JOC Article

Synthesis of a New Class of Furan-Fused Tetracyclic Compounds Using *o*-Quinodimethane Chemistry and Investigation of Their Antiviral Activity

Yuji Matsuya,[†,§] Kazushige Sasaki,[†] Mamiko Nagaoka,[†,§] Hiroko Kakuda,[†] Naoki Toyooka,[†,§] Nobuko Imanishi,[‡] Hiroshi Ochiai,[‡,§] and Hideo Nemoto*[,†,§]

Faculty of Pharmaceutical Sciences, and Department of Human Sciences and Fundamental Nursing, Faculty of Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan

nemotoh@ms.toyama-mpu.ac.jp

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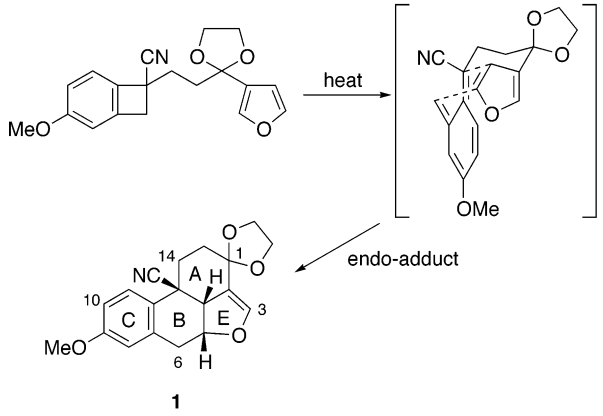
The synthesis and evaluation of antiviral activity of new furan-fused tetracyclic compounds are described. The syntheses were satisfactorily achieved on the basis of *o*-quinodimethane chemistry, using furan-containing benzocyclobutene derivatives as a substrate, in high generality and stereoselectivity. The various derivatives thus synthesized were examined on their inhibitory activity on virus growth using a hemagglutinin (HA) method, leading to a discovery of promising candidates for new antiviral drugs having high activity and good therapeutic index.

Introduction

Naturally occurring furan-fused polycyclic compounds have been reported to exhibit significant and intriguing biological activities,[1] which include antibiotic, cardiotonic, protein tyrosine kinase inhibitory, and antiviral activities as seen in halenaquinone and related natural compounds.[2] In our previous reports on the short-step synthesis of a model core structure associated with such natural products,[3] we revealed that the furan-fused tetracyclic compound **1**, which was concisely synthesized on the basis of *o*-quinodimethane chemistry (Scheme 1),[4] possessed 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. In this paper, we describe the syntheses of various derivatives of **1** as a potential lead compound using thermal cleavage of a benzocyclobutene ring and subsequent intramolecular cycloaddition, and the results of the assay for their antiviral activity.

SCHEME 1



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Results and Discussion

Modification of the A-Ring. First, modification was performed on the A-ring. The acetal structure at the 1-position seems to be a scaffold for modifications of the A-ring. However, generation of the carbonyl group by deacetalization of **1** under acid-catalyzed conditions was found to be difficult because competitive cleavage of the enol ether structure on the E-ring occurred to afford a complex mixture. Accordingly, new substrates for the thermal cycloaddition containing an oxygen function were synthesized as shown in Scheme 2. Known furanyl homoallyl alcohol **3**[5] was prepared from 3-furancarb-

† Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University.

‡ Department of Human Sciences and Fundamental Nursing, Faculty of Medicine, Toyama Medical and Pharmaceutical University.

§ TOMECS (Toyama Medicinal Chemistry Society), Japan.

(1) (a) Lee, R. H.; Slate, D. L.; Moretti, R.; Alvi, K. A.; Crews, P. *Biochem. Biophys. Res. Commun*. **1992**, *184*, 765−772. (b) Alvi, K. A.; Diaz, M. C.; Crews, P.; Slate, D. L.; Lee, R. H.; Moretti, R. *J. Org. Chem*. **1992**, *57*, 6604−6607.

