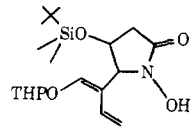
(7) Satisfactory spectral data were obtained using chromatographically homogeneous samples of all stable intermediates described herein.
(8) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.
(9) (a) MPLC (medium pressure liquid chromatography) refers to chromatography over Merck silica gel 60, 230–400 mesh, using an FMI lab pump, Altex chromatography columns, an Altex UV detector, and the indicated solvent. (b) All thin layer chromatography was performed on Merck 0.25-mm glass silica gel plates. Visualization of developed plates was by fluoresence quenching and staining with phosphomolybdic acid.
(10) Corey, E. J.; Vankateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(11) (a) This reaction was conducted in a base-treated flask (washed with aqueous sodium bicarbonate solution) owing to the lability of **11** and **12** to decomposition catalyzed by adventitious acid. (b) The remaining material (14%) is accounted for by the formation of the ene product i, of undetermined stereochemistry. For other examples of intramolecular ene reactions of acylnitroso compounds, note Keck, G. E.; Webb, R. W. *Tetrahedron Lett.* **1979**, 1185.



i

(12) Oxazine **12** was formed as an inseparable mixture of stereoisomers (corresponding to heliotridine and retronecine stereochemistry) in a ratio of ~1.3:1. Our lack of success in directing the cycloaddition to afford heliotridine stereochemistry (with the bulky *tert*-butyldimethylsilyl ether exo) is most probably due to an early, reactant-like transition state for cycloaddition of the highly reactive acylnitroso moiety. Separation of the stereoisomers was conveniently effected later in the sequence.
(13) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.
(14) (a) The bicyclic lactams **15** and **16** were obtained in a ratio of 1.3:1, reflecting little stereoselectivity in the intramolecular Diels–Alder process.[12] (b) The ring closure sequence could also be effected using the primary allylic chloride prepared from **13** by reaction with the Corey–Kim reagent[15] in dimethylformamide at 0 °C. In this case, the chromatographically pure chlorides afforded bicyclic lactams **15** and **16** in 92% isolated yield. This intramolecular alkylation was also rather sluggish, requiring 4 h at 23 °C to consume starting material after an initial deprotonation (as described above) at −78 °C.
(15) (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. (b) Corey, E. J.; Kim, C. U.; Kakeda, M. *Tetrahedron Lett.* **1972**, 4339.
(16) The appearance of the C_6 CH_2 group (pyrrolizidine numbering) proved particularly diagnostic since close models were available from previous work in our laboratories.[4] In **16** these protons appear (100 MHz, $CDCl_3$) as a doublet of doublets (J = 15, 4 Hz) at δ 2.63 and a doublet (J = 15 Hz) at 2.00, while in **15** they appear as a complex multiplet between 2.49 and 2.83.
(17) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(18) TLC comparisons of synthetic and natural materials were made on silica gel plates using 8% methanol in chloroform as eluant. The high polarity and associated tailing of these alkaloids makes TLC comparisons of limited utility, however. A more useful chromatographic comparison derived from VPC analysis using a silanized glass column of 5% OV-1 on Varaport 30. At 165 °C and 25-mL/min flow rate of nitrogen carrier gas, the retention times of naturally derived heliotridine and retronecine diacetates were 9 and 12 min, respectively. Coinjection with synthetic materials gave single sharp peaks of identical retention time.

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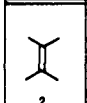
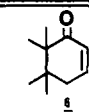
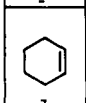
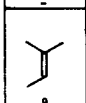
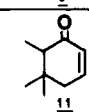
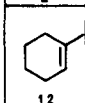
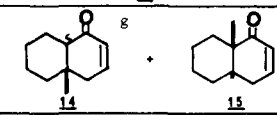
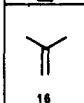
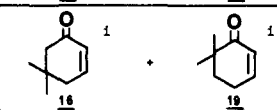
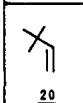
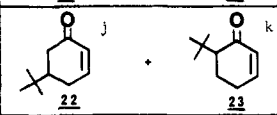
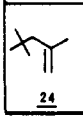
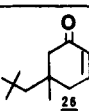
Four-Carbon Photochemical Annelation of Alkenes with 2,2,6-Trimethyl-1,3-dioxolenone

