123-54-6; 2-amino-3-cyanopyridine, 24517-64-4; diethyl (ethoxymethylene)malonate, 87-13-8.

Supplementary Material Available: ^{1}H NMR and analytical data for all compounds of the type **2**, **3**, **5**, and **8** (3 pages). Ordering information is given on any current masthead page.

One-Pot Conversion of Olefins to α,β-Unsaturated Carbonyl Compounds. An Easy Synthesis of 2-Cyclopentenone and Related Compounds

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There are few compounds that have more potential and versatility in organic synthesis than 2-cyclopentenone[1] and its higher homologues. Yet the available sources of these materials are generally tedious, multistep synthetic routes[2] or expensive commercial suppliers.[3] A conceptually attractive synthetic entry to this general class of compounds lies in the direct conversion of their parent olefins[4] through an allylic oxidation pathway. While an impressive amount of research has demonstrated the utility of such a stratagem with a variety of substrates,[4c] no approach has been generally applicable to the simple C-5 through C-8 cycloalkenes. We now report an exceedingly efficient, one-pot synthesis of the 2-cycloalkenones and other α,β-unsaturated carbonyl compounds by an in situ photooxygenation–elimination procedure.

Our synthesis is based on the decades-old observations of Schenck and co-workers,[5] which demonstrated (1) that allylic hydroperoxides are handily prepared by reaction of alkenes with photochemically generated singlet oxygen and (2) that these materials are easily converted to enones under mild conditions. More recently, other research groups[6] have shown that *activated olefins* are especially good substrates for such a conversion but simple 1,2-disubstituted ethylenes have been uniformly ignored.[7] We have found that the cycloalkenes, exemplified by cyclopentene as shown in Scheme I, are readily photooxygenated in the presence of acetic anhydride and base to yield directly cycloalkenones after aqueous workup and distillation. The examples shown in Table I illustrate that this one-pot method is general and readily applied to even those alkenes normally considered to be too unreactive toward $^1O_2$ to be useful in a preparative sense (e.g., cyclohexene). Furthermore, it has been applied to a variety of cyclic and acyclic olefins to produce α,β-unsaturated ketones, aldehydes, and esters. The last example is a replication of the work done by Conia et al. in a two-step sequence.[6a] The yield of product that we obtained by the one-pot method was somewhat higher.

In all cases examined, we found this catalyzed oxidation exceptionally easy to carry out, even on the mole scale. For some of the substrates, the two intermediates could be observed by TLC during the course of the reaction, and complete conversion to unsaturated carbonyl product required the solution to stand overnight prior to isolation. The acylation catalyst, 4-(dimethylamino)pyridine, was incorporated into the general procedure to hasten these steps of the conversion.

Scheme I

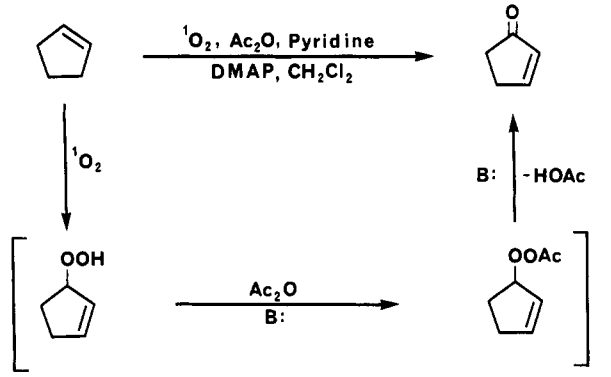
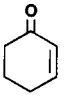
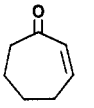
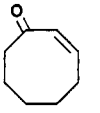
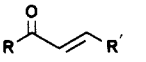
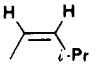
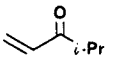
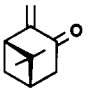
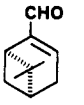
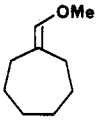
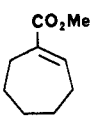


Table I. Direct Synthesis of α,β-Unsaturated Carbonyl Compounds from Olefins

olefin	product	irradiation time, h	yield,[a] %
		2	71
		10	78
		2.3[b]	85
		9[b]	88
Methyl Oleate		2	97[c]
		4.5	58
		1.5	97[d]
		2.5[b]	58[e]
		0.5[b]	77

[a] Yields are based on starting olefin and indicate the amount of distilled product obtained of ≥95% purity as judged by GC analysis. [b] In addition to the photooxygenation time, these reactions were allowed to stand overnight to ensure completion of the reaction sequence. [c] Product consists of an equal mixture of R = $(CH_2)_7CO_2CH_3$, R′ = C_7H_{15} and R = C_8H_{17}, R′ = $(CH_2)_6CO_2CH_3$. [d] Measured rotations were α-pinene $[\alpha]_D$ +47.1° (neat), pinocarvone $[\alpha]_D$ −64.5° (neat). [e] Measured rotations were β-pinene $[\alpha]_D$ −21° (neat) myrtenal $[\alpha]_D$ −14.7° (neat).

