phosphoranes.[59] In CAMEO, the treatment of the epoxide **23** with *N*-methyliminophosphorane produces three products. The first two, **24** and **25**, are deemed disfavored due to initial S_N2 attack at the more sterically hindered side of the epoxide. Resubmission of the major product, the oxazaphospholidine **26**, ultimately gives the aziridine **29** and an elimination product **28** via the intermediate **27**. The product **28** is deemed disfavored with respect to the S_N2 reaction since intramolecular cyclizations are typically faster than Grob fragmentations.[1k] Note that the weaker P–N bond in **26** is selectively cleaved to generate **27** despite the fact that cleavage of the P–O bond would result in a more stable base (amide vs alkoxide). Here, bond strength is considered to be the dominant factor for σ-phosphorane decomposition. Experimentally, **29** was obtained in 72% yield which is consistent with the predictions made by CAMEO.[59]

V. Conclusion

The capabilities of the nucleophilic module in CAMEO have been refined and extended in the treatment of ylide chemistry. Many new competitions have been addressed as well as steric effects for conjugate addition, stereochemistry of olefination, and the decomposition of unstable functionalities that are produced in many reactions of ylides. Through the continued recognition, refinement and implementation of such organizing principles, a better model is established, permitting the more accurate treatment of a broader range of chemistry.

Acknowledgment. Gratitude is expressed to the National Science Foundation for support of this work and to Procter and Gamble for a Fellowship awarded to A.G. Thanks are also given to Dr. P. Metivier for frequent synthetic consultations.

Thermal Cycloaddition Reactions of π-Delocalized Singlet Vinylcarbenes: Three-Carbon 1,1-/1,3-Dipoles. The Thermal Three-Carbon + Two-Carbon Cycloaddition

Dale L. Boger*[1] and Ronald J. Wysocki, Jr.

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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Full details of investigations defining new aspects of the scope and mechanism of the three-carbon + two-carbon cycloaddition reaction of π-delocalized singlet vinylcarbenes (three-carbon 1,1-/1,3-dipoles generated in a reversible, thermal ring opening of cyclopropenone ketals) are detailed.

In recent efforts we have detailed the reversible, thermal generation of π-delocalized singlet vinylcarbenes (three-carbon 1,1-/1,3-dipoles) from cyclopropenone ketals[2,3] and have described their well-defined participation as 2π components of an endo-selective $[{}_{\omega}2_a + {}_{\pi}2_s]$ nonlinear, cheletropic cycloaddition with selected electron-deficient olefins and as 2π components of a thermal $[{}_{\pi}2_s + {}_{\pi}4_s]$ cycloaddition with selected α-pyrones (eq 1, Scheme I).[2] Concurrent with these observations we have detailed an effective, three-carbon + two-carbon cycloaddition of the thermally generated π-delocalized singlet vinylcarbenes with electron-deficient olefins and dienes bearing two geminal electron-withdrawing substituents and have detailed three plausible mechanistic pathways that might account for this observed cycloaddition reaction (eq 2, Scheme I).[2a] Of the *five* thermal, cycloaddition reactions available to the cyclopropenone ketal $\rightleftarrows$ π-delocalized singlet vinylcarbene, which include (1) a $[{}_{\pi}2_s + {}_{\pi}4_s]$ Diels–Alder reaction of the cyclopropenone ketal,[2a,e,3b] (2) a $[{}_{\pi}2_s + {}_{\pi}4_s]$ cycloaddition of the π-delocalized singlet vinylcarbene,[2a,d] (3) an $[{}_{\omega}2_a + {}_{\pi}2_s]$ cycloaddition of the π-delocalized singlet vinylcarbene,[2a,c] (4) a [2 + 2] (olefin–olefin/olefin–carbonyl)[2a,3] dimerization, (5) and a three-carbon + two-carbon [3 + 2] cycloaddition,[2a,b,f,3b] the three-carbon + two-carbon cycloaddition has been found to proceed with the greatest facility and constitutes the exclusive reaction course observed with *all* olefin *or* diene substrates bearing two geminal electron-withdrawing substituents that have been examined to date.[2] Herein, we detail additional studies of the [3 + 2] cycloaddition reaction of π-delocalized singlet vinylcarbenes conducted with the intention of more carefully defining the mechanism and scope of this reaction.

Stepwise Dipolar or Biradical Addition–Cyclization Reaction. The absolute rate of the [3 + 2] cycloaddition reaction was determined to be sensitive to the type and extent of olefin substitution and has been shown to be insensitive to the polarity of the reaction solvent [approximate relative rate for a given substrate:

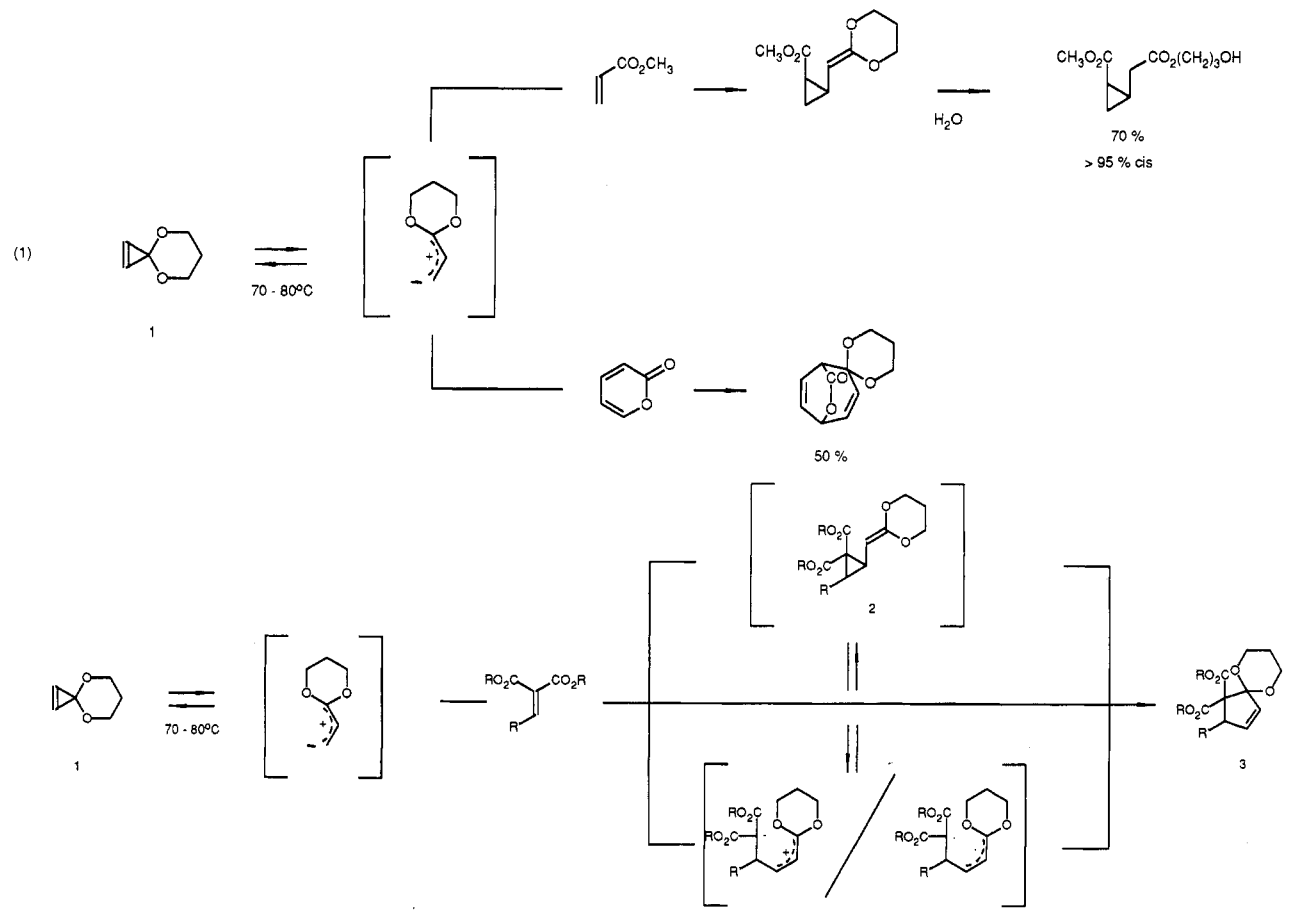
(1) National Institutes of Health research career development award recipient, 1983–88 (Grant CA 00898/01134). Alfred P. Sloan research fellow, 1985–89.

(2) (a) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695, 6713. For preliminary studies, see: (b) [3 + 2] cycloaddition: Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805. Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Org. Synth.* **1987**, *65*, 32. (c) [1 + 2] cycloaddition: Boger, D. L.; Brotherton, C. E. *Tetrahedron Lett.* **1984**, *25*, 5611. (d) [3 + 4] cycloaddition: Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425. (e) [4 + 2] cycloaddition: Boger, D. L.; Brotherton, C. E. *Tetrahedron* **1986**, *42*, 2777. (f) [3 + 2] cycloaddition with carbonyls: Boger, D. L.; Brotherton, C. E; Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 5615. (g) Transition-metal-catalyzed [2 + 2] and [1 + 2] cycloaddition: Binger, P.; Biedenbach, B. *Chem. Ber.* **1987**, *120*, 601.

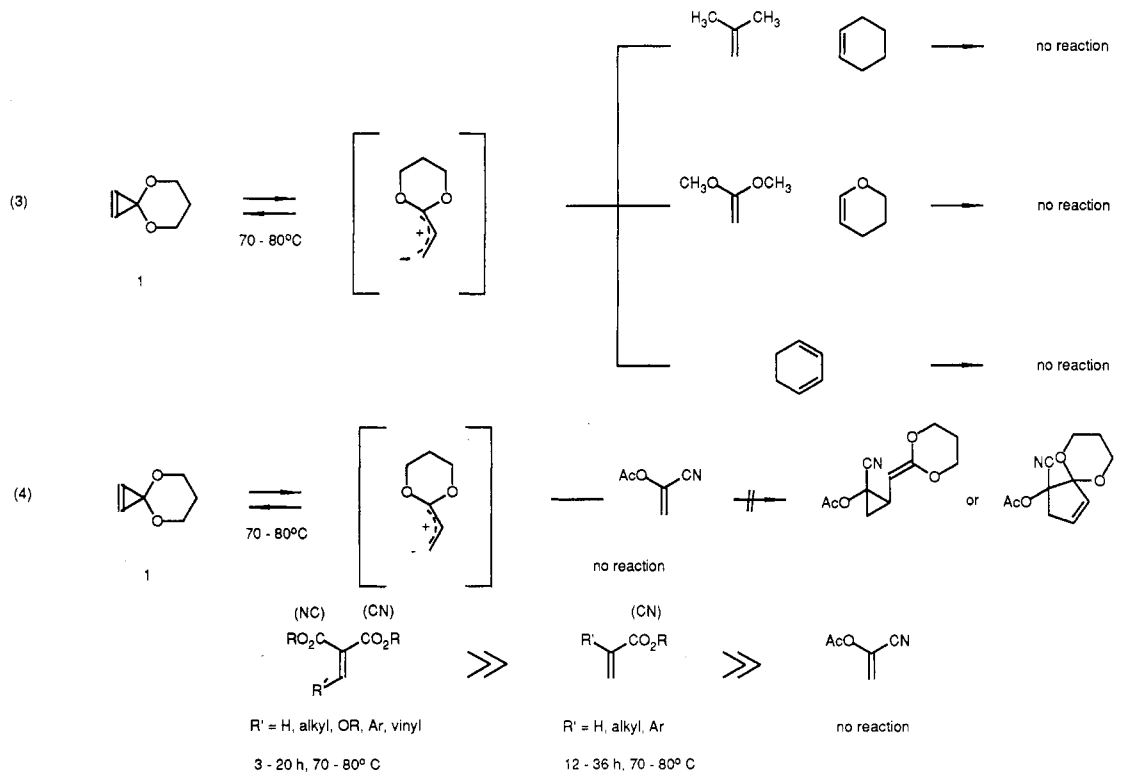
(3) For the preparation of 3,3-dimethoxycyclopropene, see: (a) Baucom, K. B.; Butler, G. B. *J. Org. Chem.* **1972**, *37*, 1730. Breslow, R.; Pecoraro, J.; Sugimoto, T. *Org. Synth.* **1977**, *57*, 41. For the first disclosure of the [4 + 2] Diels–Alder cycloaddition of cyclopropenone ketals, their participation in a single [3 + 2] and [2 + 2] cycloaddition with two, selected carbonyl compounds, and for the preparation of cyclopropenone 1,3-propanediyl ketal, see: (b) Albert, R. M.; Butler, G. B. *J. Org. Chem.* **1977**, *42*, 674. Butler, G. B.; Herring, K. H.; Lewis, P. L.; Sharpe, V. V., III; Veazey, R. L. *J. Org. Chem.* **1977**, *42*, 679.

0022-3263/88/1953-3408$01.50/0

Scheme I



Scheme II



DMF (2) > CH_3CN (1.4) > C_6H_6 (1.0) > C_5H_5N (0.9) > $C_6H_5NO_2$ (0.7)].[2a] This lack of a pronounced solvent effect on the observed rate of the [3 + 2] cycloaddition reaction is consistent with the rapid, reversible, thermal generation and subsequent rate-limiting cycloaddition of a π-delocalized singlet vinylcarbene[4-6] and is inconsistent with

Table I. Thermal Cycloaddition Reaction of Cyclopropenone Ketal 1 with 4-*E*, 4-*Z*, 5-*E*, and 5-*Z*

entry	substrate	conditions:[a] equiv of 1, solvent, temp (°C), (time (h))	products	[ratio][b]	(% yield)[c]
1	4-*Z*	4.2, C_6H_6, 80, (20)	6-*cis*:6-*trans*	[64:36]	(66)
2		4.2, CD_3CN, 80, (20)		[90:10]	(60)
3		0, C_6D_6, 80, (96)	4-*Z*:4-*E*	[100:0]	
4		0, CD_3CN, 80, (96)		[100:0]	
5	4-*E*	5.0, C_6D_6, 80, (20)	6-*cis*:6-*trans*	[27:73]	(71)
6		2.9, CD_3CN, 80, (20)		[11:89]	(58)
7		0, C_6D_6, 80, (96)	4-*Z*:4-*E*	[0:100]	
8		0, CD_3CN, 80, (71)		[0:100]	
9	6-*cis*	0, C_6D_6, 80, (96)	6-*cis*:6-*trans*	[100:0]	
10		0, CD_3CN, 80, (96)		[100:0]	
11	6-*trans*	0, C_6D_6, 80, (96)	6-*cis*:6-*trans*	[0:100]	
12		0, CD_3CN, 80, (96)		[0:100]	
13	5-*Z*	4.2, C_6D_6, 80, (24)	7-*cis*:7-*trans*	[79:21]	(76)
14		3.0, CD_3CN, 80, (24)		[81:21]	(63)
15		0, C_6D_6, 80, (69)	5-*Z*:5-*E*	[100:0]	
16		0, CD_3CN, 80, (57)		[100:0]	
17	5-*E*	1.1, C_6D_6, 80, (20)	7-*cis*:7-*trans*	[29:71]	(67)
18		1.2, CD_3CN, 80, (15)		[18:82]	(48)
19		0, C_6D_6, 80, (69)	5-*Z*:5-*E*	[0:100]	
20		0, CD_3CN, 80, (55)		[0:100]	
21	7-*cis*:7-*trans* (79:21)	0, C_6D_6, 80, (63)	7-*cis*:7-*trans*	[79:21]	
22	7-*cis*:7-*trans* (80:20)	0, CD_3CN, 80, (55)		[80:20]	
23	7-*trans*:7-*cis* (71:29)	0, C_6D_6, 80, (63)	7-*trans*:7-*cis*	[71:29]	
24	7-*trans*:7-*cis* (82:18)	0, CD_3CN, 80, (55)		[82:18]	

[a] All reactions were conducted under an inert atmosphere, at 0.05–0.5 M concentration, protected from light. [b] The product ratios were determined by ^1H NMR (300 MHz). [c] Yield of chromatographically homogeneous product isolated by chromatography (SiO_2).

