Synthesis of Bicyclic Cyclopentanols by Photoreductive Cyclization of δ,ε-Unsaturated Ketones

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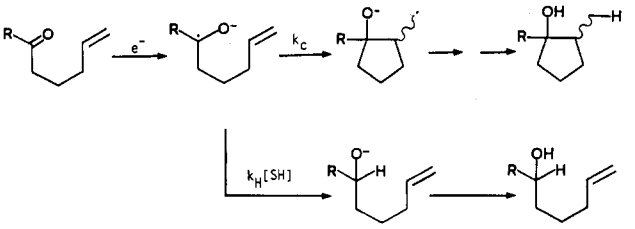
Bicyclic cyclopentanols were synthesized by intramolecular radical addition from photochemically induced electron transfer to δ,ε-unsaturated ketones. The donor was HMPA (neat) or Et_3N (in CH_3CN). Irradiation of δ,ε-ethylenic ketones and β-keto esters in HMPA led to methyl bicyclic cyclopentanols in high yields and stereoselectivity. NEt_3 was equally efficient for cyclization of corresponding acetylenic and allenic derivatives. The results are compared to those obtained by nonphotochemical methods and the nature of the excited species (donor or acceptor) is discussed.

Cyclization of δ,ε-unsaturated radicals is a very fast process which leads to cyclopentylmethyl or cyclohexyl radicals. Formation of the cyclopentane ring is highly favored according to literature data[1] and Baldwin's rules.[2] Convenient methods to prepare the starting radical involve the reduction of various functions: halides,[3] halo ketals,[4] thioethers.[5] Similarly, radical anions coming from the reduction of δ,ε-unsaturated ketones cyclize efficiently, leading to substituted cyclopentanols.[6]

It has been reeported that ketones are photochemically reduced in the presence of amines[7] and that the primary process involves a very fast electron transfer from the amine to the triplet excited state of the ketone, for aromatic[8] as well as aliphatic[9] ketones. However, no applications other than pinacol or alcohol formation from the ketone, or oxidation of the amine,[10] were described.

We have shown that hexamethylphosphoric triamide [$(Me_2N)_3PO$, HMPA], under UV irradiation, is an efficient electron donor. Although our studies essentially dealt with photoreduction of carboxylic[11] and sulfonic[12] aliphatic esters, obviously more easily reducible compounds such as aliphatic ketones were also reduced; however, side reactions lowered the yield of alcohol formation.[11]

Scheme I



In accord with the very fast cyclization process[13] one might expect that δ,ε-unsaturated ketyl radical anion produced by photoinduced electron transfer from a donor such as HMPA or tertiary amine might lead to cyclopentanol derivatives rather than to δ,ε-unsaturated alcohol or pinacol (Scheme I), just as it occurs in ground-state reduction. Owing to the mild medium conditions used in photochemical reactions, it was also interesting to compare the photochemical methodology with reported chemical or electrochemical ones.

The aim of this paper is to report various cyclization reactions conducted on this basis and their application to the synthesis of bicyclic cyclopentanol derivatives.[14]

Results

Irradiation of δ,ε-olefinic cyclopentanone **1** and cyclohexanone **3** in HMPA with low pressure mercury lamps (λ = 254 nm) led to the bicyclic cyclopentanols **2** and **4**, respectively, in high yields. Analysis of the reaction mixture could not reveal any reduction compound, such as δ,ε-olefinic alcohol, other than the cyclized one. Furthermore, only one stereoisomer having methyl and hydroxyl groups in trans configuration was obtained. Using triethylamine as donor, in a polar solvent such as acetonitrile, the same reaction occurred, but with poorer yield.

The high regio- and stereoselectivity as well as the high yield obtained in HMPA led us to test the synthetic usefulness of the reaction toward various bicyclic cyclopentanols. Starting from β-allylcyclohexanone (**5**), the mixture of cyclized isomers **6a** and **6b** was obtained, in 45% and 30% yield, respectively. Noncyclized reduction product was not detected and the 1,5 cyclization process

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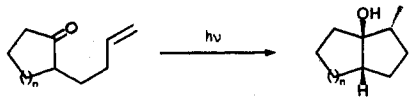
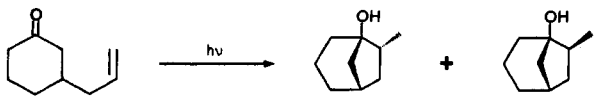
took place exclusively, as in the previous cases. Similarly, 4-cyclooctenone (7), produced bicyclo[3.3.0]cyclooctan-1-ol in 67% yield.