Clearly, the success of this approach lies in the lack of reactivity of the intermediates as well as the product to

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the photooxygenation conditions.[8] It is also interesting to note that only a catalytic amount of base is required[6b] to effect the conversions. The good to excellent yields reflect the lack of formation of significant side products.[9]

In summary, we feel this procedure offers the advantages of ease, efficiency, and thrift to a highly useful chemical conversion. Consequently, 2-cyclopentenone can now be prepared from commercially available materials in the same amount of time that it normally takes to isolate cyclopentadiene from its dimer.

Experimental Section

NMR spectra were recorded on Varian T-60, EM-360A, and CFT-20 spectrometers employing $CDCl_3$ solutions with Me_4Si as internal standard. IR spectra were determined on a Perkin-Elmer 298 spectrometer. Mass spectra were obtained on HP 5985B and Kratos MS-30 instruments. Optical rotations were measured on a Rudolph Research Autopol III polarimeter. GC was done on a Varian-Aerograph 202B instrument using 5 ft × $^1/_4$ in. columns. TLC was performed on Anatech Uniplate glass plates bearing a 250-μm layer of silica gel GF.

Methylene chloride (reagent grade) was freshly distilled from P_2O_5 prior to use. *meso*-Tetraphenylporphine (TPP) and 4-(dimethylamino)pyridine (DMAP) were used as received from the Aldrich Chemical Co. Pyridine (reagent grade) was stored over KOH prior to use. Methyl oleate was of >98% purity as prepared internally by published methods. All other materials were of reagent (or equivalent) grade and used as received from commercial sources.

Photooxygenation Apparatus. A standard immersion-well configuration[10] was used in conjunction with a General Electric LU-400 sodium vapor lamp. Due to the physical dimensions of this light source, the reactor vessel was constructed by using a ₹ 103/60 ground-glass joint. This allowed the immersion-well lamp cavity to have a 65-mm diameter, which nicely held the 400-W source. It sould be emphasized that this lamp is one of the least expensive and most efficient for sensitized photooxygenations available.[11] It has the added benefit of having a very low UV output.

General Method for Olefin Photooxygenation. 2-Cyclopenten-1-one. The immersion-well reactor having a 350-mL capacity was filled with a solution of cyclopentene (20.00 g, 0.294 mol), acetic anhydride (29.1 mL, 0.303 mol), pyridine (11.9 mL, 0.147 mol), TPP (0.021 g), and DMAP (0.716 g, 0.006 mol) in methylene chloride (270 mL). Cold tap water was circulated through the lamp jacket and on through the reflux condenser at the fastest possible rate while a gentle stream of oxygen was bubbled through the reaction mixture. After a few minutes, the lamp was turned on and the course of the reaction was monitored by temperature-programmed GC (100–195 °C at 10 °C/min on a 20% Carbowax 20 M column). After 2 h, all the cyclopentene had been consumed and 2-cyclopenten-1-one was the only product evidenced by GC and TLC. The solution was diluted with methylene chloride (270 mL) and extracted with saturated $NaHCO_3$ solution until basic (2 × 200 mL) to remove the acetic acid byproduct. The organic layer was then washed with 1 N HCl until it turned mint green and the aqueous washes were acidic (2 × 100 mL). Further extractions with saturated $CuSO_4$ (100 mL) and saturated NaCl (200 mL) followed by drying ($MgSO_4$) and concentration in vacuo at ≤30 °C gave a crude product, which was distilled from a small amount of anhydrous K_2CO_3 through a 10-cm Vigreaux column to yield colorless 2-cyclopenten-1-one: 17.06 g (71%); bp 52 °C (27 mm) [lit.[2a] bp 42–44 °C (13 mm)]; >99% GC purity. ^1H and ^{13}C NMR, IR, and mass spectra were identical with published data.

