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SYNTHESIS OF NEW POTENTIALLY ANTIVIRAL FURAN-FUSED COMPOUNDS BY THERMOLYSIS OF BENZOCYCLOBUTENE DERIVATIVES

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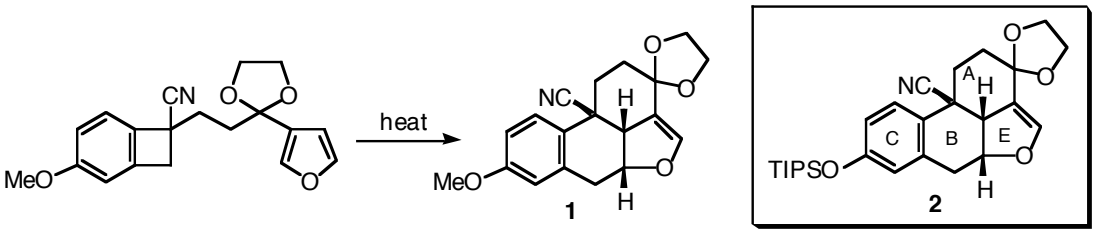
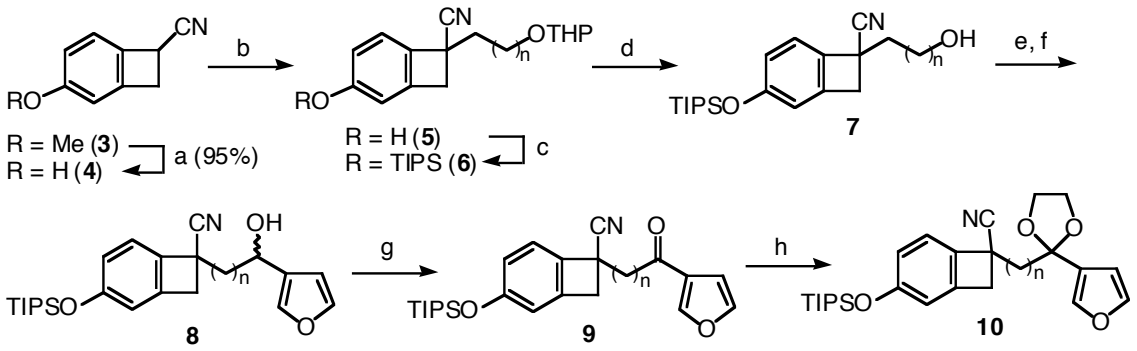
Abstract – New potentially antiviral furan-fused tetracyclic compounds were prepared using intramolecular cycloaddition of *o*-quinodimethane generated by thermolysis of benzocyclobutene derivatives. It was found that the reaction course was changed depending on the length of alkyl chain connecting quinodimethane and furan ring.

In the course of our continuous research on *o*-quinodimethane chemistry,[1] we have reported a new efficient access to the furan-fused tetracyclic compounds relating to pentacyclic polyketides, halenaquinol and halenaquinone, which are reported to exhibit significant biological activities.[2] This model study revealed a new finding that the furan-fused compound (**1**) synthesized *via* intramolecular Diels-Alder reaction of *o*-quinodimethane showed a potent antiviral activity against the Sendai virus.[3] After screening of several congeners, it was found that the TIPS derivative (**2**) possesses *ca*. 2000 times as strong activity as **1**,[3] which prompted us to investigate the structure-activity relationships in detail. In this communication, we wish to report the synthetic approach for **2** and the homologues on its A-ring by means of the intramolecular Diels-Alder reaction.



Scheme 1

To synthesize the benzocyclobutene derivatives (**10**) for thermal cycloaddition, the connection of benzocyclobutene with furan ring having various length of methylene chain was carried out as shown in Scheme 2. Readily available benzocyclobutene derivative (**3**)[4] was demethylated by treatment with iodotrimethylsilane to give the phenol (**4**), which was alkylated with several kinds of alkyl bromide in the presence of 2 eq. of LDA. Introduction of triisopropylsilyl group was performed using TIPSOTf to afford **6** in good yields. After removal of THP group with PPTs, resulting alcohol (**7**) was subjected to Swern oxidation to give the aldehyde, which was immediately treated with 3-lithiofuran, prepared from 3-bromofuran and *n*-butyllithium, to afford the adduct (**8**) as a mixture of diastereomers. Treatment of the alcohol (**8**) with PDC followed by ethylene glycol in the presence of *p*-TsOH afforded the requisite acetal (**10**), the precursors of our target polycyclic compounds *via* thermal intramolecular cycloaddition. For the compound **9a** (n = 1), the ketalization did not proceed probably due to steric hindrance.



