Notes

Study on the Reaction Mechanism of the Base-Catalyzed Intramolecular Diels–Alder Reaction of Furfuryl Propargyl Ethers

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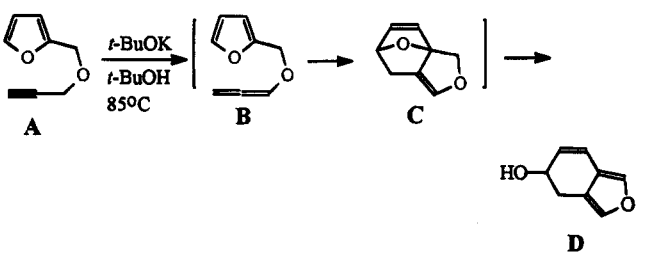
There is considerable current interest in the intramolecular Diels–Alder reaction, and it has been applied to a number of synthetic objectives with notable success.[1] The vast majority of the work reported in this area has dealt with reactions utilizing ethylenic and acetylenic dienophiles. On the other hand, the intramolecular Diels–Alder reaction of allene has received much less attention.[2] A decade ago, Kanematsu *et al.* demonstrated that the allene unit is a versatile synthon as a dienophile in the intramolecular cycloaddition due to the absence of unfavorable nonbonded interactions in the transition state.[3] Afterward, they developed a furan ring transfer reaction via the intramolecular Diels–Alder reaction of furan diene and allenyl ether dienophile and applied this reaction to the synthesis of natural products,[4] Scheme 1. For the purpose of furan ring transfer reaction, in all of their cases there were only one carbon atom and one oxygen atom connection between the furan diene and the allene dienophile for the cycloaddition. In these cases, the cycloadducts were not isolated under the reaction conditions but were further transferred to the isobenzofuran precursors via ring opening of the bridged oxygen ring of the cycloadducts. Recently, we accomplished the intramolecular Diels–Alder reactions of furans with allenyl ethers by varying the chain length and found the very high effect of the chain length on the structure and reactivity of the cycloadducts.[5]

Scheme 1



In order to investigate the reaction mechanism of the intramolecular Diels–Alder reaction of furfuryl allenyl ethers, we accomplished the base-catalyzed intramolecular cycloaddition of compounds **10a–e** and found a novel reaction involving an intramolecular Diels–Alder reaction followed by a methylthio group 1,4–migration.[6] It is the aim of this paper to discuss the reaction mechanism of the intramolecular Diels–Alder reaction of furfuryl allenyl ethers including the furan ring transfer reaction and to describe the full experimental details of the novel methylthio group 1,4–migration reaction.[6]

Results and Discussion

First of all, the furfuryl propargyl ethers **1a** and **1b** with two methyl groups at the furfurylic position were prepared for the intramolecular cycloaddition study. Metalation of furan and 2-methylfuran with *n*-BuLi in dry tetrahydofuran (THF) at 25 °C followed by addition of acetone and then propynylation of the reaction mixture with propargyl bromide in dry dimethyl sulfoxide (DMSO) and benzene at 25 °C gave compounds **1a** and **1b** in 65–70% yields, respectively. Refluxing the propargyl ethers **1a** and **1b** with *t*-BuOK in *t*-BuOH at 85 °C for 5 h gave compounds **6a** and **6b** in 70–80% yields, respectively. No detectable amount of the cycloadducts **3a** and **3b** was obtained even though the furfurylic position was blocked with two methyl groups.

Thus, we proposed that the cycloadducts **3a** and **3b**, possessing the 3,10-dioxatricyclo[5.2.1.$0^{1,5}$]deca-4,8-diene structure, are highly strained and under the reaction conditions they easily undergo ring opening of the bridged oxygen atom to form the zwitterions **4a** and **4b** as the reaction intermediates. Protonation of the alkoxide ion and nucleophilic attack on the oxonium ion by the solvent or base gave the intermediates **5a** and **5b**, which underwent aromatization to give **6a** and **6b** as the major products respectively (Scheme 2). Oxidation of **6a** and **6b** with *m*-CPBA in CH_2Cl_2 gave the lactones **7a** and **7b** in 90% yields, respectively.

In order to prove our hypothesis on the reaction mechanism of the base-catalyzed intramolecular Diels–Alder reactions of furfuryl propargyl ethers as shown in Scheme 2 and to see the effect of a methylthio group at the 5 position of the furan ring on the intramolecular Diels–Alder reaction, the furfuryl propargyl ethers **10a–e**

(1) For reviews see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 19. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (d) Ciganek, E. *Org. React.* **1984**, *32*, 1. (e) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. (f) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (g) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

(2) For some examples of the intramolecular Diels–Alder reactions of allenic dienophiles, see: (a) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315. (b) Himbert, G.; Diehl, K.; Mass, G. *J. Chem. Soc., Chem. Commun.* **1984**, 900. (c) Harrison, R. M.; Hobson, J. D.; Midgley, A. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1960. (d) Saxton, H. M.; Sutherland, J. K.; Whaley, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1449. (e) Hayakawa, K.; Yasukuchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 1837. (f) Hayakawa, K.; Nagatsugi, F.; Kanematsu, K. *J. Org. Chem.* **1988**, *53*, 860. (g) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1987**, *28*, 5895. (h) Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1989**, *30*, 6559. (i) Yoshida, M.; Hiromatsu, M.; Kanematsu ,K. *Heterocycles*, **1986**, *24*, 881. (j) Hayakawa, K.; Ohsuki, S.; Kanematsu, K. *Tetrahedron Lett.* **1986**, *27*, 947. (k) Yoshida, M.; Hiromatsu, M.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1168. (l) Yasukouchi, T.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1989**, 953. (m) Yoshida, M.; Kanematsu, K. *Heterocycles* **1987**, *26*, 3093.