The reaction scale was more than tripled with a modest decrease in isolated yield. Thus, cyclopentene (68.26 g, 1 mol) and the other reaction components (increased proportionately) in 130 mL of CH_2Cl_2 were irradiated for 3–4 h, diluted with 700 mL of CH_2Cl_2, and washed as described above. **Caution**: vigorous foaming occurs in the bicarbonate neutralization. The yield of distilled product was 53–60%. On both reaction scales, some losses to the aqueous washes were demonstrated by GC of back-extracted samples.

The other olefins (Table I) were oxidized to known compounds in the same manner (note overnight standing for some after irradiation) with the exception of methyl oleate.

Photooxygenation of Methyl Oleate. The reactor was charged with a solution of methyl oleate (20.0 g, 67.5 mmol), acetic anhydride (6.68 mL, 70.8 mmol), pyridine (2.73 mL, 33.8 mmol), TPP (50.2 mg), and DMAP (0.167 g, 1.37 mmol) in methylene chloride (325 mL). After 2 h of irradiation as described above, TLC (3:1 pentane/ether) indicated no remaining starting material and an intense UV active spot for the enone. The mixture was diluted with ether (1 L) and washed successively with 100-mL portions of water, saturated $NaHCO_3$, 1 N HCl, saturated $CuSO_4$, water, and saturated NaCl. After drying ($MgSO_4$) and concentration, the dark residue was bulb-to-bulb distilled (pot 165 °C at 0.04 mm) to afford a 1:1 mixture of methyl 9-oxo-10-octadecenoate and methyl 10-oxo-8-octadecenoate as a light yellow liquid: 20.47 g (97%); IR (neat) 2930, 2855, 1738, 1693, 1670, 1628, 1460, 1435, 1365, 1230, 1195, 1170, 1010, 978, 720 cm^{-1}; ^1H NMR δ 6.73 (dt, J = 15.5, 6.5, Hz, 1 H), 5.95, (dt, J = 15.5, 1 Hz, 1 H), 3.6 (s, 3 H, OCH_3), 2.3 (m, 6 H), 1.3 (m, 20 H), 0.87 (t, 3 H, CH_3); ^{13}C NMR 200.3, 173.9, 147.0, 146.7, 130.4, 51.2, 40.0, 39.9, 33.9, 32.4, 32.3, 31.8, 29.0 (br, intense peak), 28.1, 27.9, 24.8, 24.2, 22.6, 14.0 ppm; mass spectrum, m/z (relative intensity) 311 (4, $[M + H]^+$), 279 (9.6), 251 (7.6), 212 (7.7), 211 (8.7), 183 (11), 167 (38), 153 (34), 152 (22), 137 (48), 109 (38), 97 (100); calcd for $C_{19}H_{35}O_3$ $(M + H)^+$ M_r 311.2586, found M_r 311.2550.

Acknowledgment. We thank Professor Ernest Wenkert for first suggesting to us the synthetic potential of allylic hydroperoxide to enone conversions.

Registry No. Cyclopentene, 142-29-0; cyclohexene, 110-83-8; cycloheptene, 628-92-2; cyclooctene, 931-88-4; methyl oleate, 112-62-9; 4-methyl-2-pentene, 4461-48-7; (+)-α-pinene, 7785-70-8;

(1) (a) An excellent summary of organic synthesis based on a cyclopentenone derivative and the natural products spawning the remarkable growth in this area has recently appeared: Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480–92. (b) Extremely high asymmetric induction in the conjugate addition of a chiral malonate derivative to 2-cyclopentenone has been reported: Mukaiyama, T.; Hirako, Y.; Takeda, T. *Chem. Lett.* **1978**, 461–64. (c) For other recent and interesting conjugate additions, see: Oppolzer, W.; Pitteload, R. *J. Am. Chem. Soc.* **1982**, *104*, 6478–79. Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045–9.

(2) (a) Two commonly used preparations give 2-cyclopentenone in 20–29% yield based on cyclopentadiene starting material: "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, pp 326–28. "Vogel's Textbook of Practical Organic Chemistry, 4th ed."; Longman Inc: New York, 1978; p 870. (b) For the preparation of enones from saturated ketones, see: Garbisch, E. W., Jr. *J. Org. Chem.* **1965**, *30*, 2109–20. Ito, Y.; Hirao, T.; Saegusa, T. *Ibid.* **1978**, *43*, 1011–13. Jung, M. E.; Pan Y.-G.; Rathke, M. W.; Sullivan, D. F.; Woodbury, R. P. *Ibid.* **1977**, *42*, 3961–63 and references cited, therein.

