Acknowledgment. We thank the Science Research Council for financial support and I.C.I. Plant Protection Division for their cooperation in a CASE studentship (to A.B.).

References and Notes

(1) A. Bury, M. R. Ashcroft, and M. D. Johnson, *J. Am. Chem. Soc.*, **100**, 3217 (1978).
(2) M. P. Atkins, B. T. Golding, and P. J. Sellars, *J. Chem. Soc., Chem. Commun.*, 954 (1978).
(3) Prepared essentially by literature procedures. Cf. M. Castaing, M. Pereyre, M. Ratier, P. M. Blum, and A. G. Davies, *J. Chem. Soc., Perkin Trans. 2*, 287 (1979); R. G. Bergman, *J. Am. Chem. Soc.*, **91**, 7405 (1969).
(4) **3**: ^{13}C NMR (^{1}H decoupled, in $CDCl_3$) δ 10.7, 13.5, 14.6 (cyclopropyl ring C's), 12.1 (4 dmg Me's), 18.6 (methyl), 33.2 (br, Co–CH_2), 125.4, 137.7, 149.4, and 149.7 ppm (pyr C's and 4 dmg C=N's). **4**: ^{13}C NMR (^{1}H decoupled, in $CDCl_3$) δ 12.1 (4 Me's) 14.4, 15.1, 18.9 (cyclopropyl ring C's), 22.8 (methyl), 38.0 (br, Co–CH_2), 125.3, 137.6, 149.3, and 149.6 ppm (pyr C's and 4 dmg C=N's).
(5) (a) In $CDCl_3$ with [cobaloxime] = 0.38 mol dm^3 at 298 K: for **3** → **1** + **2**, $10^4k_1 = 3.3 \pm 0.4$ s^{-1}; for **4** → **1** + **2**, $10^5k_1 = 9.0 \pm 0.4$ s^{-1}. (b) In $CDCl_3$ with [cobaloxime] = 0.39 mol dm^{-3} at 310 K: for **1** ⇌ **1** + **2**, $10^4k_1 = 4.6 \pm 0.2$ s^{-1}, [TFA] = 0.78 M; $10^4k_1 = 2.1 \pm 0.1$ s^{-1}, [TFA] = 0.52 M. (c) In $CDCl_3$ with [cobaloxime] = 0.52 mol dm^{-3} at 295 K: for **4** → **1** + **2**, $10^3k_1 = 9 \pm 1$ s^{-1}; [TFA] = 0.21.
(6) It is not expected that the exact equilibrium mixture of **1** and **2** would be formed initially from **3** or **4** under kinetically controlled conditions. However, there is no detectable deviation from the equilibrium ratio of **1** and **2** at any stage of reactions starting from **3** or **4**.
(7) For (*R*)-**1**, $[\alpha]_D$ +60° (0.13 M, $CHCl_3$); for (*S*)-**1**, $[\alpha]_D$ −58° (0.13 M, $CHCl_3$).
(8) B. T. Golding, D. R. Hall, and S. Sakrikar, *J. Chem. Soc., Perkin Trans. 1*, 1214 (1973); B. T. Golding, P. J. Sellars, and A. K. Wong, *J. Chem. Soc., Chem. Commun.*, 570 (1977).
(9) Inversion of configuration occurs in the reactions of *p*-toluenesulfonates with (pyridine)cobaloxime(I): F. R. Jensen, V. Madan, and D. H. Buchanan, *J. Amer. Chem. Soc.*, **92**, 1414 (1970); H. L. Fritz, J. H. Espenson, D. A. Williams, and G. A. Molander, *ibid.*, **96**, 2378 (1974).
(10) Equilibrations were carried out for 5–15 half-lives with 0.13 M solutions of (*R*)- and (*S*)-**1** and (*S*)-**2** (63% enantiomeric excess) in $CHCl_3$ containing 0.1 M TFA. After equilibrations, the mixture of **1** and **2** was purified, prior to measurement of circular dichroism, from ~5% unknown product(s) of decomposition by column chromatography on silica gel.
(11) Resolved by the method of R. Rossi, P. Diversi, and G. Ingrosso, *Gazz. Chim. Ital.*, **98**, 1391 (1968); see also G. T. Pearce, W. E. Gore, and R. M. Silverstein, *J. Org. Chem.*, 41, 2797 (1976).
(12) We thank Dr. P. M. Scopes, Westfield College, for these spectra.
(13) The position of the label was confirmed by NMR spectroscopy.
(14) Unpublished results of the authors; see also M. P. Atkins, B. T. Golding, and P. J. Sellars, *Proc. Eur. Symp. Vitamin B_{12} Intrinsic Factors, 3rd, 1979*, 587 (1979).

