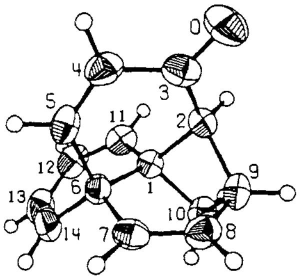


Figure 1. Computer-generated perspective drawing of the final X-ray model of **6**. The thermal ellipsoids are 50% equiprobability envelopes with hydrogens as spheres of arbitrary diameter.

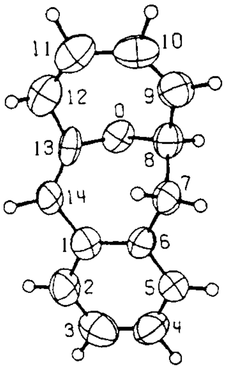
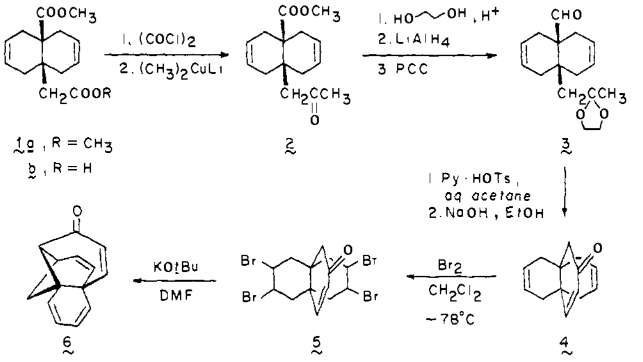
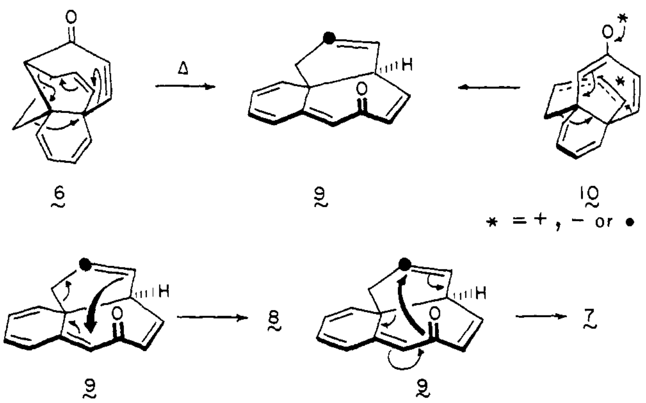


Figure 2. Computer-generated perspective drawing of the final X-ray model of **7**. The thermal ellipsoids are 50% equiprobability envelopes with hydrogens as spheres of arbitrary diameter.

Scheme I



Scheme II



a thermodynamically driven propensity for aromatization of the cyclohexadiene ring was anticipated (note that two C–C bonds must be cleaved to achieve this result), covalent incorporation of the carbonyl group with loss of the stability normally associated with a C–O double bond was not. With reference to Scheme II, this unusual behavior may be interpreted most cogently in terms of pentaenone **9**. Although **6** may be economically isomerized to **9** by three simple antiperiplanar carbon shifts as illustrated, the process need not be concerted since stepwise alternatives, e.g., via intermediate **10**, appear readily accessible. Dreiding models of **9** make clear two relevant facts: (a) strikingly, the carbonyl oxygen is positioned at a distance only 3.3 Å away from the dotted olefinic carbon atom in a geometric relationship particularly conductive to pπ–pπ overlap; (b) aromatization can be achieved by Cope rearrangement involving unsaturated centers initially 3.7 Å distant. While the latter process likely proceeds concertedly according to the dictates of orbital symmetry (six-electron sigmatropy),[7] the requisite reorganization of eight electrons to arrive at **7** (Scheme II) is not comparably favored. Nevertheless, the dominant formation of **7** (also with concurrent aromatization) belies the preferred operation of this hypothetical pathway. For the present, the proximity and relative orientation of the carbonyl group in **9** is deemed responsible for this phenomenon. On this basis, it would be of considerable interest to examine the behavior of other sterically congested molecules structurally tailored for multichannel reactivity.

Acknowledgment. L.A.P. is grateful to the National Science Foundation (Grant CHE-7900333) and I.B. to the Robert A. Welch Foundation (Grant E-594) for financial support of this research.