Sir:

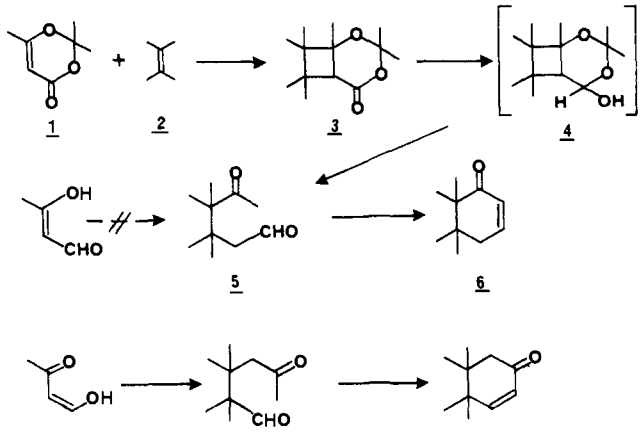
We report here a new four-carbon annelation sequence which utilizes the [2 + 2] photochemical cycloaddition of 2,2,6-trimethyl-1,3-dioxolenone (**1**) to alkenes as the key carbon-carbon bond-forming step. Subsequent mild reduction of the cyclobutane photoproducts followed by aldol cyclization provides remarkably easy access to a variety of cyclohexenones. Compound **1**, prepared in high yield from diketene and acetone by the method of Carroll and Bader,[2] can be regarded as the covalently restricted cis enol tautomer of an ester of acetoacetic acid. Because β-keto esters have been shown to be reluctant partners in [2 + 2] photoadditions to alkenes,[3] this study assumed additional interest.

Table I. Cyclohexenones from 2,2,6-Trimethyl-1,3-dioxolenone

Alkene	Cyclohexenone(s)	Yield, %[a] hν	Yield, %[a] enone[b]	ratio[c]
 2	 d 6	90	76	....
 7	 e 8	98	64	....
 9	 f 11	100	63	19:1
 12	 g + h 14 15	86	80	8:1
 16	 i + i 16 19	93	83	1:1.6
 20	 j + k 22 23	82	85	1:5
 24	 l 26	88	85	>19:1

[a] Yields of purified products, not optimized. [b] Combined yield for the two-step conversion (reduction, aldol cyclization) of photoproducts to cyclohexenones. [c] Ratio (H-H/H-T) of photoproducts, and thus cyclohexenones, as determined by a combination of chromatographic and spectroscopic techniques. [d] Note 11. [e] Note 12. [f] Note 14. [g] Note 15. [h] Note 20. [i] Note 21. [j] Note 24. [k] Note 25. [l] Note 26.

The reaction between **1** and tetramethylethylene is illustrative. Irradiation (Hanovia 450-W lamp; Corex filter) of a hexane solution of **1** and TME for 24 h yielded the cyclobutane photoadduct **3** in 90% yield.[4,5] Similarly cyclohexene yielded the corresponding adduct in 98% yield, thus establishing the viability of the photocycloaddition step. Transformation of the photoproducts into cyclohexenones was accomplished in two steps. Controlled reduction of **3** with diisobutylaluminum hydride[6] yielded keto aldehyde **5** (after spontaneous loss of acetone from hemiacetal **4** and retroaldol cyclobutanol fragmentation) which on direct exposure to aldol conditions afforded 5,5,6,6-tetramethylcyclohexenone (**6**) in 76% yield. Similar treatment of the cyclohexene photoadduct gave the *trans*-octalone **8** in 64% yield.