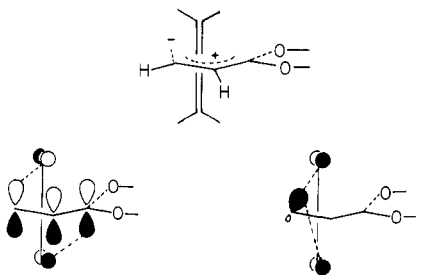


Figure 1.

expectations if the reaction were proceeding by a rate-limiting, stepwise, addition–cyclization reaction with the generation of an initial zwitterionic intermediate.[2a] Subsequent efforts to demonstrate the generation of a partially delocalized triplet vinylcarbene (biradical) by reaction with typical triplet carbene traps including neutral or electron-rich olefins and conjugated 1,3-dienes have proven unsuccessful (eq 3, Scheme II). Further verification that the stepwise, biradical addition-cyclization reaction is not operative has been derived from the failure of stoichiometric free-radical traps to inhibit or alter the observed [3 + 2] cycloaddition reaction (cf. Tables II and IV) and from the absence of an observed reaction of the thermally generated vinylcarbene with captodative olefins[7] (eq 4, Scheme II). In contrast to the observation that acrylonitrile cleanly provides a [1 + 2] cycloadduct upon thermal reaction with **1**, the addition of a C-2 electron-donating substituent (OAc) to acrylonitrile *prevented* its participation in a thermal cycloaddition reaction with the π-delocalized vinylcarbene derived from the cyclopropenone ketal **1**.

The Direct [$_\pi2_s$ + $_\pi2_a$] Cycloaddition versus Indirect [$_\pi2_s$ + $_\omega2_s$] Cycloaddition/Vinylcyclopropane Rearrangement. Having secured evidence that the [3 + 2] cycloaddition is not proceeding by the stepwise, zwitterionic addition–cyclization reaction of the π-delocalized singlet vinylcarbene or by the stepwise, biradical addition–cyclization reaction of a partially delocalized triplet vinylcarbene, we focused efforts to experimentally distinguish or detect two reasonable mechanistic alternatives: an initial [$_\pi2_s$ + $_\omega2_a$] cycloaddition to provide a doubly activated cyclopropane ketene acetal followed by an undetected vinylcyclopropane rearrangement *or* a direct, one-step cycloaddition to provide the [3 + 2] cyclopentenone ketal cycloadducts. Inspection of this last possibility suggested the potential $_\pi2_a$ participation of the π-delocalized singlet vinylcarbene in a [$_\pi2_a$ + $_\pi2_s$] three-carbon + two-carbon cycloaddition. Since the π-delocalized singlet vinylcarbene possesses a 2π three-carbon backbone, it may be viewed as potentially well-suited for participation as a three-carbon $_\pi2_a$ component of a $LUMO_{olefin}$-controlled two-carbon + three-carbon [$_\pi2_s$ + $_\pi2_a$] cycloaddition (Figure 1).

Extensive attempts to isolate or detect an initial cyclopropane ketene acetal cycloadduct **2** derived from the 2π participation of a π-delocalized singlet vinylcarbene in a nonlinear [$_\omega2_a$ + $_\pi2_s$] cheletropic cycloaddition followed by a subsequent, low-temperature vinylcyclopropane rearrangement have been unsuccessful and have suggested that this expected course of the three-carbon + two-carbon cycloaddition may not be operative.[2a,9] These observations

(4) *Carbenes*; Moss, R. A., Jones, M., Jr., Eds.; Wiley-Interscience: New York, 1982; Vol. 1 and 2.

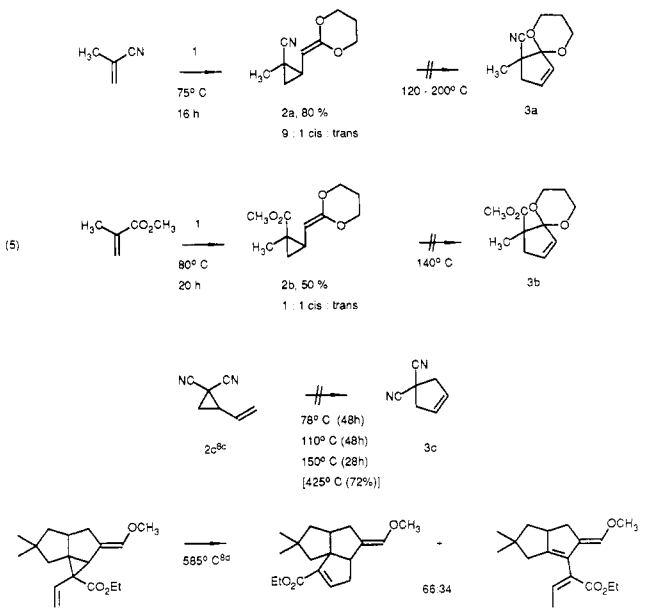
(5) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 1. The initial classification of 1,3-dipoles included systems without octet stabilization (cf. Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565) and included vinylcarbenes, ketocarbenes, ketonitrenes, as well as stabilized allylic cations. Today, such systems are regarded as $_\pi2$ reactants and no longer constitute members of the $_\pi4$ 1,3-dipoles.

(6) Steiner, G.; Huisgen, R. *J. Am. Chem. Soc.* **1973**, *95*, 5056. Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 117.

(7) Viehe, H. G.; Janousek, Z.; Merenyi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148.

(8) Review: (a) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247.

Scheme III



have been underscored by the failure of related, albeit less activated, vinylcyclopropanes to participate in vinylcyclopropane rearrangements even at elevated temperatures (eq 5, Scheme III).[2a,8,9] Confirmation of a concerted $[{}_{\pi}2_a + {}_{\pi}2_s]$ cycloaddition requires the complete maintenance of the olefin geometry in the stereochemistry of the [3 + 2] cycloadducts. In contrast, the two-step $[{}_{\omega}2_a + {}_{\pi}2_s]$ cycloaddition/vinylcyclopropane rearrangement that may proceed with the generation of zwitterionic/biradical intermediates in a non-rate-determining vinylcyclopropane (**2** → **3**) rearrangement provides the potential for loss of olefin geometry in the overall, observed [3 + 2] cycloaddition. Scheme IV summarizes the initial systems employed to study the stereoselectivity of the [3 + 2] cycloaddition reaction and the results are summarized in Table I.

The *E* and *Z* isomers of benzyl methyl (phenylmethylene)malonate (*E*- and *Z*-**4**) and benzyl methyl (methoxymethylene)malonate (*E*- and *Z*-**5**) were found to be separable by careful chromatography and proved to be configurationally stable electron-deficient substrates bearing two comparable, but different, geminal electron-withdrawing substituents suitable for participation in the [3 + 2] cycloaddition reaction. Consistent with expectations, olefinic substituents cis to the β-phenyl ring of **4** exhibit a detectable ^{1}H NMR deshielding effect derived from the induced ring current of the proximal phenyl group; e.g. **4**-*E*, 3.49 ppm (cis CO_2CH_3); **4**-*Z*, 3.35 ppm (trans CO_2CH_3).[10] Treatment of **4**-*E*, **4**-*Z*, **5**-*E*, and **5**-*Z* with the cyclopropenone ketal **1** under mild, thermal reaction conditions (70–80 °C) in a range of reaction solvents (benzene, acetonitrile) provided the [3 + 2] cycloadducts **6**-*cis*, **6**-*trans* or **7**-*cis*, **7**-*trans*, respectively, with partial (10–34%), albeit not complete, loss of olefin geometry accompanying the cycloaddition process. In the case of the [3 + 2] cycloadducts **6**, the substituents cis to the C-3 phenyl ring exhibit a pronounced downfield ^{1}H NMR chemical shift derived from a strong shielding effect of the proximal aromatic ring; e.g. **6**-*cis*, 3.72 ppm (CO_2CH_3), 4.58 and 4.10 ppm (2 d, cis CO_2CH_2Ph) vs **6**-*trans*, 2.94 ppm (cis CO_2CH_3), 5.50 and 5.15 ppm (2 d, trans CO_2CH_2Ph). For the [3 + 2] cycloadducts **7**, only the benzyl ester of **7**-*cis* exhibited an ^{1}H NMR AB quartet that may be attributed to the restricted rotation of the **7**-*cis* benzyl ester bearing two adjacent cis substituents. The initial olefin geometry of the cycloaddition substrates was found to be maintained in the predominant [3 + 2] cycloaddition product and the extent of the loss of olefin geometry for a given substrate proved independent of the substrate isomer employed. Control studies ensured that the starting olefins (**4**-*E*, **4**-*Z*, **5**-*E*, **5**-*Z*) and the product cyclopentenone ketals (**6**-*cis*, **6**-*trans*, **7**-*cis*, **7**-*trans*) were stable to the reaction conditions and do not undergo thermal isomerization (Table I). In selected instances (Table I, entries 2, 5, 6, 17) the starting olefin (4–43%) was recovered unchanged from the reaction mixture, ensuring that isomerization of the olefin in the presence of the cyclopropenone ketal **1** ⇄ π-delocalized singlet vinylcarbene does not occur under the thermal reaction conditions. In addition, in a control experiment in which the cyclopropenone ketal **1** was employed as the limiting reagent (0.5 equiv, C_6D_6, 80 °C, 12 h) the unreacted olefin **4**-*E* was recovered unchanged from the reaction mixture (84%), thus confirming the olefin configurational stability to the reaction conditions. These observations rule out the potential of an undetected but precedented,[11,12] reversible, polar addition of the π-delocalized singlet vinylcarbene to the electron-deficient olefin accounting for olefin isomerization preceding cyclization under the reaction conditions.[11] In addition, the confirmed thermal stability of the cyclopentenone ketal cycloadducts **6**-*cis*:**6**-*trans* [Table I, 0% isomerization, 80 °C] and **7**-*cis*:**7**-*trans* [Table I; 79:21 (0% isomerization); 29:71 (0% isomerization, 80 °C)] ensure that the product mixtures are not under thermodynamic control as a consequence of product, or intermediate, isomerization. Finally, the control reactions of a 1:1

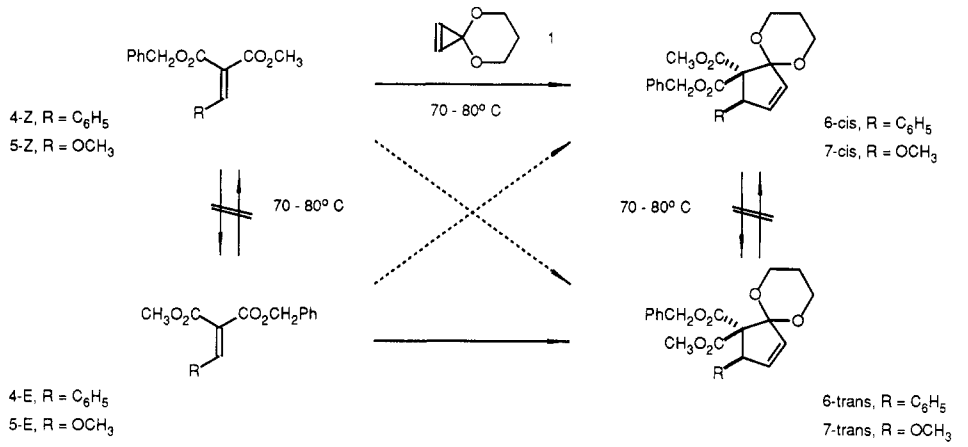
(9) (a) The [1 + 2] vinylcyclopropane ketene acetal cycloadducts **2a,b** (eq 3) would be expected rearrange at higher temperatures than those derived from olefins bearing two, geminal electron-withdrawing groups (eq 2). However, the [3 + 2] cycloadducts **3** (eq 2) are formed at 70–80 °C[2a,b] and this is at temperatures 100–130 °C lower than that at which no vinylcyclopropane rearrangement for **2a–c** is observed. Further, in the reaction of benzylidenemalonitrile with **1** at 25 °C (100–200 h),[2a] a trace (5%) of the [3 + 2] cycloaddition product was detected with no evidence of initial [1 + 2] ($[{}_{\pi}2_s + {}_{\omega}2_a]$) cycloaddition. Consequently, if the [3 + 2] cycloadducts are derived by an initial $[{}_{\pi}2_s + {}_{\omega}2_a]$ cycloaddition followed by an undetected vinylcyclopropane rearrangement, the rearrangement must be proceeding at an effective rate even at 25 °C, 135–175 °C lower than temperatures at which **2a–c** fail to rearrange. (b) To date, efforts to prepare a doubly activated cyclopropane ketene acetal by alternative routes and examine the potential for their participation in a low-temperature vinylcyclopropane rearrangement have not been successful. Boger, D. L.; Wysocki, R. J., unpublished observations. (c) For the preparation of **2c**, see: Korte, F.; Scharf, D.; Buchel, K. H. *Justus Liebigs Ann. Chem.* **1963**, *664*, 97. (d) Hudlicky, T.; Natchus, M. G.; S.-Zingde, G. *J. Org. Chem.* **1987**, *52*, 4643.

(10) The near identical ^{1}H NMR spectroscopic properties of **5**-*E* and **5**-*Z* did not permit an unambiguous isomer identification. This identification (**5**-*E* and **5**-*Z*) was derived from the unambiguous stereochemical identification of the isomeric [3 + 2] cycloadducts **7**-*cis* and **7**-*trans*. For a discussion of the stereochemistry of (alkoxyalkylidene)cyanoacetates, see: Hayashi, T.; Hori, I.; Baba, H.; Midorikawa, H. *J. Org. Chem.* **1965**, *30*, 695. Ceder, O.; Stenhede, U. *Tetrahedron* **1973**, *29*, 1585. Ilavsky, D.; Krechl, J.; Trska, P.; Kuthan, J. *Collect. Czech. Chem. Commun.* **1979**, *44*, 1423.