(3) The current price, on the basis of the largest, listed quantity (25 g), from two common sources (Fluka and Aldrich) is $213.50/mol. At the same time, the cost of cyclopentene is $13.90 to $16.35 per mol.

(4) (a) Treibs, W.; Franke, G.; Leichsensing, G.; Roder, H. *Ber.* **1953**, *86*, 616–25. (b) Reuter, J. M.; Sinha, A.; Salomon, R. G. *J. Org. Chem.* **1978**, *43*, 2438–42 and references cited therein. (c) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *Ibid.* **1969**, *34*, 3587–92 and references cited. (d) Uemura, S.; Patil, S. R. *Tetrahedron Lett.* **1982**, *23*, 4353–56; *Chem. Lett.* **1982**, 1743–46.

(5) (a) Schenck, G. O.; Neumuller, O.-A.; Eisfeld, W. *Justus Liebigs Ann. Chem.* **1958**, *618*, 202–10. (b) For review of the synthetic utility of singlet oxygen, see: Wasserman, H. H.; Ives, J. L. *Tetrahedron* **1981**, *37*, 1825–52, and references therein.

(6) (a) Rousseau G.; LePerches, P.; Conia, J. M. *Synthesis* **1978**, 67–70. (b) Fehr, C.; Galindo, J.; Ohloff, G. *Helv. Chim. Acta* **1981**, *64*, 1247–55.

(7) This may be due in part to a variety of reports describing modest conversions and low isolated yields of allylic hydroperoxides after days of irradiation under quite similar conditions to our own. However, it is clear that this earlier work did not use an immersion-well reactor, see: Bloodworth, A. J.; Eggelte, H. J. *J. Chem. Soc., Perkin Trans 1* **1981**, 1375–82. Matsuura, T.; Horinaka, A.; Yoshida, H.; Butsugan, Y. *Tetrahedron* **1971**, *27*, 3095–3100.

(8) Highly substituted enones will react with $^1O_2$: Ensley, H. E.; Carr, R. V. C.; Martin, R. S.; Pierce, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 2836–38.

(9) Cf.: ref 5b, pp 1832–34.

(10) Denny, R. W.; Nickon, A. *Org. React. (N.Y.)* **1973**, *20*, 178.

(11) This was first pointed out by Schenck and Dunlap: Schenck, G. O.; Dunlap, D. E. *Angew. Chem.* **1956**, *68*, 248–9.

(−)-β-pinene, 18172-67-3; (methoxymethylene)cycloheptane, 66051-09-0; 2-cyclopentenone, 930-30-3; 2-cyclohexenone, 930-68-7; 2-cycloheptenone, 1121-66-0; 2-cyclooctenone, 1728-25-2; methyl 9-oxo-10-octadecenoate, 87070-66-4; methyl 10-oxo-8-octadecenoate, 87070-67-5; 4-methyl-3-oxo-1-pentene, 1606-47-9; (−)-pinocarvone, 19890-00-7; (−)-myrtenal, 18486-69-6; 1-(methoxycarbonyl)-1-cycloheptene, 56745-53-0.

Diels–Alder Reaction of β-Dihydrothebaine and Its 4-Phenyl Ether with Methyl Vinyl Ketone: Synthesis of 6,14-*exo*-Ethenomorphinans[1]

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Medical Foundation of Buffalo, Inc., Buffalo, New York 14203

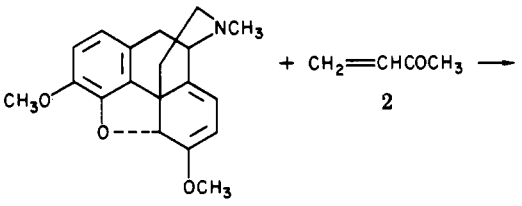
Received March 15, 1983

Bentley and co-workers[2-5] studied the Diels–Alder reaction of thebaine (1) with various dienophiles and concluded that 6,14-*endo*-etheno derivatives are formed, since the dienophiles can approach from the relatively exposed β-face of thebaine. Thus, the reaction with methyl vinyl ketone (2) formed the oripavine 3 with the stereochemistry as shown. This led these workers to synthesize a series of extremely potent 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrooripavine type analgesics.