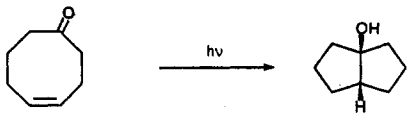


1 n=1 HMPA 2 81%
Et_3N/CH_3CN 50%

3 n=2 HMPA 4 76%

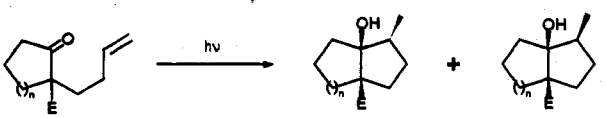


5 HMPA 6a 45% 6b 30%



7 HMPA 8 67%

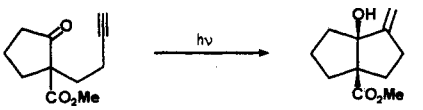
When several functional groups are present in the starting molecule, the electron transfer from donor might occur selectively to the most reducible group. Indeed, keto esters **9** and **11** could be cyclized to bicyclic compounds **10** and **12**, respectively. The cis configuration of fused bicyclic system was confirmed by infrared spectroscopy, showing an intramolecular hydrogen bonding between the hydroxyl and carboxyl groups. Excellent yields in HMPA were obtained when reaction was stopped as soon as the starting material has completely disappeared. If the irradiation was maintained after complete reduction of the carbonyl group, particularly when it was performed in a mixture HMPA–H_2O, known to be more efficient than neat HMPA for reduction of esters,[11] some amount of the corresponding cyclized hydroxy acid could be isolated. In contrast to the corresponding ketones **1** and **3**, two stereoisomers were obtained, although the cyclization remains very stereoselective. As already noticed, yields are higher in HMPA than in Et_3N/CH_3CN medium. Furthermore, a better stereoselectivity was observed in HMPA.



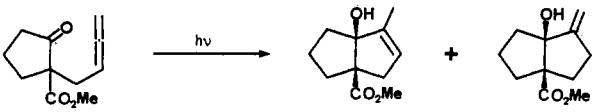
9 n=1, E=CO_2Me HMPA 10a 87% 10b 3%
Et_3N/CH_3CN 56% 4%

11 n=2, E=CO_2Et HMPA 12a 75% 12b 5%
Et_3N/CH_3CN 43% 15%

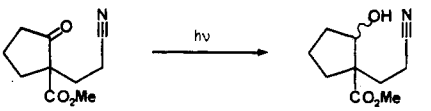
Irradiation of δ,ε-acetylenic keto ester **13** afforded the allylic bicyclic alcohol **14** in high yield, either in HMPA or Et_3N/CH_3CN, as exclusive reduction product. The corresponding allenic compound **15** irradiated in Et_3N/CH_3CN medium, afforded the cyclized products **16** and **14**, respectively, in 55% and 20% yields, with the remaining double bond in the endo and exocyclic position, respectively. In contrast with other unsaturated keto derivatives, only the carbonyl reduction product, alcohol **18**, could be isolated, with very poor yield, from the irradiation of nitrile **17**, either in HMPA or Et_3N/CH_3CN medium.



13 HMPA 14 80%
Et_3N/CH_3CN 86%



15 Et_3N/CH_3CN 16 55% 14 20%



17 HMPA or 18 10%
Et_3N/CH_3CN

Discussion

1. Photoreductive Method Compared to Chemioreductive Methods. It first appears that except for allenic and cyano derivatives **15** and **17**, which will be discussed later, only cyclized reduction products proceeding exclusively from the fastest 5-exo mode were obtained. This indicates that once electron transfer has taken place, cyclization process is faster than hydrogen transfer from the solvent. Assuming that less than 1% of the noncyclized alcohol is produced from the radical anion intermediate (Scheme I), the relative limit rate of cyclization vs. hydrogen abstraction is given by $k_c/k_H > 100$-[solvent]. With HMPA (5.7 M) as medium, $k_c/k_H > 570$. If we consider that substitution on the radical site does not modify strongly k_c (10^5 s^{-1} for 5-hexenyl radical),[13] the limit value of hydrogen transfer rate is approximately $k_H < 1.8 \times 10^2$ M^{-1} s^{-1}.

Our photoreductive method to produce the intermediate radical anion can be compared with electrochemical or chemical reduction. The stereospecific production of alcohols **2** and **4** from enones **1** and **3** is consistent with the results of electroreductive cyclization of such compounds.[6f] The high stereoselectivity of the photoreductive cyclization (**10a/10b** = 5/1) of the keto ester **9** is better than that observed in reduction with the Zn/Me_3SiCl system (**10a/10b** = 3/1).[6e] Similarly, acetylenic keto ester **13** gave exclusively the exo methylene hydroxy ester **14**, as did Zn/Me_3SiCl reduction.[6e] This cyclization has to be considered as a 5-exo-dig process, also favorable according to Baldwin's rules[2] and to numerous previously reported examples.[1c] In particular, it was established that the reductive cyclization of alkynyl ketone is indeed due to an electron transfer to the carbonyl group followed by intramolecular radical addition to triple bond.[15,16] The photochemical approach is of preparative value owing to the very simple procedure (see Experimental Section). In our hands, the difficulty of achieving cyclization by the Zn/Me_3SiCl system[6e] with the reported yields indicates