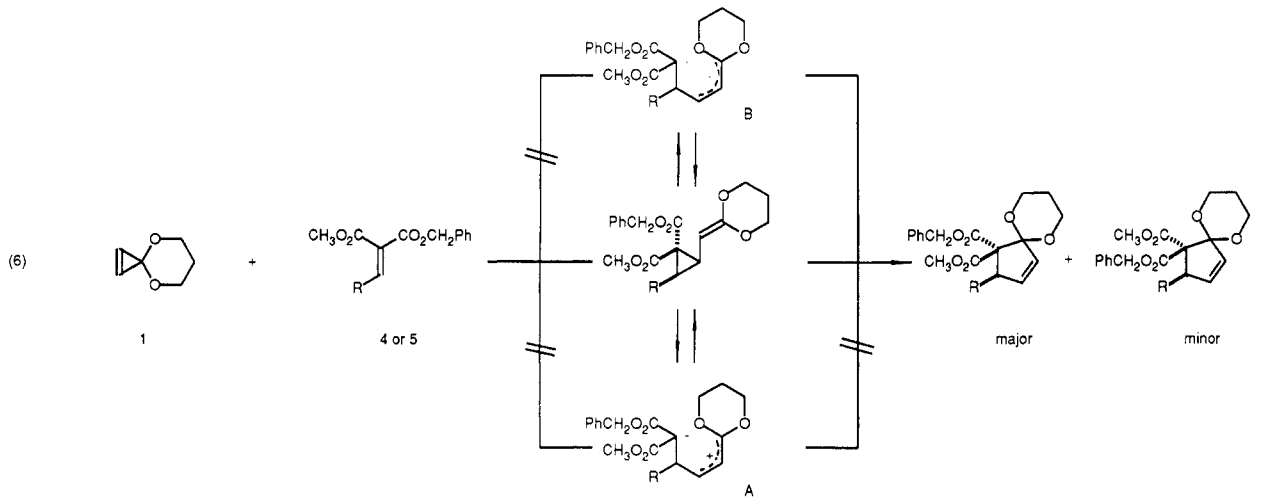
(11) Doyle, M. P.; Loh, K.-L.; Nishioka, L. I.; McVickar, M. B.; Liu, M. T. H. *Tetrahedron Lett.* **1986**, *278* 4395. See also: Lambert, J. B.; Larson, E. G.; Bosch, R. J. *Tetrahedron Lett.* **1983**, *24*, 3799. Dehmlow, E. V.; Kramer, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 706. Yang, N. C.; Marolewski, T. A. *J. Am. Chem. Soc.* **1968**, *90*, 5644.

(12) Gould, I. R.; Turro, N. J.; Butcher, J., Jr.; Doubleday, C., Jr.; Hacker, N. P.; Lehr, G. F.; Moss, R. A.; Cox, D. P.; Guo, W.; Munjal, R. C.; Perez, L. A.; Fedorynski, M. *Tetrahedron* **1985**, *41*, 1587. Turro, N. J.; Okamoto, M.; Gould, I. R.; Moss, R. A.; Lawrynowicz, W.; Hadel, L. M. *J. Am. Chem. Soc.* **1987**, *109*, 4973. Liu, M. T. H.; Subramanian, R. *J. Phys. Chem.* **1986**, *90*, 75. Liu, M. T. H. *J. Chem. Soc., Chem. Commun.* **1985**, 982. Liu, M. T. H.; Soundararajan, N.; Paike, N.; Subramanian, R. *J. Org. Chem.* **1987**, *52*, 4223.

Scheme IV



Scheme V



mixture of 4-*E*:4-*Z* and 5-*E*:5-*Z* (80 °C, C_6D_6) provided a 1:1 mixture of the isomeric [3 + 2] cycloadducts 6-*cis*:6-*trans* and 7-*cis*:7-*trans*, confirming this conclusion and further illustrating that there is no product determining preferential participation of one of the two substrate olefin isomers in the [3 + 2] cycloaddition reaction process. *The confirmed observation of partial loss of substrate olefin configuration in the [3 + 2] cycloaddition reaction rules out the direct* $[{}_{\pi}2_s + {}_{\pi}2_a]$ *cycloaddition mechanism.*

In addition, the extent of the observed loss of olefin geometry of 4-*E* and 4-*Z* or 5-*E* and 5-*Z* in the [3 + 2] cycloaddition reaction was found *to be unaffected or to decrease* with increasing solvent polarity. This clearly rules out the sole intermediacy of the zwitterionic intermediate A (eq 6, Scheme V) enroute to the [3 + 2] cycloadducts 6 and 7. Increasing the polarity of the reaction solvent would be expected to *increase* the extent of the loss of olefin geometry if the reaction were proceeding with the generation of zwitterion A. Consequently, if a single mechanism is responsible for the generation of the [3 + 2] cycloadducts, the results with 4-*E*/4-*Z* and 5-*E*/5-*Z* require that the intermediacy of the biradical B, versus zwitterion A, must be responsible for the partial loss of olefin geometry (eq 6). Morever, the observed [3 + 2] cycloaddition of 1 with 5-*E* proceeds to provide 7-*trans*:7-*cis* (70–75:30–25) in the presence of a catalytic or stoichiometric amount of a radical trap and an electron-deficient single-electron acceptor; 5–400 mol % tetramethylpiperidinyloxy free radical (Tempo) and 5–400 mol % 1,4-dinitrobenzene (Table II). No inhibition of the rate of [3 + 2] cycloaddition and no change in the product isomer ratio was observed when the reaction was conducted in the presence of stoichiometric or excess inhibitor.[13]

In recent reports,[14] Huisgen and co-workers have successfully and unambiguously established the first example of a 1,3-dipolar cycloaddition that proceeds by a two-step, addition–cyclization mechanism with the generation of a zwitterionic intermediate employing a dipolarophile/1,3-dipole combination [2,3-dicyanofumaric ester/thiocarbonyl ylide] possessing a dominant $LUMO_{dipolarophile}/HOMO_{1,3\text{-dipole}}$ interaction. In these studies, the extent of the loss of stereospecificity of the [3 + 2] cycloaddition process predictably increased with an increase in the polarity of the reaction solvent. Consequently, we have examined the thermal reaction of the cyclopropenone ketal 1 with 2,3-dicyanofumaric esters **8a** and **8b** (eq 7, Scheme VI) under a range of reaction conditions. In each instance, a single stereoisomer of the [3 + 2] cycloadduct **9** was produced which proved independent of the polarity of the reaction solvent and in which the olefin geometry of the cycloaddition substrate was presumed to be maintained in the cycloaddition product (Table III).[15] The reactions

(13) These results, in addition to the earlier studies (eq 3 and 4), rule out the potential of a stepwise addition–cyclization reaction of a triplet partially delocalized vinylcarbene required of a direct generation of the biradical B (eq 6).

(14) Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *108*, 6401. Huisgen, R.; Mloston, G.; Langhals, E. *J. Org. Chem.* **1986**, *51*, 4085. Huisgen, R.; Langhals, E.; Noth, H. *Tetrahedron Lett.* **1986**, *27*, 5475.

Scheme VI

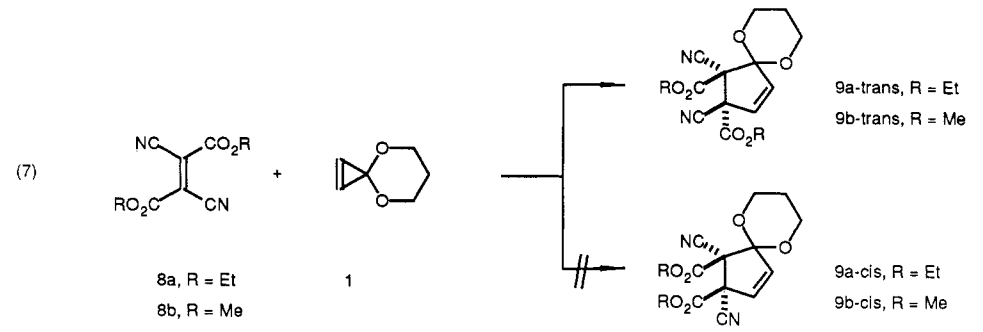
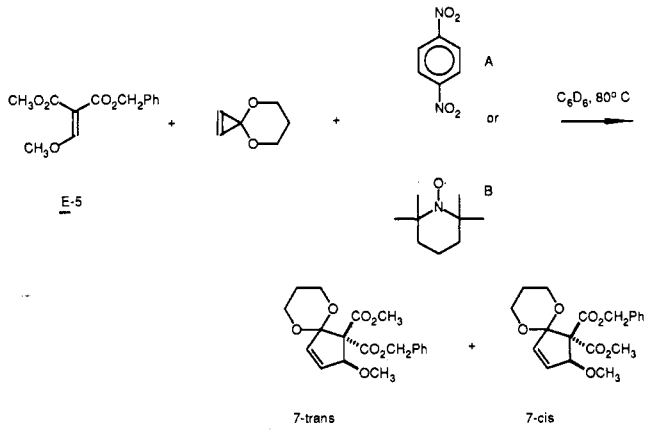


Table II



entry	inhibitor, (mol %)	conditions:[a] equiv of 1 (time (h))	products	[ratio][b]	(% yield)[c]
1		1.1 (20)	7-*trans*:7-*cis*	[71:29]	(67)
2	A, (5)	3.0 (16)		[73:27]	(62)
3	A, (20)	3.0 (16)		[73:27]	(46)
4	A, (100)	3.0 (16)		[70:30]	(66)
5	A, (400)	3.0 (16)		[75:25]	(65)
6	B, (5)	3.0 (16)		[73:27]	(45)
7	B, (20)	3.0 (16)		[74:26]	(49)
8	B, (100)	3.0 (16)		[75:25]	(64)
9	B, (400)	3.0 (16)		[71:29]	(52)

[a] All reactions were conducted (80 °C; C_6D_6) under an inert atmosphere (argon) at 0.05 to 0.5 M concentration in 5-mm NMR tubes protected from light and monitored periodically by ^1H NMR (300 MHz). [b] The 7-*trans*:7-*cis* ratio was determined by ^1H NMR (300 MHz). [c] Yield of chromatographically homogeneous product isolated by chromatography (SiO_2).

of 1 with either **8a** or **8b** proved to be much cleaner than the isolated yields recorded in Table III would indicate. Monitoring the reaction of **8b** with 1 in acetonitrile-d_3 by ^1H NMR indicates clean disappearance of the **8b** methyl ester [3.96 ppm (s)] with the concurrent appearances of *only* two methyl ester signals [3.84 ppm (s) and 3.75 ppm (s)] which can be attributed to **9b**. In addition, the olefinic ^1H NMR proton signals of **9b** [6.94 ppm (d, J = 5.8 Hz) and 6.50 ppm (d, J = 5.8 Hz)] are the only ^1H NMR signals appearing in the 7.0–4.5 ppm region. Despite the clean conversions, adventitious water present in the workup and chromatographic purification of **9a**, **9b** is responsible for

Table III. Thermal Cycloaddition Reaction of Cyclopropenone Ketal 1 with Diethyl and Dimethyl 2,3-Dicyanofumarate (8a and 8b)

entry	substrate	conditions: equiv of 1, solvent, temp (°C), (time, h)	products	%, yield[a]
1	**8a**	1.5, C_6H_6, 80, (7.5)	**9a**-*trans*	66
2	**8a**	1.2, CD_3CN, 80, (4)	**9a**-*trans*	50–52
3	**8a**	1.2, DMF-d_7, 80, (4)	**9a**-*trans*	44
4	**8b**	2.1, C_6H_6, 80, (9)	**9b**-*trans*	30
5	**8b**	1.1, CD_3CN, 80, (4)	**9b**-*trans*	32
6	**8b**	1.1, DMF-d_7, 80, (3)	**9b**-*trans*	28
7	**8a**	0, C_6H_6, CD_3CN, 80, (10–15)	**8a**[b]	
7	**8b**	0, CD_3CN, 80, (27)	**8b**[b]	
9	**9a**-*trans*	0, C_6D_6, CD_3CN, 80, (39–43)	**9a**[b]	
		0, DMF-d_7, 80, (29)		
10	**9b**-*trans*	0, C_6D_6, CD_3CN, 80, (42)	**9b**[b]	

[a] Yield of chromatographically homogeneous product isolated by chromatography (SiO_2). The [3 + 2] cycloadducts **9a** and **9b** have proven unstable to the conditions of chromatographic purification; see ref 15 and 16. Monitoring the reactions by ^1H NMR indicated conversions of 85–100% for **9a** and **9b**. [b] 0% isomerization.

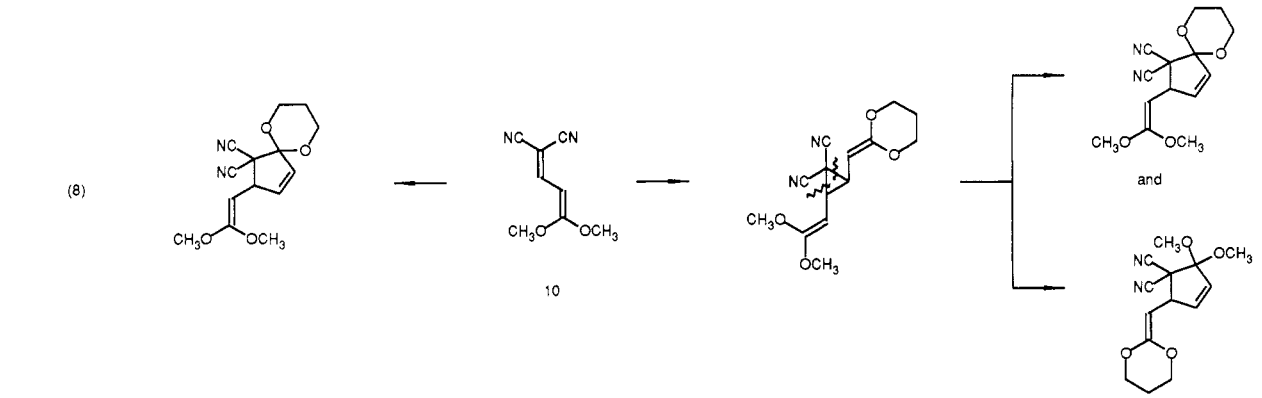
the low isolated yields recorded in Table III.[16] Thus, in contrast to the efforts of Huisgen[14] and in contrast to the reaction of 1 with electron-deficient olefins bearing two geminal electron-withdrawing substituents (cf. Scheme IV), the reaction of the thermally generated π-delocalized singlet vinylcarbene derived from 1 with the 2,3-dicyanofumarate esters **8a/8b** has proven to be stereospecific.

