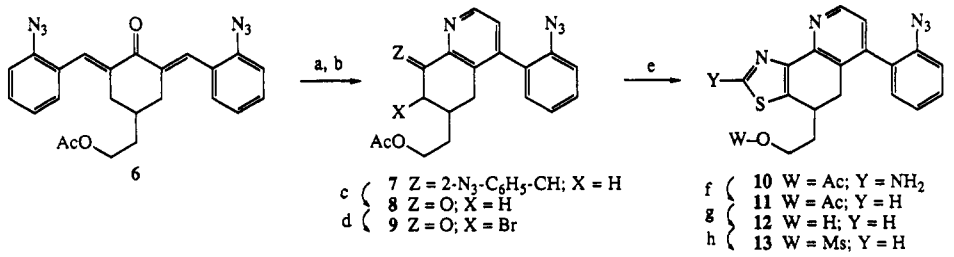
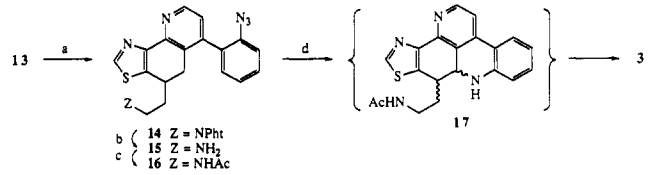
**Scheme II**[a]



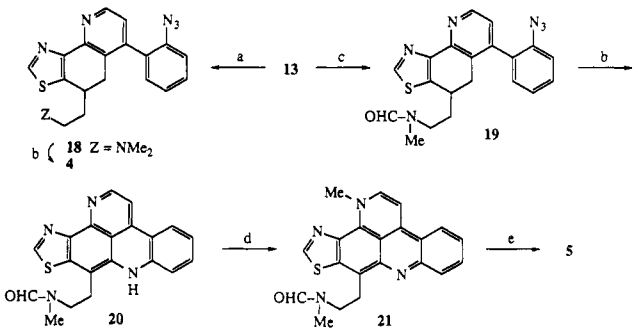

[a] (a) Ethyl vinyl ether, $Yb(fod)_3$, $(CH_2Cl)_2$, reflux, 99%; (b) $HONH_3^+Cl^-$, MeCN, reflux, 61%; (c) $O_3$, $CH_2Cl_2$/MeOH, -78 °C, then $Me_2S$, -78 °C to room temperature, 78%; (d) pyridinium tribromide, AcOH, 50 °C, 70%; (e) thiourea, EtOH, 35 °C, 15 min, 95%; (f) *i*-AmONO, DMF, 80 °C, 82%; (g) $K_2CO_3$, MeOH, 94%; (h) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 99%.

**Scheme III**[a]




[a] (a) K-phthalimide, DMF, 50 °C, 84%; (b) $N_2H_4 \cdot H_2O$, MeOH, room temperature, 30 min, 94%; (c) $Ac_2O$, pyridine, room temperature, 86%; (d) *hν*, 9:1 chlorobenzene/acetophenone, 110 °C, 62% chromatographed.

**Scheme IV**[a]




[a] (a) 40% aqueous $Me_2NH$, DMF, 86%; (b) *hν*, 9:1 chlorobenzene/acetophenone, 110 °C, 61% (chromatographed) for **4**, 63% (chromatographed) for **20**; (c) MeNHCHO, NaH, 0 °C, 77%; (d) MeI, $K_2CO_3$, PhH, 70 °C, 99%; (e) $POCl_3$, then $NaBH_4$, DME, 87%.

Fully synthetic nordercitin[15] was obtained from **13** by mesylate displacement with dimethylamine and photolysis (61% chromatographed yield) of the intermediate **18**.[17] The synthesis of dercitin itself required selective N-methylation of the pyridine ring. It was surmised that such selectivity might be achieved within the domain of compound **19**, where the highly nucleophilic side chain dimethylamino group, which would interfere with the methylation step, is present in latent form. It was further assumed that the feeble nucleophilicity of the dihydroacridine segment of the molecule should permit full expression of the well-established 20-fold greater reactivity of the pyridine nitrogen vs its thiazole counterpart toward methyl iodide.[18] These expectations were realized. Thus, reaction of **13** with *N*-sodio-*N*-methylformamide[19] generated amide **19**,[15] which was converted into the aromatized pentacyclic compound **20**[15] in 63% chromatographed yield by the now familiar photolytic step. Treatment of **20** with MeI provided derivative **21**[15] in quantitative yield. The formamide was best reduced to a dimethylamine by the method of Kuehne,[20] a transformation that secured fully synthetic dercitin[15] in 87% yield.[17] The overall yields of **4** and **5** from **6** were 12.5% and 10.0% over 10 steps and over 12 steps, respectively.