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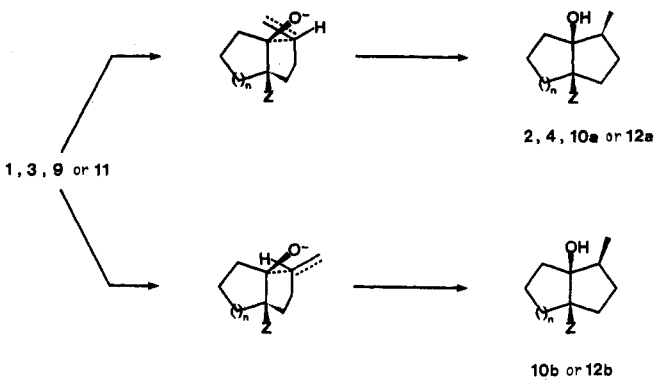
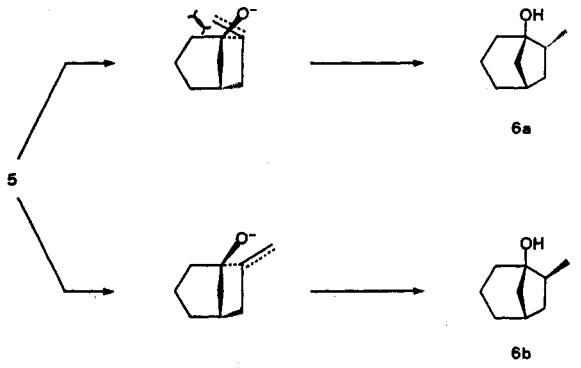
Scheme II



Scheme III

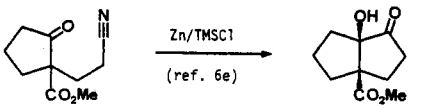


that in such heterogeneous conditions the reaction is not easy to reproduce.

The behavior of the allenic derivative **15** is interesting because the two compounds **14** and **16**, derived from the two allowed 5-exo-dig and 5-endo-dig cyclization modes,[2] were obtained, in contrast to other results: the 5-exo-dig closure took place exclusively from electroreductive cyclization of allenic cyclopentanone.[6d]

2. Stereoselectivity. The cis configuration of the ring fusion is well-documented.[17] The same stereospecificity was already observed in reductive cyclization of unsaturated ketones.[6a,f] The relative stereochemistry of the hydroxyl and exo-methyl substituents deserves further comments. In the special case of a ketyl radical anion intermediate, the stereoselectivity is well-rationalized considering repulsive electrostatic interaction between negative oxygen and partial negative charge carried by the terminal sp^2 carbon atom in the C_5 cyclic transition state, according to the stereoelectronic approach to this transition state.[1b,6f] In other words, we can assume that stereochemistry will be governed by the size of the dihedral angle between the C–O bond and the "olefinic" bond in the transition state. The transition state which has the greater dihedral angle will be favored (Scheme II). For α-substituted ketone **1** (or **3**, **9**, and **11**), the favored transition state is that leading to compound **2** (or **4**, **10a**, and **12a**). The poor stereoselectivity observed for the β-substituted ketone **5** is due to additional steric factors; in this more strained tricyclic system, steric interactions are more important precisely in the transition state having the more favorable dihedral angle (Scheme III): so, electrostatic factors responsible for the high stereoselectivity of reaction of compounds **1**, **3**, **9**, and **11** are balanced by steric factors for reaction of compound **5**.

3. Case of Cyano Derivative 17. Cyclization of the 4-cyanobutyl radical is known to be slower than that of the 5-hexenyl radical (respectively 3.9×10^3 s^{-1} and 10^5 s^{-1} at 25 °C[13]). The production of noncyclized alcohol **18** from the cyano ester **17**, in our reaction conditions, indicate that hydrogen transfer from the solvent now competes with the cyclization process. However, the cyclization of the same compound occurred very efficiently when submitted to other reductive conditions: indeed compound **17**, treated by the Zn/Me_3SiCl system, was reported to give exclusively the bicyclic derivative **19** in high yield,[6e] although the solvent used, THF, was also a very good hydrogen donor. Furthermore, olefinic or acetylenic ketones and keto esters gave essentially the same results whatever the reducing way used. Although we cannot exclude that some cyclization with subsequent decomposition took place, owing to the very incomplete balance of the reaction, a reasonable explanation of these different behaviors could be the following: in the chemical reduction, a wide excess of reducing agent is used (20 equiv of Zn powder);[6e] the slower rate of cyclization of cyano radical allows a second electron transfer leading finally to an intramolecular nucleophilic addition. Such a bielectronic mechanism is also supported by the Zn/Me_3SiCl reductive cyclization of dicarbonyl analogues.[6e] With photochemical reducing conditions, a two electron process is very improbable, because the requisite condition to have an electron transfer is to produce an excited state (donor or acceptor, see below); so, two electron transfers to the substrate would require an excited state concentration high enough to allow two consecutive bimolecular reactions, which is not reasonable to envisage in our irradiation conditions.