Two important conclusions may be drawn from these observations. First, the observed [3 + 2] cycloaddition of the π-delocalized singlet vinylcarbene derived from 1 with **8a,b** cannot be proceeding by way of a stepwise, addition–cyclization reaction with the initial, direct generation of a zwitterionic intermediate. As demonstrated in the observations of Huisgen,[14] such a process would be expected to exhibit a solvent-dependent loss of [3 + 2] stereoselectivity. Second, the complete maintenance of the substrate olefin geometry is consistent with the $_\pi 2_a$ participation of the π-delocalized singlet vinylcarbene in a direct, concerted [$_\pi 2_s$ + $_\pi 2_a$] cycloaddition but contrasts the results derived with substrates *E*-/*Z*-**4** and *E*-/*Z*-**5**. Thus, while the observations with **8a,b** would ordinarily be considered strong support for a concerted cycloaddition reaction, it is more accurately attributed to the *expected* increased barrier to C^1–C^2 bond rotation *and* a reinforcing increased rate of final five-membered ring cyclization

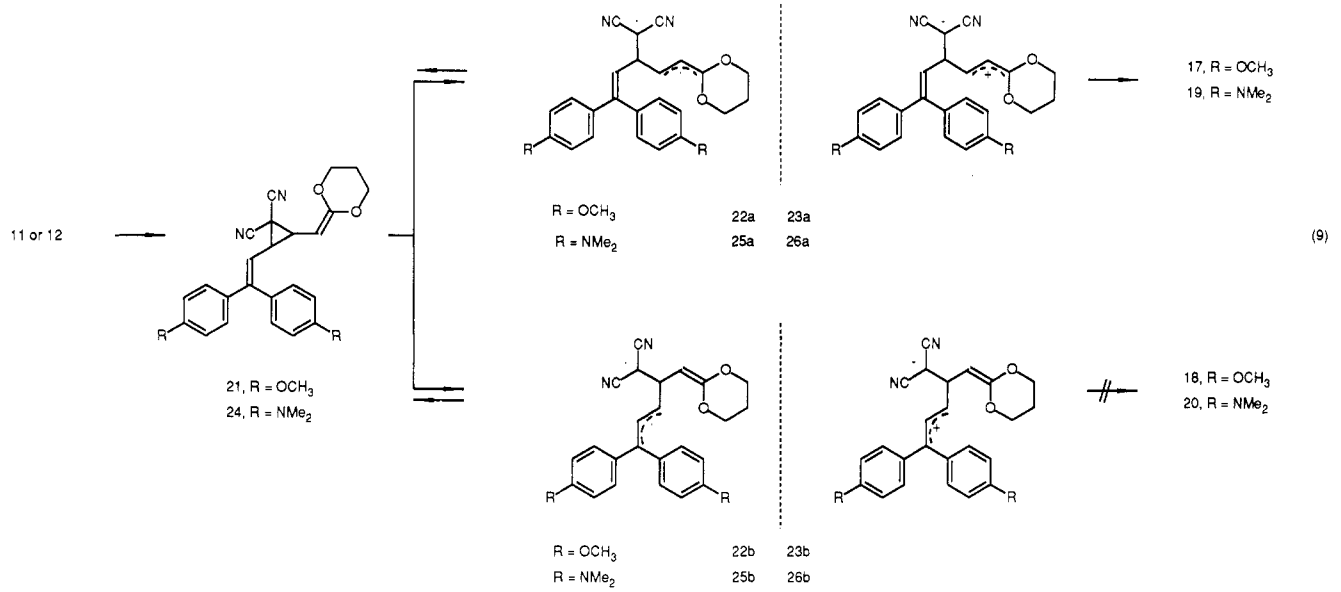
(15) The comparable low-energy conformations (MacroModel, Version 1.5; Allinger MM2) of **9a**-*trans* (–16.12 kcal/mol) and **9a**-*cis* (–16.19 kcal/mol) suggest that if the [3 + 2] cycloaddition reaction of 1 with **8a** were proceeding with the generation of a biradical or a zwitterionic intermediate, a mixture of **9a**-*trans* and **9a**-*cis* would be observed *and* that the observation of a single [3 + 2] cycloadduct isomer may be taken to reflect the maintenance of the initial olefin geometry in the [3 + 2] cycloaddition reaction.

(16) The instability of the products **9a**, **9b** to water was found in the attempts to thermally isomerize **9b**. Methyl ester **9b**, warmed at 80 °C in CD_3CN with a trace amount of atmospheric moisture present, was consumed within a few hours to give an unidentified ring-opened product. For related observations, see: Noordstrand, A. A. P.; Steinberg, H.; de Boer, Th. J. *Tetrahedron Lett.* **1975**, 2611. Wiering, P. G.; Steinberg, H. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 394.

Scheme VII



Scheme VIII



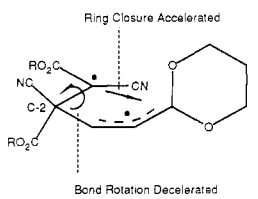
(entropic effect) of an intermediate biradical or zwitterion that accompanies the C^2-quaternary substitution.[17] If a two-stage [$_\pi2_s$ + $_\omega2_a$] cycloaddition/vinylcyclopropane rearrangement is operative, the preceding observations with *E*-/*Z*-**4** and *E*-/*Z*-**5** and the lack of an observed solvent effect suggested that this must be a biradical intermediate.

The reaction of the cyclopropenone ketal **1** with the 2,3-dicyanofumaric esters **8a** and **8b** does represent the first successful examples of tetrasubstituted olefins participating in a cycloaddition reaction ([3 + 2] cycloaddition) with the π-delocalized singlet vinylcarbene and this reactivity may be attributed to the electron-deficient character and minimal steric hindrance of the tetrasubstituted olefinic substrates.

Investigations Designed to Indirectly Observe an Undetected [$_\pi2_s$ + $_\omega2_\alpha$] Cycloaddition. Having established that the [3 + 2] cycloaddition is not proceeding by direct [$_\pi2_s$ + $_\pi2_a$] cycloaddition, we initiated efforts to trap and indirectly detect the potential [$_\pi2_s$ + $_\omega2_a$] vinylcyclopropane ketene acetal cycloadduct through the examination of the thermal reaction of **1** with the dienes **10–12**. Provided the [3 + 2] cycloaddition is observed, a direct or stepwise addition–cyclization reaction of the π-delocalized singlet vinylcarbene with **10–12** would provide a single [3 + 2] cycloadduct while a reaction proceeding with the initial generation of a [1 + 2] vinylcyclopropane ketene acetal cycloadduct ([$_\omega2_a$ + $_\pi2_s$] cycloaddition) followed by subsequent biradical or zwitterionic rearrangement to the [3 + 2] cyclopentenone ketal cycloadducts possesses the capabilities of providing *two*, distinguishable [3 + 2] cycloadducts (eq 8, Scheme VII).

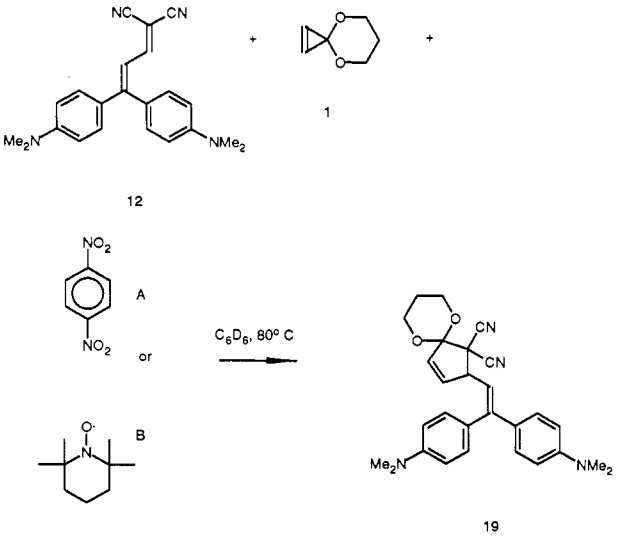
Although initial attempts to study the reaction of **1** with the exceptionally reactive diene **10** proved unmanageable,[18] the reaction of the cyclopropenone ketal **1** with the dienes **11** and **12** were examined. If diene **11** would provide the [1 + 2] cycloadduct **21**, subsequent biradical vinylcyclopropane rearrangement of **21** would predominantly and perhaps exclusively provide **17** through the preferential formation of the biradical **22a** [$(RO)_2C^\bullet$ > (p-$CH_3OC_6H_4)_2C^\bullet$, **22a** > **22b**] (eq 9, Scheme VIII). A

(17) This is illustrated with the biradical intermediate below.



(18) Schubert, H.; Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 553. An improved, more convenient preparation of **10** was devised: Treatment of (methoxymethylene)malononitrile with dimethoxyethylene (1.3 equiv, 60 °C, THF, 10 h) provided **10** (22%). The reaction of **10** with cyclopropenone ketal **1** (80 °C, benzene or CD_3CN) provided no distinguishable reaction products.

Table IV



entry	inhibitor, (mol %)	conditions:[a] equiv of 1, solvent, (time, h)	% yield[b]
1		2.7, C_6H_6, (4)	92 (- -)
2	A, (5)	3.0, C_6D_6, (3.8)	nd (>95)
3	A, (20)	3.0, C_6D_6, (3.8)	nd (>95)
4	A, (100)	3.0, C_6D_6, (3.8)	82 (>95)
5	A, (400)	3.0, C_6D_6, (4.3)	nd (>95)
6	B, (5)	3.0, C_6D_6, (16)	95 (>95)
7	B, (20)	3.0, C_6D_6, (16)	83 (>95)
8	B, (100)	3.0, C_6D_6, (16)	88 (- -)
9	B, (400)	3.0, C_6H_6, (12)	75 (- -)

[a] All reactions were run under an inert atmosphere (argon) and protected from light (80 °C). Reactions conducted in C_6D_6 as solvent were run in 5-mm ^1H NMR tubes and monitored periodically by ^1H NMR (300 MHz). [b] Yield of chromatographically homogeneous product isolated by chromatography (SiO_2). The percent yield in parentheses refers to the estimated percent conversion determined by ^1H NMR of the crude reaction product.

zwitterionic vinylcyclopropane rearrangement of **21** would be expected to provide a mixture of **17** and **18** as a result of competitive formation of two zwitterionic intermediates, **23a** versus **23b**, and would result from the comparable resonance stabilization of the two potential dipolar intermediates [$(RO)_2C^+ \cong (p\text{-}CH_3OC_6H_4)_2C^+$, **23a** ≅ **23b**]. In contrast, the diene **12** would be expected to provide the [1 + 2] cycloadduct **24** and a subsequent biradical *or* dipolar vinylcyclopropane rearrangement of **24** would predominantly or exclusively provide **20** through the preferential formation of the resonance-stabilized biradical[19] [$(p\text{-}Me_2NC_6H_4)_2C^{\bullet} \leftrightarrow (p\text{-}Me_2\dot{N}^+{=}C_6H_4){=}C(C_6H_4NMe_2) \gg (RO)_2C^{\bullet}$] *or* resonance-stabilized zwitterion [$(p\text{-}Me_2NC_6H_4)_2C^+ \leftrightarrow (p\text{-}Me_2N^+{=}C_6H_4){=}C(C_6H_4NMe_2) > (RO)_2C^+$, **26b > 26a**] (eq 9). Treatment of dienes **11** and **12** with the cyclopropenone ketal **1** (80 °C; C_6H_6, CH_3CN, DMF-d_7) cleanly provided the [3 + 2] cycloadducts **17** and **19** in exceptionally high yields (86–92%) as the *exclusive* reaction products (Scheme IX). No trace of the [3 + 2] cycloadducts **18** or **20** was detected. In the case of diene **12**, this observation clearly rules out the intermediacy of the [1 + 2] cycloadduct **24** as an initial, and undetected, reaction product. In addition, the observed [3 + 2] cycloaddition of **1** with diene **12** proceeds to provide **19** in the presence of catalytic or stoichiometric amounts of radical traps: 5–400 mol % Tempo and 5–400 mol %

(19) Creary, X.; Mehrsheikh-Mohammadi, M. E.; McDonald, S. *J. Org. Chem.* **1987**, *52*, 3254.

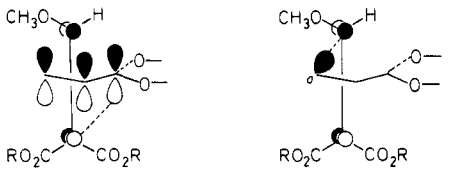


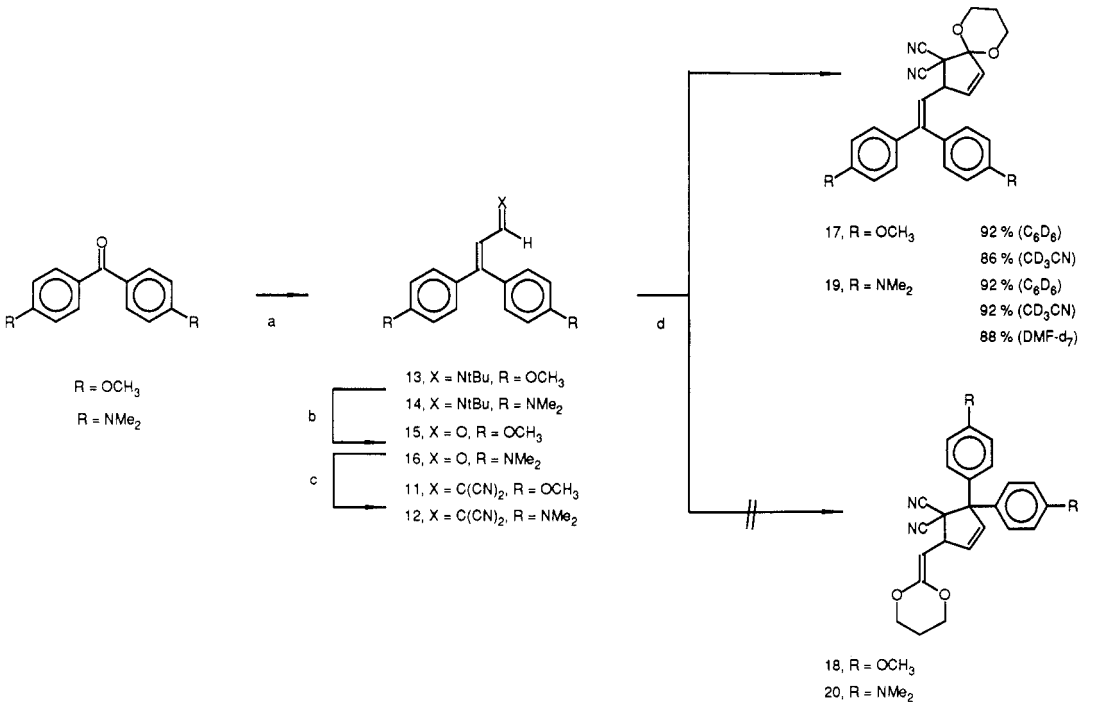
Figure 2.