Supplementary Material Available: Data collection and processing parameters, atomic coordinates, thermal parameters, bond distances, bond angles, and torsion angles in **7** (4 pages). Ordering information is given on any current masthead page.

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(7) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie, Academic Press: Weinheim/Bergstr., New York, 1970.

Anthracycline Synthesis with Fischer Carbene Complexes[1]

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The clinical effectiveness of the anthracycline antitumor agents daunomycin (**5a**) and adriamycin (**5b**) has led to a substantial number of reports on the total synthesis of their corresponding aglycones, **6a** and **6b**.[2,3] The 11-deoxy analogues of **6a** and **6b** (R_4 = H) are of current interest due to improved therapeutic indices, and there have very recently been several reports on their total syntheses,[2,3b,4,5] We have envisioned an approach to an-

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(1) This work was presented at the 186th National Meeting of the American Chemical Society, Washington, D.C., Aug 28–Sept 2, 1983.

(2) For comprehensive reviews see: "Anthracycline Antibiotics"; El Khadem, H. S., Ed.; Academic Press: New York, 1982. Arcamone, F. *Med. Chem. (Academic)* **1981**, *17*. Kametani, T.; Fukumoto, K. *Med. Res. Rev.* **1981**, *1*, 23–72.

(3) For more recent synthetic approaches, see: (a) Tamariz, J.; Schwager, L.; Stibbard, J. H. A.; Vogel, P. *Tetrahedron Lett.* **1983**, 1497. (b) Rao, A. V. R.; Reddy, K. B.; Mehendale, A. R. *J. Chem. Soc., Chem. Commun.* **1983**, 564. (c) Broadhurst, M. J.; Hassal, C. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2227. (d) Kimball, S. D.; Kim, K. S.; Mohanty, D. K.; Vanotti, E.; Johnson, F. *Tetrahedron Lett.* **1982**, 3871. (e) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825. (f) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378. (g) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *Ibid.* **1981**, *103*, 5263.

(4) (a) Hauser, F. M.; Prasanna, S.; Combs, D. W. *J. Org. Chem.* **1983**, *48*, 1328. (b) Rao, A. V. R.; Mehendale, A. R.; Reddy, K. B. *Tetrahedron Lett.* **1982**, 2415. (c) Rao, A. V. R.; Deshpande, V. H.; Reddy, N. L. *Ibid.* **1982**, 775. (d) Jung, M. E.; Node, M.; Pfluger, R. W.; Lyster, M. A.; Lowe, J. A., III *J. Org. Chem.* **1982**, *47*, 1150. (e) Gesson, J. P.; Mondon, M. *J. Chem. Soc., Chem. Commun.* **1982**, 421. (f) Alexander, J.; Flynn, D. L.; Mitscher, L. A.; Veysoglu, T. *Tetrahedron Lett.* **1981**, 3711. (g) Kimball, S. D.; Walt, P. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561. (h) Yadau, J.; Corey, P.; Hsu, C. T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, 811.

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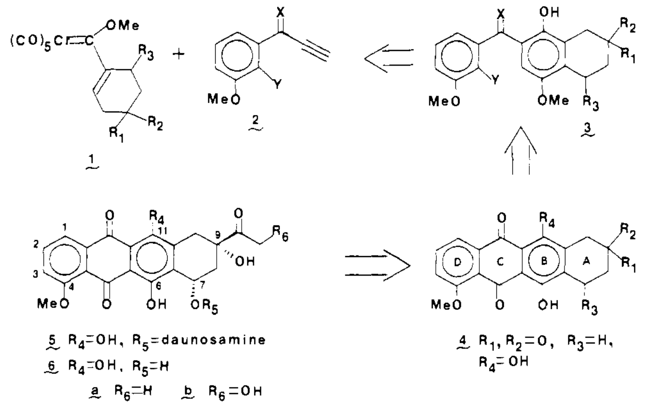
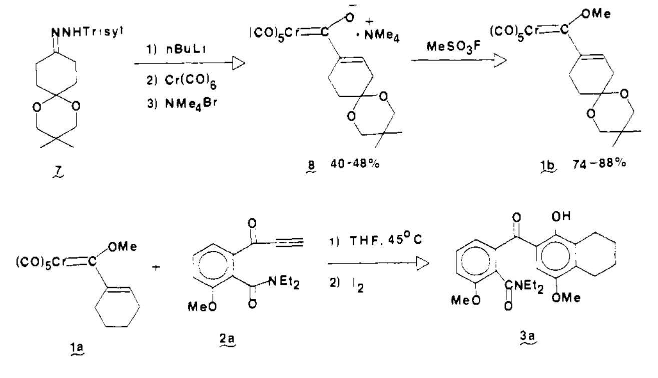
Scheme I



