduct **61** and *endo*-Adduct **63**

If the furan moiety can be replaced with an oxazole ring, the construction of novel tetracyclic framework containing the isoquinoline and oxazole ring is expected (Scheme 11). The substrates for such thermal reactions were prepared from the bromo-BCB **64** (X = H or CN). The bromides **64** were reacted with TosMIC under alkaline condition to afford the isocyanides **65**, which were further converted to the oxazole derivatives **66** upon treatment with aldehydes and *tert*-BuOK (R = H or Ph). However, attempts on the thermal reactions of these substrates **66** ended in failure. The desired tetracyclic compounds **68** could not be detected, and the toluene derivatives **69** were isolated in 23–60% yields, via the sigmatropic rearrangement exemplified in Scheme 4. These results suggested that the oxazole ring did not have a

sufficient reactivity toward the [4+2] cycloaddition in the OQM chemistry.¹⁴



Scheme 11. Attempt on the Cycloaddition of Oxazole Instead of Furan

Finally, several furan-fused tetracyclic compounds, as well as several BCBs, were found to exhibit interesting bioactivity on enhancement of hyperthermia-induced apoptosis of human lymphoma cells.¹⁵ These findings suggest that the furan-fused tetracyclic compounds may be applied to a cancer therapy, in addition to the treatment of viral infections and Alzheimer's disease.

(2) 2,3-BENZODIAZEPINE DERIVATIVES

As mentioned in the "INTRODUCTION" section, the ring cleavage of BCBs generally requires high temperature over 100 °C. However, the energy barrier of these electrocyclic processes has been reported to depend on the electronic nature of the substituents on the benzylic positions (Figure 7). In general, electron-donating groups bring about acceleration effects on the ring-opening, and the hydroxy-BCB and the dioxy-BCB have been reported to undergo the ring cleavage at 80 °C and 40 °C, respectively.^{1b,1c,16} Especially the oxy-anion substituent dramatically accelerates the ring fission,¹⁷ and the OQM can be generated even at -25 °C with a strong outward torquoselectivity.¹⁸ In relation to these effects, our group has also reported that the silylmethyl group can significantly accelerate the OQM formation by the σ -donating effects of a C-Si bond.¹⁹

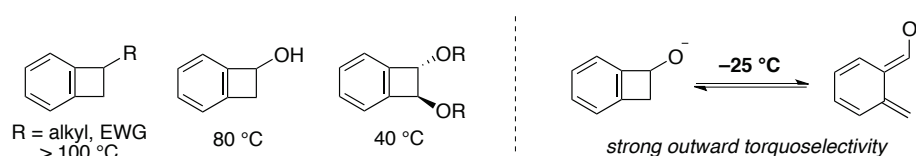


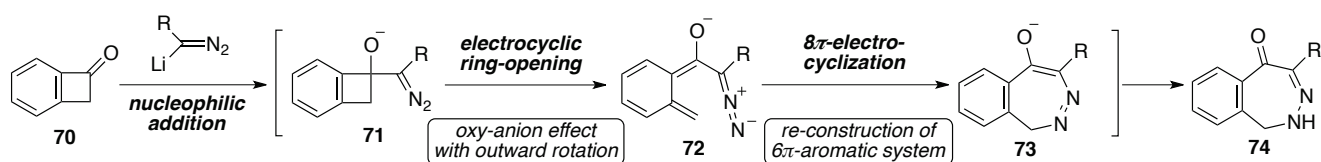
Figure 7. Temperatures Required for the OQMs Formation from BCBs

If these acceleration effects are well applicable, extremely mild OQM formation and subsequent transformation process can be established. In fact, several examples applying the oxy-anion effects for the construction of carbocyclic skeleton have been reported so far.²⁰ As a recent application for the

construction of heterocyclic skeleton, facile transformation of benzocyclobutenones into the 2,3-benzodiazepine nucleus is described herein.