1,4-dinitrobenzene (Table IV). This control observation confirms the earlier conclusion that the observed [3 + 2] cycloaddition reaction of **12** is not proceeding by a stepwise, biradical addition–cyclization reaction of a triplet partially delocalized vinylcarbene. It is remarkable that of the potential reaction pathways available to the reaction of **1** with dienes **11** and **12** including [4 + 2], [1 + 2], [3 + 4], and [3 + 2] cycloaddition, the clean, rapid [3 + 2] cycloaddition reaction is the exclusive reaction course observed.

An Alternative Mechanism. Consequently, in the examination of alternative reaction mechanisms for the [3 + 2] cycloaddition reaction that could account for the (1) partial, albeit not complete, loss of substrate olefin geometry in the course of the cycloaddition, (2) the lack of solvent dependency on the rate *and* stereoselectivity of the cycloaddition reaction, (3) the lack of observation of alternative and preferential formation of rearrangement products [alternative [3 + 2] cycloadducts derived from an initial, undetected [1 + 2] cycloadduct], and (4) the lack of inhibition of the cycloaddition reaction by free-radical traps, we have considered a single-electron transfer/combination reaction mechanism. Reversible, thermal generation of the π-delocalized singlet vinylcarbene,[20] single-electron transfer from the electron-rich π-delocalized singlet vinylcarbene to the electron-deficient substrate with generation of the π-delocalized cation-radical **28**, a distonic cation-radical, and substrate radical-anion, biradical (or dipolar) combination, and subsequent zwitterion (or biradical) combination, provides an attractive mechanism that accounts for *all* observations to date. Moreover, the single-electron transfer [3 + 2] cycloaddition reaction mechanism does accomodate the preferential and unexpectedly facile participation of electron-deficient substrates that are not readily accomodated by a simple cycloaddition mechanism ([1 + 2] or [3 + 2]) and that would not be expected to be optimal substrates for participation in a simple stepwise addition–cyclization reaction proceeding through the initial generation of biradical or zwitterionic intermediates. *Such substrates, e.g. 5-E/Z, would be expected to preferentially produce stabilized substrate radical-anions* (eq 10, Scheme X). Consequently, in an initial effort to establish the viability of the single-electron transfer/combination mechanism, the reaction of **27** with the cyclopropenone ketal **1** was examined with the potential of isolating products derived from the rearrangement of the cyclopropylmethyl radical (eq 11, Scheme X). Treatment of **27** with the cyclopropenone ketal **1** (80 °C; C_6H_6) cleanly and exclusively produced the [3 + 2] cycloadduct **30** (89%) without the detection of products that could be derived from rearrangement of the radical-anion intermediate **29**. Consequently, the operative single electron transfer/combination mechanism requires that the substrate anion-radical and cation-radical **28** combination occur at a rate faster than the cyclopropylmethyl radical rearrangement.[21] Studies to define this aspect of

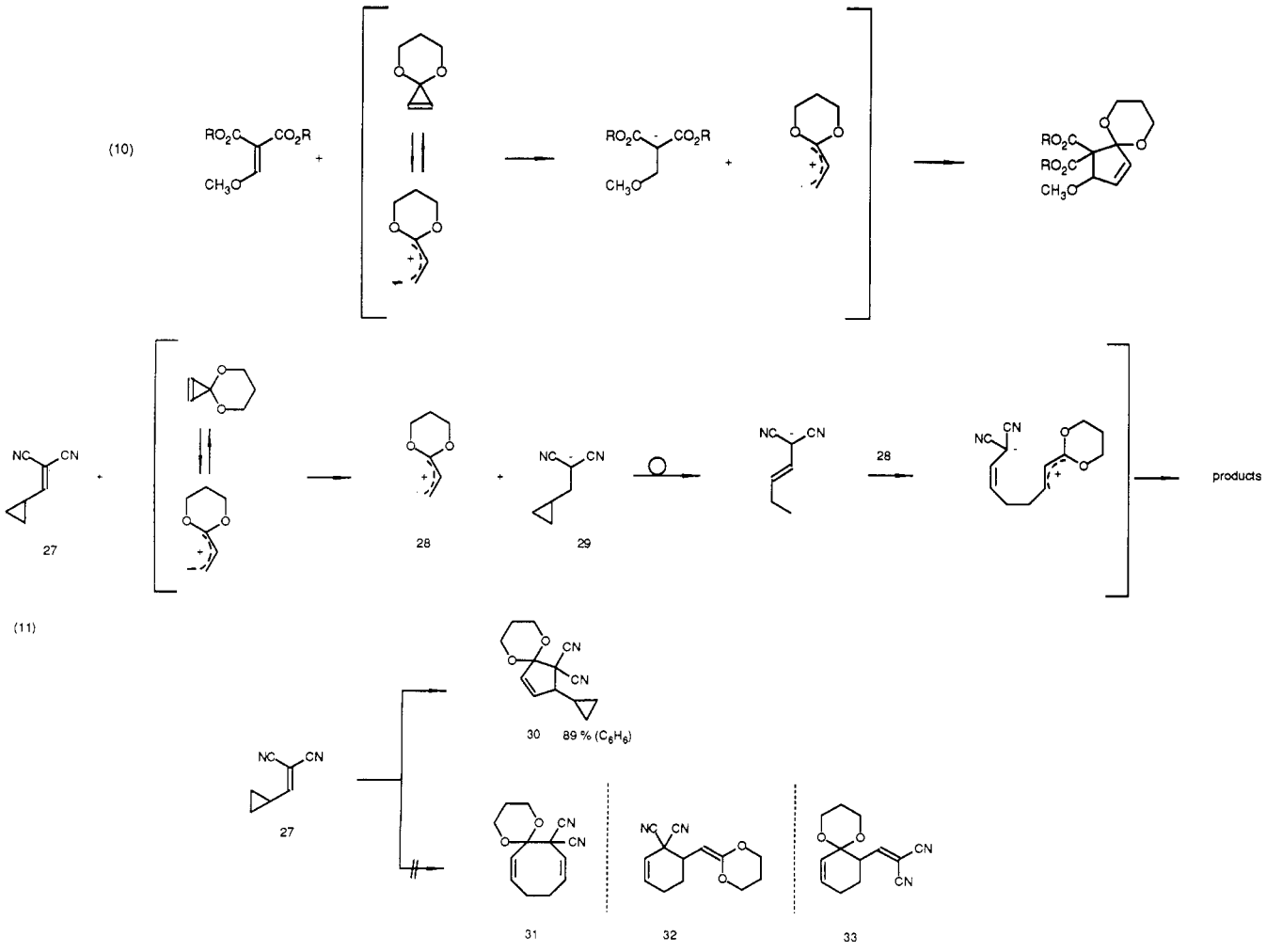
(20) Single-electron transfer from **1** to the electron-deficient substrate with generation of a cyclopropenone ketal radical-cation may precede ring opening to provide **28**. At present we are not able to distinguish between the two pathways to **28**.

Scheme IX[a]



[a] (a) R = OCH_3: 1.05 equiv of $Me_3SiCH(Li)CH{=}N\text{-}t\text{-}Bu$, THF, −78 °C (1 h), −23 °C (2 h). For R = NMe_2: 1.2 equiv of $CH_2(Li)CH{=}N\text{-}t\text{-}Bu$, THF, −78 to 25 °C (12 h). (b) Citric acid or acetic acid, H_2O, 15–30 min. (c) 1.0 equiv of malononitrile, 0.1 equiv of piperidinium acetate, CH_2Cl_2, 25 °C (2–10 h). (d) 3.0 equiv of 1, 80 °C (4–9 h).

Scheme X



the single-electron transfer mechanism as well as studies to distinguish whether the partial loss of substrate olefin geometry is the consequence of a mechanism of single-electron transfer, combination, and subsequent cyclization *or* the result of restricted bond rotation of the resulting substrate anion-radical preceding formation of a highly organized transition state (e.g. Figure 2) are in progress.

Conclusion

The [3 + 2] cycloaddition reactions of the π-delocalized singlet vinylcarbene reversibly and thermally generated in situ from the cyclopropenone ketal 1 may proceed with partial, albeit not complete, loss of substrate olefin geometry in a process in which the rate *and* stereoselectivity of the reaction has proven independent of the solvent polarity. These observations and the lack of the observation of the preferential formation of alternative [3 + 2] cycloadducts derived from a potentially undetected [1 + 2] cycloadduct, the lack of observed reaction with triplet carbene traps and captodative olefins, and the lack of inhibition of the [3 + 2] cycloaddition reaction by the addition of stoichiometric radical traps rule out: (1) a concerted $[_{\pi}2_a + {}_{\pi}2_s]$ cycloaddition mechanism; (2) a stepwise addition–cyclization mechanism of a singlet π-delocalized vinylcarbene proceeding with the intermediate generation of a zwitterionic intermediate; (3) a stepwise addition–cyclization mechanism of a triplet partially delocalized vinylcarbene proceeding with the intermediate generation of a biradical intermediate; and (4) the prospect of initial $[_{\omega}2_a + {}_{\pi}2_s]$ cycloaddition followed by biradical or zwitterionic vinylcyclopropane rearrangement of the undetected [1 + 2] cycloadduct. Moreover, the experimental observations are consistent with a single-electron transfer/anion-radical and cation-radical combination mechanism. The continued exploration and application of the thermal cycloaddition reactions of the cyclopropenone ketal (1) and π-delocalized singlet-vinylcarbenes are in progress.

Experimental Section

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian FT-80, Varian XL-200, Nicolet NT-200, Nicolet NT-470, or General Electric QE-300 instrument, and chemical shifts are reported in parts per million relative to internal tetramethylsilane (0.00 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian XL-200 (50 MHz), and chemical shifts are reported in parts per million relative to chloroform-*d* (77.0 ppm). Infrared spectra (IR) were recorded on a Perkin-Elmer 1420 spectrometer and a Perkin-Elmer 1800 Fourier transform spectrometer. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron-impact mass spectra (EIMS) and chemical-ionization mass spectra (CIMS) were recorded on a Finnigan 4000 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Kratos MS-50 spectrometer. Medium-pressure liquid chromatography (MPLC)[22a] and flash chromatography[22b] were performed on 230–400-mesh silica gel. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Benzene (C_6H_6) was distilled from calcium hydride. Methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide. Benzene-d_6 (C_6D_6), acetonitrile-d_3 (CD_3CN), and *N,N*-dimethylformamide-d_7 (DMF-d_7) were obtained from Aldrich Chemical Co. and used without further purification. Diisopropylamine was distilled from calcium hydride. *n*-Butyllithium (*n*-BuLi) was titrated with menthol in benzene at room temperature with 2,2′-dipyridyl as an indicator.[22c] All extraction and chromatographic solvents [ethyl ether (Et_2O), ethyl acetate (EtOAc), methylene chloride (CH_2Cl_2), and hexane] were distilled prior to use. All reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen (N_2) or argon.

(*E*)- and (*Z*)-Benzyl Methyl (Phenylmethylene)malonate (4-*E* and 4-*Z*). A solution of benzyl methyl malonate (2.45 g, 11.8 mmol)[23] in benzene (50 mL) was treated with benzaldehyde (1.56 g, 14.8 mmol, 1.2 equiv) and piperidine (0.130 mL, 1.3 mmol, 0.1 equiv). A reflux condenser equipped with a Dean-Stark trap charged with benzene was attached and the reaction solution was warmed at reflux with azeotropic removal of water (12 h). The cooled reaction solution was diluted with benzene (50 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 5.0 × 15.0 cm, CH_2Cl_2 eluant) afforded 4-*E* and 4-*Z* (1.68 g, 3.49 g theoretical, 48%) as a 1:1 mixture as estimated by ^{1}H NMR. The *E* and *Z* isomers (4-*E* and 4-*Z*) were separated by MPLC (SiO_2, 1.5 × 1000 cm, 1:1 $CHCl_3$–CH_2Cl_2 eluant) to afford pure 4-*E* (587 mg) as a faint yellow oil and pure 4-*Z* (506 mg) as a faint yellow oil. For 4-*E*: ^{1}H NMR (C_6D_6, 80 MHz, ppm) 7.87 (s, 1 H, *H*C=CCO_2CH_3), 7.35–6.90 (m, 10 H, C_6H_5), 5.13 (s, 2 H, $OCH_2C_6H_5$), 3.49 (s, 3 H, OCH_3); IR (neat) ν_{max} 3033, 2950, 1719, 1625, 1498, 1450, 1378, 1260, 1083, 830 cm^{-1}. For 4-*Z*: ^{1}H NMR (C_6D_6, 80 MHz, ppm) 7.81 (s, 1 H, *H*C=CCO_2CH_3), 7.25–6.75 (m, 10 H, C_6H_5), 5.15 (s, 2 H, $OCH_2C_6H_5$), 3.35 (s, 3 H, OCH_3); IR (neat) ν_{max} 3033, 2953, 2844, 1735, 1627, 1577, 1498, 1437, 1388, 1260, 1082, 1062, 745 cm^{-1}. For 4-*E* and 4-*Z* (1:1): EIMS, *m/e* (relative intensity) 296 (M^+, 1), 264 (4), 158 (16), 130 (21), 91 (base); CIMS (isobutane), *m/e* (relative intensity) 297 (M + H^+, 100); HRMS, *m/e* 296.1039 ($C_{18}H_{16}O_4$ requires 296.1048).

(*E*)- and (*Z*)-Benzyl Methyl (Methoxymethylene)malonate (5-*E* and 5-*Z*). A solution of acetic anhydride (1.73 mL, 18.4 mmol, 2.0 equiv), trimethyl orthoformate (1.1 mL, 10.1 mmol, 1.1 equiv), and benzyl methyl malonate (1.90 g, 9.13 mmol)[23] was treated with anhydrous zinc chloride (0.1 g, 0.73 mmol, 0.08 equiv). A reflux condenser equipped with a Dean-Stark trap charged with 0.5 mL of trimethyl orthoformate and 0.4 mL of acetic anhydride was attached and the reaction mixture was warmed at 100 °C with the distillative removal of methanol (21 h). The cooled reaction solution was concentrated in vacuo and filtered through a short column of silica gel (5.0 × 5.0 cm, CH_2Cl_2). Evaporation of the solvent in vacuo afforded a mixture of 5-*E* and 5-*Z* (1.00 g, 2.28 g theoretical, 44%) as a colorless oil. The *E* and *Z* isomers (5-*E* and 5-*Z*) were separated by MPLC (SiO_2, 1.5 × 1000 cm, 3:1 $CHCl_3$–CH_2Cl_2 eluant) to give pure 5-*E* (116 mg), pure 5-*Z* (107 mg) and remaining mixed fractions. For 5-*E*: ^{1}H NMR (C_6D_6, 200 MHz, ppm) 7.20 (s, 1 H, CH_3OCH=C), 7.16 (m, 5 H, C_6H_5), 5.22 (s, 2 H, $OCH_2C_6H_5$), 3.42 (s, 3 H, OCH_3), 2.78 (s, 3 H, OCH_3); ^{1}H NMR (CD_3CN, 80 MHz, ppm) 7.60 (s, 1 H, CH_3OCH=C), 7.36 (s, 5 H, C_6H_5), 5.18 (s, 2 H, $OCH_2C_6H_5$), 3.91 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3); IR (neat) ν_{max} 3030, 3005, 2956, 1735, 1637, 1437, 1389, 1270, 1203, 1137, 1090 cm^{-1}. For 5-*Z*: ^{1}H NMR (C_6D_6, 200 MHz, ppm) 7.20 (s, 1 H, CH_3OCH=C), 7.16 (m, 5 H, C_6H_5), 5.12 (s, 2 H, $OCH_2C_6H_5$), 3.47 (s, 3 H, OCH_3), 2.76 (s, 3 H, OCH_3); ^{1}H NMR (CD_3CN, 80 MHz, ppm) 7.60 (s, 1 H, CH_3OCH=C), 7.36 (s, 5 H, C_6H_5), 5.16 (s, 2 H, $OCH_2C_6H_5$), 3.91 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3); IR (neat) ν_{max} 3030, 2980, 2950, 1720, 1624, 1501, 1439, 1397, 1366, 1285, 1202, 1093, 756 cm^{-1}. For 5-*E* and 5-*Z* (1:1): EIMS, *m/e* (relative intensity) 250 (M^+, 1), 143 (base), 91 (84); CIMS (isobutane), *m/e* (relative intensity) 251 (M + H^+, base); HRMS, *m/e* 250.0839 ($C_{13}H_{14}O_5$ requires 250.0841).