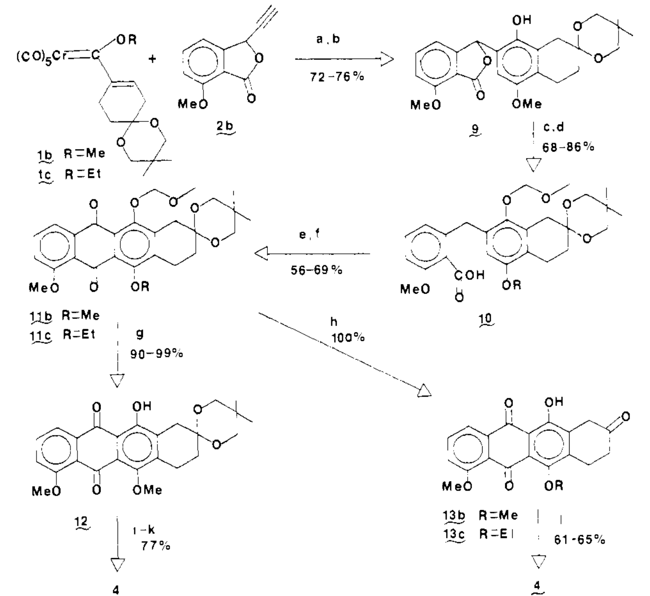
Scheme II



thracyclines involving the benzannulation reaction of chromium carbene complexes and acetylenes. This novel and intriguing reaction was first reported by Dötz,[6] and recently we have examined the scope of the reactions of α,β-unsaturated complexes such as **1a**.[7] The particular approach utilizing this benzannulation that is indicated in Scheme I has the potential to solve the three major synthetic problems associated with this family of natural products. These are the regioselectivity, the introduction of the C-7 hydroxyl, and a convergent approach to both the 11-oxy (R_4 = OH) and 11-deoxy (R_4 = H) members of the family.

In this communication we will establish the efficacy of the benzannulation reaction of chromium carbene complexes as the key step in a general synthetic approach to anthracyclinones. To this end we chose as an initial target the tetracyclic trione **4**,[8] which has previously been converted to daunomycinone (**6a**) in three steps.[9] The final ring to be closed on the way to **4** is the C ring, and thus the B ring is to be made by the benzannulation of the carbene complex **1** with the acetylene **2**. The problem of the relative regiochemistry of the A and D rings reduces to the regiochemistry of the alkyne incorporation since cyclization can only occur in one direction for complex **1**. We have previously examined the regiochemistry of the alkyne incorporation and expect that with the terminal alkyne **2** only the 2-substituted tetrahydronaphthol **3** will be produced.[7,10]

Scheme III[a]



[a] (a) THF, 45 °C, 12 h; (b) 2 equiv of $[Fe(DMF)_3Cl_2][FeCl_4]$ in THF; (c) excess Et_2N-*i*-Pr, $ClCH_2OCH_3(CH_2Cl_2)$, 3 h; (d) Zn, pyridine, $CuSO_4 \cdot 7H_2O$ (10% KOH), reflux 24 h;[15] (e) 1.2 equiv of $(CF_3CO)_2O$, 8 equiv of 2,6-di-*tert*-butylpyridine (CH_2Cl_2), 0–25 °C, 4 h; (f) Triton B (MeOH), 1 atm O_2, 25 °C, 5 min; (g) 1.2 equiv of $CF_3CO_2H(CH_2Cl_2)$, 25 °C, 12 h; (h) 4 equiv of H_2SO_4 (acetone), 56 °C, 1 h; (i) 10 equiv of AgO, excess 6 N HNO_3 (acetone), 15 min; (j) 1% aqueous $NaHSO_3$; (k) 10% aqueous H_2SO_4 (acetone), 45 °C, 10 h; (l) 1:1 48% HBr/HOAc, 55 °C, 2 h.