17 19

4. On the Photoredox Process. Chemioselectivity. Photochemically induced electron transfer may be considered as a classical redox process in which one of the reactant is an excited species. We have already demonstrated that excited HMPA is able to transfer one electron to a nonactivated ester ($E_{red} \sim -3$ V/SCE).[11] Obviously, aliphatic ketones ($E_{red} \sim -2.4$ V/SCE)[18a] can be reduced in the same manner. The ability to transfer an electron to or from an excited molecule can be estimated by using the Rehm–Weller equation,[19] which gives the free enthalpy change of the process, according to electrochemical parameters and the excited state energy. With triethylamine as donor ($E_{ox} = 0.78$ V/SCE),[18b] almost all the light is absorbed by the ketone: $A_9/A_{Et_3N} = 4.2/1$ ([9] = 3.5×10^{-2} M; $[Et_3N] = 0.175$ M; $\epsilon_{254}^{9} = 68$; $\epsilon_{254}^{Et_3N} = 3.26$). The electron transfer from triplet as well as singlet excited ketone ($E_s \sim 88$ kcal.mol^{-1}[20]) is actually a favored process ($\Delta G \ll 0$). When irradiation is performed in HMPA ($E_{ox} \sim 1.29$ V/SCE),[11] the amount of light absorbed by the donor (HMPA) is significant, if not the major one: $A_9/A_{HMPA} = 2/1$ ([HMPA] = 5.7 M; $\epsilon_{254}^{HMPA} \sim 0.3$; [9] = 5×10^{-2} M). Whereas electron transfer to excited ketone is now much less favorable ($\Delta G > 0$), a highly negative ΔG value indicating a very fast electron transfer is obtained if we consider donor (HMPA) excitation (~110 kcal/

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mol[11]). The nature of the excited redox compound (oxidant in CH_3CN/Et_3N, reductant in HMPA) is confirmed by the following experimental observations: compound **9** did not react when irradiated in neat Et_3N ($A_{Et_3N} > A_9$) or with dilute HMPA (5 equiv) in CH_3CN ($A_9 \gg A_{HMPA}$).

A better chemioselectivity could be expected, in reduction of keto ester derivatives, using Et_3N as donor, which is able to reduce a carbonyl group but not a carboxyl one. Except for 5-digonal cases (cyclization of **13** and **15**), where good yields were obtained in each medium, HMPA gave better results than CH_3CN/Et_3N. Probably in the latter case, side reactions between intermediates, products, and/or the medium can occur.

In summary, the photoreductive cyclization of δ,ϵ-unsaturated ketones is a very efficient and general reaction when the unsaturation is a carbon–carbon multiple bond. The behavior of compounds can be considered to be similar, whatever the way used to produce the intermediate radical anion: chemical reduction, electroreduction, photoreduction. The latter has the advantage of being carried out in very mild and homogeneous conditions, without reproducibility problem, and constitutes an advantageous complementary methodology to reach cyclic compounds.

Experimental Section

All experiments were run under an argon atmosphere. ^1H NMR spectra were obtained on a Bruker CW 80 (80 MHz) instrument, in $CDCl_3$, employing Me_4Si as an internal standard. ^{13}C NMR spectra were taken in $CDCl_3$ on a Bruker WP 60 spectrometer at 15.08 MHz. IR spectra were obtained as solutions in $CHCl_3$ on a SP 2000 Philips spectrophotometer. UV spectra were taken on a Beckman spectrophotometer. Mass spectra were run on a JEOL spectrometer at 70 eV and microanalysis by the service de microanalyses, Université de Reims. Uncorrected melting points were taken on a Kofler bank. TLC and flash chromatography were accomplished with Merk silica gel 60. Preparative HPLC was performed on a Jobin-Yvon modulprep chromatograph with Merck silica 60 H. Gas chromatograms were obtained on a Girdel instrument (SE 30 6%/Chromosorb WAW HMDS, 160–190 °C). Preparative irradiations were conducted in a merry-go-round type system equipped with 12 low-pressure mercury Philips TUV 15 lamps (254 nm); 10-mm o.d. quartz tubes were used. The solution were degased by bubbling in argon for 15 min. Solvents such as ether and THF were distilled from sodium benzophenone. Benzene, DMF, Me_2SO, HMPA, CH_3CN, and triethylamine were distilled from CaH_2.