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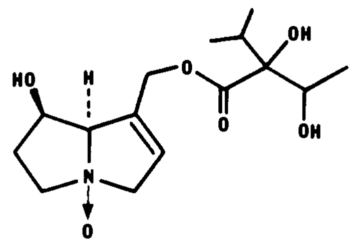
Synthetic Studies on Pyrrolizidine Alkaloids. 1. (±)-Heliotridine and (±)-Retronecine via Intramolecular Dienophile Transfer

Sir:

The pyrrolizidine alkaloids constitute an exceptionally large class of naturally occurring materials which have attracted the attention of synthetic organic chemists with increasing frequency in recent years.[1] The large number of such naturally occurring alkaloids, their deceptively simple structural features, and a remarkable range and potency of biological effects have all served to make these materials unusually attractive synthetic targets. Particularly intriguing are the changes in biological activity which accompany relatively minor modifications in structure. Thus, indicine *N*-oxide[2] [**1**, an oxidized trachelanthic acid ester of retronecine (**2**)] shows extremely promising antitumor activity, while the very similar heliotrine



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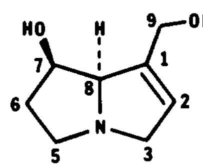

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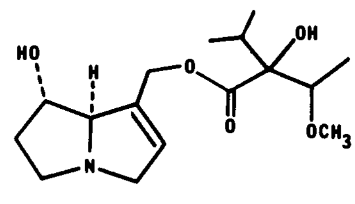
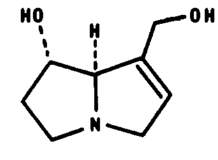


3



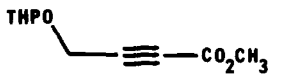
4

[**3**, an ester of heliotridine (**4**)] is an established carcinogen.

Although considerable progress has been made recently, by a number of groups,[3] in developing synthetic approaches to somewhat simpler, less oxidized pyrrolizidines, little progress has been described toward more complex examples such as heliotridine and retronecine. Presently we report the synthesis of retronecine and heliotridine by a route which relies heavily on the previously described intramolecular dienophile transfer technique[4] to simultaneously form one key carbon nitrogen bond (N–C_8, pyrrolizidine numbering), establish the $\Delta_{1,2}$ double bond, and functionalize C_3 appropriately for eventual formation of the N–C_3 bond.

The known,[5] readily available acetylenic ester **5**, upon addition to 1.2 equiv of lithium divinylcuprate at −78 °C in tetrahydrofuran, reaction at −78 °C for 4.25 h, and quenching with methanol (−78 °C), affords, after dilution with ether, filtration through Florisil, and normal extractive workup, diene ester **6** as a single isomer in quantitative yield: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.42 (dd, J = 18, 10 Hz, 1 H, C_4 vinyl), 5.93 (s, 1 H, C_2 vinyl), 5.80 (d, 1 H, J = 18 Hz, C_5 vinyl), 5.40 (d, 1 H, J = 10 Hz, C_5 vinyl), 4.83 (s, 2 H, CH_2), 4.69 (br s, 1 H, OCHO), 3.72 (s, 3 H, OCH_3), 4.00–3.33 (m, 4 H, CH_2O), 1.59 (m, 4 H, CH_2CH_2); mass spectrum (CI, methane) *m/e* 227. Ester **6** was reduced (2.0 equiv of *i*Bu_2AlH in ether, 0 °C, 0.25 h) to dienol **7**, which was oxidized with excess active manganese dioxide[8] in benzene containing anhydrous Celite (23 °C, 48 h) to afford the labile dienal **8**, used immediately in the subsequent step after filtration and concentration under reduced pressure.

Addition of aldehyde **8** to a cold (−78 °C) solution of the lithium enolate[4] of **9** (prepared by addition of **9** to 1.1 equiv of lithium diisopropylamide in 4:1 THF-hexamethylphosphoramide at −78 °C), followed by warming to −25 °C over 45 min, quenching (−25 °C) with methanol, and normal extractive workup, cleanly afforded alcohol **10** [IR (film, partial) 3400 (br), 1650 (br); NMR (90 MHz, $CDCl_3$, partial) δ 7.87–7.18 (m, 8 H, aromatic), 6.20 (dd, J = 18, 11 Hz, 1 H, $CH{=}CH_2$), 5.54 (d, J = 9 Hz, 1 H, vinyl), 5.33 (d, J = 18 Hz, 1 H, $CH{=}CH_2$), 5.03 (d, 1 H, J = 11 Hz, $CH{=}CH_2$), 4.79 (br q, J = 6 Hz, 1 H, methine), 2.69 (s, 3 H, CH_3), 2.44 (d, J = 6 Hz, 2 H, $CH_2C{=}O$), 2.15 (s, 3 H, CH_3)] which was readily converted[10] (*tert*-butyldimethylchlorosilane, imidazole, dimethylformamide, 23 °C, 12 h) into its *tert*-butyldimethylsilyl ether derivative **11**. This key intermediate, formed in 64% overall yield from **7** after purification by column (MPLC) chromatography,[9] now contains all carbons and the nitrogen destined to appear in the final alkaloid products, as well as differentially protected hydroxyl moieties destined to appear at C_7 and C_9.