The success of this general strategy will also be dependent on the functional group compatibility of the benzannulation reaction. The C ring in **4** is a quinone, and thus the correct oxidation state for the propargylic carbon in **2** is a ketone (X = O). However, the reaction of the acetylene **2a** with the carbene complex **1a** gave only a 17% yield of the annulated product **3a** in a tetrahydrofuran (30% in acetonitrile) (Scheme II). Other electron-deficient acetylenes such as phenyl ethynyl ketone and methyl propiolate also gave poor yields with **1a** in tetrahydrofuran (17% and 22%, respectively).[7] An additional problem would be that the electrophilic ring closure in the corresponding intermediate **3** (X = O) would likely require harsh conditions.[11] Attention was thus turned to other analogues of the acetylene **2**.

The benzannulation reaction proceeds nicely with the ethynyl lactone **2b**[12a] and the cyclohexenylcarbene complex **1b** to give the tetrahydronaphthol **9** in the range of 72–76% yield (69% in acetonitrile) after an oxidative workup with ferric chloride–DMF complex[12b] to remove the chromium tricarbonyl group. The complex **1b** can be prepared according to Fischer's general method[13] and as indicated in Scheme II was prepared via the isolation of the salt **8**[14] necessitated by separation problems. This is not usually the case, for example, **1a** can be prepared by the same method in a single step in 61% overall yield.[7] The final ring was closed by treating the acid **10** with trifluoroacetic anhydride in the presence of excess 2,6-di-*tert*-butylpyridine (Scheme III). The intermediate anthrone was oxidized directly with oxygen in the presence of Triton B to the anthraquinone **11b**.[5a] The methoxymethyl ether of **11b** can be selectively cleaved to give dimethyl

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(5) For total syntheses of alkavinone, a related 11-deoxy anthracyclinone, see: (a) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. (b) Pearlman, B. A.; McNamara, J. M.; Itasan, I.; Hatkeyama, S.; Sekizaki, H.; Kishi, Y. *Ibid.* **1981**, *103*, 4248. (c) Confalone, P. N.; Pizzolato, G. J. *Ibid.* **1981**, *103*, 4251. (d) Li, T.; Wu, Y. L. *Ibid.* **1981**, *103*, 7007. (e) Boeckman, R. K., Jr.; Sum, F. W. *Ibid.* **1982**, *104*, 4604.

(6) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644.

(7) Wulff, W. D.; Chan, K. S.; Tang, P. C., unpublished results.

(8) (a) Kende, A. S.; Rizzi, J.; Riemer, J. *Tetrahedron Lett.* **1979**, 1201. (b) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378. (c) Tamura, Y.; Wada, A.; Sasho, M.; Fukunaga, K.; Maeda, H.; Kita, Y. *J. Org. Chem.* **1982**, *47*, 4376.

(9) Kende, A. S.; Tsay, Y. G.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967.

(10) Wulff, W. D.; Tang, P. C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677.

(11) Rao, A. V. R.; Deshpande, V. H.; Reddy, N. L. *Tetrahedron Lett.* **1980**, 2661.

(12) (a) The lactone **2b** can be prepared in 42% yield from *N*,*N*-diethyl-*o*-methoxybenzamide and propargyl aldehyde in one step. (b) Tobinaga, S.; Kotani, E. *J. Am. Chem. Soc.* **1972**, *94*, 309.

(13) Fischer, E. O.; Schubert, U.; Kleine, W.; Fischer, H. *Inorg. Syn.* **1979**, *19*, 164.

(14) Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580.

(15) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799.

ether **12** and subsequently oxidatively demethylated[8b] with silver oxide and hydrolyzed to give the desired tetracyclic trione **4** in 77% yield. This oxidation could not be successfully scaled up, and as an alternative we found that the dimethyl ether **13b** could be cleanly demethylated selectively at the 6-position with 1:1 HBr/HOAc to give in larger scales the trione **4**, which had ^1H NMR, IR, and mass spectra identical with those of an authentic sample. That the 6-methoxyl in **13b** is selectively cleaved can also be established by the same conversion for **13c** prepared from the ethoxycarbene complex **1c**. The synthesis of the tetracyclic trione **4** was achieved in nine steps from commercially available starting materials in 8% overall yield and is thus comparable to the other syntheses of this intermediate.[8]

The synthesis of the intermediate **4** not only represents a formal synthesis of daunomycinone **6a**[9] but also demonstrates that the strategy of utilizing the benzannulation of cyclohexenyl chromium carbene complexes as outlined in Scheme II is a viable approach to anthracycline synthesis. Moreover, it can be anticipated to be a powerful approach since fully functionalized aglycones (i.e., **6a**) could be obtained directly from the corresponding cyclization of more highly functionalized carbene complexes and since it could at the same time provide for a convergent synthesis for both the 11-oxy and 11-deoxy anthracyclines due to the fact that the benzannulated product **9** has the oxygens in the incipient 6- and 11-positions differentially protected.