Synthesis of Starting Materials. A. Preparation of Compounds 9 and 11.[21] The alkyl 2-oxocycloalkanecarboxylate (7.03 mmol, 1 equiv) was added dropwise to a stirred solution of *t*-BuOK (0.82 g, 7.31 mmol, 1.04 equiv) in dry Me_2SO (30 mL). After 1 h, 4-bromo-1-butene (1.04 g, 7.73 mmol, 1.1 equiv) was added dropwise. After 20 h at room temperature the solution was diluted with water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with water (30 mL), dried over magnesium sulfate, and evaporated, and the crude product was purified by flash chromatography.

Methyl 1-(3-buten-1-yl)-2-oxocyclopentanecarboxylate (9):[6e] purification by flash chromatography (90/10 hexane/ethyl acetate); oil, yield 86%; IR 1750, 1725, 1640, 995, 910 cm^{-1}; ^1H NMR δ 1.60–2.90 (m, 10 H), 3.75 (s, 3 H), 4.90–5.20 (m, 2 H), 5.55–6.10 (m, 1 H); ^{13}C NMR 19.61, 29.20, 32.90, 33.15, 37.94, 52.45, 60.28, 115.17, 137.69, 171.00, 214.49; MS $C_{11}H_{16}O_3$, *m/e* (relative intensity) 197 ($M^+ + 1$, 1), 196 (M^+, 0.2), 142 (100), 123 (24), 110 (78), 95 (36), 81 (22), 67 (48), 55 (28); UV (CH_3CN) 215 (ϵ_{max} 234), 280 (ϵ_{max} 114) and ϵ_{254} 68.

Ethyl 1-(3-buten-1-yl)-2-oxocyclohexanecarboxylate (11): purification by flash chromatography (96/4 hexane/ethyl acetate); oil, yield 81%; IR 1730, 1710, 1645, 995, 915 cm^{-1}; ^1H NMR δ 1.30 (t, 3 H, J = 7 Hz), 1.40–2.80 (m, 12 H), 4.25 (q, 2 H, J = 7 Hz), 4.85–5.20 (m, 2 H), 5.55–6.10 (m, 1 H); ^{13}C NMR 14.14, 22.64, 27.62, 28.65, 33.99, 36.18, 41.10, 60.65, 61.20, 114.74, 138.18, 172.00, 207.68; MS $C_{13}H_{20}O_3$, calcd 224.1411, found 224.1386; *m/e* (relative intensity) 225 ($M^+ + 1$, 2), 224 (M^+, 0.8), 170 (88), 141 (27), 124 (100), 109 (21), 81 (42), 68 (24), 67 (25).

B. Preparation of 13 and 15. To a solution of *t*-BuOK (0.820 mg, 7.3 mmol, 1.05 equiv) in Me_2SO (50 mL) was added the methyl 2-oxocyclopentane carboxylate (0.998 g, 7 mmol, 1 equiv). The solution was stirred at room temperature for 1 h, and 4-bromo-1-butyne was added (0.982 mg, 7.7 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 14 h. The solution was diluted with water (30 mL). A mixture of **13** and **15** was obtained and separated by HPLC (85/15 hexane/ethyl acetate).

Methyl 1-(3-butyn-1-yl)-2-oxocyclopentanecarboxylate (13): oil, yield 10%; IR 3320, 2120, 1750, 1730, 1150, 650 cm^{-1}; ^1H NMR δ 1.5–3 (m, 11 H), 3.7 (s, 3 H); ^{13}C NMR 14.51, 19.60, 32.60, 33.02, 37.76, 52.51, 69.09, 84.35, 171.20, 213.94; MS $C_{11}H_{14}O_3$, calcd 194.0979, found 194.0961; *m/e* (relative intensity) 194 (M^+, 1), 142 (95), 110 (80), 79 (75), 67 (95), 55 (100).

Methyl 1-(2,3-butadien-1-yl)-2-oxocyclopentanecarboxylate (15): oil, yield 5%; IR 1960, 1750, 1730, 1150, 850 cm^{-1}; ^1H NMR δ 1.5–3 (m, 8 H), 3.7 (s, 3 H), 4.5–5.1 (m, 3 H); ^{13}C NMR 19.68, 31.59, 32.04, 36.26, 51.35, 65.27, 73.54, 84.01, 160.40, 208.16, 213.71; MS $C_{11}H_{14}O_3$, calcd 194.0889, found 194.0915; *m/e* (relative intensity) 194 (M^+, 5), 166 (35), 151 (23), 135 (100), 110 (85), 78 (4), 67 (30).