1 2 3 4 5 6

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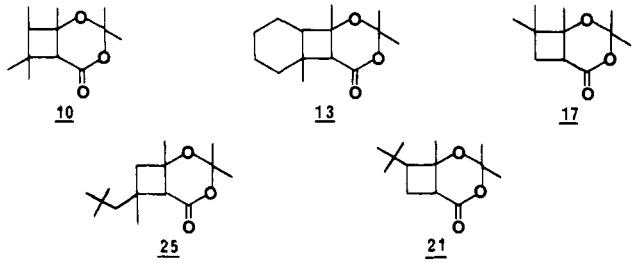
Recent disclosures from these laboratories have shown that formyl acetone (and other acyclic α-formyl ketones) undergo smooth photoaddition to alkenes *exclusively* through that hydrogen-bonded enol tautomer enolized toward the aldehyde carbon.[1a,7] It is of interest that in the present case the keto aldehyde intermediates (e.g., **5**) and thus the final cyclohexenones (e.g., **6**) are the same as would have arisen had the *alternate enol tautomer* of formyl acetone been involved in the initial photocycloaddition. It is also worth noting that the sense of the reaction is to yield differently substituted products from those obtained with other four-carbon cyclohexenone annelation units such as methyl vinyl ketone (Robinson annelation),[8] 1-methoxy-3-trimethylsiloxybutadiene (Diels-Alder),[9] and formylacetone (photoannelation),[1a,7] and as such represents a complementary process.

The results obtained from the reaction of **1** with several unsymmetrical alkenes indicate a remarkable range of regioselectivities in the photoaddition step. For instance trisubstituted alkenes **9** and **12** lead to a preponderence of the head-head regioisomers (**10** and **13** respectively), while 1,1-disubstituted alkenes such as **16** and **24** favor either head-tail (**17**) or head-head (**25**) regiochemistry depending on the degree of steric bulk of the alkene substituents. The single monosubstituted alkene studied, 3,3-dimethylbutene (**20**), favors the head-tail orientation **21**. A rationale for this broad spectrum of regioselectivities is unclear at this time.[10] The complex mixture of steric and electronic factors which governs regiochemical preferences in photocycloadditions seems to be particularly sensitive to substitution at the β position of the unsaturated carbonyl photopartner. Further examination of this rather subtle point is planned.



Although the full scope of this interesting process remains to be established, several further observations are pertinent. Smooth photoaddition has been obtained with oxygenated alkenes such as ethyl vinyl ether and isopropenylacetate as well as with cyclopentenes and cyclobutenes. Moreover, the 6-ethyl homologue of **1**, prepared by γ-alkylation of **1** (LDA, THF-HMPA, CH_3I),[27] is an equally active photopartner.

In summary, it is seen that alkenes can be converted into 5- and 6-substituted cyclohexenones in three laboratory steps with good efficiency and regioselectivity. The sense of the initial photoaddition is to provide photochemical access to that formylacetone enol tautomer which is not available from formylacetone itself (a reactivity "umpolung"), and which thus complements existing methods.

References and Notes

(1) (a) Paper No. 6 in the series of photochemical annelations. Part 5: Baldwin, S. W.; Wilkinson, J. M. *Tetrahedron Lett.* **1979,** 2657. (b) Supported in part by the National Institutes of Health (GM 26266).

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(4) Typically the alkene and **1** were present in a 3:1 molar ratio, although ratios as low as 1.5:1 have been employed. The [**1**] was generally 0.5–2.0% in hexane, methylene chloride, or acetonitrile, or mixtures thereof, with irradition times of 12–24 h.

(5) Typically the IR spectra of photoproducts showed a strong absorption at ~1740 cm^{-1} in contrast to two strong absorptions at 1715 and 1640 cm^{-1} for the starting material **1**. In addition the NMR resonances for the cyclobutane proton adjacent to the carbonyl appeared in the region δ 2.6–2.9 with expected multiplicities, while remaining cyclobutane resonances appeared at δ 1.9–2.5. The stereochemistry of the cyclobutane–lactone ring fusion was assumed to be cis in all cases by analogy to related literature reports for β-substituted 4-oxaenones. See Margaretha, P. *Helv. Chim. Acta.* **1974,** *57,* 2237.

(6) Schmidlin, J.; Wettstein, A. *Helv. Chim. Acta.* **1963,** *46,* 2799. Reproduceable reduction results were obtained by treating a hexane solution of the photoproducts with 2 equiv of Dibal in hexane at −60 °C for 1 h. Quenching with a large excess of methanol, followed by warming to room temperature, treatment with dilute HCl, and a standard ether workup, afforded the crude keto aldehydes (or β-hydroxycyclohexanones) in 60–90% yield. Cyclodehydration could be accomplished by several standard methods, although in our hands the most reliable involved heating a 1% benzene solution of the keto aldehyde with 5% TsOH for 2–3 h with azeotropic removal of water.