These practical syntheses dramatically increase the availability of the new natural products. In addition, they confirm the structure of **5** and define a general entry to the thiazolopyridoacridine alkaloids. The synthetic plan should permit introduction of diverse structural variations into side chain and ring system analogues of **1–5**, facilitating eventual medicinal chemistry work. From a chemical standpoint, this work reaffirms the value of our pyridine-forming reaction and of photochemical transformations of azides in the construction of complex polycyclic heteroaromatic molecules. Further ramifications of these principles will be described in due course.

**Acknowledgment.** We thank the National Institutes of Health (CA-55268), the National Science Foundation (CHE 91-16820), the Robert A. Welch Foundation (C-1007), and the donors of the Petroleum Research Fund, administered by the American Chemical Society (AC-20399), for support of our research.

**Supplementary Material Available:** Listings of spectral data for selected compounds (4 pages). Ordering information is given on any current masthead page.

(18) Metzeger, J. V. *Chem. Heterocycl. Compd.* **1979**, *34-1*, 125.
(19) This reaction was conveniently carried out in *N*-methylformamide as the solvent.
(20) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* **1977**, *42*, 2082.

## Total Synthesis of Calicheamicin $\gamma_1^I$

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As one of Nature's most extraordinary molecular constructions, with phenomenal biological activity and a fascinating mode of action, calicheamicin $\gamma_1^I$ (**1**, Figure 1)[1,2] has captured the imagination of synthetic organic chemists around the world.[3-6]

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(1) Isolation and structure: Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. Lee, M. D.; Dunne, T. S.; Chang, C. C.; Siegel, M. M.; Morton, G. O.; Ellestad, G. A.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 985. Review: Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res.* **1991**, *24*, 235.
(2) For isolation and structures of the related esperamicins, see: Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

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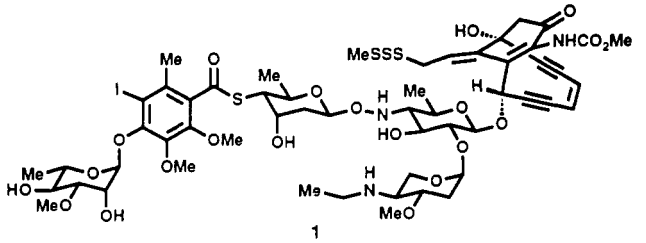

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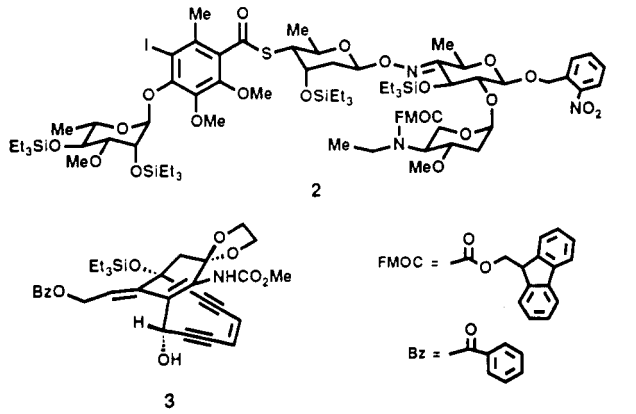
**Figure 1.** Molecular structure of calicheamicin $\gamma_1^I$ (**1**).



2 3

**Figure 2.** Advanced key intermediates **2** and **3** for the construction of calicheamicin $\gamma_1^I$ (**1**).

Herein we report the first total synthesis of this molecule in its naturally occurring enantiomeric form.

The convergent synthesis of calicheamicin $\gamma_1^I$ (**1**) required as advanced intermediates the oligosaccharide fragment **2** and the aglycon precursor **3** (Figure 2). These intermediates were synthesized in enantiomerically pure forms by modifications and extensions of procedures previously reported from these laboratories.[4,5] Crucial to the success of this total synthesis were (a) the ready access to fragments **2** and **3** in gram quantities; (b) a stereospecific and efficient coupling of the two key segments; and (c) the specific sequence of high-yielding reactions described below.

Photodeprotection of *o*-nitrobenzyl glycoside **2**[7] (Hanovia mercury lamp, THF–$H_2O$) generated the corresponding lactol (82% yield, ca. 1:1 anomeric mixture by $^1H$ NMR, plus 16% starting material, chromatographically separated), which was converted to the trichloroacetimidate **4** (Figure 3), according to Schmidt's procedure (NaH catalyst, $Cl_3CCN$),[8] in high yield.