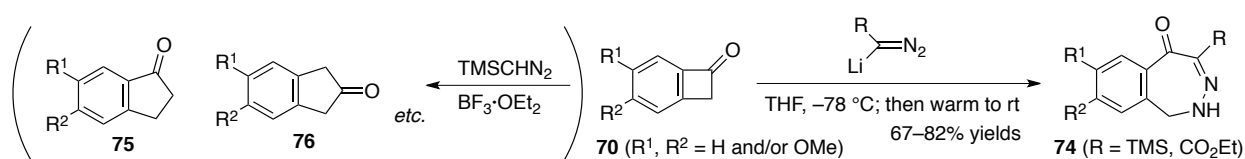
(2)-1. Insertion of diazomethylene into benzocyclobutenones²¹

The concept of 2,3-benzodiazepine construction through tandem electrocyclic reactions including OQM chemistry is depicted in Scheme 12. The nucleophilic addition of diazomethylene anion to benzocyclobutenone **70** will give the adduct oxy-anion **71**, which will undergo the 4π -electrocyclic ring-opening at quite low temperature with an exclusive outward rotation of the oxide group. The diazomethylene group will be inevitably forced to orient to an inner side to form OQM **72**, whose geometry is crucial for the subsequent 8π -electrocyclization. Reconstruction of 6π -aromatic system will be an effective driving force for the 8π -electrocyclization to form the 2,3-benzodiazepine ring system **73**. Overall, the diazomethylene unit is inserted into the four-membered ring of BCB to furnish **74**.



Scheme 12. Overview of Tandem Electrocyclic Reactions for Construction of 2,3-Benzodiazepines

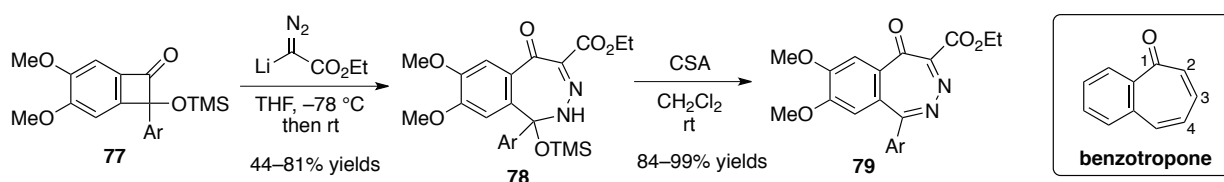
This concept was realized as shown in Scheme 13.²¹ Various substituted benzocyclobutenones were reacted with diazomethylene anion generated from TMS-diazomethane or ethyl diazoacetate at $-78\text{ }^{\circ}\text{C}$ and then immediately warmed to room temperature for 1 h, to provide the 2,3-benzodiazepine derivatives **74** in satisfactory yields. On the other hand, the reaction with TMS-diazomethane under a Lewis acid condition resulted in one-carbon homologation accompanied by N_2 elimination to afford some indanone derivatives **75**, **76**, etc. Because diazo compounds are unstable and easily eliminate N_2 gas under harsh conditions, the anion-mediated OQM formation under the extraordinarily mild condition enables the diazo reagents to act as a C–N–N three-atom source without N_2 elimination. The initial adduct (diazo-alcohol, **71**) could be isolated by quenching the reaction at $-78\text{ }^{\circ}\text{C}$, but this diazo-alcohol gave rise to only complicated mixture under heating condition ($80\text{ }^{\circ}\text{C}$).²¹



Scheme 13. Reaction of Benzocyclobutenones with Diazomethylene Compounds

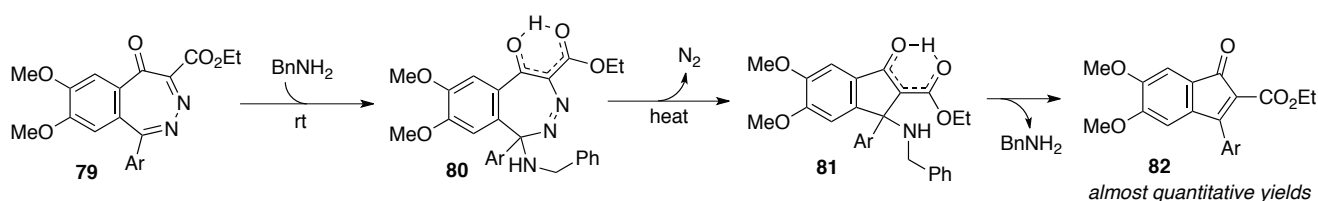
(2)-2. Application for 3,4-diazabenzotropone compounds and their reactivity²²