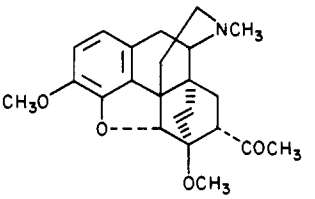
As part of an on-going program on analgesics in the morphine/morphinan area, we have reported[6] a practical synthesis of β-dihydrothebaine (**4a**) from thebaine (1). The Diels–Alder reaction of β-dihydrothebaine with **2** was of considerable interest to us, since this could provide an entry into a novel class of potential analgesic intermediates. Interestingly, Bentley[5] had mentioned in a review article that β-dihydrothebaine (**4a**) undergoes a Diels–Alder reaction with **2**. He assigned endo stereochemistry to the adduct **5** presumably by analogy with the oripavines. No experimental details have since appeared in the literature.

We have reexamined this reaction. A close examination of the Dreiding models of thebaine and β-dihydrothebaine shows that the strain on the thebaine molecule is considerably released by opening the 4,5-α-epoxide ring. Thus the addition of the dienophile to the exposed face of the diene in **4a** can be envisioned from both faces, unlike in the closed ring system of thebaine (1). In our hands the reaction between β-dihydrothebaine and **2** proved to be very sluggish and did not give the adduct as a clean product under a variety of conditions. In some instances, the adduct was formed as evidenced by NMR, but the yield was extremely poor.

Better results were obtained when the 4-phenyl ether **4b** was substituted for **4a**, since the adduct **6b** was isolated



1 (thebaine) 2



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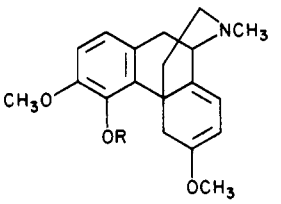
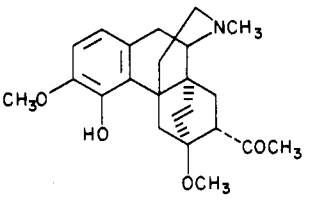
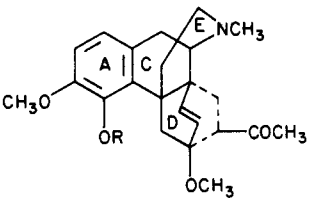


4a, R = H = β-dihydrothebaine
b, R = Ph

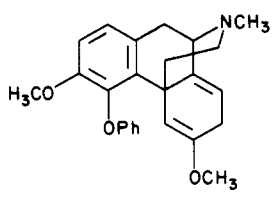


5

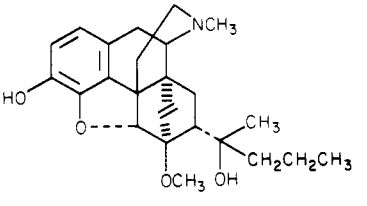


6a, R = H
b, R = Ph

in 33% yield (procedure A) after chromatography. On the basis of a report by Hudlicky[7] that Diels–Alder reaction can be conducted under mild reaction conditions by adsorbing a solution of the diene and dienophile on silica gel or alumina, **4b** was reacted with **2** on an alumina column (procedure B) and the yield was increased to 80%. On scale-up, this procedure gave poor yields and the following simplified procedure was therefore developed. The product **6b** could be readily prepared, albeit in lower but reproducible yields, by refluxing a slurry of **4b**, alumina (neutral, grade 1), **2**, and benzene for 20 h, as long as **2** was added at intervals. This process had the added advantage that the reaction could be readily carried out by using a mixture of **4b** and **7**. Fractional crystallization of the product after workup gave 41% of the Diels–Alder product.



7



8 (etorphine)

It was apparent from the results of a large series of experiments that the Diels–Alder reaction between **4b** and **2** was more complicated than the facile reaction observed between thebaine and **2**. Therefore a crystalline sample

(1) Part 7 in the series Novel Opiates and Antagonists. For part 6, see: Quick, J.; Herlihy, P.; Howes, J. F., submitted for publication.
(2) Bentley, K. W. In "The Alkaloids"; Manski, R. H. F., Ed.; Wiley: New York, 1971; Vol. 13, p 1.
(3) Bentley, K. W.; Hardy, D. G.; Crocker, H. P.; Haddlesey, D. I.; Mayor, P. A. *J. Am. Chem. Soc.* **1967**, *89*, 3312 and references cited therein.
(4) Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3267.
(5) Reference 2, p 120.
(6) Razdan, R. K.; Portlock, D. E.; Dalzell, H. C.; Malmberg, C. *J. Org. Chem.* **1978**, *43*, 3604.
(7) Hudlicky, M. *J. Org. Chem.* **1974**, *39*, 3460.

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