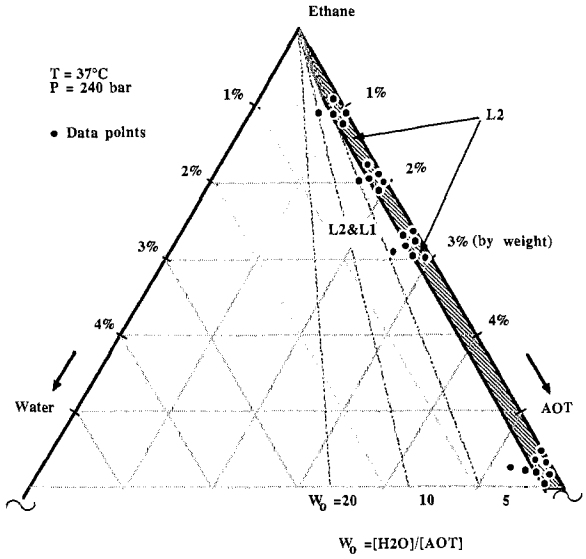

Figure 1. Ethane-rich corner of the ethane–AOT–water ternary phase diagram. L2 is the reverse micelle in supercritical ethane phase; L1 is a liquid phase which containing AOT, water, and ethane.

formation depends on the AOT and water concentration as shown in Figure 1. W_0 in supercritical ethane at these conditions exhibits behavior different from larger liquid *n*-alkane systems.[14] First, the maximum W_0 is dependent on AOT concentration; second, W_0 is much lower than for other hydrocarbon systems. The low W_0 values observed in both supercritical ethane and propane are tentatively explained in terms of the "packing ratio" model described by Mitchell and Ninham.[15,16] The area occupied by the polar head groups remains constant at fixed pH and ionic content. In contrast, the greater penetration of the surfactant tails and the larger volume solvated by the supercritical fluid result in an interfacial surfactant layer which will have higher curvature; thus only smaller micelles can exist.

As the supercritical ethane density is reduced, the single micellar phase is destroyed and two phases are formed consisting of an AOT–water-rich liquid phase and a predominantly ethane upper phase. As shown in Figure 2, the minimum ethane density for micelle stability decreases as the temperature is increased; this suggests that the increase in thermal energy is sufficient to offset the loss of ethane solvating power at the lower fluid density. The density range over which dissolution and micellization occurs differs for subcritical liquid and supercritical ethane; this can also be attributed to the temperature difference of the two phases.

There are several interesting possible technological applications of supercritical fluid micelles or microemulsions. Diffusion coefficients are up to 10^2 higher in the continuous supercritical fluid phase than in liquids. Similarly, viscosity is up to 10^2 lower in such fluids. This combination of properties should allow very high mass transfer rates in extractions from liquid or porous solid phases or high overall rates for interfacial reaction processes. By changing the size or shape of the micelle by varying the fluid density, the selectivity of the micelle core in extractions or the properties of the micelle environment for chemical reactions can be changed. Also, supercritical fluid density is a much less constrained variable than temperature in controlling micellar phase behavior; in contrast to liquid systems where pressure and temperature have only moderate utility. A small decrease in density could be used to alter the phase behavior and thus "unload" the micelle contents for final product recovery after extraction. The step could be reversed by a small increase in density to rapidly reform the micelles. Equivalent control is absent in liquid systems

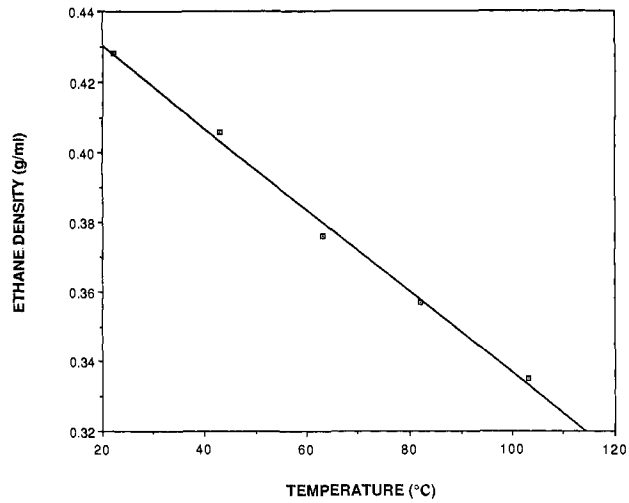

Figure 2. Minimum supercritical ethane (T_c = 32.4 °C) density required for the formation of stable reverse micelles as a function of temperature. Densities correspond closely to those for the pure ethane at similar conditions.

where ionic strength or pH are typically used to manipulate phase behavior. Further studies are in progress aimed at both the investigation of reverse-micelle phase behavior and properties and the development of separation and chromatographic processes utilizing the unique solvating characteristics of both the supercritical fluids and reverse-micellar phases.