C. Preparation of Methyl 1-(2-Cyanoethyl)-2-oxocyclopentanecarboxylate (17).[6e] To a solution of *t*-BuOK (0.112 g, 1 mmol, 0.1 equiv) in DME (5 mL) was added the methyl-2-oxocyclopentanecarboxylate (1.42 g, 10 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 1 h. Acrylonitrile (0.657 mL, 10 mmol, 1 equiv) in DME (1.5 mL) was added to the preceeding solution. The mixture was stirred at room temperature and extracted with water (10 mL) and ether (3 × 20 mL). The product was purified by flash chromatography (70/30 hexane/ethyl acetate): yield 55%; IR 2400, 1750, 1730, 1230, 1190, 800 cm^{-1}; ^1H NMR δ 1.5–3 (m, 10 H), 3.7 (s, 3 H); ^{13}C NMR 13.11, 19.60, 29.50, 33.87, 37.82, 52.84, 58.81, 119.29, 160.46, 213.58; MS $C_{10}H_{13}NO_3$, *m/e* (relative intensity) 195 (M^+, 3), 167 (35), 164 (20), 152 (10), 127 (100), 108 (95), 97 (50), 67 (65).

D. Preparation of 1 and 3.[22] These two compounds were prepared by dealkoxycarbonylation of **9** and **11**, respectively.

Dry sodium cyanide (0.5 g, 10.19 mmol, 1 equiv) was added to a stirred solution of **10a** or **10b** (10.19 mmol, 1 equiv) in dry Me_2SO (5 mL). After warming (**10a** at 150 °C for 1.5 h, and **10b** at 160 °C for 8.5 h), the cooled solution was diluted with water (30 mL) and extracted with ether (3 × 20 mL). The organic layer was washed with water (20 mL) and dried (magnesium sulfate). Ether was distilled off at 760 mmHg, and the crude product was purified by flash chromatography.

2-(3-Buten-1-yl)cyclopentanone (1):[6f] purification by flash chromatography (90/10 pentane/ether); oil, yield 74%; IR 1735, 1640, 995, 915 cm^{-1}; ^1H NMR δ 1.00–2.50 (m, 11 H), 4.85–5.25 (m, 2 H), 5.50–6.10 (m, 1 H); ^{13}C NMR 20.76, 28.96, 29.63, 31.63, 38.12, 48.45, 115.11, 138.18, 221.05; MS $C_9H_{14}O$, *m/e* (relative intensity) 138 (M^+, 13), 84 (100), 83 (43).

2-(3-Buten-1-yl)cyclohexanone (3):[6f] purification by flash chromatography (95/5 pentane/ether); oil, yield 70%; IR 1710, 1645, 1000, 920 cm^{-1}; ^1H NMR δ 1.00–2.60 (m, 13 H), 4.80–5.20 (m, 2 H), 5.50–6.10 (m, 1 H); ^{13}C NMR 25.01, 28.11, 28.65, 31.33, 33.99, 42.13, 49.96, 114.80, 138.66, 212.97; MS $C_{10}H_{16}O$, *m/e* (relative intensity) 152 (M^+, 9), 98 (100), 97 (20), 83 (24), 70 (32), 55 (23).

E. Preparation of 3-Allylcyclohexanone (5) and Cyclooct-4-en-1-one (7). These compounds were prepared according to described procedure.[23,24]

Photoreductive Cyclization. A. General Procedure. 1. Irradiations in HMPA. A solution of ketone (5 mmol) in dry HMPA (100 mL) was degased by argon bubbling and irradiated (five 1-cm o.d. quartz tubes) at 254 nm until complete disappearance of the starting material (checked by TLC) (1.5–2.5 h). An ice-cold solution of 3 M HCl (200 mL) was added slowly to the irradiated solution, previously cooled. The mixture was ex-

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tracted several times with ether. The organic layer was washed with diluted HCl and water and dried over magnesium sulfate. Ether was distilled off. The crude product was purified by flash chromatography or preparative TLC.

2. Irradiation in CH_3CN–Et_3N. A solution of ketone in dry acetonitrile (3.5×10^{-2} M) was degassed by argon bubbling. Triethylamine (5 equiv) was added, and the solution was irradiated at 254 nm, until complete disappearance of the starting material (2–3.5 h). Acetonitrile and triethylamine were distilled off, and the crude product was purified by preparative TLC.

B. Products. 2-Methylbicyclo[3.3.0]octan-1-ol (2):[6f] purification by flash chromatography (65/35 pentane/ether); mp 57–59 °C; IR 3610, 3460, 915, 905 cm^{-1}; ^1H NMR δ 0.95 (d, 3 H, J = 6 Hz), 0.90–2.30 (m, 12 H), 1.60 (br s, 1 H); ^{13}C NMR 13.42, 25.92, 30.05, 32.60, 35.09, 36.18, 45.59, 51.72, 92.95; MS $C_9H_{16}O$, m/e (relative intensity) 140 (M^+, 13), 111 (34), 98 (37), 97 (100), 84 (82), 83 (31), 55 (28).

