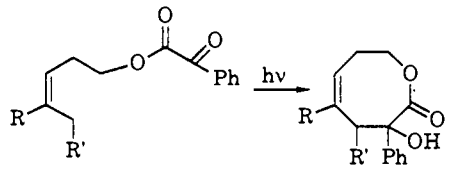
proton NMR and TLC. Lactone **17** was a mixture of stereoisomers at the newly-generated stereogenic center α to the carbonyl group.

Keto ester **18** cyclized to hydroxy lactone **19** in 49% yield. The cyclization of keto ester **18** to an eight-membered-ring lactone rather than a six-membered-ring lactone was unexpected. A 1,9-hydrogen atom abstraction reaction via the syn rotamer of the ester followed by rapid closure of the proximate biradical nicely rationalizes this result. Similarly, keto ester **20** cyclized exclusively to the eight-membered-ring lactone **21** in 31% yield.



18: R=H, R'=Me **19**: R=H, R'=Me
20: R=Me, R'=H **21**: R=Me, R'=H

The results presented herein demonstrate the potential of using either photochemically generated 1,4-biradicals or 1,9-hydrogen abstractions for ring-forming reactions. Extension to other photochemical reactions that proceed by way of 1,4-biradicals is in progress. Although the synthetic utility of this strategy remains to be determined, seven- and eight-membered oxacyclic rings are common subunits in certain families of marine natural products,[13]

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Regioselective and Endo-Stereoselective [3 + 2] Cycloaddition of Dipolar Trimethylenemethane to Electron-Deficient Olefin

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Stereoselective synthesis of five-membered carbocycles continues to attract the interest of organic chemists,[1,2] We report that the thermal [3 + 2] cycloaddition of a substituted dialkoxy trimethylenemethane (TMM, **2**) to an electron-deficient olefin proceeds endo-stereoselectively with retention of the olefin geometry, providing a single-step synthesis of substituted cyclopentanes (Scheme I). Some examples of successful regiocontrol in the cycloaddition to unsymmetrical olefins are also described. The present cycloaddition of a 4π-electron TMM to an olefin[3] shares an important characteristic with the Diels-Alder reaction in that the reaction proceeds under predictable regio- and stereocontrol.

We have previously shown[4] that thermolysis of (*E*)-ethylidenecyclopropane **1a** at 60-100 °C reversibly and stereospecifically generates a dipolar, 4π-electron (*E*)-TMM **2a**, which is stereochemically stable under the conditions of its [3 + 2] cycloaddition to olefins (vide infra).[5] In order to investigate the stereochemical behavior of **2a** in the cycloaddition, we examined its reaction with dimethyl maleate. When a 1 M C_6D_6 solution of an equimolar mixture of **1a** and the maleate was heated at 80 °C for 24 h under nitrogen, the ketene acetals (**4a** and **5a**) were formed in 88% yield with a ratio of 95:5. By ^{1}H NMR analysis ($^3J_{HH}$, NOE, and COSY) combined with chemical derivatization,[6] the major isomer was assigned to be **4a**. In no case did we note isomerization of either the starting olefin or the product under the reaction conditions. The stereochemsitry of the product in conjunction with the *E* geometry of **2a** strongly suggested that the major cycloaddition pathway involves an endo transition state (**3**), wherein the acetal and the ester groups are located close to each other.[7] Various other observations (vide infra) are also consistent with the endo transition state. The stereoisomer **5a** may be due to an alternative exo transition state.

Several important observations were made. The endo:exo isomer ratio (**4a**:**5a**) exhibited notable dependence on the solvent polarity (Table I, entry 1), decreasing dramatically from 97:3 to 73:27[8] as the polarity of the solvent was increased from octane (ϵ = 1.9) to DMSO-d_6 (ϵ = 46.6). The results suggest that polar interactions between the directing groups control the stereochemistry. This solvent dependency stands in contrast to the very small solvent effects in the Diels-Alder reaction.[9] Polar solvent also accelerated the cycloaddition, which may be in part due to accelerated cycloaddition and in part due to accelerated TMM formation, which is about 100 times faster in DMSO than in an alkane solvent.[4] The product yield was little influenced by the solvent variation, however. The cycloadditions to methyl *trans*-crotonate (entry 2) and methacrylate (entry 3) proceeded with virtually complete endo selectivity, but with poor regioselectivity. However, a high level of regiocontrol was achieved with the aid of substituent steric effects. Thus, the isopropyl TMM **1b** reacted with methyl *trans*-crotonate to give a single endo adduct, with other isomers accounting for only 4% of the cycloadducts (entry 4). On the other hand, a cis olefin reacts regio-randomly even with **1b** (entry 5), and a bulky cis substituent on the olefin acceptor severely retards the cycloaddition (entry 7). These observations are also in agreement with the endo transition state **3**. Alternatively, methyl (*E*)-4,4-dimethyl-2-pentenoate, bearing a bulky olefinic substituent, reacted with **1a** to give a single cycloadduct (>97% isomeric purity, entry 6). In general, an olefin substituent trans to the ester group appears to ensure high endo selectivity