Acknowledgment. We thank the Department of Energy, Office of Basic Energy Sciences, for support of this work through Contract DE-AC06-76RLO-1830.

(14) Delord, P.; Larche, F. C. In *Reverse Micelles*; Luisi, P. L., Straub, B. E., Eds.; Plenum Press: New York, 1984; pp 137–141.
(15) Evans, D. F.; Mitchell, D. J.; Ninham, B. W. *J. Phys. Chem.* **1986**, *90*, 2817–2825.
(16) Mitchell, D. J.; Ninham, B. W. *J. Chem. Soc., Faraday Trans. 2* **1981**, *77*, 601–629.

Asymmetric Induction in Grignard and Hetero-Diels–Alder Reactions of Chiral α,β-Unsaturated Carbonyl Compounds[1]

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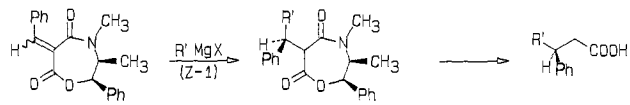
The diastereoselective addition of nucleophiles to α,β-unsaturated carbonyl derivatives is an important method in asymmetric synthesis of enantiomerically pure compounds.[2] The 6-benzylidene-oxazepane-5,7-dione **1**, which was introduced by Mukaiyama[3] is an effective chiral acceptor. Thus, the addition of Grignard reagents to **1** leads to **2** which after hydrolysis affords 3-substituted carboxylic acids **3** with high enantiomeric excess.



Z-1
E-1 2 3

†Organische Chemie.
‡Anorganische Chemie.
(1) Intra- and Intermolecular Hetero-Diels–Alder Reactions. 15. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 14: Tietze, L. F.; Voss, E. *Tetrahedron Lett.* **1986**, *27*, 6181.
(2) Tomioka, K.; Koga, K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 3A, p 201.
(3) Mukaiyama, T.; Takeda, T.; Osaki, M. *Chem. Lett.* **1977**, 1165. Mukaiyama, T.; Takeda, T.; Fujimoto, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3368.

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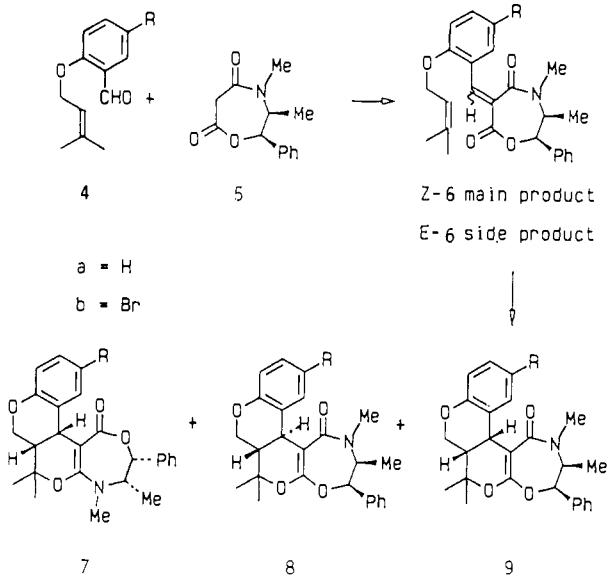
We have shown[4a] that 6-arylideneoxazepane-5,7-diones like (*Z*)-**6a** can be used in a very selective intramolecular hetero-Diels–Alder reaction.[5] Heating of (*Z*)-**6a** in the presence of diethylaluminum chloride leads in a 78% yield to the cis adduct **9a** with an induced diastereoselectivity[6] of >98%. In addition, 1% of the trans adduct **8a** and 2% of constitutional isomer **7a** were found.[7] In this paper



we give an explanation for the high asymmetric induction in both reactions, which contradicts the hitherto assumed mechanism;[3,4a] however, the products have the correct configuration.