Reaction of 1 with 4-*E*: *trans*-Benzyl Methyl 2-Phenyl-6,10-dioxaspiro[4.5]dec-3-ene-1,1-dicarboxylate (6-*trans*). In Benzene-d_6. A solution of (*E*)-benzyl methyl (phenylmethylene)malonate (4-*E*, 86 mg, 0.29 mmol) in benzene-d_6 (0.3 mL) was treated with cyclopropenone 1,3-propanediyl ketal (1,

(21) Recent studies have demonstrated the substantial stabilization imparted to free radicals adjacent to anionic centers; cf. Kornblum, N.; Chen, S. I.; Kelly, W. J. *J. Org. Chem.* **1988**, *53*, 1830. Consequently, it is not unlikely that the rate of the ring-opening cyclopropylmethyl radical rearrangement of the radical anion **29** is slower than that of the unstabilized cyclopropylmethyl radical.

(22) (a) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247. (b) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. (c) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165. Vedejs, E.; Engler, D. A.; Teleschew, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(23) Commercially available from Aldrich Chemical Co.

162 mg, 1.45 mmol, 5.0 equiv) under nitrogen. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (20 h). The reaction solution was cooled to room temperature and concentrated in vacuo, and the residue was filtered through a short column of silica gel (1 × 5 cm, CH_2Cl_2). Evaporation of the solvent in vacuo and flash chromatography (SiO_2, 1.5 × 10 cm, CH_2Cl_2 eluant) of the residue afforded recovered **4-*E*** (4 mg, 0% isomerized), cyclopropenone 1,3-propanediyl ketal dimer, and an inseparable mixture of **6-*trans*** and **6-*cis*** (84.1 mg, 118 mg theoretical, 71% at 96% conversion, 73:27, respectively, by ^1H NMR) as a colorless oil. For **6-*trans***: ^1H NMR ($CDCl_3$, 470 MHz, ppm) 7.50–7.20 (m, 10 H, C_6H_5), 6.69 (dd, 1 H, J = 6.2, 2.8 Hz, CCH=C*H*CH), 6.14 (dd, 1 H, J = 6.2, 1.0 Hz, CC*H*=CHCH), 5.50 (d, 1 H, J = 12.5 Hz, OC*H*HC$_6$H$_5$), 5.15 (d, 1 H, J = 12.5 Hz, OCH*H*C$_6$H$_5$), 4.96 (dd, 1 H, J = 2.8, 1.0 Hz, CCH=CHC*H*), 4.20–3.90 (m, 4 H, OCH_2CH$_2$CH_2O), 2.94 (s, 3 H, OCH_3), 2.25–2.15 (m, 1 H, OCH$_2$C*H*HCH$_2$O), 1.22 (m, 1 H, OCH$_2$CH*H*CH$_2$O); IR (neat) ν_{max} 3062, 3033, 2953, 2870, 1732, 1627, 1604, 1495, 1455, 1434, 1376, 1352, 1337, 1270, 1216, 1155, 1125, 911, 758, 736 cm^{-1}; EIMS, m/e (relative intensity) 408 (M^+, 2), 376 (1), 273 (9), 91 (base); CIMS (isobutane), m/e (relative intensity) 409 ($M + H^+$, base), 297 (51), 225 (67); HRMS, m/e 408.1573 ($C_{24}H_{24}O_6$ requires 408.1573).

Reaction of 1 with 4-*E* in Acetonitrile-d_3. A solution of (*E*)-benzyl methyl (phenylmethylene)malonate (**4-*E***, 120 mg, 0.405 mmol) in acetonitrile-d_3 (0.4 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 132 mg, 1.18 mmol, 2.9 equiv) under nitrogen. The reaction solution was sealed, shielded from light, and warmed at 80 °C (20 h). The reaction solution was cooled to room temperature and concentrated in vacuo, and the residue was filtered through a short column of silica gel (1 × 6 cm, CH_2Cl_2). Evaporation of the solvent in vacuo and flash chromatography (SiO_2, 2.0 × 12 cm, CH_2Cl_2 eluant) of the residue afforded recovered **4-*E*** (37.6 mg, 0.127 mmol, <4% isomerized), cyclopropenone 1,3-propanediyl ketal dimer and an inseparable mixture of **6-*trans*** and **6-*cis*** (96.5 mg, 165 mg theoretical, 58% at 85% conversion, 89:11, respectively, by ^1H NMR) as a colorless oil.

Reaction of 1 with 4-*Z*: *cis*-Benzyl Methyl 2-Phenyl-6,10-dioxaspiro[4.5]dec-3-ene-1,1-dicarboxylate (6-*cis*). In Acetonitrile-d_3. A solution of (*Z*)-benzyl methyl (phenylmethylene)malonate (**4-*Z***, 120 mg, 0.405 mmol) in acetonitrile-d_3 (0.4 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 132 mg, 1.18 mmol, 2.9 equiv) under nitrogen. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (20 h). The reaction solution was cooled to room temperature and concentrated in vacuo, and the residue was filtered through a short column of silica gel (1 × 5 cm, CH_2Cl_2). Evaporation of the solvent in vacuo and flash chromatography (SiO_2, 1.5 × 12 cm, CH_2Cl_2 eluant) of the residue afforded recovered **4-*Z*** (8 mg, <5% isomerized), cyclopropenone 1,3-propanediyl ketal dimer and an inseparable mixture of **6-*cis*** and **6-*trans*** (99 mg, 165 mg theoretical, 60%, 90:10, respectively, by ^1H NMR) as a colorless oil. For **6-*cis***: ^1H NMR ($CDCl_3$, 470 MHz, ppm) 7.30–7.10 (m, 10 H, C_6H_5), 6.73 (dd, 1 H, J = 6.2, 2.8 Hz, CCH=C*H*CH), 6.16 (dd, 1 H, J = 6.2, 1.0 Hz, CC*H*=CHCH), 4.96 (dd, 1 H, J = 2.8, 1.0 Hz, CCH=CHC*H*), 4.58 (d, 1 H, J = 12.5 Hz, OC*H*HC$_6$H$_5$), 4.10 (d, 1 H, J = 12.5 Hz, OCH*H*C$_6$H$_5$), 4.10 (m, 2 H, OCHH_{eq}CH$_2$CHH_{eq}O), 3.95 (m, 2 H, OCHH_{ax}CH$_2$CHH_{ax}O), 3.72 (s, 3 H, OCH_3), 2.0 (m, 1 H, OCH$_2$CH*H*CH$_2$O), 1.38 (m, 1 H, OCH$_2$C*H*HCH$_2$O); IR (neat) ν_{max} 3062, 3033, 2951, 2869, 1732, 1625, 1605, 1495, 1455, 1273, 1217, 1155, 1109, 1058, 758, 701 cm^{-1}; EIMS, m/e (relative intensity) 408 (M^+, 9), 376 (3), 273 (12), 183 (12), 91 (base); CIMS (isobutane), m/e 409 ($M + H^+$, base); HRMS, m/e 408.1568 ($C_{24}H_{24}O_6$ requires 408.1573).

Reaction of 1 with 4-*Z* in Benzene. A mixture of (*Z*)-benzyl methyl (phenylmethylene)malonate (**4-*Z***, 53 mg, 0.179 mmol) in dry benzene (0.15 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 85 mg, 0.76 mmol, 4.2 equiv) under nitrogen. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (20 h). The reaction mixture was cooled to room temperature and concentrated in vacuo, and the residue was filtered through a short column of silica gel (1 × 4 cm, CH_2Cl_2). Evaporation of the solvent in vacuo and flash chromatography (SiO_2, 1.5 × 10 cm, CH_2Cl_2 eluant) of the residue afforded cyclopropenone 1,3-propanediyl ketal dimer and an inseparable mixture of **6-*cis*** and **6-*trans*** (48 mg, 73 mg theoretical, 66%, 64:36, respectively, by ^1H NMR) as a colorless oil.

Reaction of 1 with 5-*E*: *trans*-Benzyl Methyl 2-Methoxy-6,10-dioxaspiro[4.5]dec-3-ene-1,1-dicarboxylate (7-*trans*). In Benzene-d_6. A mixture of (*E*)-benzyl methyl (methoxymethylene)malonate (**5-*E***, 28.6 mg, 0.11 mmol) in benzene-d_6 (0.3 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 13.2 mg, 0.12 mmol, 1.1 equiv) under nitrogen. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (20 h). The reaction mixture was cooled to room temperature and concentrated in vacuo, and the residue was filtered through a short column of silica gel (1 × 3 cm, CH_2Cl_2). Evaporation of the solvent in vacuo and flash chromatography (SiO_2, 1 × 9 cm, CH_2Cl_2 eluant) of the residue afforded recovered **5-*E*** (12.2 mg, 0.048 mmol, 0% isomerized) and an inseparable mixture of **7-*trans*** and **7-*cis*** (19.1 mg, 39.8 mg theoretical, 48%, at 80% conversion, 82:18, respectively, by ^1H NMR) as a colorless oil. For **7-*trans***: ^1H NMR (C_6D_6, 470 MHz, ppm) 7.15 (m, 5 H, C_6H_5), 6.33 (dd, 1 H, J = 6.2, 2.0 Hz, CCH=C*H*CHOCH$_3$), 5.99 (dd, 1 H, J = 6.2, 1.3 Hz, CC*H*=CHCHOCH$_3$), 5.39 (dd, 1 H, J = 2.0, 1.3 Hz, CCH=CHC*H*OCH$_3$), 5.15 (s, 2 H, OCH_2C$_6$H$_5$), 3.70 (m, 4 H, OCH_2CH$_2$CH_2O), 3.38 (s, 3 H, OCH_3), 3.37 (s, 3 H, OCH_3), 1.65 (m, 1 H, OCH$_2$C*H*HCH$_2$O), 0.68 (m, 1 H, OCH$_2$CH*H*CH$_2$O); IR (neat) ν_{max} 2952, 2875, 1734, 1457, 1436, 1362, 1309, 1269, 1248, 1224, 1115, 1099, 1059, 1005 cm^{-1}. **7-*cis*/*trans*** mixture: EIMS, m/e (relative intensity) 362 (M^+, 1.4), 331 (5.5), 303 (20), 227 (77.8), 91 (base); CIMS (isobutane), m/e (relative intensity) 363 ($M + H^+$, 43), 332 (19), 331 (base); HRMS, m/e 362.1366 ($C_{19}H_{22}O_7$ requires 362.1366).

Reaction of 1 with 5-*E* in Acetonitrile-d_3. A solution of (*E*)-benzyl methyl (methoxymethylene)malonate (**5-*E***, 21.8 mg, 0.087 mmol) in acetonitrile-d_3 (0.5 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 12 mg, 0.11 mmol, 1.2 equiv) under nitrogen. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (15 h). The reaction mixture was cooled to room temperature and concentrated in vacuo, and the residue was filtered through a short column of silica gel (0.5 × 4 cm, CH_2Cl_2). Evaporation of the solvent in vacuo and flash chromatography (SiO_2, 1 × 10 cm, CH_2Cl_2 eluant) of the residue afforded an inseparable mixture of **7-*trans*** and **7-*cis*** (21 mg, 31.5 mg theoretical, 67%, 71:29, respectively, by ^1H NMR) as a colorless oil.

Reaction of 1 with 5-*Z*: *cis*-Benzyl Methyl 2-Methoxy-6,10-dioxaspiro[4.5]dec-3-ene-1,1-dicarboxylate (7-*cis*). In Benzene-d_6. A mixture of (*Z*)-benzyl methyl (methoxymethylene)malonate (**5-*Z***, 9.0 mg, 0.036 mmol) in benzene-d_6 (0.2 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 16.5 mg, 0.15 mmol, 4.2 equiv) under nitrogen. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (24 h). The reaction mixture was cooled to room temperature and concentrated in vacuo, and the residue was filtered through a short column of silica gel (0.5 × 2 cm, CH_2Cl_2). Evaporation of the solvent in vacuo and flash chromatography (SiO_2, 1 × 10 cm, CH_2Cl_2 eluant) of the residue afforded an inseparable mixture of **7-*cis*** and **7-*trans*** (10 mg, 13 mg theoretical, 76%, 79:21, respectively, by ^1H NMR) as a colorless oil. For **7-*cis***: ^1H NMR (C_6D_6, 470 MHz, ppm) 7.15 (m, 5 H, C_6H_5), 6.33 (dd, 1 H, J = 6.2, 2.2 Hz, CCH=C*H*CHOCH$_3$), 5.98 (dd, 1 H, J = 6.2, 1.2 Hz, CC*H*=CHCHOCH$_3$), 5.58 (d, 1 H, J = 12.2 Hz, OC*H*HC$_6$H$_5$), 5.39 (dd, 1 H, J = 2.2, 1.2 Hz, CCH=CHC*H*OCH$_3$), 5.17 (d, 1 H, J = 12.2 Hz, OCH*H*C$_6$H$_5$), 3.70 (m, 4 H, OCH_2CH$_2$CH_2O), 3.47 (s, 3 H, OCH_3), 3.45 (s, 3 H, OCH_3), 1.65 (m, 1 H, OCH$_2$C*H*HCH$_2$O), 0.68 (m, 1 H, OCH$_2$CH*H*CH$_2$O); IR (neat) ν_{max} 2952, 2932, 2874, 1736, 1452, 1363, 1265, 1096 cm^{-1}.