(1) [3 + 2] construction of five-membered carbocycles: (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389 and references therein. (c) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (d) Cekovic, Z.; Saicic, R. *Tetrahedron Lett.* **1986**, *27*, 357. Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558. (e) Herndon, J. W.; Wu, C.; Harp, J. J.; Kreutzer, K. A. *Synlett.* **1991**, 1. (f) Beak, P.; Wilson, K. D. *J. Org. Chem.* **1987**, *52*, 3826. (g) Gray, B. D.; McMillan, J. A.; Moore, M. *Tetrahedron Lett.* **1987**, *28*, 689. (h) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695. Boger, D. L.; Brotherton-Pleiss, C. E. *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 147-219. (i) Marino, J. P.; Laborde, E. *J. Am. Chem. Soc.* **1985**, *107*, 734. (j) Beal, R. B.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391. (k) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825. (l) Rosenblum, M.; Watkins, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 6322 and references therein. (m) Eidenschink, R.; Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 292. (n) Boche, G.; Martens, P. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 724. (o) Tokuyama, H.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.*, in press.

(2) (a) Reviews on TMM: Little, R. D.; Masjedizadeh, M. R.; Moeller, K. D.; Dannecker-Doerig, I. *Synlett* **1992**, 107. Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 486. Dowd, P. *Acc. Chem. Res.* **1972**, *5*, 242. (b) Metal-mediated TMM chemistry: Noyori, R.; Yamakawa, M.; Takaya, H. *Tetrahedron Lett.* **1978**, 4823 and references cited therein. Binger, P.; Buchi, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. Aumann, R.; Uphoff, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 357. Lewis, R. T.; Motherwell, M. B.; Shipman, M. J. *J. Chem. Soc., Chem. Commun.* **1988**, 948. Yamago, S.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1112. Yamago, S.; Nakamura, E. *Tetrahedron* **1989**, *45*, 3081. (c) Reviews on [3 + 2] cycloadditions: Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley & Sons: New York, 1984; Vols. 1 and 2. Little, R. D. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 239-270.

(3) Review: Nakamura, E. *Organic Synthesis in Japan, Past, Present, and Future*; Noyori, R., Ed.; Tokyo Kagaku Dozin: Tokyo, 1992; pp 273-282.

(4) Nakamura, E.; Yamago, S.; Ejiri, S.; Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 3183.

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(6) Stereochemistry in Table I was unequivocally established by NMR and/or chemical correlation, except in entries 3 and 5 (partially assigned and assigned by analogy, respectively). See the supplementary material for details.

(7) Note that the structure of **3** is not meant to represent the exact geometry of the transition state, which may well be quite flexible.

(8) Product ratios in Table I were determined by capillary GC and by ^{1}H NMR.

(9) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, Germany, 1988. Cf. Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469.

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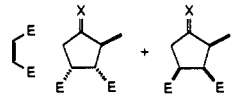
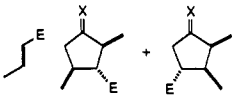
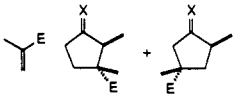
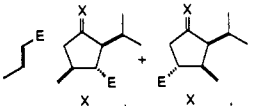
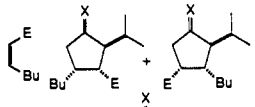
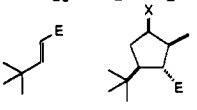
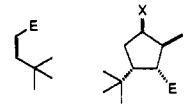
Table I. Regio- and Stereoselective [3 + 2] Cycloaddition[a]

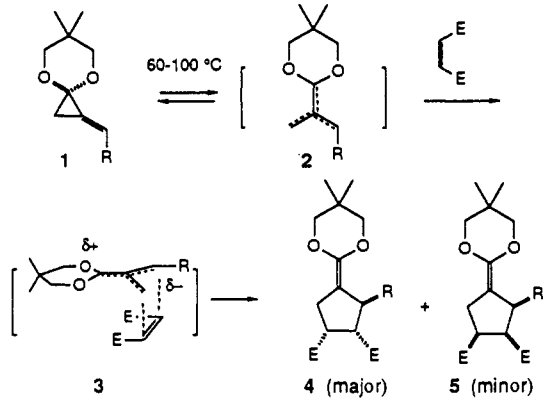
entry	1	olefin	cycloadducts[b] E = COOMe, X = C(OCH$_2$CMe$_2$CH$_2$O)	solvent[c]	%yield (product ratio)
1	1a			octane (1.9)	77 (97:3)
				benzene (2.3)	88 (95:5)
				toluene (2.6)	86 (97:3)
				DME (7.2)	85 (92:8)
				ClCH$_2$CH$_2$Cl (10.4)	74 (92:8)
				DMF (36.7)	72 (80:20)
				acetonitrile (37.5)	78 (80:20)
				DMSO-d6 (46.6)	73 (73:27)
2	1a			toluene	81 (50:50)
3	1a			toluene	72 (1:1)
4	1b			CD_3CN	71 (96:4)
5	1b			CD_3CN	80 (1:1)
6	1a			CD_3CN	89 (>97:3)
7	1a			CD_3CN	not detected

