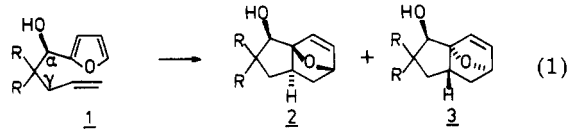
Communications

Stereochemical Control in the Intramolecular Diels–Alder Reaction with Furan

Summary: The intramolecular Diels–Alder reaction of a substituted furan has been carried out in excellent yield (95%) with high stereoselectivity when sterically demanding groups are present on the bridging chain.

Sir: In connection with studies directed toward the synthesis of prostaglandin intermediates we required an intramolecular Diels–Alder reaction of a dienophile tethered to a furan ring by a three-carbon chain.[1,2] We have previously reported on some of the factors controlling this reaction on model compounds (eq 1).[1] With proper sub-



(1)

stituents present on the bridging chain, high yields (>90%) of Diels–Alder adducts could be obtained; however, epimeric mixtures with respect to the OH on the bridging chain in 1 always resulted. For this reaction to be useful for the synthesis of prostaglandin intermediates we required a more highly functionalized tethering chain (i.e., oxygen functionality at both the α and γ carbons in 1) and stereochemical control of the substituents on this chain. We now report a successful solution to these problems.

The synthesis of the desired Diels–Alder precursor is depicted in Scheme I (see paragraph at the end of paper about supplementary material). Addition of the anion generated from 2-carbethoxydithiane[3] to furfural to yield 4[4] could be carried out in 81% yield only when the magnesium salt[5] was used (presumably this prevents the retroreaction).[6] Protection of the alcohol as the THP derivative and conversion of the ester group to an aldehyde ($LiAlH_4$; NCS, Me_2S, 76% yield from 4) afforded 5[4] (R = THP) as a mixture of THP isomers (2:1). The major THP isomer crystallized out of the mixture and was used for the rest of the synthetic sequence. Addition of vinylmagnesium bromide to this protected aldehyde produced a 3:1 ratio of 6:7[4] (R = THP; 90%). The isomer ratio could be increased to 8:1 (R = THP, 86%) by low-temperature addition of vinyl lithum instead of the Grignard. The stereochemical assignments of 6 and 7 were based on ^1H NMR coupling constants of their cyclization products (vide infra) and correlation with an X-ray crystal structure of **9D** (Figure 1, see paragraph at the end of paper about supplementary material).

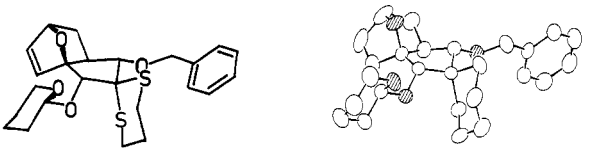
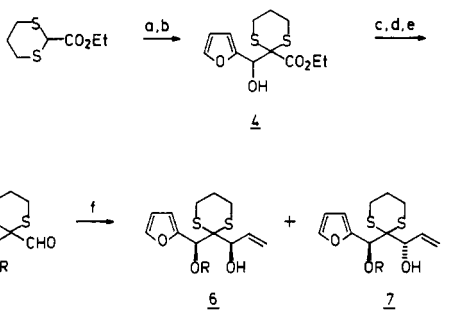


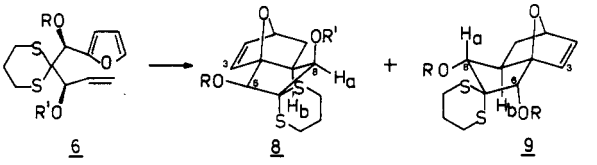
Figure 1.

Scheme I[a]



[a] (a) LDA, -20 °C/$MgBr_2$; (b) furfural; (c) DHP, pyridinium tosylate, CH_2Cl_2; (d) $LiAlH_4$, THF, Δ; (e) NCS, Me_2S, Et_3N, -35 °C; (f) *t*-BuLi, vinylbromide, THF, -78 °C.

Table I. Substituent Effects on Diels–Alder Product Isomer Ratios of 8 and 9



	R	R′	8:9	% yield 8 + 9 (time, days)	δ H_a[a] (*J*, Hz) 8	9
A	H	H	1:1	95 (2)	4.02 (4.8)[b]	3.80 (8.8)[b]
B	Ac	Ac	1:3.4	80 (4)	5.87 (6.1)[c]	5.70 (8.8)[c]
C	Bn	Bn	1[d]:99	82 (3)		3.74 (10.1)[c]
D	THP	Bn	1[d]:99	91 (2)		4.08 (10.1)[c]

[a] 250-MHz spectra referenced to either $CHCl_3$ or benzene. [b] $CDCl_3$ used as solvent. [c] Benzene-d_6 used as solvent. [d] This isomer was not detected.