(3) Hayakawa, K.; Yodo, M.; Ohsuki, S.; Kanematsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6735.

(4) (a) Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689. (b) Yamaguchi, Y.; Hayakawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1987**, 515. (c) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1987**, *52*, 2040. (d) Yamaguchi, Y.; Tatsuta, N.; Hayakawa, K.; Kanematsu, K. *J. Chem. Soc., Chem. Commun.* **1989**, 470. (e) Yamaguchi, Y.; Tatsuta, N.; Soejima, S.; Hayakawa, K.; Kanematsu, K. *Heterocycles* **1990**, *30*, 223. (f) Kanematsu, K.; Soejima, S. *Heterocycles* **1991**, *32*, 1483.

(5) Wu, H. J.; Lin, S. H.; Lin, C. C. *Heterocycles* **1994**, *38*, 1507.

(6) Wu, H. J.; Shao, W. D.; Ying, F. H. *Tetrahedron Lett.* **1994**, *35*, 729.

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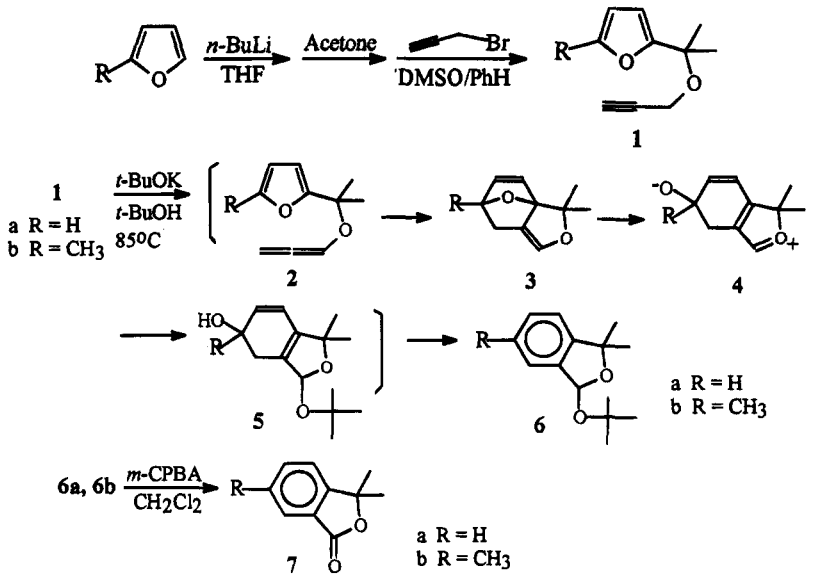
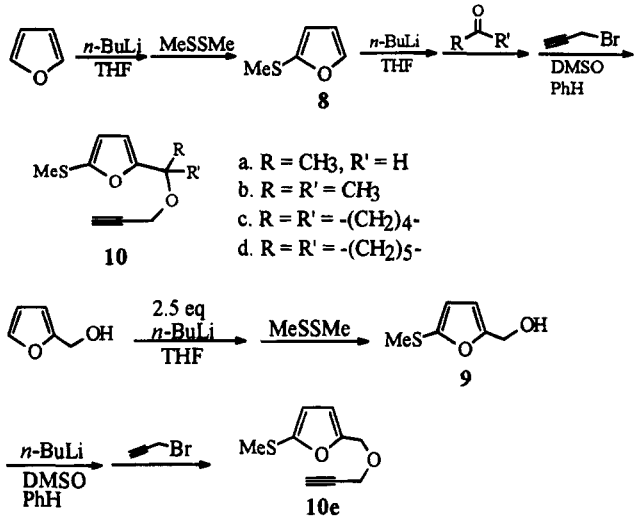
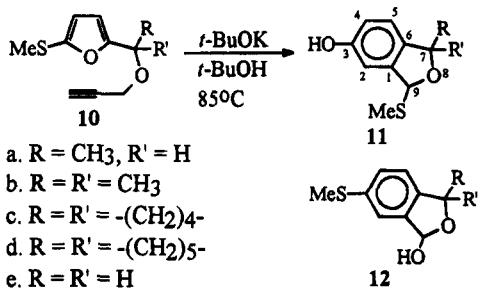
Scheme 2