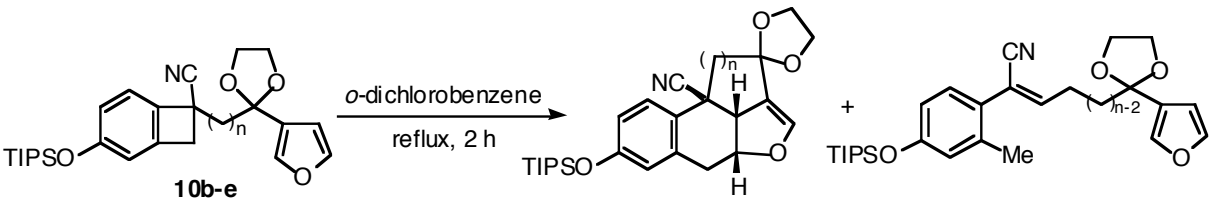
Reagents and conditions: (a) TMSI, MeCN, reflux; (b) LDA, THF, -78°C, then $BrCH_2(CH_2)_nOTHP$, -25°C; (c) TIPSOTf, Et_3N, CH_2Cl_2, 0°C; (d) PPTs, EtOH, 60°C; (e) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then Et_3N; (f) 3-lithiofuran, Et_2O, -20°C; (g) PDC, MS 4A, CH_2Cl_2, rt; (h) ethylene glycol, *p*-TsOH, benzene, reflux.

	Yield (%)					
	5	**6**	**7**	**8** (in 2 steps)	**9**	**10**
n = 1 (**a**)	77	89	79	35	41	0
n = 2 (**b**)	79	96	91	43	46	65
n = 3 (**c**)	95	91	85	45	63	65
n = 4 (**d**)	83	97	68	59	34	44
n = 6 (**e**)	79	98	76	58	42	34

Scheme 2 Preparation of the Substrates for Thermal Cycloaddition

With four substrates (**10b-e**) for thermal cycloaddition in hand, we explored their conversion into tetracyclic system by intramolecular Diels-Alder reaction of *o*-quinodimethane generated by thermal ring opening of the benzocyclobutene, and the results are summarized in Scheme 3. All the reactions were performed in refluxing *o*-dichlorobenzene (bp 180°C) for 2 h. The substrate (**10b**) afforded our desired cycloadduct (**2**) in good yield with an exclusive stereoselectivity.[5] On the other hand, for the substrates (**10c-e**) having longer alkyl chain, the efficiency for the formation of tetracyclic products (**11**) obviously decreased. Instead, substituted toluene derivatives (**12**)[6] were formed dominantly, which were sole products in the cases of **10d** (n = 4) and **10e** (n = 6) as a substrate. The stereostructure of the product (**11c**)

was unambiguously determined by X-Ray analysis of the corresponding desilylated compound (**13**) (Figure 1).[7]



Substrate	Result
10b (n = 2)	**2** (62%), **12b** (0%)
10c (n = 3)	**11c** (18%), **12c** (46%)
10d (n = 4)	**11d** (0%), **12d** (71%)
10e (n = 6)	**11e** (0%), **12e** (78%)

Scheme 3 Thermolysis of the Compounds (**10b-e**)

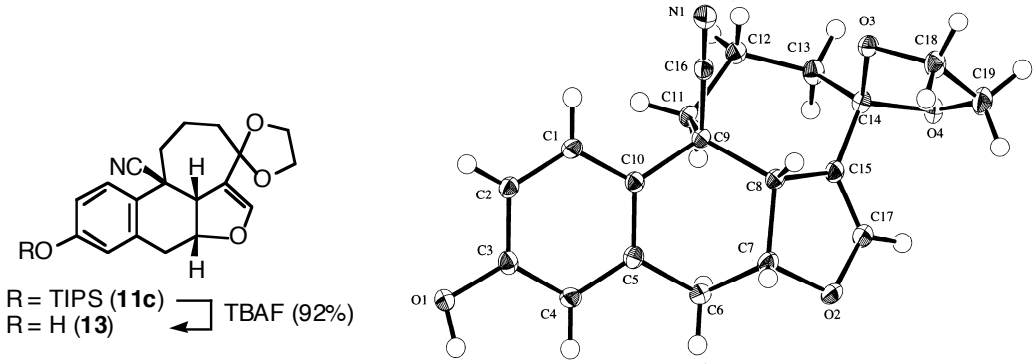
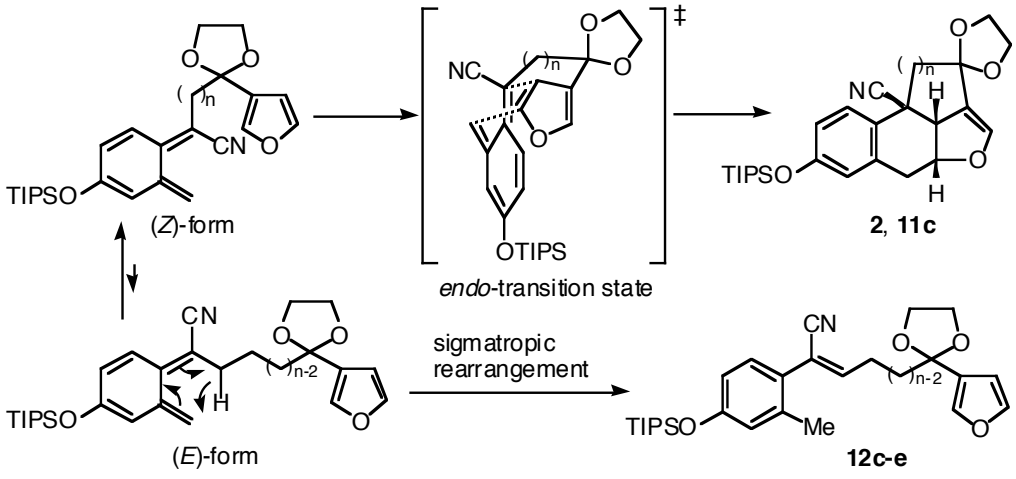