9-Methylbicyclo[4.3.0]nonan-1-ol (4):[6f] purification by flash chromatography (70/30 pentane/ether); oil; IR 3610, 3460, 965, 915, 885 cm^{-1}; ^1H NMR δ 0.85 (d, 3 H, J = 6 Hz), 0.90–2.20 (m, 14 H), 1.20 (br s, 1 H); ^{13}C NMR 12.69, 20.46, 21.25, 23.61, 24.28, 27.74, 28.35, 44.86, 45.53, 78.32; MS $C_{10}H_{18}O$, m/e (relative intensity) 154 (M^+, 15), 111 (100), 98 (71), 97 (32), 83 (23), 55 (28).

7-Methylbicyclo[3.2.1]octan-1-ol (6a and 6b). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.92; H, 11.39. Separation was by preparative TLC (80/20 pentane/ether; three migrations). The structure of the two isomers **6a** and **6b** was determined according to ref 25.

Major isomer 6a: mp 120–124 °C; IR 3600, 3430, 940, 900, 865 cm^{-1}; ^1H NMR δ 0.98 (d, 3 H, J = 6.5 Hz), 0.90–2.60 (m, 12 H), 1.25 (br s, 1 H); ^{13}C NMR 11.88, 19.40, 31.43, 33.33, 34.84 (2 C), 41.56, 47.46, 78.99; MS $C_9H_{16}O$, m/e (relative intensity) 140 (M^+, 13), 110 (28), 98 (90), 97 (99), 84 (22), 83 (43), 82 (30), 79 (58), 71 (23), 70 (100), 69 (38), 67 (62), 55 (73), 53 (28).

Minor isomer 6b: mp 61–63 °C; IR 3610, 3440, 940, 900, 865 cm^{-1}; ^{1}NMR δ 0.92 (d, 3 H, J = 6 Hz), 0.80–2.30 (m, 12 H), 1.30 (br s, 1 H); ^{13}C NMR 18.54, 19.84, 30.89, 33.11, 37.77, 38.31, 40.91, 42.92, 78.99; MS $C_9H_{16}O$, m/e (relative intensity) 140 (M^+, 12), 98 (60), 97 (99), 96 (24), 95 (26), 84 (20), 83 (55), 82 (44), 81 (37), 79 (39), 71 (34), 70 (69), 69 (67), 68 (27), 67 (60), 57 (54), 56 (28), 55 (100), 53 (24).

Bicyclo[3.3.0]octan-1-ol (8):[6f] purification by flash chromatography (80/20 pentane/ether); Oil; IR 3610, 3440, 975, 925, 910 cm^{-1}; ^1H NMR δ 1.00–2.10 (m, 13 H), 1.65 (s, 1 H); ^{13}C NMR 25.92, 33.39, 41.95, 52.33, 91.55; MS $C_8H_{14}O$, m/e (relative intensity) 126 (M^+, 4), 97 (100), 84 (91), 83 (31), 55 (21).

Methyl 4-Methyl-5-hydroxybicyclo[3.3.0]octane-1-carboxylate (10a and 10b).[6e] Purification was by preparative TLC (85/15/hexane/ethyl acetate, double migration). The structure of the two isomers was determined according to ref 25.

Major isomer 10a: oil; IR 3580, 3490, 1705 cm^{-1}; ^1H NMR (400 MHz) δ 1.00 (d, 3 H, J = 6.5 Hz), 1.15–2.55 (m, 10 H), 2.00 (m, 1 H), 2.58 (br s, 1 H), 3.72 (s, 3 H); ^{13}C NMR 13.24, 24.89, 30.66, 35.33, 35.64, 38.07, 45.11, 51.91, 62.11, 94.16, 177.33; MS $C_{11}H_{18}O_3$, m/e (relative intensity) 198 (M^+, 15), 166 (68), 142 (83), 139 (26), 138 (50), 121 (41), 111 (48), 110 (100), 109 (22), 97 (51), 96 (23), 71 (26), 70 (29), 69 (23), 67 (23), 55 (28).

Minor isomer 10b: oil; IR 3580, 3500, 1710 cm^{-1}; ^1H NMR (400 MHz) δ 1.00 (d, 3 H, J = 6 Hz), 1.25–2.40 (m, 10 H), 1.76 (m, 1 H), 2.60 (br s, 1 H), 3.72 (s, 3 H); ^{13}C NMR 13.05, 23.31, 33.09, 36.06, 37.58, 39.89, 44.08, 51.97, 62.78, 93.01, 177.32; MS $C_{11}H_{18}O_3$, m/e (relative intensity) 198 (M^+, 8), 166 (47), 142 (60), 139 (23), 138 (48), 121 (35), 111 (42), 110 (100), 109 (21), 97 (47), 96 (25), 95 (20), 79 (25), 69 (20), 67 (30), 58 (23), 55 (35).