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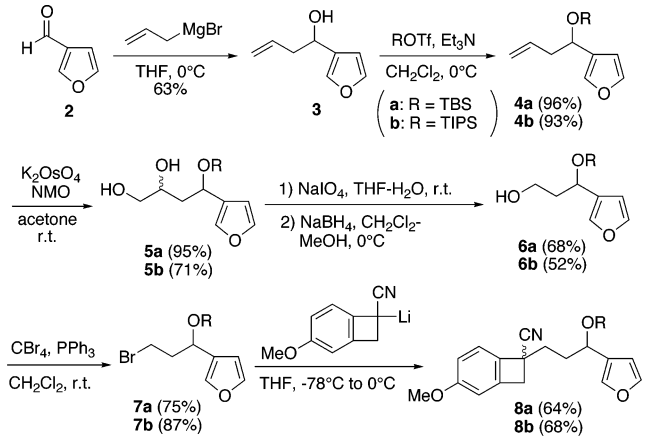
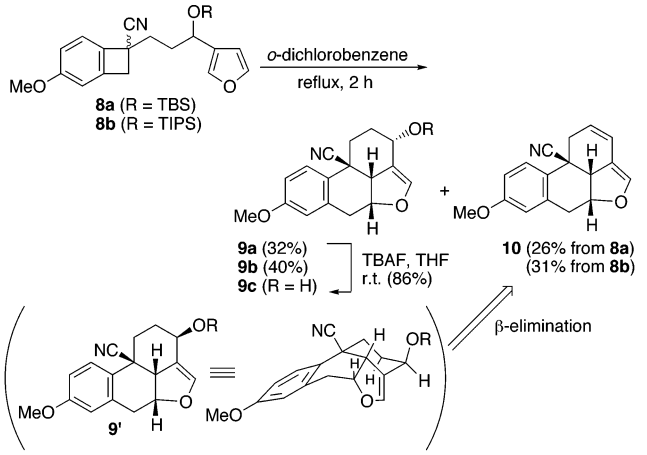
SCHEME 2



SCHEME 3



aldehyde (**2**) by the Grignard addition. This alcohol was converted into silyl ethers **4a** and **4b**, which were subjected to oxidative cleavage followed by reduction with sodium borohydride to give the primary alcohols **6a** and **6b**. Treatment with tetrabromomethane and triphenylphosphine afforded the corresponding bromides **7a** and **7b**, and the reaction of the bromides with a lithiated benzocyclobutene derivative proceeded successfully to furnish the required substrates **8a** and **8b** for the next thermal reaction.

Thermal cycloaddition of **8a** and **8b** was performed in refluxing *o*-dichlorobenzene for 2 h, and the results are summarized in Scheme 3. In both cases, expected tetracyclic products **9a** and **9b** were obtained concomitant with olefin **10**, which might be formed as a result of β-elimination of the silyloxy group. The other stereoisomers could not be detected, implying that the cycloaddition proceeded via the endo transition state as shown in Scheme 1, exclusively. Also, it is suggested that the major precursor of **10** is the epimeric product **9′**,[6] which can be rationally explained by the fact that the silyloxy group in **9′** has axial orientation, facilitating its elimination

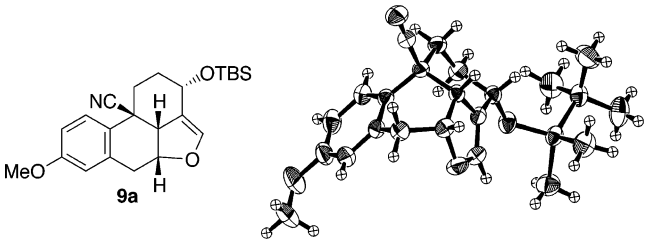
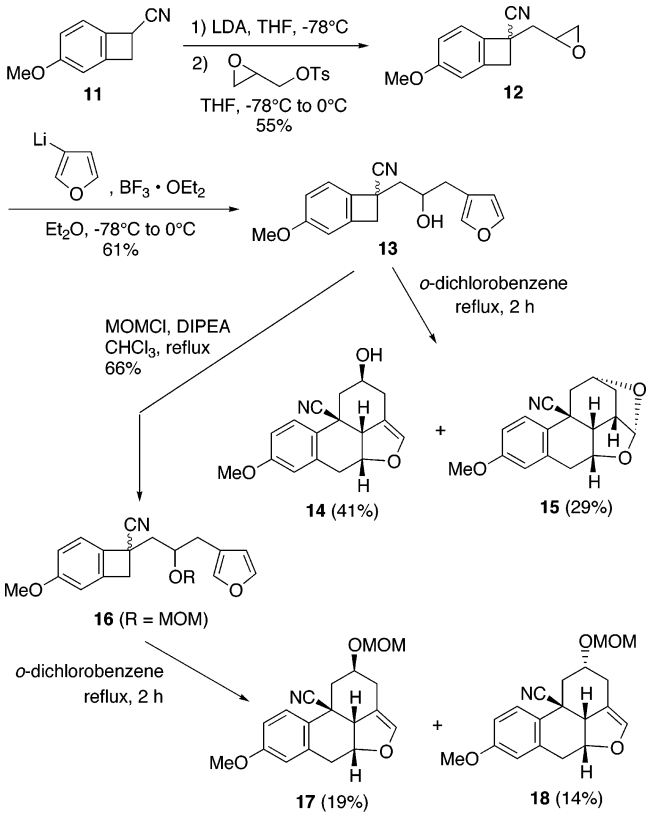


FIGURE 1. ORTEP drawing of compound **9a**.