Reaction of 1 with 5-*Z* in Acetonitrile-d_3. A solution of (*Z*)-benzyl methyl (methoxymethylene)malonate (**5-*Z***, 26 mg, 0.10 mmol) in acetonitrile-d_3 (0.3 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 35 mg, 0.31 mmol, 3.0 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (16 h). The reaction mixture was cooled to room temperature and concentrated in vacuo, and the residue was filtered through a short column of silica gel (1 × 5 cm, $CHCl_3$). Evaporation of the solvent in vacuo and flash chromatgraphy (SiO_2, 1.5 × 12 cm, CH_2Cl_2 eluant) of the residue afforded cyclopropenone 1,3-propanediyl ketal dimer and an inseparable mixture of **7-*cis*** and **7-*trans*** (21.2 mg, 37.6 mg theoretical, 58%, 81:19, respectively, by ^1H NMR) as a colorless oil.

Reaction of 1 with (*E*)-Diethyl 2,3-Dicyanofumarate (8a): *trans*-Diethyl 1,2-Dicyano-6,10-dioxaspiro[4.5]dec-3-ene-1,2-dicarboxylate (9a-*trans*). In Benzene. A solution of (*E*)-diethyl 2,3-dicyanofumarate (**8a**, 40.0 mg, 0.180 mmol)[24] in dry benzene (0.5 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 30.0 mg, 0.268 mmol, 1.5 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (7.5 h). The reaction mixture was cooled to room temperature and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 7.0 cm, CH_2Cl_2 eluant) afforded cyclopropenone 1,3-propanediyl ketal dimer and **9a**-*trans* (39.8 mg, 60.1 mg theoretical, 66%) as a tan foam: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 6.61 (d, 1 H, J = 6.0 Hz, CCH=C*H*CCN), 6.49 (d, 1 H, J = 6.0 Hz, CC*H*=CHCCN), 4.31 (q, 2 H, J = 7.2 Hz, OCH_2CH$_3$), 4.30 (q, 2 H, J = 7.2 Hz, OCH_2CH$_3$), 4.15 (m, 2 H, OC*H*HCH$_2$C*H*HO), 3.99 (m, 2 H, OCH*H*CH$_2$CH*H*O), 2.20 (m, 1 H, OCH$_2$C*H*HCH$_2$O), 1.69 (dt, J = 13.0, 3.0 Hz, 1 H, OCH$_2$CH*H*CH$_2$O), 1.32 (t, 3 H, J = 7.2 Hz, OCH$_2$CH_3), 1.31 (t, 3 H, J = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz, ppm) 163.1 (*C*=O), 162.7 (*C*=O), 131.3 (HC=CHCCN), 130.3 (HC=*C*CCN), 113.7 (*C*≡N), 113.6 (*C*≡N), 109.7 (O*C*O), 64.1 (O*C*H$_2$), 63.9 (O*C*H$_2$), 63.3 (O*C*H$_2$), 62.3 (O*C*H$_2$), 56.8 (O=*C*CCN), 24.2 (*C*H$_2$), 13.7 (*C*H$_3$), 13.6 (*C*H$_3$); IR (neat) ν_{max} 3096, 2984, 2894, 2243, 1758, 1625, 1466, 1446, 1369, 1335, 1259, 1196, 1172, 1124, 1089, 1048, 1023, 916, 848, 774, 725 cm^{-1}; EIMS, m/e (relative intensity) 261 (base), 203 (19), 175 (53); CIMS (isobutane), m/e (relative intensity) 335 (M + H$^+$, base); HRMS, m/e 334.1165 ($C_{16}H_{18}N_2O_6$ requires 334.1165).

In Acetonitrile-d_3. A solution of (*E*)-diethyl 2,3-dicyanofumarate (**8a**, 36 mg, 0.162 mmol)[24] in acetonitrile-d_3 (0.3 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 22 mg, 0.196 mmol, 1.2 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (4 h). The reaction mixture was cooled to room temperature and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 8.0 cm, CH_2Cl_2 eluant) of the brown residue afforded cyclopropenone 1,3-propanediyl ketal dimer and **9a**-*trans* (28.0 mg, 54.1 mg theoretical, 52%) as a tan foam.

In *N*,*N*-Dimethylformamide-d_7 (DMF-d_7). A solution of (*E*)-diethyl 2,3-dicyanofumarate (**8a**, 33.0 mg, 0.149 mmol)[24] in DMF-d_7 (0.3 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 22.0 mg, 0.196 mmol, 1.2 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (4 h). The reaction mixture was cooled to room temperature and poured onto 10 mL of water. The mixture was extracted with CH_2Cl_2 (4 × 10 mL). The organic layers were combined, washed with water (5 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 7.0 cm, CH_2Cl_2 eluant) of the brown residue afforded cyclopropenone 1,3-propanediyl ketal dimer and **9a**-*trans* (22.0 mg, 49.8 mg theoretical, 44%) as a tan foam.

Reaction of 1 with (*E*)-Dimethyl 2,3-Dicyanofumarate (8b): *trans*-Dimethyl 1,2-Dicyano-6,10-dioxaspiro[4.5]dec-3-ene-1,2-dicarboxylate (9b-*trans*). In Acetonitrile-d_3. A solution of (*E*)-dimethyl 2,3-dicyanofumarate (**8b**, 35.5 mg, 0.182 mmol)[24] in acetonitrile-d_3 (0.3 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 22 mg, 0.196 mmol, 1.1 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (24 h). The reaction mixture was cooled to room temperature and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 6.0 cm, CH_2Cl_2 eluant) of the tan residue afforded cyclopropenone 1,3-propanediyl ketal dimer (16.8 mg) and **9b**-*trans* (17.8 mg, 56 mg theoretical, 32%) as a pale green foam: ^1H NMR ($CDCl_3$, 470 MHz, ppm) 6.68 (d, 1 H, J = 6.2 Hz, CCH=C*H*CCO$_2$CH$_3$), 6.58 (d, 1 H, J = 6.2 Hz, CC*H*=CCO$_2$CH$_3$), 4.35–4.31 (ddt, 1 H, J = 1.0, 3.1, 11.8 Hz, OCHH_{eq}CH$_2$CH$_2$O), 4.20–4.16 (ddt, 1 H, J = 1.5, 3.7, 11.8 Hz, OCH$_2$CH$_2$CHH_{eq}O), 4.07–3.98 (dq, 2 H, J = 3.6, 11 Hz, OCHH_{ax}CH$_2$CHH_{ax}O), 3.86 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 2.25 (m, 1 H, OCH$_2$CHH_{eq}CH$_2$O), 1.69 (m, 1 H, OCH$_2$CHH_{ax}CH$_2$O); IR (neat) ν_{max} 3094, 2959, 2890, 2257, 1751, 1625, 1437, 1336, 1260, 1172, 797 cm^{-1}; EIMS, m/e (relative intensity) 275 (3), 247 (base); CIMS (isobutane), m/e (relative intensity) 363 (M + $C_4H_9^+$, base), 307 (M + H$^+$, 28); CIHRMS (isobutane), m/e 307.0929 ($C_{14}H_{15}N_2O_6$ requires 307.0930).

Reaction of 1 with *E*-8b in *N*,*N*-Dimethylformamide-d_7 (DMF-d_7). A solution of (*E*)-dimethyl 2,3-dicyanofumarate (**8b**, 44.3 mg, 0.23 mmol)[24] in dry DMF-d_7 (0.4 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 27.5 mg, 0.25 mmol, 1.09 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (16 h). The reaction mixture was concentrated in vacuo and filtered through a short column of silica gel (1 × 10 cm, CH_2Cl_2). Evaporation of the solvent in vacuo and flash chromatography (SiO_2, 1.0 × 6.0 cm, CH_2Cl_2 eluant) of the residue afforded cyclopropenone 1,3-propanediyl ketal dimer and **9b**-*trans* (20 mg, 70.4 mg theoretical, 28%) as a pale green foam.

Reaction of 1 with *E*-8b in Benzene. A solution of (*E*)-dimethyl 2,3-dicyanofumarate (**8b**, 33 mg, 0.17 mmol)[24] in dry benzene (0.3 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 40 mg, 0.36 mmol, 2.1 equiv) under argon. The mixture was sealed, shielded from light, and warmed at 80 °C (9 h). The reaction mixture was diluted with benzene (2 mL) and filtered, and the filtrate was concentrated in vacuo. Flash chromatography (SiO_2, 1 × 8.0 cm, CH_2Cl_2 eluant) of the brown residue afforded **9b**-*trans* (15.6 mg, 52 mg theoretical, 30%) as a colorless oil.

2-Cyano-5,5-bis(4-methoxyphenyl)-2,4-pentadienenitrile (11). A stirred solution of diisopropylamine (1.4 mL, 1.01 g, 10.0 mmol, 1.05 equiv) in anhydrous tetrahydrofuran (30 mL) under argon (0 °C) was treated with *n*-butyllithium (2.3 M in hexanes, 4.3 mL, 9.89 mmol, 1.04 equiv). After 15 min, 2-(trimethylsilyl)acetaldehyde *tert*-butylimine (1.70 g, 9.93 mmol, 1.05 equiv)[25] was added to the solution of freshly generated lithium diisopropylamide and the resulting solution was stirred at 0 °C (20 min). The reaction solution was cooled to −78 °C and added (via cannula) to a slurry of 4,4′-dimethoxybenzophenone (2.30 g, 9.5 mmol) in anhydrous tetrahydrofuran (10 mL) cooled to −78 °C. The reaction mixture was stirred at −78 °C (1 h) and −23 °C (2 h) and allowed to warm to room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in water (10 mL) and acidified to pH 4.5 with solid citric acid, and the resulting mixture was stirred for 0.5 h (25 °C). The reaction mixture was extracted with ether (3 × 15 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and saturated aqueous NaCl (1 × 10 mL), dried (K_2CO_3), and concentrated in vacuo. Flash chromatography (SiO_2, 4 × 12 cm, CH_2Cl_2 eluant) afforded **15** (1.86 g, 2.56 g theoretical) as a pale yellow oil.[26]

A solution of **15** (1.86 g, 7.27 mmol) in dichloromethane (20 mL) was treated with malononitrile (480 mg, 7.27 mmol, 1.0 equiv), acetic acid (0.040 mL, 0.7 mmol, 0.1 equiv), and piperidine (59 mg, 0.69 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 2 h and diluted with dichloromethane (20 mL). The reaction mixture was washed with 5% aqueous hydrochloric acid (1 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and dried Na_2SO_4). Flash chromatography (SiO_2, 4 × 12 cm, CH_2Cl_2 eluant) afforded **11** (1.03 g, 3.00 g theoretical, 34%) as yellow plates (hexane): mp 118.5–119 °C; ^1H NMR ($CDCl_3$, 470 MHz, ppm) 7.47 (d, 1 H, J = 12.1 Hz, (NC)$_2$C=C*H*), 7.36, 7.14, 7.00, and 6.91 (4 d, 8 H, J = 8.5 Hz, C$_6H_4$), 7.07 (d, 1 H, J = 12.1 Hz, *H*C=CAr$_2$), 3.90 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3); IR (melt) ν_{max} 2950, 2851, 2221, 1660, 1556, 1513, 1503, 1252, 1173, 1028, 834 cm^{-1}; EIMS, m/e (relative intensity) 316 (M$^+$, base), 301 (8), 290 (10); CIMS (isobutane), m/e (relative intensity) 307 (M + H$^+$, base); HRMS, m/e 316.1205 ($C_{20}H_{16}H_2O_2$ requires 316.1212). Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.92; H, 5.10; N, 8.86. Found: C, 75.85; H, 5.32; N, 8.63.

Reaction of 2-Cyano-5,5-bis(4-methoxyphenyl)-2,4-pentadienenitrile (11) with 1: 2-[2′,2′-Bis(4-methoxyphenyl)-ethenyl]-6,10-dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile (17). In Acetonitrile-d_3. A mixture of 2-cyano-5,5-bis(4-methoxyphenyl)-2,4-pentadienenitrile (**11**, 42.1 mg, 0.13 mmol) in acetonitrile-d_3 (0.15 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 44.2 mg, 0.39 mmol, 3.0 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (22 h). The reaction mixture was cooled to room tem-

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(26) The product contained ca. 5% 4,4′-dimethoxybenzophenone.

perature and concentration in vacuo afforded a deep orange oil. Flash chromatography (SiO_2, 1.5 × 15 cm, CH_2Cl_2 eluant) afforded **17** (47.3 mg, 55.6 mg theoretical, 86%) as an orange foam: ^1H NMR ($CDCl_3$, 470 MHz, ppm) 7.24, 7.14, 6.95, and 6.82 (4 d, 8 H, J = 8.7 Hz, C_6H_4), 6.44 (dd, 1 H, J = 6.2, 1.8 Hz, CC*H* = CHCH), 6.00 (dd, 1 H, J = 6.2, 2.4 Hz, CCH=C*H*CH), 5.87 (d, 1 H, J = 10.7 Hz, HCC*H*=CAr_2), 4.26–3.96 (m, 5 H, OCH_2, *H*CCH=CAr_2), 3.85 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 2.20 (m, 1 H, OCH_2CHHCH_2O), 1.65 (dt, 1 H, J = 13, 3.4 Hz, OCH_2CHHCH_2O); IR (neat) ν_{max} 2963, 2934, 2838, 2252, 1606, 1512, 1287, 1249, 1173, 1032, 834 cm^{-1}; EIMS, m/e (relative intensity) 428 (M^+, 71), 265 (59), 219 (base); CIMS (isobutane), m/e (relative intensity) 485 (M + $C_4H_9^+$, base) , 429 (M + H^+, 42); HRMS, m/e 428.1718 ($C_{26}H_{24}N_2O_4$ requires 428.1736).

In Benzene-d_6. A solution of **11** (46.4 mg, 0.147 mmol) in benzene-d_6 (0.2 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 48 mg, 0.429 mmol, 2.9 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (20 h). Flash chromatography (SiO_2, 2.5 × 10 cm, CH_2Cl_2 eluant) afforded **17** (59.2 mg, 64.0 mg theoretical, 92%) as an orange foam.