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Infrared Spectrum and Photochemistry of Methoxychlorocarbene

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Oxygen-substituted carbenes have drawn considerable attention.[2] Interaction between the carbene unoccupied p orbital and the adjacent oxygen lone pair is thought to stabilize the singlet state relative to the triplet[3] and to increase the nucleophilicity in oxycarbenes.[4] The simplest member of this family, hydroxymethylene, has been suggested as an intermediate in formaldehyde photochemistry, although it has eluded spectroscopic detection.[5] Alkoxycarbenes have similarly been implicated as photoproducts of cyclobutanones and certain other cyclic ketones.[6] Methoxychlorocarbene (**1**) was proposed by Hine and co-workers in 1953[7] to be an intermediate in the alkaline methanolysis of chloroform. More recently, the groups of Moss[8] and Stevens[9] have investigated the reactions of **1** generated by thermolysis of 3-chloro-3-methoxydiazirine (**2**). Two aspects of the chemistry of **1** are of particular note. First, methoxychlorocarbene (**1**) is the premier example of an ambiphilic singlet carbene.[4,8,9] The substituent effects produce a species exhibiting both electrophilic and nucleophilic proclivities. Second, **1** does not thermally rearrange to acetyl chloride, but rather generates methyl chloride and CO if untrapped.[9] Although the mechanism of this reaction is uncertain, carbocations have been suggested as intermediates in the decomposition of other alkoxychlorocarbenes.[10] This is in striking contrast to non-halogen-substituted oxycarbenes, which generally undergo alkyl migration to give the corresponding carbonyl compounds,[6,11] albeit likely via biradicals.

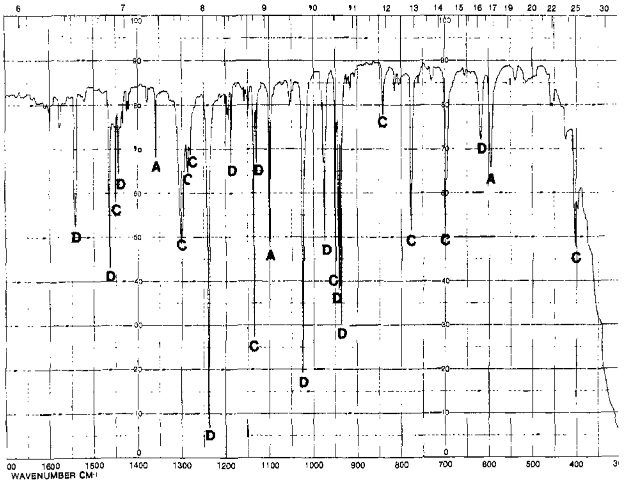
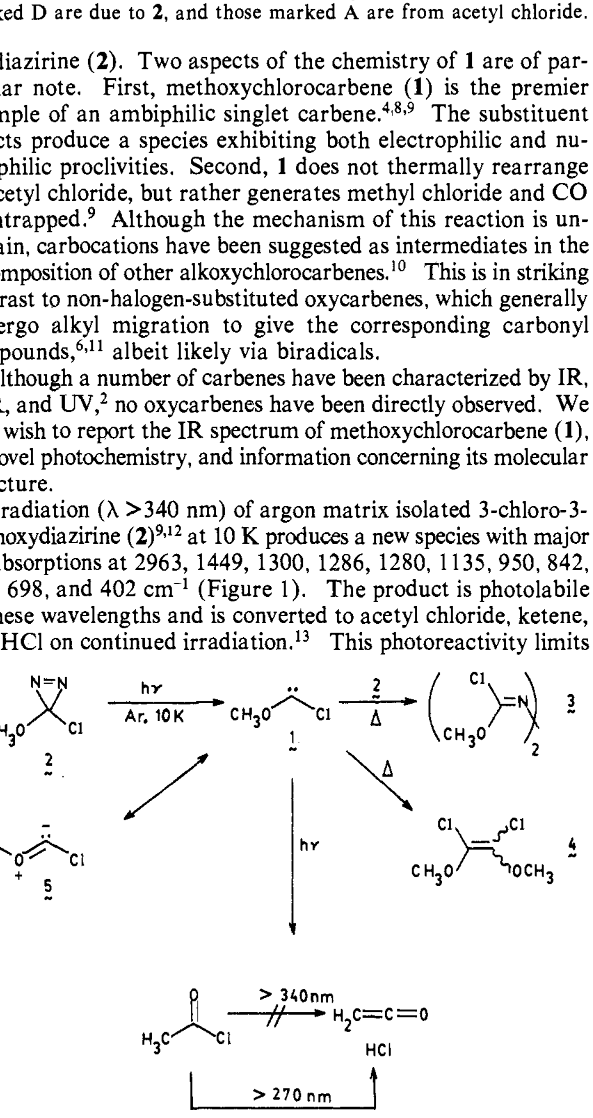