SCHEME 4



much more than that of **9** because of 1,3-diaxial repulsion or the presence of an adjacent anti-hydrogen for E2 elimination. The derivative **9c** having a free hydroxyl group was also prepared by desilylation of **9a**. The stereostructure of **9a** was confirmed by X-ray crystallographic analysis (Figure 1),[7] and the structure of **9b** was presumed by the similarity of the NMR spectra to that of **9a**. In addition, conversion of **9c** to **10** in refluxing *o*-dichlorobenzene was observed, which supported the stereostructure of **10**.

Next, we investigated the synthesis of oxygen-containing derivatives at the 15-position on the A-ring according to Scheme 4. Benzocyclobutene derivative **11** was lithiated with LDA and was allowed to react with racemic glycidyl tosylate to give the epoxide **12**, which was subjected to oxirane-ring opening with 3-lithiofuran, prepared from 3-bromofuran and *n*-butyllithium, to afford a requisite substrate **13**.

It was found that thermolysis of **13** gave rise to a novel pentacyclic product **15** in addition to a normal cycload-

(6) The diastereomers of the substrate **8a** (or **8b**) were indistinguishable in the spectral data (^{1}H and ^{13}C NMR) and on the TLC, so the ratio of the diastereomers could not be estimated. It should be noted that the diastereomeric ratio of the starting materials **8** does not reflect the product ratio of **9** and **9′** (or **10**) because the chiral center bearing the cyano group in **8** is canceled out during formation of the *o*-quinodimethane intermediate.

(7) Details of the crystallographic data are provided in the Supporting Information.

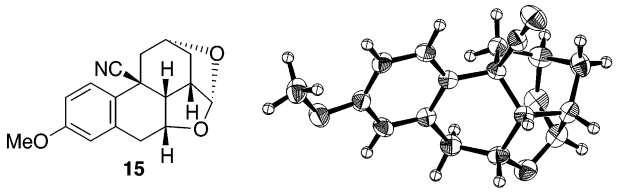


FIGURE 2. ORTEP drawing of compound **15**.

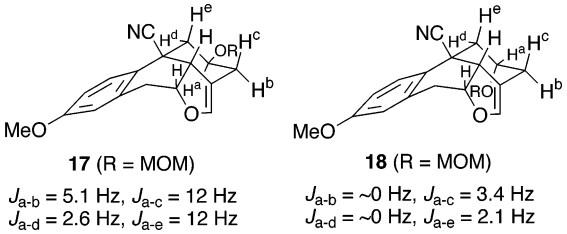


FIGURE 3. Coupling constant correlations of products **17** and **18**.

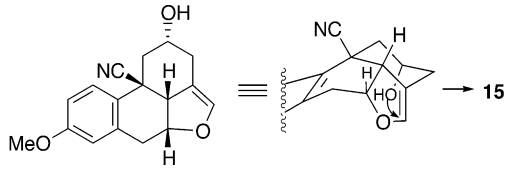
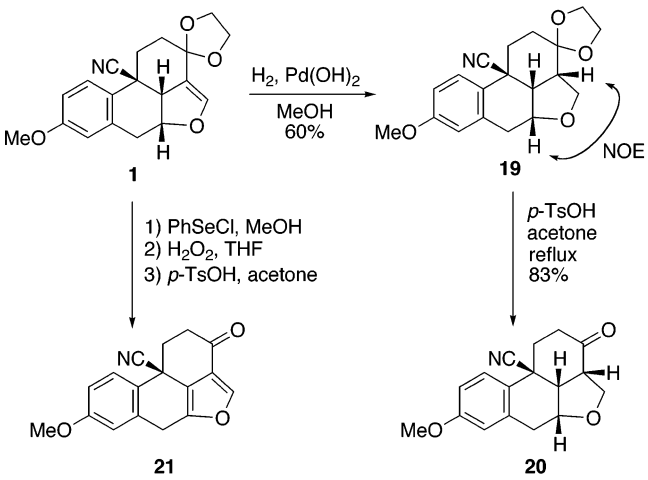


FIGURE 4. Presumed process for the formation of the cyclic acetal **15**.