The core structure of the 2,3-benzodiazepine derivatives **74** can be regarded as a 4,5-dihydro-3,4-diazabenzotropone skeleton. Thus, the benzocyclobutenones having a higher oxidation state than **70** should provide a fully conjugated diazabenzotropone nucleus. Actually, the trimethylsiloxy substrates **77** were prepared and subjected to the 2,3-benzodiazepine-forming reaction conditions afforded **78**, which were transformed into the 3,4-diazabenzotropone compounds **79** upon treatment with CSA in good yields (Scheme 14).²²



Scheme 14. Synthetic Application for 3,4-Diazabenzotropones **79**

The seven-membered ring in **79** contains two electronegative nitrogen atoms and one keto group, and also an electron-withdrawing ester substituent, and thus exhibits a highly electron-deficient property. Therefore, the 5-position of **79** can function as a highly active electron acceptor and receive various nucleophiles. For example, the reaction of **79** with catalytic amount of BnNH_2 easily proceeded to give the adduct **80**, which underwent nitrogen extrusion to furnish indenone derivatives **82** in almost quantitative yields (Scheme 15).²² As an interesting bioactivity of 3,4-diazabenzotropones **79**, induction of DNA fragmentation of human lymphoma U937 cells has been reported (Figure 8).²²



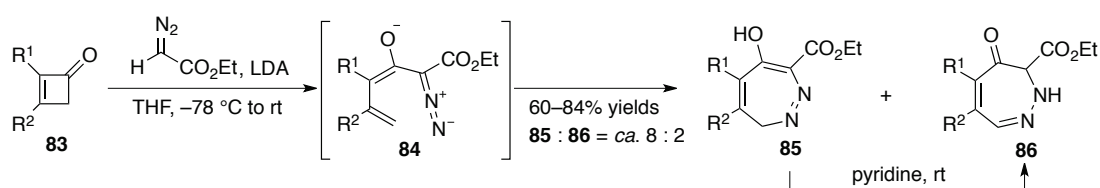
Scheme 15. Nitrogen Extrusion Reaction of 3,4-Diazabenzotropones **79**



Figure 8. Effects of 3,4-Diazabenzotropones **79** on DNA Fragmentation of Human Lymphoma Cells

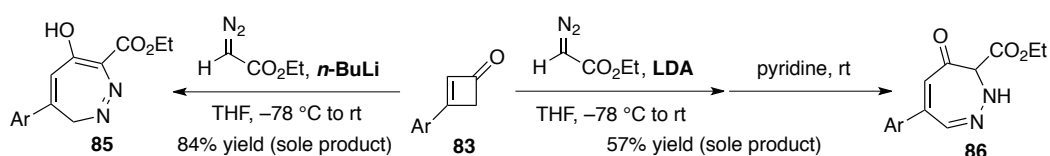
(2)-3. Application for monocyclic 1,2-diazepine compounds²³

The 2,3-benzodiazepine-forming reaction mentioned above was applicable for monocyclic cyclobutenones **83** to produce monocyclic 1,2-diazepine derivatives **85** and **86** via the diazo-diene intermediate **84** in satisfactory yields (Scheme 16). Although **85** and **86** seemed to be simple tautomers at a glance, these isomers could be separated and stably isolated by a column chromatography. After several experiments, the isomer **85** was found to easily isomerize to **86** by treatment with amine bases such as pyridine.²³



Scheme 16. Application for the Monocyclic 1,2-Diazepine Syntheses

Because LDA was used for generation of lithiated diazoacetate in the preliminary survey of the reaction conditions, it was expected that diisopropylamine originated from LDA participated in the isomerization of **85** to **86**. Use of *n*-BuLi instead of LDA as a base suppressed the formation of the minor isomer **86** as expected, and the enol isomer **85** was obtained in 84% yield as a sole product. Conversely, one-pot treatment with pyridine after the reaction using LDA as a base gave the keto isomer **86** solely in 57% yield. Thus, selective synthesis of two isomers **85** and **86** could be accomplished (Scheme 17).²³



Scheme 17. Selective Synthesis of Two 1,2-Diazepine Isomers **85** and **86**

CONCLUSION

In this review, we focused on recent applications of *o*-quinodimethane chemistry involving thermolysis of benzocyclobutene derivatives for the construction of furan-fused tetracyclic compounds and 2,3-benzodiazepine derivatives, mainly including our research results. The obtained heterocycles exerted a wide range of biological activities, and expected to be a new seed for novel drug discovery. These strategies based on the *o*-quinodimethane chemistry will further contribute to both the heterocyclic chemistry and medicinal chemistry in future.

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