Both **6A** and **7A** underwent the intramolecular Diels–Alder reaction in high yield when heated at 80 °C (for 2 days and 4 days, respectively), but each led to a 1:1 mixture of epimeric products (Tables I and II). To determine if the epimer ratio could be influenced, we undertook a systematic study of protecting groups. Table I describes our results for isomer **6**. Heating the diacetyl derivative **6B** begins to favor formation of isomer **9B** over **8B** (The overall reaction rate was slower, requiring 4 days to achieve an 80% yield.). This trend continues when either two benzyl groups are used (**6C**) or when THP and benzyl groups are used (**6D**). In these latter cases isomer **9** was formed exclusively (no 8 detected by ^1H NMR).

To ascertain which chiral center (C-6 or C-8) had the greater influence on the stereochemical outcome of the cyclization we examined the effect of the same series of protecting groups on the cyclization of **7**. It is clear from these results (Table II) that the dominating stubstituent

(1) (a) Sternbach, D. D.; Rossana, D. M., *Tetrahedron Lett.* **1982**, *23*, 303. (b) Sternbach, D. D.; Rossana, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 5853. (c) Onan, K. D.; Sternbach, D. D.; Rossana, D. M., submitted for publication.

(2) For related examples, see: Parker, K. A.; Adamchuck, M. R. *Tetrahedron Lett.* **1978**, 1689. Van Royen, L. A.; Mijnheer, R.; DeClercq, P. J. *Ibid.* **1983**, *24*, 3145; **1983**, *23*, 3283. Grootaert, W.; DeClercq, P. J. *Ibid.* **1982**, *23*, 3291.

(3) Eliel, E. L.; Hartmann, A. A. *J. Org. Chem.* **1972**, *37*, 505.

(4) These compounds exhibited satisfactory spectral data (^1H NMR, ^{13}C NMR, IR) and C, H analysis.

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(6) Deprotonation of the hydroxyl group in 4 with KH led to a rapid retroreaction to furfural and 2-carbethoxydithiane.

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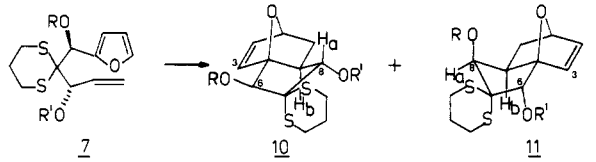
Table II. Substituent Effects on Diels–Alder Product Isomer Ratios of 10 and 11



7 10 11

	R	R′	10:11	% yield 10 + 11 (time, days)	δ H_a[a] (J, Hz) 10	11
A	H	H	1:1	95 (4)	3.65 (9.2)[b]	4.20 (4.9)[b]
B	Ac	Ac	2:1	90 (2)	5.80 (10.0)[c]	6.00 (6.5)[c]
C	Bn	Bn	1.1:1	84 (2)	4.10 (9.1)[c]	4.01 (5.0)[c]
D	THP	Bn	9:1[d]	89 (3)	4.13 (9.1)[c]	

[a] 250-MHz spectra referenced to either $CHCl_3$ or benzene. [b] $CDCl_3$ used as solvent. [c] Benzene-d_6 used as solvent. [d] Traces of this isomer were observed in the NMR spectrum of the mixture. This value represents an upper limit.

is at C-8. When both alcohols are protected the α-stereochemistry (pseudoequatorial) predominantes at C-8. This is the same trend that is observed with isomer **6**. Apparently the stereochemical preference at C-6 is also α. Thus in the cyclization of isomer **6** both effects are additive while in the cyclization of isomer **7** the steric effects are opposing, thus accounting for a somewhat smaller ratio.

The stereochemical assignments of these isomers are based on ^1H NMR data and correlation with an X-ray crystal structure of **9D**[7] (Figure 1). The X-ray results determined that all the compounds in Table I were derived from **6**, thus defining **7** as the precursor for the compounds in Table II. The stereochemical outcome of the intramolecular Diels–Alder reaction (i.e.; **8** vs. **9** and **10** vs. **11**) could be determined by examination of the coupling between H_a and H_b. Isomers **9** and **10** exhibited 8–10-Hz coupling, consistent with the dihedral angle of 164 (3)° obtained from the X-ray data of **9D**. The opposite configuration at C-8 in isomers **8**,**11** produced a much smaller coupling of 4–6.5 Hz, indicative of the smaller dihedral angle between the hydrogens in these isomers.

In summary, we have found that the desired Diels–Alder adduct **9D** can be produced in high yield. These results required two stereoselective reactions. First, the stereoselective addition of vinyl lithium to an aldehyde, and second, a stereoselective intramolecular Diels–Alder reaction. Synthetic applications of compound **9D** are in progress.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation for partial support of this work.