[a] The reactions were carried out at 100–120 °C for 55–75 h under nitrogen except in entries 1 and 2 (80 °C, 20–35 h). The yields are based on pure isolated products after hydrolysis of the ketene acetals except in entries 2, 5, and 7, where they are based on NMR analysis. The product ratios were determined by capillary GC analysis on OV-1 or on OV-17. [b] In entry 5, X = C(OCH$_2$CH$_2$CH$_2$O). [c] The dielectric constants are for protio solvents: Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972.

even in a very polar solvent (cf. entries 4 and 6). Finally, we note that hydrolysis of the ketene acetal to the corresponding ester proceeds with high stereoselectivity (generally >90%). Thus, the cycloaddition and hydrolysis set four stereogenic centers with excellent stereocontrol.[10]

In summary, we have found a general, stereospecific, regio- and stereoselective thermal [3 + 2] cycloaddition reaction involving a 6π-electron transition state. The observed levels of selectivities may be better than those of its [4 + 2] counterpart, the uncatalyzed Diels–Alder reaction, and the reaction is unique among known all-carbon [3 + 2] cycloadditions.[1,2,11] Mechanistic and synthetic studies continue in these laboratories.

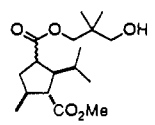
Scheme I



Acknowledgment. We thank the Ministry of Education, Science, and Culture of Japan and the Yamada Science Foundation for financial support.

Supplementary Material Available: Listings of experimental procedures, physical properties of the cycloadducts, and stereochemical assignments (17 pages). Ordering information is given on any current masthead page.

(10) Typical reaction procedure: Isopropylidenecyclopropane **1b** and methyl crotonate (1.1 equiv) in CD_3CN (0.5 mL/mmol of **1b**) were heated in a sealed tube at 100–120 °C for 50 h (>97% pure by capillary GC analysis). Careful NMR analysis indicated the regioisomeric ratio to be 96:4. Hydrolysis of the crude product (addition of 40 μL of 10% v/v aqueous AcOH) followed by purification on silica gel afforded a 95:3:2 isomeric mixture of cyclopentanecarboxylic acid ester **i** in 71% yield. This isomeric ratio indicates that the hydrolysis proceeded with >30:1 selectivity. The cycloaddition reaction is remarkably insensitive to the reaction conditions, and the acetals derived from neopentyl glycol and 1,3-propanediol (Table I, entry 5) may be employed with equal success.



i

(11) There is one previous report of endo-selective thermal [3 + 2] cycloaddition of TMM (with 3:1 selectivity): Little, L. D.; Bukhari, A.; Venegas, M. G. *Tetrahedron Lett.* **1979**, 305.

Photochemistry of α-Keto Phosphate Esters: Photorelease of a Caged cAMP

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We report our results on a phosphate photoprotecting (or *cage*) group that rapidly releases phosphate ($k_r > 10^8$ s^{-1}) in nearly quantitative yield by efficient photolysis of the *caged* phosphate. As a demonstration of this strategy, cAMP was generated with an efficiency of 34% and a first-order rate constant of 3×10^8 s^{-1} by irradiation of benzoin cAMP, a caged nucleotide.

The recent interest in *caged* phosphates as precursors capable of rapid release of nucleotides and other biologically active phosphates to study the kinetics of muscle action by ATP,[1] calcium channel activation by GTP,[2] and visual excitation by the inositol phosphate cascade[3] has drawn attention to the need for better photolabile groups.[4] To date, the most commonly chosen *cage*

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(4) (a) Engels, J.; Schlaeger, E. *J. Med. Chem.* **1977**, *20*, 907; *Experientia* **1978**, *34*, 14–15. (b) Nerbonne, J. M.; Richard, S.; Nargeot, J.; Lester, H. A. *Nature* **1984**, *310*, 74. (c) Nargeot, J.; Nerbonne, J. M.; Engels, J.; Lester, H. A. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 2395. (d) Kaplan, J. H.; Forbush, B.; Hoffman, J. B. *Biochemistry* **1978**, *17*, 1929. (e) McCray, J. A.; Trentham, D. R.; Reid, G. P.; Walker, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 7170. (f) McCray, J. A.; Trentham, D. R. *Annu. Rev. Biophys. Chem.* **1989**, *18*, 239.

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