duct **14**. The structure of **15** was unambiguously determined by X-ray crystallographic analysis (Figure 2).[7] On the other hand, the MOM-protected substrate **16** afforded two tetracyclic adducts **17** and **18**, the stereochemistry of which were presumed by the coupling constant correlations in their ^{1}H NMR spectra (Figure 3). The structure of **14** was supported by the fact that the ^{1}H NMR spectra of **14** and **17** were very much alike in coupling patterns and chemical shifts. As shown in Figure 4, the formation of **15** would be rationalized considering that the isomer of **14** having an axial hydroxyl group readily underwent cyclization due to the proximity of the free hydroxyl group to the enol ether structure on the E-ring.

Modification of the E-Ring. Our next subject is modification of the E-ring composed of the dihydrofuran structure. Transformation of the lead compound **1** to a corresponding tetrahydrofuran derivative was first examined by means of catalytic hydrogenation. This transformation was achieved in a stereoselective manner using palladium hydroxide as a catalyst. The stereostructure of the product **19** was determined by NOE experiment as shown in Scheme 5, and the result implied that the hydrogenation occurred from the less hindered convex face of the substrate having a cage-type conformation. Compound **19** was further transformed into ketone **20** by treatment with *p*-TsOH in acetone. In addition to this reductive transformation, aromatization of the dihydrofuran system of **1** was also achieved in a three-step sequence, providing **21**, which has already been described in our previous paper.[3b]

SCHEME 5



Modification of the C-Ring. The C-ring of the lead compound **1** consists of an aromatic ring bearing a methoxy group at the 9-position. Several variants on this position were synthesized according to Schemes 6 and 7. The benzocyclobutene derivative **11** was demethylated by treatment with trimethylsilyl iodide, and the phenolic compound **22** thus obtained was alkylated with an alkyl bromide having a three-carbon chain to afford **23**. Treatment of the phenol **23** with TBSOTf gave the corresponding silyl ether **24** in good yield. After removal of THP group, the resulting alcohol **25** was oxidized with PDC and subsequently treated with 3-lithiofuran to give the alcohol **26**, which was converted into the ketone **27** by reoxidation. The compound **28** obtained by ketalization of the ketone was subjected to thermal cycloaddition to furnish new tetracyclic derivative **29a** having a silyloxy group at 9-position with an exclusive stereoselectivity. A free-hydroxy derivative **29b** and TIPS derivative **29c** were also synthesized from **29a**. A 9-unsubstituted derivative **33** was synthesized as shown in Scheme 7. A commercially available benzocyclobutene **30** was coupled with a known furan-containing alkyl bromide **31**[3b] to give **32**, the thermolysis of which afforded **33** as a sole stereoisomer again. The ^{1}H NMR spectra of the products **29a**−**c** and **33** showed good similarity to that of the lead compound **1**.

Evaluation of the Bioactivity. The antiviral activity of the furan-fused tetracyclic compounds obtained in this study was surveyed using the assay method of hemagglutinin (HA) titers.[8] 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 Table 1.

As can be seen in the table, most of the test compounds more or less exhibited the antiviral activity, and some of them were much more potent than the lead compound **1**. On the other hand, the compounds **15**, **20**, and **21** showed no or much less activity as compared to **1**, which suggested the importance of the ethylene ketal at the 1-position, the dihydrofuran structure at the E-ring, and the presumably rigid open-cage conformation of the molecule. Among all of the congeners examined in this