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(10) For discussions of the general problems in predicting regiochemistry in enone–alkene photocycloadditions, see: (a) Eaton, P. E. *Acc. Chem. Res.* **1968,** *1,* 50. (b) Bauslaugh, P. G. *Synthesis* **1970,** 287. (c) de Mayo, P. *Acc. Chem. Res.* **1971,** *4,* 41.

(11) The following spectral data were obtained for the low melting 5,5,6,6-tetramethylcyclohexenone (**6**): bp 80 °C (0.25 mmHg); IR ($CHCl_3$) 1670, 1380, and 1370 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (s, 6 H), 1.10 (s, 6 H), 2.28 (m, 2 H), 6.00 (dt, J = 9.5, 2.5 Hz, 1 H), 6.74 (dt, J = 9.5, 4.0 Hz, 1 H). All new compounds gave satisfactory elemental analyses (±0.4%).

(12) Isomerization to the more stable *trans*-octalone **8** occurred during aldol cyclization: mp 69–69.5 °C, lit.[13] 70–72 °C.

(13) Johnson, W. S.; Bass, J. D.; Williamson, K. L. *Tetrahedron* **1963,** *19,* 861.

(14) Coxon, J. M.; Garland, R. P.; Hartshorn, M. P. *Aust. J. Chem.* **1970,** *23,* 2531.

(15) The mixture of *cis*- and *trans*-methyloctalones **14** and **15** (ratio 4:3) was reduced by catalytic hydrogenation to give the dihydro compounds which were compared (NMR and MS) to literature values for authentic samples of *cis*- and *trans*-10-methyldecalones[16–18] and *cis*-9-methyldecalone.

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(20) An authentic sample of **15** prepared according to the literature was identical in all respects with minor isomer **15**: Zurflüh, R.; Tamm, Ch. *Helv. Chim. Acta* **1972,** *55,* 2495.

(21) Structure assignments were made by comparison with authentic **18**[22] and **19**.[23]

(22) (a) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976,** *41,* 636. (b) "The Sadtler Standard Spectra"; Sadtler Research Laboratories: Philadelphia, 1966; NMR Vol. 3, No. 1789.

(23) Berzin, V. B.; Vul'fson, N. S.; Isaeva, L. G.; Sizoi, M. N. *J. Org. Chem. USSR* **1975,** *11,* 322.

(24) (a) Moreau, P.; Casadevall, E. *C.R. Acad. Sci. Paris, Ser. C* **1971,** *272,* 801. (b) Barieux, J. J.; Gore, J. *Bull Soc. Chim. Fr.* **1971,** 1649.

(25) (a) Matoba, K.; Yamazaki, T. *Yakugaku Zasshi* **1973,** *93,* 1406. (b) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1956,** *78,* 4604. The hydrogenation product from **23** was identical in all respects with an authentic sample of 2-*tert*-butylcyclohexanone kindly supplied by Professor E. Eliel.

(26) The structure of cyclohexenone **26** was assigned on the basis of the following spectral evidence: IR (film) 1680 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (s, 9 H), 1.02 (s, 3 H), 1.16 (s, 2 H), 1.40–2.42 (complex, 4 H), 5.96 (m, 1 H), 6.80 (m, 1 H). In addition conversion of the photoproduct **25** into the symmetrical 5-methyl-5-neopentylcyclohexane-1,3-dione (CH_3OH–H_2O; H_2SO_4, 70 °C) provided ready spectral confirmation of the H–H substitution pattern of **25**: NMR ($CDCl_3$) δ 1.01 (s, 9 H), 1.08 (s, 3 H), (s, 2 H), 2.63 (s, 4 H), 3.33 (s, 2 H).

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Received September 24, 1979

NMR of Individual Sites in Protein Crystals. Magnetic Ordering Effects

Sir:

We report a new method for obtaining NMR spectra of individual sites in protein *crystals* which permits direct extraction of static, and in principle dynamic, molecular structural parameters.

0002-7863/80/1502-3635$01.00/0