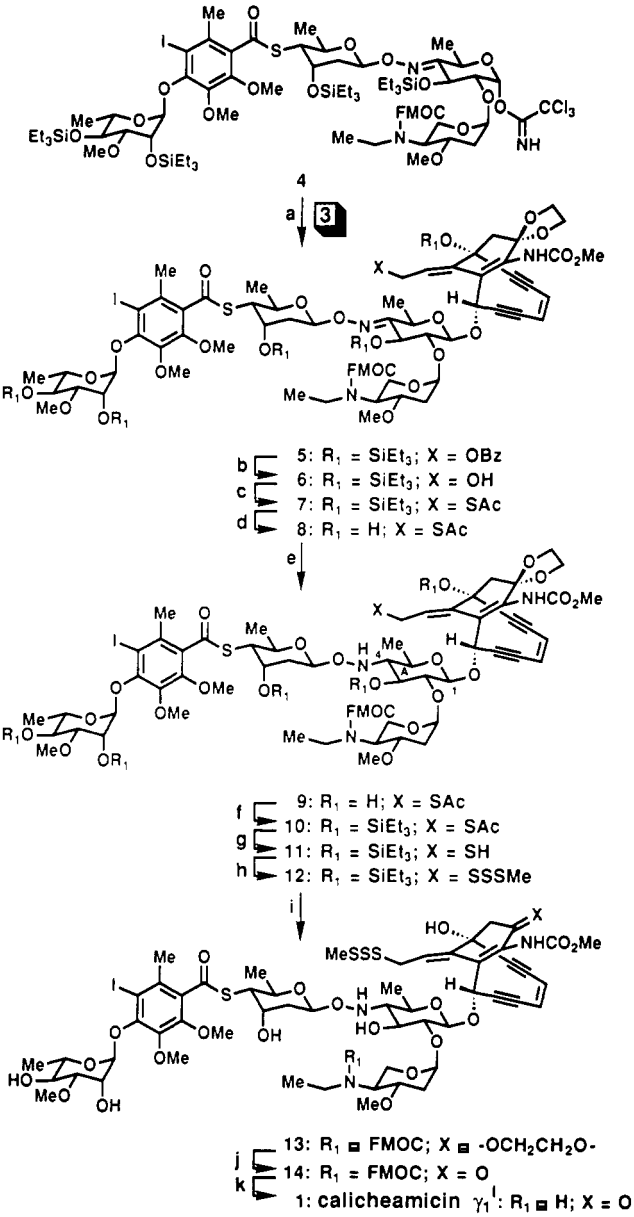


**Figure 3.** Total synthesis of calicheamicin $\gamma_1^I$ (**1**). Reagents and conditions: (a) 1.0 equiv of **4**, 1.4 equiv of **3**, 3.0 equiv of $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, −40 °C, 1.75 h, 76% (45% **5**, plus 31% monodesilylated product; this product was quantitatively converted to **5** with 5.0 equiv of $Et_3SiOTf$, 10.0 equiv of $^iPr_2NEt$, $CH_2Cl_2$, 0 °C, 1 h); (b) 4.0 equiv of DIBAL, $CH_2Cl_2$, −78 °C, 1 h, 88%; (c) 15.0 equiv of $PPh_3$, 12.0 equiv of DEAD, 13.0 equiv of AcSH, THF, 0 °C, 0.5 h, 96%; (d) excess HF·pyr, THF–$CH_2Cl_2$ (6:1), 0 °C, 3 h, 94%; (e) 10.0 equiv of $NaCNBH_3$, 2.0 equiv of $BF_3{\cdot}OEt_2$, THF, −40 °C, 3.5 h, 80% (2:1 mixture of isomers, 75% conversion); (f) 20.0 equiv of $Et_3SiOTf$, 40.0 equiv of $^iPr_2NEt$, $CH_2Cl_2$, 0 °C, 2 h; then excess AcOH, EtOAc–$H_2O$ (100:1), 25 °C, 24 h, 75%; (g) 3.0 equiv of DIBAL, $CH_2Cl_2$, −90 °C, 0.5 h; (h) 7.0 equiv of *N*-(methyldithio)phthalimide, $CH_2Cl_2$, 0 → 25 °C, 15 h, 75% (over two steps); (i) excess HF·pyr, THF–$CH_2Cl_2$ (5:1), 0 → 25 °C, 18 h, 90%; (j) 1.0 equiv of $TsOH{\cdot}H_2O$, THF–$H_2O$ (20:1), 25 °C, 18 h, 70%; (k) $Et_2NH$–THF–$H_2O$ (5:25:1), 25 °C, 1.5 h, 90%.