The 6-arylideneoxazepane-5,7-diones **1** and **6** can easily be obtained via condensation of **5** with benzaldehyde or benzaldehyde derivatives **4**, respectively, in the presence of $TiCl_4$,[3] ethylene diammonium diacetate,[4a] (EDDA), or piperidine/acetic acid.[4a] However, in contrast to the description in the literature,[3] the main products are the *Z* isomers (*Z*)-**1** and (*Z*)-**6**. Thus, the reaction of **5** with benzaldehyde in acetonitrile gave a 10:1 mixture of (*Z*)-**1**/(*E*)-**1** (EDDA, 91% yield), with **4a** a 50:1 mixture of (*Z*)-**6a**/(*E*)-**6a** (EDDA, 98%), and with **4b** a 13:1 mixture of (*Z*)-**6b**/(*E*)-**6b** (piperidine/acetic acid, 93%). The configuration of these compounds was determined by ^{13}C NMR and X-ray analysis. Whereas the chemical shifts of the relevant atoms in the ^1H and ^{13}C NMR of the *E*/*Z* isomers of **1**, **6a**, and **6b** did not show significant differences, the coupling constants $J_{6a\text{-}H/C\text{-}7}$ and $J_{6a\text{-}H/C\text{-}5}$, respectively, allowed an unambiguous structure determination.[8] Thus, for (*Z*)-**6b**, $J_{6a\text{-}H/C\text{-}7}$ = 12 Hz and for (*E*)-**6b**, $J_{6a\text{-}H/C\text{-}7}$ = 7.5 Hz were found. For $J_{6a\text{-}H/C\text{-}5}$ the values are interchanged (*Z*, 7 Hz; *E*, 11 Hz).

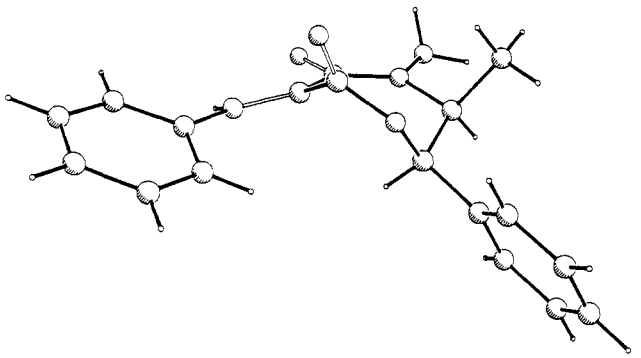


Figure 1. Molecular structure of (*Z*)-**1** in the crystal. The two molecules in the asymmetric unit adopt very similar conformations.

The X-ray structure[9] of (*Z*)-**1** shows that the oxazepane ring displays a pseudoboat conformation in the crystal (Figure 1). In this conformation the attack at the β-carbon of the α,β-unsaturated carbonyl moiety from the *si* face is hindered. That means that the reaction takes place syn to the bulkier groups at the stereogenic centers in (*Z*)-**1**. Another even more evident reason for the high selectivity may be the upward flexion of the lactone (57.4°) and the amide carbonyl group (31.5°). Thus, the formation of a chelate could only occur from the *re* face; also it may be considered that the Grignard reagent attacks at a carbonyl oxygen first.