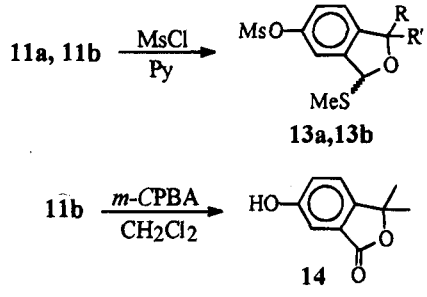
Scheme 3



Scheme 4



Scheme 5



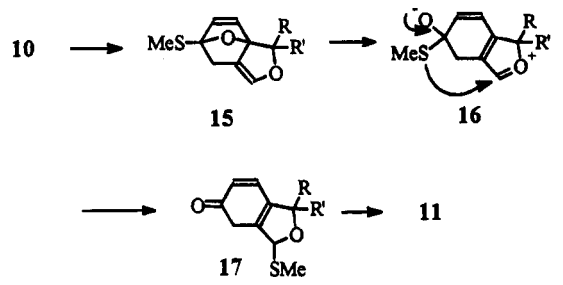
were prepared for the cycloaddition reaction. Metalation of furan with *n*-BuLi in dry THF at 25 °C followed by addition of dimethyl disulfide gave 2-methylthiofuran (**8**) in 80% yield. Reaction of **8** with *n*-BuLi in dry THF at 25 °C followed by addition of acetaldehyde, acetone, cyclopentanone, and cyclohexanone and then propynylation of the reaction mixture with propargyl bromide in dry DMSO and benzene at 25 °C, gave the furfuryl propargyl ethers **10a**, **10b**, **10c**, and **10d** in 65–75% yields, respectively (Scheme 3). Metalation of furfuryl alcohol with 2.5 equiv of *n*-BuLi in dry THF at 25 °C followed by addition of dimethyl disulfide gave compound **9** in 75% yield. Treatment of **9** with *n*-BuLi in dry DMSO and benzene at 25 °C followed by addition of propargyl bromide gave the furfuryl propargyl ether **10e** in 85% yield.

Refluxing the propargyl ether **10a** with *t*-buOK in *t*-BuOH at 85 °C for 5 h gave the rearranged product **11a** in 90% yield. The ^{1}H and ^{13}C NMR spectra of **11a** revealed that **11a** was a mixture of two diastereomers in a ratio of 1:1. The structure of the product of this intramolecular Diels–Alder reaction was assigned to be **11a** instead of **12a**, based on the ^{1}H and ^{13}C NMR spectra of **11a**. Reactions of the propargyl ethers **10b**, **10c**, **10d**, and **10e** under the same reaction conditions gave the rearranged products **11b**, **11c**, **11d**, and **11e** in 80–90% yields, respectively (Scheme 4).

To prove the structure of the product of this reaction to be **11** instead of **12**, some chemical transformations of the reaction products were performed. Mesylation of **11a** and **11b** with methanesulfonyl chloride in pyridine at room temperature for 3 h gave compounds **13a** and **13b**, respectively. The ^{1}H NMR spectra of **13a** and **13b** revealed that the aromatic protons shifted downfield from δ 6.96–6.71 to 7.22–7.10 whereas the chemical shift of the methine proton at C_9 almost remained unchanged. Oxidation of **11b** with *m*-chloroperbenzoic acid in dichloromethane at room temperature gave the lactone **14** (Scheme 5). The molecular structure of the rearranged products **11b** was proven by X-ray analysis of the crystalline compound **11b**.[7]

(7) The author has deposited atomic coordinates for **11b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

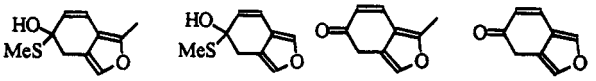
Scheme 6



In all cases of the base-catalyzed intramolecular Diels–Alder reactions of **10a–e**, no detectable amount of the corresponding cycloadducts **15a–e** was obtained. The intramolecular Diels–Alder reactions of **10a–e** gave **11a–e** as the major products, presumably via the corresponding cycloadducts **15a–e** and zwitterions **16a–e**. Repelling the methylthio group by the alkoxide ion followed by nucleophilic attack of the methylthio group on the oxonium ion gave the rearranged intermediates **17a–e**, which underwent aromatization to give **11a–e**, respectively (Scheme 6).

Thus, this novel reaction, involving an intramolecular Diels–Alder reaction followed by a methylthio group migration, supports our hypothesis on the reaction mechanism of the intramolecular Diels–Alder reactions of furfuryl allenyl ethers as shown in Scheme 2.

In the cases of the base-catalyzed intramolecular Diels–Alder reaction of **10a** and **10e**, we did not obtain the corresponding furan ring transfer reaction products **18** and **19** or **20** and **21**. These results might imply that the methylthio group migration from C_3 to C_9 proceeded faster than the furan ring transfer reaction, i.e., the abstraction of the protons on C_7 by the *tert*-butoxide base.



Finally, according to the above results, we propose here in general that the furan ring transfer reactions, discovered by Kenematsu *et al.*,[4] may proceed via a zwitterion, such as **4**, as the reaction intermediates.