Ethyl 7-Methyl-6-hydroxybicyclo[4.3.0]nonane-1-carboxylate (12a and 12b). Purification was by preparative TLC (90/10 hexane/ethyl acetate).

Major isomer 12a; oil; IR 3460, 1690 cm^{-1}; ^1H NMR δ 0.90 (d, 3 H, J = 6 Hz), 1.25 (t, 3 H, J = 7 Hz), 0.80–2.30 (m, 13 H), 3.80 (br s, 1 H), 4.15 (q, 2 H, J = 7 Hz); ^{13}C NMR 13.05, 14.14, 20.58, 21.00, 26.59, 26.83, 28.35, 29.02, 42.49, 54.57, 60.89, 78.98, 179.69; MS $C_{13}H_{22}O_3$, m/e (relative intensity) 226 (M^+, 3), 170 (100), 136 (22), 135 (62), 124 (44), 123 (22), 121 (21), 111 (29), 110 (31), 81 (21), 67 (31), 55 (40). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.86; H, 9.71.

Minor isomer 12b: oil; IR 3500, 1700 cm^{-1}; ^1H NMR δ 0.90 (d, 3 H, J = 6 Hz), 1.25 (t, 3 H, J = 7 Hz), 0.80–2.50 (m, 13 H), 3.40 (br s, 1 H), 4.15 (q, 2 H, J = 7 Hz); ^{13}C NMR 12.51, 14.15, 23.13, 23.50, 28.60, 32.06, 33.63, 34.67, 36.43, 56.70, 60.41, 80.87, 177.89; MS $C_{13}H_{22}O_3$, m/e (relative intensity) 226 (M^+, 2), 170 (100), 136 (21), 135 (43), 124 (41), 123 (21), 121 (25), 111 (27), 110 (30), 81 (22), 67 (31), 55 (41). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.02; H, 9.60.

Methyl 4-methylene-5-hydroxybicyclo[3.3.0]octane-1-carboxylate (14): oil; IR 3600, 1730, 800 cm^{-1}; ^1H NMR δ 1.5–2.6 (m, 10 H), 2.8 (br s, 1 H), 3.7 (s, 3 H), 5.1 (m, 2 H); ^{13}C NMR 23.46, 29.64, 30.29, 33.32, 35.76, 41.12, 51.74, 62.31, 90.86, 156.84, 176.40; MS $C_{11}H_{16}O_3$, calcd 196.1100, found 196.1101; m/e (relative intensity) 196 (M^+, 2), 178 (100), 136 (40), 120 (95), 109 (85), 91 (35), 79 (45).

Methyl 4-methyl-5-hydroxybicyclo[3.3.0]oct-3-ene-1-carboxylate (16): oil; IR 3640, 1730, 800 cm^{-1}; ^1H NMR δ 1.2–2.5 (m, 12 H), 3.7 (s, 3 H), 5.5 (m, 1 H); MS $C_{11}H_{16}O_3$, calcd 196.1100, found 196.1100; m/e (relative intensity) 196 (M^+, 2), 178 (85), 136 (40), 129 (100), 109 (98), 79 (50).

Methyl 1-(2-cyanoethyl)-2-hydroxycyclopentane-1-carboxylate (18): mixture of isomers, identical with an authentic sample obtained by $NaBH_4$ reduction of compound **17**; oil; IR 3640, 2260, 1730, 1060 cm^{-1}; ^1H NMR δ 1.5–2.5 (m, 11 H), 3.7 (s, 3 H), 4.5 (m, 1 H); ^{13}C NMR 13.66, 20.45, 32.29, 32.54, 32.90, 52.27, 57.10, 80.01, 119.47, 162.88, 175.27; MS $C_{10}H_{15}NO_3$, m/e (relative intensity) 197 (M^+, 2), 140 (27), 121 (30), 108 (100), 97 (30), 84 (40), 67 (15).

Registry No. **1**, 22627-57-2; **2**, 101327-91-7; **3**, 16178-83-9; **4**, 101327-92-8; **5**, 20498-05-9; **6a**, 101327-93-9; **6b**, 101327-94-0; **7**, 6925-14-0; **8**, 52318-93-1; **9**, 82343-68-8; **10a**, 87635-98-1; **10b**, 84109-86-4; **11**, 61771-76-4; **12a**, 104323-49-1; **12b**, 104323-50-4; **13**, 87635-96-9; **14**, 87635-97-0; **15**, 104323-51-5; **16**, 104323-52-6; **17**, 87636-00-8; **18**, 104323-53-7; HMPA, 680-31-9; 4-bromo-1-butene, 5162-44-7; methyl 2-oxocyclopentanecarboxylate, 10472-24-9; ethyl 2-oxocyclohexanecarboxylate, 1655-07-8; 4-bromo-1-butyne, 38771-21-0; acrylonitrile, 107-13-1; triethylamine, 121-44-8.

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