Similar arguments apply to the intramolecular hetero-Diels–Alder reaction of (*Z*)-**6a** and (*Z*)-**6b**. Thus, the cycloaddition occurs via an exo-*Z**-syn transition state,[10] by attack of the dienophile from the *re* face, yielding **9a** and **9b**, respectively, with i-de[6] >98%. To exclude the possibility that **9a** or **9b** be obtained via an endo-E*-syn transition state of (*E*)-**6a** or (*E*)-**6b**, which could be formed intermediately by a fast isomerization, pure (*E*)-**6b** was used in the cycloaddition. This compound shows a completely different behavior in the Lewis acid catalyzed transformation (Et_2AlCl, 83 °C, 1,2-dichloroethane). Thus, the reaction is about 4 times slower and yields a mixture of all eight possible isomers, providing **9b** in only 2% yield. However, if the cycloaddition of (*E*)-**6b** is performed under interval irradiation with UV light (λ_{max} > 300 nm), **9b** is formed in a 57% yield almost exclusively, indicating that an isomerization of (*E*)-**6b** to (*Z*)-**6b** takes place prior to the Diels–Alder reaction. Thus, irradiation of pure (*Z*)-**6b** or (*E*)-**6b** at 0 °C provides a 2.5:1 mixture of (*Z*)-**6b**/(*E*)-**6b**. The discussion about the possible conformations of the transition states in the Grignard and hetero-Diels–Alder reactions was so far based on the X-ray of crystalline (*Z*)-**1**. However, the value of $J_{2,3} \leq 1$ Hz in the ^1H NMR spectra of (*Z*)-**1**, (*Z*)-**6a**, and (*Z*)-**6b** indicates an orthogonal orientation of H-2 and H-3 in solution, which is also found in the crystals. Also the low reactivity of (*Z*)-**6a** and (*Z*)-**6b** compared to other arylidene 1,3-dicarbonyl compounds[11] shows that the heterodiene and the α-carbonyl group in (*Z*)-**6a** and (*Z*)-**6b** are not coplanar, again consistent with the structure in the crystal. Thus the conformation of (*Z*)-**1**, (*Z*)-**6a**, and (*Z*)-**6b** in solution and in the crystalline state can be assumed to be similar. The experimental results of the described additions clearly show that the usual explanation for a diastereofacial differentiation at a prochirality

(4) (a) Tietze, L. F.; Brand, S.; Pfeiffer, T. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 784. The reaction is the first example of an intramolecular hetero-Diels–Alder reaction of a heterodiene with a removable chiral auxiliary. The intermolecular reaction with chiral heterodienes has also been described: (b) Tietze, L. F.; Glüsenkamp, K. H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 887. Schmidt, R.; Maier, M. *Tetrahedron Lett.* **1985**, *26*, 2065. In addition chiral heterodienophiles such as glyoxylates, imines, sulfines, *N*-sulfinylcarbonates, and α-chloronitroso compounds as well as chiral enol ethers and chiral Lewis acids have been employed. (c) Jurczak, J.; Tkacz, M. *J. Org. Chem.* **1979**, *44*, 3347. Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. van den Broek, L. A. G. M.; Porskamp, P. A. T. W.; Haltiwanger, R. C.; Zwanenburg, B. *J. Org. Chem.* **1984**, *49*, 1691. Whitesell, J. K.; James, D.; Carpenter, J. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1449. Felber, H.; Kresze, G.; Braun, H.; Vasella, H. *Tetrahedron Lett.* **1984**, *25*, 5381. Posner, G. H.; Wetlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667. Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

(5) For recent excellent reviews on the asymmetric induction in Diels–Alder reactions, see: Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods 1986*; Scheffold, R., Ed.; Springer Verlag: Berlin, Heidelberg, 1986; Vol. 4. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York 1984; Vol. 3B, p 455. Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876.

(6) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1042.

(7) The noncatalyzed reaction of (*Z*)-**6a** (1,2-dichlorobenzene, 100 °C, 18 h) affords 45% of **9a**, 24% of **8a**, and 21% of **7a**. The structure of **7a**, **8b**, and **9a** were determined by X-ray analysis; the structure of **7a** given in ref 4a had to be revised.

(8) Vögeli, U.; Herz, D.; von Philipsborn, W. *Org. Magn. Reson.* **1980**, *13*, 200. Kingsbury, C. A.; Draney, D.; Sopchik, A.; Rissler, W.; Durham, D. *J. Org. Chem.* **1976**, *41*, 386.

(9) Crystal data for (*Z*)-**1**: space group $P2_1$, a = 9.191 (1) Å, b = 16.567 (2) Å, c = 11.465 (4) Å, β = 101.93 (2)°, Z = 4, R = 0.047 for 3042 reflections with $F_o > 4\sigma(F_o)$. Full details of the structure determination will be published elsewhere.

(10) Exo/endo, orientation of the chain relative to the heterodienes; *E**/*Z**, configuration of the heterodiene in the assumed transition state. The reacting carbonyl has a higher priority than the nonreacting. Syn/anti, orientation of hydrogens at the prochirality centers.