Crude trichloroacetimidate **4** was then coupled with the aglycon derivative **3**[7] (1.4 equiv) in $CH_2Cl_2$ under the influence of $BF_3{\cdot}Et_2O$ at −40 °C[9] to afford the desired product **5** (Figure 3) in 76% yield.[10] The correct stereochemical outcome of this

(3) For a review on the chemistry and biology of the enediyne anticancer antibiotics, see: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.

(4) Oligosaccharide fragment: Nicolaou, K. C.; Groneberg, R. D.; Miyazaki, T.; Stylianides, N. A.; Schultze, T. J.; Stahl, W. *J. Am. Chem. Soc.* **1990**, *112*, 8193.

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(6) For selected synthetic studies from other laboratories on the calicheamicins and esperamicins, see: (a) Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 3253. (b) Haseltine, J. N.; Cabal, M. P.; Mantlo, N. B.; Iwasawa, N.; Yamashita, D. S.; Coleman, R. S.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1991**, *113*, 3850. (c) Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544. (d) Magnus, P.; Lewis, R.; Bennett, F. *J. Am. Chem. Soc.* **1992**, *114*, 2560. (e) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631. (f) Schreiber, S. L.; Kiessling, L. L. *Tetrahedron Lett.* **1989**, *30*, 433. (g) Schoenen, F. J.; Porco, J. A., Jr.; Schreiber, S. L.; Van Duyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765. (h) Yang, D.; Kim, S.-H.; Kahne, D. *J. Am. Chem. Soc.* **1991**, *113*, 4715. (i) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. (j) Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851. (k) Skrydstrup, H.; Audrain, H.; Ulibarri, G.; Grierson, D. S. *Tetrahedron Lett.* **1992**, *33*, 4563.

(7) Details for the preparation of this intermediate will be described in the forthcoming full account of this work.

(8) (a) Grandler, G.; Schmidt, R. R. *Carbohydr. Res.* **1985**, *135*, 203. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212 (review).

(9) (a) Nicolaou, K. C.; Schreiner, E. P.; Stahl, W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 585. See also: (b) Nicolaou, K. C.; Schreiner, E. P.; Iwabuchi, Y.; Suzuki, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 340. (c) Halcomb, R. L.; Boyer, S. H.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 338.

glycosidation reaction ($\beta$-glycoside bond as shown in **5**) was anticipated from precedent in trichloroacetimidate chemistry[11] and was confirmed by a value of 7.4 Hz for coupling constant $J_{1,2}$ (anomeric proton, ring A) of compound **9** (Figure 3) obtained after reduction of the oxime bond (C=N). At this juncture the first sulfur atom of the trisulfide moiety was introduced as a thioacetate by a two-step procedure involving DIBAL-induced removal of the benzoate group to generate selectively the allylic alcohol **6** (88% yield) followed by Mitsunobu reaction using AcSH as the nucleophile[5,6a,b] to give compound **7** in 96% yield. Attempts to reduce the C=N bond in ring A revealed the need for desilylation prior to this crucial operation. All five silyl groups were, therefore, removed using excess HF·pyr, leading to pentaol **8** (94% yield) in preparation for the next step.

Reduction of the C=N bond in **8** with excess $NaCNBH_3$ in the presence of $BF_3{\cdot}Et_2O$ in THF proceeded smoothly[9a,b] to afford a mixture of **9** (4$\alpha$-epimer, major) and its 4$\beta$-epimer (**9**-epi, minor) in 80% total yield (ca. 2:1 ratio of isomers, ca. 75% conversion). Rapid flash chromatography separated the desired isomer **9** from its 4$\beta$-epimer (**9**-epi), but not from starting material **8**, suggesting further purification at a subsequent step. At this point it was also recognized that reprotection of the free hydroxyl groups was desirable for the pending steps leading to the establishment of the trisulfide moiety. Thus, the mixture of **9** + **8** (ca. 2:1 ratio) was fully silylated by exposure to $Et_3SiOTf$-$^iPr_2NEt$ followed by treatment of the crude product mixture with excess $AcOH-H_2O$ in EtOAc furnishing pentasilyl ether **10** together with the oxime derivative **7** in 75% total yield. Reaction of this mixture (**10** + **7**, ca. 2:1) with 3.0 equiv of DIBAL in $CH_2Cl_2$ at −90 °C gave selectively the corresponding mixture of thiols (**11**, plus oxime thiol). Exposure of this mixture to excess *N*-(methyldithio)-phthalimide[12,13] followed by flash chromatography afforded trisulfide **12** in 75% yield (two steps, based on the content of **9** in the starting mixture **9** + **8**).