Conclusions

In summary, first of all, in the intramolecular Diels–Alder reaction of **1a** and **1b**, we proposed the zwitterions **4a** and **4b** to be the reaction intermediates of the cycloaddition. Second, the base-catalyzed intramolecular Diels–Alder reactions of the furfuryl propargyl ethers **10a–e** gave **11a–e**, respectively, a novel reaction involving an intramolecular Diels–Alder reaction followed by a methylthio group 1,4-migration. These results prove the intramolecular cycloaddition to proceed via the zwitterions **16a–e** as the reaction intermediates. Finally, we propose in general that the furan ring transfer reactions proceed via the corresponding zwitterions as the reaction intermediates.

Experimental Section

General. Melting points were determined in capillary tubes with a Laboratory Devices melting point apparatus and were uncorrected. Infrared spectra were recorded in $CHCl_3$ solutions or on neat thin films between NaCl disks on a Nicolet 520 spectrometer. ^1H NMR spectra were measured in $CDCl_3$ solutions on a JEOL FX-100 FT, a Varian UNITY-300FT or a Brucker AM-400FT spectrometer and were referenced to chloroform (δ 7.26 ppm) or tetramethylsilane (δ 0.00 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a Varian UNITY-300FT or a Brucker AM-400FT spectrometer with the center line of internal $CDCl_3$ (δ 77.0 ppm) as reference. The multiplicities of ^{13}C signals were determined by DEPT techniques. Mass spectra were taken on a JOEL JMS-D100 or TRIO-2000 mass spectrometer. High resolution mass values were taken on a JEOL JMS-D300 mass spectrometer. Elemental analyses were performed at the microanalysis laboratory of National Taiwan University using a Perkin-Elmer 240C analyzer. X-ray analysis was carried out on a Nicolet R3m/V instrument at the Department of Chemistry, National Tsing Hua University. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2 mm) were used, and column chromatography was done by using Merck Kieselgel 60 (70-200 mesh) as the stationary phase.

Preparation of Furfuryl Propargyl Ethers 1a and 1b. To a solution of 2-methylfuran (2.00 g, 24.4 mmol) in dry THF (50 mL) was added *n*-BuLi (12 mL, 30 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. To this solution was added dry acetone (1.55 g, 26.8 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. After evaporation of the solvent under reduced pressure, dry DMSO (20 mL) and dry benzene (20 mL) were added to dissolve the reaction mixture. To this solution was then added propargyl bromide (8.70 g, 73.2 mmol), and the reaction mixture was stirred at 25 °C for 5 h. After addition of saturated NH_4Cl (20 mL) and extraction with ether (5 × 20 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **1b** (3.1 g, 70%): IR (film) 3300, 2120, 1500 cm^{-1}; ^1H NMR (400 MHz) δ 6.15 (d, 1H, J = 2.4 Hz), 5.89 (d, 1H, J = 2.4 Hz), 3.86 (d, 2H, J = 2.2 Hz), 2.33 (t, 1H, J = 2.2 Hz), 2.28 (s, 3H), 1.56 (s, 6H); ^{13}C NMR δ 154.3, 152.0, 108.3, 105.7, 81.1, 73.4, 73.0, 51.3, 25.6, 13.6; DEPT δ 108.3 (CH), 105.7 (CH), 73.0 (CH), 51.3 (CH_2), 25.6 (CH_3), 13.6 (CH_3); LRMS (EI, 30 eV) *m/z* (rel int) 178 (M^+, 5), 123 (100); HRMS (EI) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0982. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.18; H, 7.92. Found: C, 74.40; H, 7.74.

The same reaction conditions and procedure were applied to the synthesis of **1a** (65%, oily): IR (film) 3300, 2120, 1500 cm^{-1}; ^1H NMR (400 MHz) δ 7.39 (m, 1H), 6.32 (m, 1H), 6.28 (m, 1H), 3.86 (d, 2H, J = 2.2 Hz), 2.34 (t, 1H, J = 2.2 Hz), 1.59 (s, 6H); ^{13}C NMR δ 156.4, 142.2, 109.9, 107.4, 81.0, 73.7, 73.1, 51.5, 25.6; DEPT δ 142.2 (CH), 109.9 (CH), 107.4 (CH), 73.1 (CH), 51.5 (CH_2), 25.6 (CH_3); LRMS (EI, 30 eV) *m/z* (rel int) 164 (M^+, 30), 149 (100), 109 (52); HRMS (EI) calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0824. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.88; H, 7.26.

Intramolecular Diels–Alder Reaction of 1a and 1b. Compound **1a** (3.28 g, 20 mmol) was dissolved in 2-methyl-2-propanol (100 mL) in a round-bottomed flask. Potassium *tert*-butoxide (4.5 g, 40 mmol) was added to the solution, and the reaction mixture was refluxed at 85 °C for 5 h. After cooling, saturated NH_4Cl (60 mL) was added, and the reaction mixture was extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **6a** (2.62 g, 80%): IR (film) 1600, 1055 cm^{-1}; ^1H NMR (400 MHz) δ 7.32–7.11 (m, 4H), 6.34 (s, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.36 (s, 9H); ^{13}C NMR δ 148.0, 138.9, 128.7, 127.5, 122.8, 120.3, 99.8, 85.2, 74.6, 30.8, 29.2, 28.8; DEPT δ 128.7 (CH), 127.5 (CH), 122.8 (CH), 120.3 (CH), 99.8 (CH), 30.8 (CH_3), 29.2 (CH_3), 28.8 (CH_3); LRMS (EI, 30 eV) *m/z* (rel inten) 220 (M^+, 5), 147 (100); HRMS (EI) calcd for $C_{14}H_{20}O_2$ 220.1464, found 220.1472. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.38; H, 9.15. Found: C, 76.65; H, 9.31.