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SCHEME 6

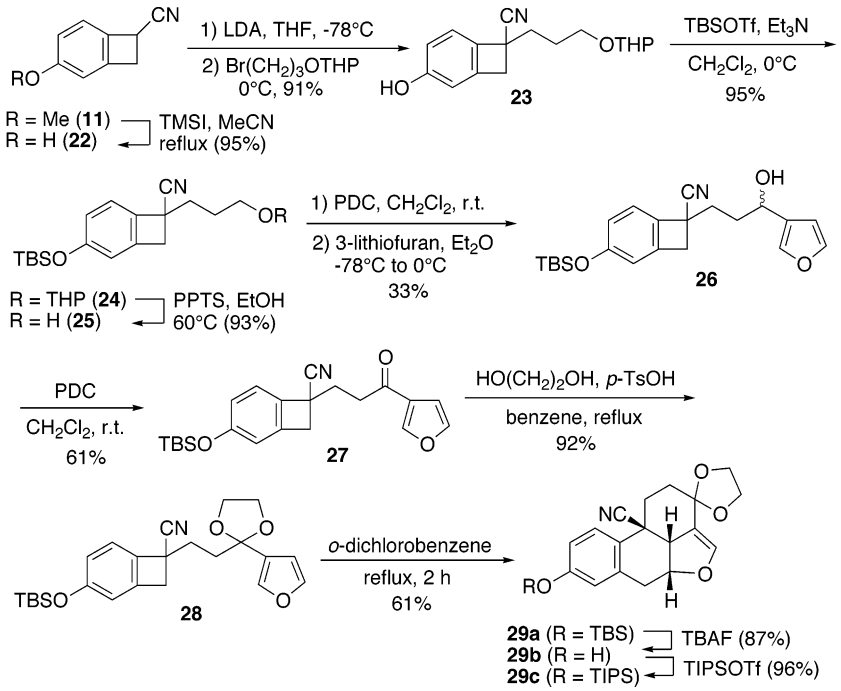


TABLE 1. The Effect of Synthesized Furan-Fused Tetracyclic Compounds on the Growth of HVJ in LLC-MK2 Cells[a]

	HA titers in culture supernatants in the presence of the indicated sample concentrations (μg/mL)[b]						MIC (α)[c]	MCC (β)[d]	therapeutic index (α/β)
compound	2000	1000	500	250	125	62.5	(μg/mL)	(μg/mL)	
1	16	32	32	32	32	64	2000	62.5	32
9b	64	64	64	64	64	64			
9c	4	4	4	32	64	64	500	125	4
10				<4	<4	<4	12.5		
14		<4	4	4	16	64	125		
15		64	64	128	128	128			
17		<4	4	4	4	8	62.5		
18		<4	<4	4	4	4	62.5		
19	4	4	4	16	64	64	250	>2000	<0.125
20	128	256	512	512					
21					256	256			
29a	<4	8	32	64	64	64	1000	>2000	<0.5
29b				32	32				
29c						<4			
33	<4	<4	<4	<4	32	32	250	125	2

	sample concentrations (μg/mL)						MIC (α)[c]	MCC (β)[d]	therapeutic index (α/β)
compound	5	2.5	1.25	0.6	0.3	0.15	(μg/mL)	(μg/mL)	
29c	<4	<4	4	8	32	128	0.6	125	0.0048

[a] The virus was adsorbed on the medium 1 h before the sample was added and was 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 compounds more active than the lead compound (**1**) are shown. [d] The maximum cytotoxic concentrations (MCC) of the compounds having less toxicity than **1** are shown.

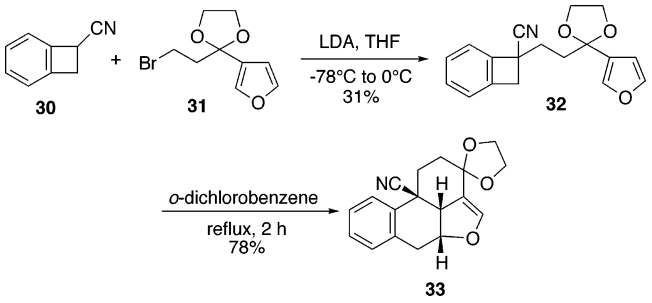
study, we found the triisopropylsilyloxy derivative **29c** to have the most potent inhibitory activity for the virus growth. Accounts of the substituent effects toward the bioactivity are currently under consideration. The cytotoxic assay of several compounds was performed using the MTT method,[9] and the results are summarized as the maximum cytotoxic concentrations (MCC) as well as the calculated therapeutic indexes. Thus, we could find several derivatives having more potent antiviral activity than the lead compound **1**, and, especially, the TIPS derivative **29c** was revealed to have the lowest MIC value and good therapeutic index.

Conclusion

In this paper, we have demonstrated that the intramolecular [4+2] cycloaddition of *o*-quinodimethane generated by the thermal ring opening of benzocyclobutene derivatives is a promising method for constructing a new class of antiviral furan-fused tetracyclic compounds. This synthetic methodology has the advantages of conciseness, short-step sequence, high generality, and high endo-

(9) Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55−63.

SCHEME 7



selectivity. Evaluation of the antiviral activity of new derivatives mentioned above gave several findings regarding the structure−activity relationships. Further efforts to search for more efficient derivatives are currently ongoing in our laboratory.

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Supporting Information Available: Synthetic procedure and characterization data for all new compounds, including ^{1}H and ^{13}C NMR spectra, crystallographic data for **9a** and **15**, and procedure for the bioassay. This material is available free of charge via the Internet at http://pubs.acs.org.

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