Registry No. **4**, 91280-56-7; (*R**,*R**)-**5** (R = THP), 91265-48-4; (*R**,*S**)-**5** (R = THP), 91265-49-5; **6A**, 91265-50-8; **6B**, 91265-51-9; **6C**, 91265-52-0; **6D**, 91265-53-1; **6** R = THP, R^1 = H, 91265-54-2; **7A**, 91265-55-3; **7B**, 91265-56-4; **7C**, 91265-57-5; **7D**, 91326-48-6; **7** R = THP, R^1 = H, 91326-49-7; **8A**, 91265-58-6; **8B**, 91265-59-7; **8C**, 91265-60-0; **8D**, 91265-61-1; **9A**, 91326-50-0; **9B**, 91326-51-1; **9C**, 91326-52-2; **9D**, 91326-53-3; **10A**, 91326-54-4; **10B**, 91326-55-5; **10C**, 91326-56-6; **10D**, 91326-57-7; **11A**, 91326-58-8; **11B**, 91326-59-9; **11C**, 91326-60-2; **11D**, 91265-62-2; 2-carboethoxydithiane, 20462-00-4; 1,2-dibromoethane, 106-93-4; magnesium bromide, 7789-48-2; 2-carboethoxydithiane lithium enolate, 79348-08-6; furfural, 98-01-1; ethyl (*R**,*R**)-3-(2-furyl)-2-oxo-3-(2-tetrahydropyranyloxy)propanoate 1,3-propanedithio acetal, 91265-63-3; dihydropyran, 25512-65-6; ethyl (*R**,*S**)-3-(2-furyl)-2-oxo-3-(2-tetrahydropyranyloxy)propanoate 1,3-propanedithio acetal, 91265-64-4; 1-(2-furyl)-3-hydroxy-1-(2-tetrahydropyranyloxy)-2-propanone 1,3-propanedithio acetal, 91265-65-5.

Supplementary Material Available: Full experimental details along with spectral data for the compounds in Scheme I; crystal data for **9D** including tables of atomic coordinates, thermal parameters, bond lengths and valency angles, and torsion angles (20 pages). Ordering information is given on any current masthead page.

(7) Crystallographic parameters appear in the supplementary material section. Publication of complete crystallographic details is planned.

Daniel D. Sternbach,* Debby M. Rossana
Department of Chemistry
Duke University
Durham, North Carolina 27706

Kay D. Onan
Department of Chemistry
Northeastern University
Boston, Massachusetts 02115
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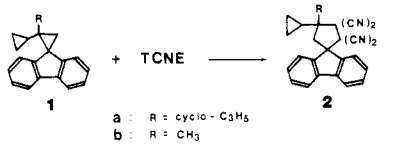
Facile Thermal [$_\sigma$2 + $_\pi$2] Cycloadditions of Some Cyclopropanes with TCNE. A Remarkable Effect of the Fluorene Unit Fused in a Spiro Fashion[1]

Summary: The fact that **1a**, as well as similarly spiro-activated **1b** and **5**, readily reacted with TCNE to afford a [$_\sigma$2 + $_\pi$2] cycloadduct, whereas **3** was practically unreactive, suggests an initial electron transfer in the cycloaddition.

Sir: Efficient [$_\sigma$2 + $_\pi$2] cycloadditions between cyclopropanes and ethylenes would be a promising way to prepare five-membered carbocycles. In fact, several reports describe such cycloadditions,[2] and all previous results indicate that the [$_\sigma$2 + $_\pi$2] cycloaddition successfully occurs when the donor–acceptor pairing of the reactants is properly attained.[3] We report here that certain cyclopropanes react very readily with TCNE in such a manner. The extremely reactive cyclopropanes carry a fluorene unit, linked in a spiro fashion to the cyclopropane, and good cation-stabilizing substituents on the three-membered ring. Remarkably, the lack of the fluorene unit resulted in a marked reduction in the reactivity.

On being mixed in an appropriate solvent, 1,1-dicyclopropyldibenzo[*d*,*f*]spiro[2.4]heptane (**1a**) and TCNE gave



a colored solution, but the color faded after a short period of time. The time required to give the colorless solution depended on the polarity of the solvent used (less than 1 s in acetonitrile or in nitromethane, 1–2 s in acetone, ca.

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(2) (a) Magrill, D. S.; Altmann, J.; Ginsberg, D. *Isr. J. Chem.* **1969**, *7*, 479. (b) Martini, T.; Kampmeier, L. A. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 236. (c) Nishida, S.; Moritani, I.; Teraji, T. *J. Chem. Soc., D* **1971**, 36. (d) Kataoka, F.; Nishida, S. *Chem. Lett.* **1980**, 1115. (e) Noordstrand, A. A. P.; Steinberg, H.; de Boer, Th. J. *Tetrahedron Lett.* **1975**, 2611. (f) Wiering, P. G.; Steinberg, H. *J. Org. Chem.* **1981**, *46*, 1663. (g) Wiering, P. G.; Verhoeven, J. W.; Steinberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 7675. See also: (h) Berkowitz, W. F.; Grenetz, S. C. *J. Org. Chem.* **1976**, *41*, 10.

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