The same reaction conditions and procedure were applied to the formation of **6b** (70%, oily): IR (film) 1600, 1060 cm^{-1}; ^1H NMR (400 MHz) δ 7.11–6.99 (m, 3H), 6.29 (s, 1H), 2.35 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H), 1.35 (s, 9H); ^{13}C NMR δ 145.4 139.1, 137.4, 129.7, 123.2, 120.1, 99.7, 85.1, 74.6, 30.9, 29.3, 28.9, 21.2; DEPT δ 129.7 (CH), 123.2 (CH), 120.1 (CH), 99.7 (CH), 30.9 (CH_3), 29.3 (CH_3), 28.9 (CH_3), 21.2 (CH_3); LRMS (EI, 30 eV) *m/z* (rel int) 234 (M^+, 4), 161 (100); HRMS (EI) calcd for $C_{15}H_{22}O_2$

234.1620, found 234.1626. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.65; H, 9.55.

Oxidation of 6a and 6b with *m*-CPBA. To a solution of **6a** (3.00 g, 13.6 mmol) in CH_2Cl_2 (50 mL) was added *m*-chloroperbenzoic acid (*m*-CPBA) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h. After addition of 0.1 N NaOH (30 mL) and extraction with chloroform (4 × 20 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **7a** (2.0 g, 90%): IR (film) 1760, 1280, 1040 cm^{-1}; ^1H NMR δ 7.78–7.34 (m, 4H), 1.58 (s, 6H); ^{13}C NMR δ 169.7, 154.8, 134.0, 128.8, 125.5, 125.0, 120.6, 85.3, 27.2; DEPT δ 134.0 (CH), 128.8 (CH), 125.5 (CH), 120.6 (CH), 27.2 (CH_3); LRMS (EI, 30 eV) *m/z* (rel int) 162 (M^+, 9), 147 (100); HRMS (EI) calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0673.

Spectral data for **7b** (90%): IR (film) 1755, 1280, 1180 cm^{-1}; ^1H NMR δ 7.58 (s, 1H), 7.42 (d, 1H, J = 7.8 Hz), 7.24 (d, 1H, J = 7.8 Hz), 2.39 (s, 3H), 1.58 (s, 6H); ^{13}C NMR δ 169.8, 152.8, 138.9, 135.1, 125.5, 125.3, 120.3, 85.2, 27.2, 21.1; DEPT δ 135.1 (CH), 125.5 (CH), 120.3 (CH), 27.2 (CH_3), 21.1 (CH_3); LRMS (EI, 30 eV) *m/z* (rel int) 176 (M^+, 100), 161 (15), 160 (19); HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0844.

2-Methylthiofuran. To a solution of furan (5.0 g, 73 mmol) in dry THF (100 mL) was added *n*-BuLi (46 mL, 75 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. To this solution was added dimethyl disulfide (8.3 g, 88 mmol) at 0 °C, and the reaction mixture was stirred at 25 °C for 4 h. After addition of saturated NH_4Cl (80 mL) and extraction with ether (5 × 40 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by distillation to give **8** (7.0 g, 80%): bp 130–132 °C (760 mmHg); IR (film) 1500, 740 cm^{-1}; ^1H NMR δ 7.46 (m, 1H), 6.41 (m, 1H), 6.35 (m, 1H), 2.36 (s, 3H); ^{13}C NMR δ 147.1, 144.5, 114.0, 111.2, 18.5; DEPT δ 144.5 (CH), 114.0 (CH), 111.2 (CH), 18.5 (CH_3); LRMS (EI, 30 eV) *m/z* (rel inten) 114 (M^+, 100), 99 (18), 67 (30).