Figure 1. Infrared spectrum obtained on irradiation (λ >340 nm) of argon matrix isolated (1:700; 10 K) 3-chloro-3-methoxydiazirine (**2**). Bands marked C are assigned to methoxychlorocarbene (**1**), those marked D are due to **2**, and those marked A are from acetyl chloride.

Although a number of carbenes have been characterized by IR, ESR, and UV,[2] no oxycarbenes have been directly observed. We now wish to report the IR spectrum of methoxychlorocarbene (**1**), its novel photochemistry, and information concerning its molecular structure.

Irradiation (λ >340 nm) of argon matrix isolated 3-chloro-3-methoxydiazirine (**2**)[9,12] at 10 K produces a new species with major IR absorptions at 2963, 1449, 1300, 1286, 1280, 1135, 950, 842, 777, 698, and 402 cm^{-1} (Figure 1). The product is photolabile at these wavelengths and is converted to acetyl chloride, ketene, and HCl on continued irradiation.[13] This photoreactivity limits



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(1) Recipient of a Camille and Henry Dreyfus Foundation Grant for Newly Appointed Young Faculty in Chemistry.

(2) Jones, M., Jr.; Moss, R. A. "Carbenes"; Vol. I, 1973, Vol. II, 1975, Wiley: New York, 1973, 1975; Vol. I, II, and references cited therein.

(3) Mueller, P. H.; Rondan, N. G.; Houk, K. N. Harrison, J. F.; Hooper, D.; Willen, B. H.; Liebman, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 5049.

(4) Rondan, N. G.; Houk, K. N.; Moss, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1770.

(5) Sodeau, J. R.; Lee, E. K. C. *Chem. Phys. Lett.* **1978**, *57*, 71.

(6) Yates, P.; Loutfy, R. O. *Acc. Chem. Res.* **1975**, *8*, 209 and references therein.

(7) Hine, J.; Pollitzer, E. L.; Wagner, H. *J. Am. Chem. Soc.* **1953**, *75*, 5607.

(8) Moss, R. A.; Shieh, W.-C. *Tetrahedron Lett.* **1978**, 1935. Moss, R. A.; Fedorynski, M.; Shieh, W.-C. *J. Am. Chem. Soc.* **1979**, *101*, 4736.

(9) Smith, N. P.; Stevens, I. D. R. *Tetrahedron Lett.* **1978**, 1931; *J. Chem. Soc., Perkin Trans. 2* **1979**, *213*, 1298.

(10) Skell, P. S.; Keating, J. T. In "Carbonium Ions"; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1970; Vol. 2, p 617.

(11) Ayral-Kaloustian, S.; Agosta, W. C. *J. Org. Chem.* **1982**, *47*, 284.

(12) Matrix samples were prepared in dilutions of 1:600 to 1:1000 in argon and deposited from the gas phase onto a 2.54-cm CsI window cooled by an Air Products, Inc., Displex 202 refrigerator. Irradiations were performed with a Varian EIMAC 300-W high-pressure Xe arc lamp through a water filter and appropriate cutoff filters. Infrared spectra were recorded on a Beckman 4250 spectrometer.

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