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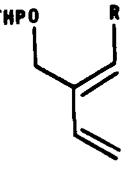
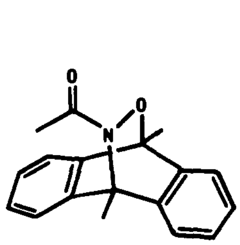


6 R = CO_2CH_3
7 R = CH_2OH
8 R = CHO



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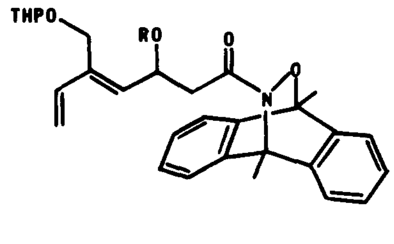
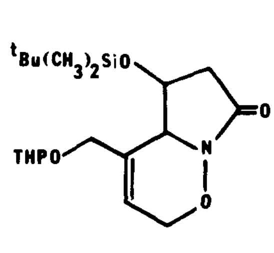


10 R = H
11 R = $Si(CH_3)_2{}^tBu$



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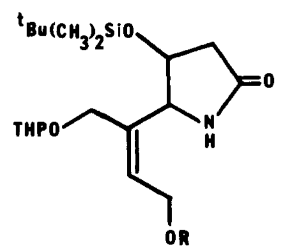
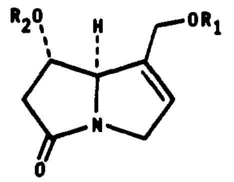
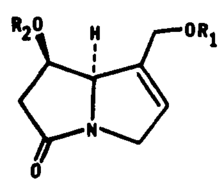


13 R = H
14 R = SO_2CH_3



15 R_1 = THP, R_2 = $Si(CH_3)_2{}^tBu$
17 R_1, R_2 = H



16 R_1 = THP, R_2 = $Si(CH_3)_2{}^tBu$
18 R_1, R_2 = H

Intramolecular transfer of the acylnitroso dienophile was cleanly effected essentially as previously described[4] by thermolysis (benzene, 80 °C, 4.5 h) of **11** to afford (86% after purification by MPLC[9]) the 1,2-oxazine derivative **12**.[11,12] Reductive cleavage of the nitrogen-oxygen bond in **12** was very cleanly effected without interference from other potentially sensitive functionality by reaction[13] with excess 6% sodium amalgam (dry ethanol, 4 equiv of Na_2HPO_4, 0 °C, 5 h) to afford hydroxylactam **13** (R_f[9] 0.125 vs. 0.58 for **12**, 8% methanol–chloroform) in 90% isolated yield after purification by filtration through a short silica gel column. Conversion of this material into **2** and **4** clearly requires two operations which are interrelated: reductive removal of the lactam carbonyl and ring closure to form the N–C_3 bond (pyrrolizidine numbering). These seemingly routine operations are in fact considerably more difficult than a cursory examination might suggest. Reduction of the amide function in **13** is not easily accomplished directly owing to the lability of other functionality in **13** under vigorous reduction conditions. Activation of the allylic alcohol in **13** followed by base-induced intramolecular alkylation is frustrated by several significant problems, including a geometry for S_N2 attack which precludes normal allylic activation, the lability of the β-silyloxyamide under conditions which allow for deprotonation at carbon, and a significant amount of strain in the resulting ring-closed product. Although some progress has been made in our laboratories toward a solution involving initial reduction of **13**, the synthesis was completed most expeditiously as follows. Hydroxylactam **13** was converted (2 equiv each of methanesulfonyl chloride and triethylamine, CH_2Cl_2, 0 °C, 5 min) into the corresponding mesylate **14**, which, after extractive workup and drying but without purification, was added (as a tetrahydrofuran solution, ~0.2 M) to 1.0 equiv of lithium diisopropylamide in tetrahydrofuran (0.065 M) at −78 °C. Warming to 23 °C over 1.5 h and reaction at 23 °C for a further 2.5 h afforded, after purification by MPLC,[9] the easily separable bicyclic lactams **15** and **16** (R_f[9] 0.27 and 0.15, respectively, in 35% THF–hexanes) in 50% overall yield from **12**.[14] A tentative assignment of stereochemistry proved possible from the 100-MHz ^1H NMR spectra[16] of **15** and **16**, which was confirmed by conversion into (±)-heliotridine and (±)-retronecine, respectively. Further reactions were conducted using each isomer separately.