General Procedure for the Preparation of 5-(Methylthio)-2-furfuryl Propargyl Ethers 10a–d. To a solution of 2-methylthiofuran (5.0 g, 43 mmol) in dry THF (100 mL) was added *n*-BuLi (21 mL, 52 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h. To this solution was added acetaldehyde (1.9 g, 44 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. After evaporation of the solvent under reduced pressure, dry DMSO (40 mL) and dry benzene (40 mL) were added to dissolve the reaction mixture. To this solution was added propargyl bromide (8.70 g, 73.2 mmol), and the reaction mixture was stirred at 25 °C for 5 h. After addition of saturated NH_4Cl (50 mL) and extraction with ether (5 × 50 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **10a** (6.15 g, 72%): IR (film) 3300, 2160, 1095 cm^{-1}; ^1H NMR (300 MHz) δ 6.36 (d, 1H, J = 3 Hz), 6.28 (d, 1H, J = 3 Hz), 4.67 (*q*, 1H, J = 6 Hz), 4.18–4.00 (doublet of AB quartet, 2H, J = 16, 2.4 Hz), 2.43 (t, 1H, J = 2.4 Hz), 2.41 (s, 3H), 1.54 (d, 3H, J = 6 Hz); ^{13}C NMR δ 157.1, 147.1, 114.5, 109.4, 79.9, 74.2, 69.3, 55.5, 19.4, 18.7; DEPT δ 114.5 (CH), 109.4 (CH), 74.2 (CH), 69.3 (CH), 55.5 (CH_2), 19.4 (CH_3), 18.7 (CH_3); LRMS *m/z* (rel int) 196 (M^+, 45), 141 (100). Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.44; H, 6.08.

The same reaction conditions and procedure were applied to the preparation of **10b–d**.

α,α-Dimethyl-5-(methylthio)-2-furfuryl propargyl ether (10b): 76% yield; IR (film) 3300, 2160, 1095 cm^{-1}; ^1H NMR (300 MHz) δ 6.31 (d, 1H, J = 3 Hz), 6.23 (d, 1H, J = 3 Hz), 3.87 (d, 1H, J = 2.4 Hz), 2.38 (s, 3H), 2.31 (t, 1H, J = 2.4 Hz), 1.55 (s, 6H); ^{13}C NMR δ 158.7, 147.0, 114.4, 109.1, 80.9, 73.9, 73.1, 51.6, 25.6, 18.7; DEPT δ 114.4 (CH), 109.1 (CH), 73.1 (CH), 51.6 (CH_2), 25.6 (CH_3), 18.7 (CH_3); LRMS *m/z* (rel int) 210 (M^+, 30), 195 (25), 155 (100). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 62.58; H, 6.83.

α,α-Tetramethylene-5-(methylthio)-2-furfuryl propargyl ether (10c): 68% yield; IR (film) 3300, 2150, 1060 cm^{-1}; ^1H NMR (300 MHz) δ 6.35 (d, 1H, J = 3 Hz), 6.27 (d, 1H, J = 3 Hz), 3.90 (d, 2H, J = 2.4 Hz), 2.41 (s, 3H), 2.34 (t, 1H, J = 2.4 Hz), 2.14–1.66 (m, 8H); ^{13}C NMR δ 158.1, 147.0, 114.3, 109.4, 85.1, 80.0, 73.1, 52.2, 36.0, 23.1, 18.7; DEPT δ 114.3 (CH), 109.4 (CH), 80.0 (CH), 52.2 (CH_2), 36.0 ($2CH_2$), 23.1 ($2CH_2$), 18.7 (CH_3); LRMS *m/z* (rel inten) 236 (M^+, 15), 189 (16), 181 (100). Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 66.28; H, 6.74.

α,α,-(Pentamethylene)-5-(methylthio)-2-furfuryl propargyl ether (10d): 65% yield; IR (film) 3300, 2150, 1070 cm^{-1}; ^1H NMR (300 MHz) δ 6.36 (d, 1H, J = 3 Hz), 6.28 (d, 1H, J = 3 Hz), 3.88 (d, 2H, J = 2.4 Hz), 2.40 (s, 3H), 2.32 (t, 1H, J = 2.4 Hz), 1.97~1.70 (m, 6H), 1.43~1.38 (m, 4H); ^{13}C NMR δ 158.3, 146.8, 114.3, 109.7, 81.1, 75.4, 72.8, 50.6, 33.6, 25.4, 22.0, 18.6; DEPT δ 114.3 (CH), 109.7 (CH), 75.4 (CH), 50.6 (CH_2), 33.6 ($2CH_2$), 25.4 (CH_2), 22.0 ($2CH_2$), 18.6 (CH_3); LRMS *m/z* (rel inten) 250 (M^+, 4), 211 (18), 195 (100). Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 66.95; H, 7.31.

5-(Methylthio)-2-furfuryl Alcohol (9). To a solution of furfuryl alcohol (8.0 g, 81 mmol) in dry THF (100 mL) was added *n*-BuLi (129 mL, 206 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h. To this solution was added dimethyl disulfide (11.5 g, 122 mmol) at 0 °C, and the reaction mixture was stirred at 25 °C for 4 h. After addition of saturated NH_4Cl (90 mL) and extraction with ether (5 × 40 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **9** (8.6 g, 74%): IR (film) 3500–3200, 1500, 1010 cm^{-1}; ^1H NMR (300 MHz) δ 6.31 (d, 1H, J = 3 Hz), 6.19 (d, 1H, J = 3 Hz), 4.48 (s, 2H), 3.20 (s, 1H), 2.33 (s, 3H); ^{13}C NMR δ 156.4, 146.9, 114.9, 109.2, 56.9, 18.6; DEPT δ 114.9 (CH), 109.2 (CH), 56.9 (CH_2), 18.6 (CH_3); LRMS *m/z* (rel inten) 144 (M^+, 100), 127 (78), 97 (20).