Figure 1 ORTEP Drawing of the Compound (**13**)

These results are rationalized as follows. The cycloadducts (**2**, **11c**) possessing all-*cis* relative configurations can be formed *via endo*-transition state from thermodynamically preferable (*Z*)-*o*-quinodimethane. This transition state energy would be affected by the ring-size corresponding to A-ring (Scheme 4).



Scheme 4 Plausible Reaction Pathway

In the cases of **10c-e**, higher energy level of the transition state compared to **10b** (six-membered ring) would diminish the reaction rate toward the cycloaddition, consequently sigmatropic [1,5] rearrangement from (*E*)-*o*-quinodimethane[8] could predominate over the cycloaddition.

The synthetic study of the other congeners of **2** is now ongoing in our laboratory,[9] and details of the biological evaluations of them, including **11c**, will be reported in due course.

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

1. H. Nemoto and K. Fukumoto, *Tetrahedron*, 1998, **54**, 5425.
2. (a) N. Toyooka, M. Nagaoka, H. Kakuda, and H. Nemoto, *Synlett*, 2001, 1123. (b) N. Toyooka, M. Nagaoka, E. Sasaki, H. Qin, H. Kakuda, and H. Nemoto, *Tetrahedron*, 2002, **58**, 6097.
3. Unpublished data. The results of the bioassay for these compounds will be reported elsewhere in near future.
4. T. Kametani, Y. Kato, T. Honda, and K. Fukumoto, *J. Am. Chem. Soc*., 1976, **98**, 8185.
5. The stereostructure of this compound was presumed based on the comparison of the NMR spectra with those of the compound (**1**), the structure of which was confirmed by X-Ray analysis; See, ref. 2. NMR data for **2**: ^{1}H-NMR (300 MHz, $CDCl_3$) □: 7.16 (1H, d, *J* = 8.1Hz), 6.82 (1H, d, *J* = 8.1Hz), 6.78 (1H, s), 6.00 (1H, d, *J* = 1.7Hz), 5.29 (1H, d, *J* = 10Hz), 4.02-4.00 (1H, m), 3.93-3.85 (4H, m), 3.25 (1H, dd, *J* = 16, 3.0Hz), 3.12 (1H, dd, *J* = 16, 1.6Hz), 2.88 (1H, dt, *J* = 15, 3.1Hz), 2.52 (1H, td, *J* = 15, 3.1Hz), 1.92-1.84 (2H, m), 1.30-1.17 (3H, m), 1.08 (18H, d, *J* = 6.6Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) □: 156.10, 142.98, 136.71, 126.71, 122.97, 122.40, 121.92, 118.46, 110.30, 104.68, 79.75, 65.28, 63.65, 51.17, 35.20, 33.94, 31.28, 29.69, 17.88, 12.60.
6. The corresponding *E*-isomers could not be detected in all cases, and the geometries were presumed based on the reaction mechanism.
7. The compound (**13**) was recrystallized from AcOEt-hexane to form a colorless needle crystal ($C_{19}H_{19}NO_4$, mp 222-223°C) which has approximate dimensions of 0.35 x 0.10 x 0.10 mm (a primitive monoclinic cell, space group $P2_1/n$ with unit cell parameters: *a* = 7.7330(6) *Å*, *b* = 10.4605(6) *Å*, *c* = 19.007(1) *Å*, □ = 90.959(1)°, *V* = 1537.3(2) *Å*^{3}, Z = 4, D_{calc} = 1.41 g/cm^3). The data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo-K□ radiation (□ = 0.71069 *Å*). Of the 18177 reflections which were collected, 4728 were unique (R_{int} = 0.029). The

structure was solved by direct methods (SIR97), and full-matrix least-squares refinement was based on 4493 observed reflections ($I > -3.00\sigma(I)$, $2\theta < 60.06$) and 220 variable parameters ($R = 0.057$, $R_w = 0.109$, $R1 = 0.039$ for $I > 2.0\sigma(I)$ data).

8. The first description concerning [1,5] sigmatropic rearrangement of *o*-quinodimethanes; T. Kametani, M. Tsubuki, Y. Shiratori, Y. Kato, H. Nemoto, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, 1977, **42**, 2672.
9. For example, removal and several transformations of the cyano group, which plays an important role for lowering LUMO energy level of the quinodimethanes in the inverse electron-demand Diels-Alder step, are being examined.