2-Cyano-5,5-bis[4-(dimethylamino)phenyl]-2,4-pentadienenitrile (12). A stirred solution of diisopropylamine (1.4 mL, 1.01 g, 10.0 mmol, 1.28 equiv) in anhydrous tetrahydrofuran (20 mL) under argon (0 °C) was treated with *n*-butyllithium (2.1 M in hexanes, 4.5 mL, 9.45 mmol, 1.20 equiv). After 15 min, acetaldehyde *tert*-butylimine (925 mg, 9.35 mmol, 1.19 equiv)[25] was added to the solution of freshly generated lithium diisopropylamide, and the resulting solution was stirred at 0 °C (15 min). The reaction solution was added via cannula to a slurry of 4,4′-bis(dimethylamino)benzophenone (2.10 g, 7.83 mmol)[23] in anhydrous tetrahydrofuran (40 mL) cooled to −78 °C. The reaction mixture was stirred at −78 °C (1 h) and was allowed to warm to room temperature. After 12 h, the reaction mixture was concentrated in vacuo and the residue was treated with aqueous acetic acid (8 M, 10 mL) and stirred (15 min). The resulting mixture was diluted with water (15 mL) and was extracted with ether (3 × 20 mL). The ether layers were combined and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), saturated aqueous NaCl (1 × 30 mL), and dried ($MgSO_4$). Concentration in vacuo afforded a red oil which by ^1H NMR indicated a 1:1 mixture of the desired aldehyde **16** and starting ketone. This red mixture was taken up into dichloromethane (30 mL) and was treated with malononitrile (520 mg, 7.87 mmol, 1.0 equiv), acetic acid (0.040 mL, 0.71 mmol, 0.09 equiv), and piperidine (0.070 mL, 0.71 mmol, 0.09 equiv). The reaction mixture was stirred for 10 h and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 12 cm, 9:1 CH_2Cl_2/hexane eluant) afforded diene **12** (1.15 g, 2.68 g theoretical, 43%) as a red powder. An analytical sample was prepared by crystallization from dichloromethane–ether to give dark violet needles (mp 195–197 °C): ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.47 (d, 1 H, J = 12.3 Hz, NCC=C*H*), 7.35, 7.19, 6.74, and 6.65 (4 d, 8 H, J = 9.0 Hz, C_6H_4), 6.96 (d, 1 H, J = 12.3 Hz, *H*C=CAr), 3.07 (s, 6 H, NCH_3), 3.06 (s, 6 H, NCH_3); IR (KBr) ν_{max} 2908, 2211, 1599, 1518, 1445, 1371, 1322, 1270, 1216, 1191, 1175, 1128, 946, 866, 821 cm^{-1}; EIMS, m/e (relative intensity) 342 (M^+, base), 316 (10), 170 (17); CIMS (isobutane), m/e (relative intensity) 399 (M + $C_4H_9^+$, 8), 381 (M + $C_3H_3^+$, 3), 343 (M + H^+, base); HRMS, m/e 342.1846 ($C_{22}H_{22}N_4$ requires 342.1845).

Reaction of 2-Cyano-5,5-bis[4-(dimethylamino)phenyl]-2,4-pentadienenitrile (12) with 1: 2-[2′,2′-Bis[4-(dimethylamino)phenyl]ethenyl]-6,10-dioxaspiro[4.5]dec-3-ene-1,1-dicarbonitrile (19). In Acetonitrile-d_3. A solution of diene **12** (40 mg, 0.12 mmol) in acetonitrile-d_3 (0.4 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 94 mg, 0.84 mmol, 7.0 equiv) under argon. The reaction was sealed, shielded from light, and warmed at 80 °C (10 h). The reaction was cooled to room temperature and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 12 cm, CH_2Cl_2 eluant) afforded **19** (48.8 mg, 53.1 mg theoretical, 92%) as a green oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.18, 7.09, 6.75, 6.62 (4 d, 8 H, J = 8.4 Hz, C_6H_4), 6.39 (dd, 1 H, J = 6.5, 1.5 Hz, C*H*C=CHCHCH=CAr_2), 6.01 (dd, 1 H, J = 6.5, 2.4 Hz, CCH=C*H*CHCH=CAr_2), 5.77 (d, 1 H, J = 10.0 Hz, CHC*H*=CAr_2), 4.30–3.85 (m, 5 H, OCH_2, HC=CHC*H*CH=CAr_2), 2.17 (m, 1 H, OCH_2CHHCH_2O), 1.63 (dt, 1 H, J = 13.6, 3.3 Hz, OCH_2CHHCH_2O); IR (neat) ν_{max} 3042, 2966, 2882, 2805, 2252, 1684, 1607, 1523, 1481, 1446, 1362, 1303, 1267, 1245, 1226, 1194, 1166, 1114, 1064, 1040, 1025, 947, 910, 821 cm^{-1}; EIMS, m/e (relative intensity) 454 (M^+, 15), 304 (12), 232 (39), 149 (17), 128 (32), 56 (base); CIMS (isobutane), m/e (relative intensity) 511 (M + $C_4H_9^+$, 61), 455 (M + H^+, base), 428 (8); HRMS, m/e 454.2367 ($C_{28}H_{30}N_4O_2$ requires 454.2369). Anal. Calcd for $C_{28}H_{30}N_4O_2$: C, 73.91; H, 6.65; N, 12.32. Found: C, 73.52; H, 6.75; N, 12.05.

Reaction in Benzene. A mixture of diene **12** (34.0 mg, 0.099 mmol) in dry benzene (0.4 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 30.0 mg, 0.268 mmol, 2.7 equiv) under argon. The reaction was sealed, shielded from light, and warmed at 80 °C (4 h). The reaction was cooled to room temperature and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 10.0 cm, CH_2Cl_2 eluant) of the green residue afforded **19** (41.3 mg, 45.1 mg theoretical, 92%) as a green oil.

Reaction in DMF-d_7. A mixture of diene **12** (46.0 mg, 0.135 mmol) in DMF-d_7 (0.4 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 60.0 mg, 0.541 mmol, 4.0 equiv) under argon. The reaction was sealed, shielded from light, and warmed at 80 °C (4 h). Reaction was cooled to room temperature. Flash chromatography (SiO_2, 2.0 × 12 cm, CH_2Cl_2/hexane, 9:1, eluant) of the reaction solution afforded **19** (54.1 mg, 61.3 mg theoretical, 88%) as a dark green oil.

(Cyclopropylmethylene)malonitrile (27). A solution of cyclopropanecarboxaldehyde[27] (220 mg, 3.14 mmol) in dichloromethane (10 mL) was treated with malononitrile (209 mg, 3.14 mmol, 1.0 equiv), acetic acid (0.018 mL, 0.31 mmol, 0.10 equiv), and piperidine (0.031 mL, 0.31 mmol, 0.10 equiv) and the mixture was stirred for 40 min at room temperature. The reaction mixture was concentrated in vacuo. Flash chromatography (SiO_2, 1.0 × 12 cm, CH_2Cl_2 eluant) of the residue afforded **27** (217 mg, 371 mg theoretical, 59%) as a light pink oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 6.63 (d, 1 H, J = 11.5 Hz, C=C*H*CH), 2.14 (qd, 1 H, J = 11.5, 4.0 Hz, C=CHC*H*), 1.52 (m, 2 H, CH*H*CH*H*), 1.08 (m, 2 H, C*H*HC*H*H); IR (neat) ν_{max} 3033, 2233, 1598, 1234, 1197, 1066, 957, 867 cm^{-1}; EIMS, m/e (relative intensity) 118 (M^+, 19), 91 (base), 64 (30); CIMS (isobutane), m/e (relative intensity) 175 (M + $C_4H_9^+$, 10), 119 (M + H^+, base); HRMS, m/e 118.0534 ($C_7H_6N_2$ requires 118.0531).

Reaction of 1 with (Cyclopropylmethylene)malononitrile (27). Preparation of 2-Cyclopropyl-6,10-dioxaspiro[4.5]-dec-3-ene-1,1-dicarbonitrile (30). A solution of (cyclopropylmethylene)malononitrile (**27**, 52 mg, 0.44 mol) in dry benzene (1.0 mL) was treated with cyclopropenone 1,3-propanediyl ketal (**1**, 81 mg, 1.6 equiv) under argon. The reaction mixture was sealed, shielded from light, and warmed at 80 °C (20 h). The reaction was cooled to room temperature and concentrated in vacuo. Flash chromatography (SiO_2, 1.0 × 12 cm, CH_2Cl_2 eluant) of the pink residue afforded **30** (90 mg, 101 mg theoretical, 89%) as a white solid. An analytical sample was prepared by recrystallization from ether–hexane (mp 123–125 °C): ^1H NMR ($CDCl_3$, 470 MHz, ppm) 6.41 (dd, 1 H, J = 6.3, 2.2 Hz, CCH=C*H*CH), 6.08 (dd, 1 H, J = 6.3, 1.9 Hz, CC*H*=CHCH), 4.20 (m, 2 H, $OCHHCH_2CHHO$), 4.07 (td, 1 H, J = 10.7, 3.5 Hz, $OCHHCH_2CH_2O$), 3.97 (td, J = 10.7, 3.5 Hz, OCH_2CH_2CHHO), 2.63 (dt, 1 H, J = 10.2, 2.0 Hz, CCH=CHC*H*CH), 2.19 (m, 1 H, OCH_2CHHCH_2O), 1.65 (dp, 1 H, J = 13.6, 3.5 Hz, OCH_2CHHCH_2O), 1.07 (m, 1 H, CCH=CHCHC*H*), 0.82 (m, 1 H, cyclopropyl-H), 0.71 (m, 1 H, cyclopropyl-H), 0.60 (hextet, 1 H, J = 5.0 Hz, cyclopropyl-H), 0.34 (hextet, 1 H, J = 5.0 Hz, cyclopropyl-H); IR (KBr) ν_{max} 3082, 3007, 2992, 2882, 2252, 1619, 1347, 1292, 1246, 1206, 1157, 1126, 1085, 1024, 839, 808 cm^{-1}; EIMS, m/e (relative intensity) 230 (M^+, 1), 190 (19), 132 (33), 131 (37), 126 (base); CIMS (isobutane), m/e (relative intensity) 231 (M + H^+, base), 87 (27); HRMS, m/e 230.1053 ($C_{13}H_{14}N_2O_2$ requires 230.1055). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.73; H, 6.13; N, 12.13.

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CA 42056) and the Alfred P. Sloan Foundation.

Registry No. 1, 60935-21-9; 4-*Z*, 114995-75-4; 4-*E*, 114995-74-3; 5-*Z*, 114995-77-6; 5-*E*, 114995-76-5; 6-*cis*, 114995-79-8; 6-*trans*, 114995-78-7; 7-*cis*, 114995-81-2; 7-*trans*, 114995-80-1; 8a, 35234-88-9; 8b, 35234-87-8; 9a-*trans*, 114995-82-3; 9b-*trans*, 114995-83-4; 11, 114995-84-5; 12, 114995-86-7; 15, 19618-37-2; 16, 17665-72-4; 17, 114995-85-6; 19, 114995-87-8; 27, 114995-88-9; 28, 114995-91-4; 28 (dipole), 114995-90-3; 29, 114995-92-5; 30, 114995-89-0; A, 100-25-4; B, 2564-83-2; $PhCH_2O_2CCH_2CO_2CH_3$, 52267-39-7; PhCHO, 100-52-7; $(CH_3O)_3CH$, 149-73-5; $(CH_3)_3SiCH_2CH{=}NBu\text{-}t$, 73198-78-4; $(CH_3OC_6H_4\text{-}4)_2CO$, 90-96-0; $CH_2(CN)_2$, 109-77-3; $CH_3CH{=}NBu\text{-}t$, 7020-80-6; $(Me_2NC_6H_4\text{-}4)_2CO$, 90-94-8; cyclopropanecarboxaldehyde, 1489-69-6.

Supplementary Material Available: Full details of the attempted thermal isomerization (control studies) of 4-*E*, 4-*Z*, 5-*E*, 5-*Z*, 6-*cis*, 6-*trans*, 7-*cis*, and 7-*trans* and details of the attempted reaction of 1 with 1-cyanovinyl acetate are provided (3 pages). Ordering information is given on any current masthead page.

Oxidation of Thymines by Peroxosulfate Ions in Water

Toshio Itahara,* Yukiko Fujii, and Miki Tada

Institute of Chemistry, College of Liberal Arts, Kagoshima University, Korimoto, Kagoshima 890, Japan

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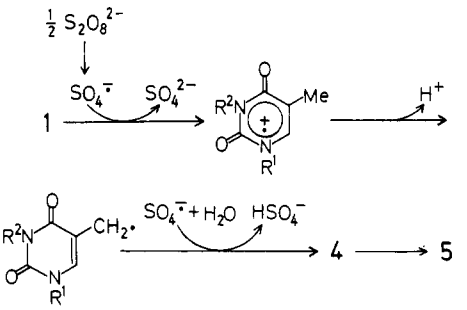
Oxidation of thymines by sodium peroxodisulfate in water at 85 °C gave the corresponding 5-(hydroxymethyl)uracils and 5-formyluracils. The reaction may proceed via thymine cation radicals. On the other hand, oxidation of thymines by potassium peroxomonosulfate in water gave the corresponding *cis*-5,6-dihydroxy-5,6-dihydrothymines and 5-hydroxy-5-methylbarbituric acids. Furthermore, treatment of thymine with both potassium peroxomonosulfate and hydrogen peroxide in water gave *cis*-6-hydroperoxy-5-hydroxy-5,6-dihydrothymine.

Many peroxides such as hydrogen peroxide,[1] hydroperoxythymines,[2] fatty acid hydroperoxides,[3] and benzoyl peroxide[4] are known to have mutagenic and carcinogenic activity. Therefore, damage of nucleic acids by peroxides is of interest. Oxidation of nucleic acid bases and their derivatives by peroxides such as hydrogen peroxide[5,6] and *m*-chloroperbenzoic acid[7] has been extensively investigated. Furthermore, reaction of them with peroxodisulfate ion ($S_2O_8^{2-}$) has been reported by several groups of workers.[8,9] However, little attention has been paid to isolation of products[10] of the oxidation by $S_2O_8^{2-}$ except for the reaction in alkaline solution.[8] This paper describes the oxidation of thymines (1) by sodium peroxodisulfate ($Na_2S_2O_8$) and potassium peroxomonosulfate ($KHSO_5$) in water. Treatment of 1 with $Na_2S_2O_8$ in water at 85 °C resulted in the selective oxidation of the 5-methyl group

Scheme I



of 1, whereas oxidation of 1 by $KHSO_5$ in water gave the corresponding *cis*-5,6-dihydroxy-5,6-dihydrothymines (8) and 5-hydroxy-5-methylbarbituric acids (9).

Results and Discussion

The N-methylated thymines **1b–d** were prepared by treatment of sodium salts of thymine (**1a**) with methyl iodide in dimethylformamide. Droplet countercurrent chromatography was used for preparative separation of a mixture of 1-methylthymine (**1b**), 3-methylthymine (**1c**), and 1,3-dimethylthymine (**1d**). Separation with $CHCl_3$–MeOH–H_2O (5:5:3) by the descending method resulted in the isolation of them. However, **1c** was obtained only in very low yield. Therefore, synthesis of **1c** according to the method for preparation of 3-methyluracil[11] was attempted. Treatment of the sodium salt of 2-thiothymine (**2**) with methyl iodide in dimethylformamide gave 2-(methylthio)pyrimidine (**3**), which was reacted with hydrochloric acid to give **1c**.

Treatment of thymines **1a–d** with $Na_2S_2O_8$ in water at 85 °C under nitrogen or in air gave the corresponding 5-(hydroxymethyl)uracils **4a–d** and 5-formyluracils **5a–d**

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