5-(Methylthio)-2-furfuryl Propargyl Ether (10e). To a solution of **9** (3.0 g, 20 mmol) in dry DMSO (30 mL) and dry benzene (30 mL) was added *n*-BuLi (10 mL, 25 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 0.5 h. To this solution was added propargyl bromide (7.4 g, 62 mmol), and the reaction mixture was stirred at 25 °C for 5 h. After addition of saturated NH_4Cl (30 mL) and extraction with ether (5 × 30 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **10e** (3.2 g, 85%): IR (film) 3300, 2150, 1080 cm^{-1}; ^1H NMR (300 MHz) δ 6.37–6.33 (*m*, 2H), 4.52 (s, 2H), 4.14 (d, 2H, J = 2 Hz), 2.49 (t, 1H, J = 2 Hz), 2.40 (s, 3H); ^{13}C NMR δ 152.9, 142.5, 114.5, 111.6, 79.1, 74.8, 62.9, 56.6, 18.4; DEPT δ 114.5 (CH), 111.6 (CH), 74.8 (CH), 62.9 (CH_2), 56.6 (CH_2), 18.4 (CH_3); LRMS *m/z* (rel int) 182 (M^+, 40), 127 (100). Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.54; H, 5.44.

General Procedure for the Intramolecular Diels–Alder Reaction of the 5-(Methylthio)-2-furfuryl Propargyl Ethers 10a–e. To a solution of **10a**, **10b**, **10c**, **10d**, or **10e** (10 mmol) in 2-methyl-2-propanol (100 mL) was added potassium *tert*-butoxide (3.4 g, 30 mmol) at 25 °C, and the reaction mixture was refluxed at 85 °C for 5 h. After cooling, saturated NH_4Cl (40 mL) was added, and the reaction mixture was extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give the corresponding reaction products **11a**, **11b**, **11c**, **11d**, or **11e**, respectively. These compounds **11a–e** showed characteristic IR bands near 3500–3300, 1620, and 1000 cm^{-1}. Compound **11a** was obstained as a mixture of diastereomers in a ratio of 1:1.

1-Methyl-3-(methylthio)-5-hydroxy-1,3-dihydroisobenzofuran (11a): 82% yield; ^1H NMR (300 MHz) δ 10.23 (brs, 1H), 6.94–6.74 (m, 3H), 6.37 and 6.29 (s, 1H), 5.40 and 5.26 (q, 1H, J = 6 Hz), 1.98 and 1.87 (s, 3H), 1.50 and 1.42 (d, 3H, J = 6 Hz); ^{13}C NMR δ 156.3 and 156.1, 139.6 and 139.2, 134.9 and 134.8, 121.7 and 121.6, 116.3, 109.1 and 108.9, 88.6 and 88.2, 79.9 and 79.6, 22.3, and 21.5, 12.3 and 11.1; DEPT δ 121.7 and 121.6 (CH), 116.3 (CH), 109.1 and 108.9 (CH), 88.6 and 88.2 (CH), 79.9 and 79.6 (CH), 22.3 and 21.5 (CH_3), 12.3 and 11.1 (CH_3); LRMS *m/z* (rel int) 196 (M^+, 5), 195 (20), 149 (100). Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.04; H, 6.21.

1,1-Dimethyl-3-(methylthio)-5-hydroxy-1,3-dihydroisobenzofuran (11b): 85% yield; ^1H NMR (300 MHz) δ 6.96–6.71 (m, 3H), 6.31 (s, 1H), 5.42 (brs, 1H), 2.00 (s, 3H), 1.54 (s, 3H), 1.45 (s, 3H); ^{13}C NMR δ 155.8, 139.3, 139.2, 121.4, 116.2, 109.0, 87.0, 86.2, 29.4, 29.3, 11.8; DEPT δ 121.4 (CH), 116.2 (CH), 109.0 (CH), 87.0 (CH), 29.4 (CH_3), 11.8 (CH_3); LRMS *m/z* (rel int) 210 (M^+, 5), 163 (100). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 62.64; H, 6.91.

1,1-Tetramethylene-3-(methylthio)-5-hydroxyl-1,3-dihydroisobenzofuran (11c): 88% yield; ^{1}H NMR (300 MHz) δ 10.06 (brs, 1H), 6.98–6.77 (m, 3H), 6.33 (s, 1H), 1.95 (s, 3H), 1.97–1.78 (m, 8H); ^{13}C NMR δ 156.1, 139.6, 137.1, 121.4, 116.5, 108.9, 96.8, 87.1, 41.3, 41.2, 24.9, 24.8, 11.6; DEPT δ 121.4 (CH), 116.5 (CH), 108.9 (CH), 87.1 (CH), 41.3 (CH_2), 41.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 11.6 (CH_3); LRMS *m/z* (rel int) 236 (M^+, 5), 189 (100). Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 66.33; H, 6.94.