(11) Tietze, L. F.; Stegelmeier, H.; Harms, K.; Brumby, T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 863.

center by steric interaction with the bulkier groups on the stereogenic centers must be looked at with great care.

Supplementary Material Available: Tables of positional and thermal parameters and bond lengths and angles for (*Z*)-**1** (5 pages). Ordering information is given on any current masthead page.

"Remote Control" of Flavin Reactivities by an Intramolecular Crown Ring Serving as a Metal-Binding Site

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Coenzymes are prosthetic groups in enzymes and catalyze the enzyme-mediated reactions in the active sites. Although some of them are capable of catalyzing the reactions even in the absence of apoenzymes, the activities are mostly controlled through the interactions with apoenzymes.[1-5] In particular, allosteric effects by which some catalytic activities of enzymes may be regulated are quite intriguing from a bioorganic viewpoint: that is, binding of an effector to a remote, allosteric site induces activity changes in the active sites.[6] In order to mimic such allosteric functions in synthetic systems, we previously synthesized a crown ether flavin mimic (**1**).[7] The crown ether cavity in **1** is recognized as a binding site not only for spherical metal cations but ammonium cations and others through hydrogen bonding, and the resulting complexation changed the spectral and catalytic behaviors. Roseoflavin (**2**), isolated from a culture medium of Streptomyces strain No. 768,[8] has a dimethylamino group at the 8-position instead of a methyl group in conventional flavin coenzymes and shows an antiflavin reactivity.[9,10] This occurs because the isoalloxazine ring loses its oxidizing ability owing to intramolecular charge transfer from the 8-(dimethylamino) group to the pteridine moiety.[11,12] This finding suggests a new strategy to design flavins (**3**) with the allosteric functionality: that is, the oxidizing ability of **3** should be greatly reduced, as seen in **2**, when the 8-sulfonamide group is dissociated. Furthermore, this dissociation equilibrium can be "remote-controlled" by the metal binding to the crown ether portion.[7,13] Obviously, the molecular design in this paper is stimulated by two preceding concepts, "remote functionalization" in steroid photochemistry[14] and "lariat ethers" in crown ether chemistry.[15-17]

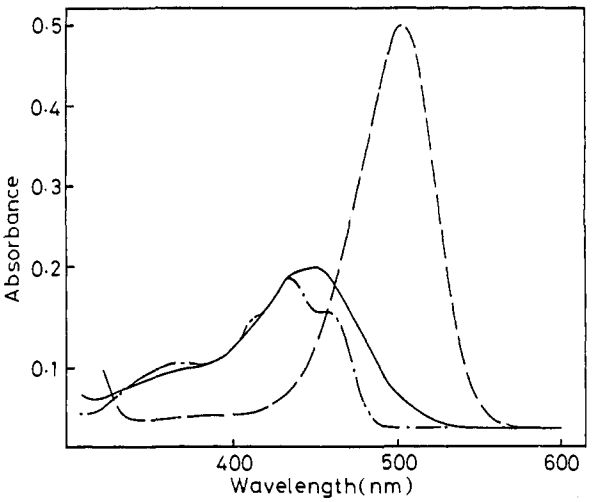
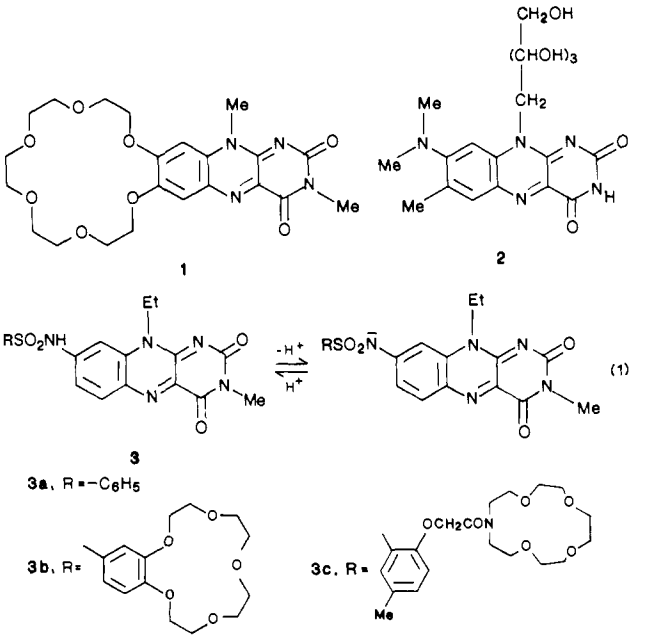