Removal of the protecting groups in **15** was accomplished by methanolysis of the tetrahydropyranyl ether (reflux, 3 h) catalyzed by pyridinium *p*-toluenesulfonate,[17] followed by reaction with 2.0 equiv of tetra-*N*-butylammonium fluoride[10] (THF, 23 °C, 5 min) to afford dihydroxylactam **17** (R_f[9] 0.14 vs. 0.69 for **15**, 8% methanol–chloroform) in essentially quantitative yield. Reduction with lithium aluminum hydride (5.0 molar equiv) in refluxing tetrahydrofuran for 4 h then gave, after quenching with sodium sulfate decahydrate–Celite, filtration (washing with tetrahydrofuran containing ~10% triethylamine), and evaporation, (±)-heliotridine, whose identity and purity were firmly established by direct spectroscopic (^1H NMR, ^{13}C NMR) comparisons with natural material. Acetylation (excess acetic anhydride in pyridine) furnished the corresponding diacetate, which was likewise spectroscopically and chromatographically[18] (TLC, VPC) identical with the diacetate prepared from natural material.

A parallel sequence with bicyclic lactam **16** furnished, via the intermediacy of dihydroxylactam **18**, (±)-retronecine, whose identity was confirmed by direct spectral and chromatographic comparisons with natural material as outlined above.

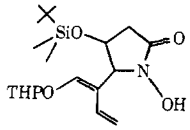
The differentially protected diol intermediates in the synthetic approach outlined herein would appear to be ideally suited for eventual conversion into various ester derivatives of **2** and **4** with high biological activity, such as indicine *N*-oxide (**1**). Efforts in this regard are in progress in our laboratories and will be reported in due course.

Acknowledgment. We are indebted to Professor C. C. J. Culvenor for generous authentic samples of heliotridine and retronecine which were invaluable in verifying our synthetics. Financial support of this research by the National Institutes of Health (through NCI Grant 1 R01 CA24166) is gratefully acknowledged.

References and Notes

(1) For an excellent account of the chemistry and pharmacology of this class of compounds, note Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North-Holland Publishing Co.: Amsterdam, 1968.
(2) Kugelman, M.; Liu, W. C.; Axelrod, M.; McBride, T. J.; Rao, K. V. *Lloydia* **1976**, *39*, 125.
(3) For recent synthetic approaches to this class of alkaloids note: (a) Stevens, R. V.; Luh, Y.; Shev, J. T. *Tetrahedron Lett.* **1976**, 3799. (b) Danishevsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 7712, 4783. (c) Borch, R. F.; Ho, B. C. *J. Org. Chem.* **1977**, *42*, 1225. (d) Mariano, P. S.; Osborn, M. E.; Mariano, D. D.; Gunn, B. C.; Pettersen, R. C. *Ibid.* **1977**, *42*, 2903; (e) Glass, R. S.; Deardorff, D. R.; Gains, L. H. *Tetrahedron Lett.* **1978**, 2965. (f) Wilson, S. R.; Sawicki, R. A. *Ibid.* **1978**, 2969. (g) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330.
(4) Keck, G. E. *Tetrahedron Lett.* **1978**, 4767.
(5) Warrener, R. N.; Cain, E. N. *Aust. J. Chem.* **1971**, *24*, 785.
(6) This material is prone to Diels–Alder dimerization on heating or prolonged storage. Hence solutions of **8** were concentrated under reduced pressure with minimal heating, and the ester was reduced promptly to dienol **7**, which could be stored indefinitely at −20 °C.

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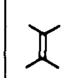
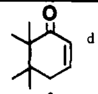
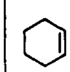
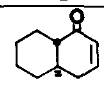
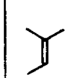
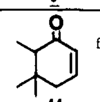
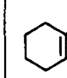
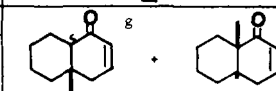
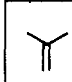
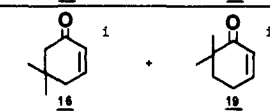
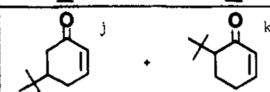
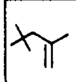
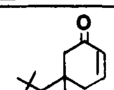
Four-Carbon Photochemical Annelation of Alkenes with 2,2,6-Trimethyl-1,3-dioxolenone

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**	 **6** [d]	90	76	....
 **7**	 **8** [e]	98	64	....
 **9**	 **11** [f]	100	63	19:1
 **12**	 **14** [g] + **15** [h]	86	80	8:1
 **16**	 **18** [i] + **19** [i]	93	83	1:1.6
 **20**	 **22** [j] + **23** [k]	82	85	1:5
 **24**	 **26** [l]	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.