1,1-Pentamethylene-3(methylthio)-5-hydroxyl-1,3-dihydroisobenzofuran (11d): 84% yield; ^{1}H NMR (300 MHz) δ 8.84 (brs, 1H), 6.98–6.76 (m, 3H), 6.33 (s, 1H), 2.01 (s, 3H), 1.87–1.30 (m, 10H); ^{13}C NMR δ 155.9, 139.3, 138.9, 121.6, 116.0, 109.1, 87.6, 86.8, 37.9, 25.0, 22.5, 22.3, 11.7; DEPT δ 121.6 (CH), 116.0 (CH), 109.1 (CH), 86.8 (CH), 37.9 ($2CH_2$), 25.0 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 11.7 (CH_3); LRMS *m/z* (rel int) 250 (M^+, 5), 203 (100), 186 (20). Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 67.32; H, 7.38.

1-(Methylthio)-6-hydroxyl-1,3-dihydroisobenzofuran (11e): 80% yield; ^{1}H NMR (300 MHz) δ 7.66 (brs, 1H), 7.05 (d, 1H, J = 7.8 Hz), 6.85 (d, 1H, J = 7.8 Hz), 6.82 (s, 1H), 6.43 (s, 1H), 5.19–5.03 (AB quartet, 2H), 1.99 (s, 3H); ^{13}C NMR δ 155.9, 139.1, 129.7, 121.5, 116.0, 108.8, 89.6, 72.5, 11.5; DEPT δ 121.5 (CH), 116.0 (CH), 108.8 (CH), 89.6 (CH), 72.5 (CH_2), 11.5 (CH_3), LRMS *m/z* (rel int) 182 (M^+, 8), 135 (100). Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.10; H, 5.38.

Mesylation of 11a and 11b. To a solution of **11a** (1.0 g, 5.0 mmol) in pyridine (20 mL) was added methanesulfonyl chloride (0.90 g, 7.6 mmol) at 0 °C, and the reaction mixture was stirred at 25 °C for 3 h. After addition of saturated NH_4Cl (20 mL) and extraction with ether (5 × 20 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **13a** (1.2 g, 88%). Compound **13a** was obtained as a mixture of diastereomers in a ratio of 1:1. Spectral data for **13a**: IR ($CHCl_3$) 1620, 1380, 1170 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.25–7.19 (m, 3H), 6.44 and 6.34 (s, 1H), 5.44 and 5.33 (q, 1H, J = 6 Hz), 3.18 and 3.17 (s, 3H), 2.09 and 1.96 (s, 3H), 1.56 and 1.49 (d, 3H, J = 6 Hz); ^{13}C NMR δ 148.9 and 148.8, 142.5 and 142.3, 140.9 and 140.5, 122.4 and 122.2, 122.1, 116.4 and 116.1, 88.2 and 87.6, 79.4 and 79.0, 37.4, 21.9 and 21.0, 12.6 and 11.2; DEPT δ 122.4 and 122.2 (CH), 122.1 (CH), 116.4 and 116.1 (CH), 88.2 and 87.6 (CH), 79.4 and 79.0 (CH), 37.4 (CH_3), 21.9 and 21.0 (CH_3), 12.6 and 11.2 (CH_3); LRMS *m/z* (rel int) 274 (M^+, 6), 227 (100). Anal. Calcd for $C_{11}H_{14}O_4S_2$: C, 48.16; H, 5.14. Found: C, 47.92; H, 5.02.

The same reaction conditions and procedure were applied to the transformation of **11b** to **13b**. Spectral data for **13b**: IR ($CHCl_3$) 1620, 1380, 1170 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.22–7.10 (m, 3H), 6.32 (s, 1H), 3.13 (s, 3H), 2.00 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H); ^{13}C NMR δ 148.8, 146.1, 140.0, 122.7, 121.9, 116.5, 86.7, 86.1, 37.5, 29.1, 29.0, 12.0; DEPT δ 122.7 (CH), 121.9 (CH), 116.5 (CH), 86.7 (CH), 37.5 (CH_3), 29.1 (CH_3), 29.0 (CH_3), 12.0 (CH_3); LRMS *m/z* (rel int) 288 (M^+, 7), 241 (100). Anal. Calcd for $C_{12}H_{16}O_4S_2$: C, 49.98; H, 5.59. Found: C, 49.72; H, 5.64.

Oxidation of 11b with *m*-CPBA. To a solution of **11b** (1.0 g, 4.7 mmol) in CH_2Cl_2 (20 mL) was added *m*-chloroperbenzoic acid (0.83 g, 4.8 mmol) at 25 °C, and the reaction mixture was stirred at 25 °C for 4 h. After addition of 0.1 N NaOH (10 mL) and extraction with chloroform (4 × 20 mL), the organic layer was washed with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography to give **14** (0.5 g, 65%): IR (film) 3400–3200, 1740, 1320 cm^{-1}; ^{1}H NMR (300 MHz) δ 11.20 (brs, 1H), 7.39–7.20 (m, 3H), 1.64 (s, 6H); LRMS *m/z* (rel inten) 178 (M^+, 18), 163 (100); HRMS (EI) calcd for $C_{10}H_{10}O_3$ 178.0630, found 178.0642.

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Supporting Information Available: NMR spectra for **6a,b**, **11a–e**, and **13a** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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