Figure 1. Absorption spectra of **3c** (1.03×10^{-5} M) in acetonitrile at 30 °C: (- - -) neutral **3c** ([CF_3COOH] = 2.32×10^{-5} M); (- - -) anionic **3c** ([1,8-diazabicyclo[5.4.0]-7-undecene] = 1.70×10^{-5} M), (—) **3c**·Ca^{2+} complex ([$Ca(ClO_4)_2$] = 7.65×10^{-3} M).



3a-c were synthesized by the reaction of 3-methyl-8-chloro-10-ethylisoalloxazine with the corresponding sulfonamides in sulfolane in the presence of potassium carbonate.[8] The products were identified by IR, NMR, and elemental analysis. In acidic aqueous solution **3a-c** gave a yellow color characteristic of "regular" flavins (λ_{max} 433 nm for **3a**, 435 nm for **3b**, and 436

(1) Walsh, C. In *Enzymatic Reaction Mechanism*; W. H. Freeman: San Francisco, 1979.
(2) Bruice, T. C.; Benkovic, S. J. In *Bioorganic Mechanisms*; Benjamin: New York, 1966.
(3) Jencks, W. P. In *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969.
(4) Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 1762.
(5) For a comprehensive review on coenzyme model catalyses, see: Shinkai, S. *Prog. Polym. Sci.* **1982**, *8*, 1.
(6) For allosteric effects in organic chemistry, see the following papers and references cited therein: (a) Rebek, J., Jr.; Costello, T.; Marshall, L.; Wattley, R.; Gadwood, R. C.; Onan, K. *J. Am. Chem. Soc.* **1985**, *107*, 7481. (b) Rebek, J., Jr.; Costello, T.; Wattley, R. *Ibid.* **1985**, *107*, 7487.
(7) (a) Shinkai, S.; Ishikawa, Y.; Shinkai, H.; Tsuno, T.; Manabe, O. *Tetrahedron Lett.* **1983**, *24*, 1539. (b) Shinkai, S.; Ishikawa, Y.; Shinkai, H.; Tsuno, T.; Makishima, H.; Ueda, K.; Manabe, O. *J. Am. Chem. Soc.* **1984**, *106*, 1801.
(8) Otani, S.; Takatsu, M.; Nakano, M.; Kasai, S.; Miura, T.; Matsui, K. *J. Antibiot.* **1974**, *27*, 88.
(9) Kasai, S.; Kubo, Y.; Yamanaka, S.; Hirota, T.; Sato, H.; Tsuzukida, Y.; Matsui, K. *J. Nutr. Sci. Vitaminol.* **1978**, *24*, 339.
(10) Kasai, S.; Miura, R.; Matsui, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2877.
(11) Song, P.-S.; Walker, E. B.; Vierstra, R. D.; Poff, K. L. *Photochem. Photobiol.* **1980**, *32*, 393.
(12) (a) Shinkai, S.; Kameoka, K.; Honda, N.; Ueda, K.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1985**, 673. (b) Shinkai, S.; Kameoka, K.; Honda, N.; Ueda, K.; Manabe, O.; Lindsey, J. *Bioorg. Chem.* **1986**, *14*, 119.
(13) Yamashita, T.; Nakamura, H.; Takagi, M.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1550.
(14) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170 and references cited therein.
(15) Schultz, R. A.; Dishong, D. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1982**, *104*, 625.
(16) Dishong, D. M.; Diamond, C. J.; Cinoman, M. I.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 586.
(17) Gustowski, D. A.; Echegoyen, L.; Goli, D. M.; Kaifer, A.; Schultz, R. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 1633.
(18) The reaction of 3-methyl-8-chloro-10-alkylisoalloxazine with amines was investigated in detail by Yoneda and co-workers: Yoneda, F.; Shinozuka, K.; Hiromatsu, K.; Matsushita, R.; Sakuma, Y.; Hamana, M. *Chem. Pharm. Bull.* **1980**, *28*, 3576.

0002-7863/87/1509-0923$01.50/0