Finally, deprotection of **12** by sequential exposure to (i) HF·pyr (**12** → **13**, 90% yield); (ii) $TsOH{\cdot}H_2O$ (**13** → **14**, 70% yield); and (iii) $Et_2NH$ (**14** → **1**, 90% yield) furnished calicheamicin $\gamma_1^I$ (**1**). Synthetic calicheamicin $\gamma_1^I$ (**1**) exhibited identical physical and spectroscopic data (TLC, HPLC, $[\alpha]^{25}_D$, $^1H$ and $^{13}C$ NMR, mass, IR and UV spectra) with those of an authentic sample.[14]

The reported total synthesis is remarkably efficient considering the complexity of the target molecule, and in addition to opening a synthetic route to calicheamicin $\gamma_1^I$ (**1**), it provides an entry into a new family of designed variations of the natural substance.[15]

**Acknowledgment.** We wish to express our many thanks to Drs. Gary Siuzdak, Dee H. Huang, and Raj Chadha for mass spectrometric, NMR spectroscopic, and X-ray crystallographic assistance, respectively. This work was financially supported through a NATO (SERC, U.K.) fellowship (to A.L.S.), through a visiting scientist fellowship from Toray Co., Japan (to K.S.), by the National Institutes of Health, by the University of California, San Diego, and by The Scripps Research Institute.

**Supplementary Material Available:** A listing of selected physical data for compounds **5**–**9**, **9**-epi, **12**, **13**, and **1** (12 pages). Ordering information is given on any current masthead page.

(10) Partial loss of one of the $SiEt_3$ groups (unassigned) occurred under these conditions; the desilylated coupling product was quantitatively converted to **5** by exposure to excess $Et_3SiOTf$-$^iPr_2NEt$ leading to a combined yield of 76% for this reaction.

(11) Trichloroacetimidate **4** (predominantly the $\alpha$-anomer, thermodynamic product) is apparently undergoing stereoselective glycosidation to afford the $\beta$-anomer **5** (see ref 8).

(12) (a) Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 57, 211. (b) Sullivan, A. B.; Boustany, K. *Int. J. Sulfur Chem., Part A* **1971**, *1*, 207.

(13) For previous applications of this sequence to form the trisulfide unit of similar systems, see: (a) Magnus, P.; Lewis, R. T.; Bennett, F. *J. Chem. Soc., Chem. Commun.* **1989**, 916 (calicheamicinone model system). (b) References 5 and 6a,b (calicheamicinone).

(14) We thank Drs. G. A. Ellestad and D. B. Borders of Lederle Laboratories for an authentic sample of natural calicheamicin $\gamma_1^I$ (**1**).

(15) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

## Novel Free Radical Ring-Forming Reaction of Dichlorocyclobutanones and Sequential Ring Expansion

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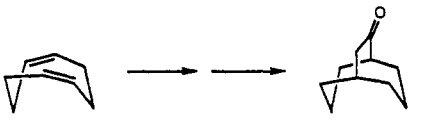
*Received July 22, 1992*

We have discovered an unusual reaction sequence that interpolates the elements of ketene into a 1,5-diene and forms a new seven-membered-ring ketone, as illustrated for 1,5-cyclooctadiene (eq 1). Since we are unaware of any comparable sequence in the literature, our findings are reported here.



71% (1)

The new reaction makes use of the regio- and chemoselective cycloaddition of dichloroketene to an olefin to form the dichlorocyclobutanone adduct (Scheme I).[1,2] In the key step, tri-*n*-butyltin hydride reduction of the adduct leads to free radical addition to the second double bond of the diene,[3,4] followed by reduction of the second chloride.[5] When the cyclobutanone product is treated with trimethylsilyl iodide,[6] ring opening occurs to yield the seven-membered keto iodide. The iodide can then either be reduced with tin hydride to yield the saturated ketone or the iodide can be eliminated with DBU to give the enone. This sequence is illustrated in Scheme I, where readily available *endo*-6-vinylbicyclo[2.2.1]hept-2-ene is transformed to the interesting and unusual tricyclo[6.2.1.$0^{6,10}$]undec-2-en-4-one. The yields in each step are quite reasonable. Further examples of the new reaction are shown in Table I.

Alkyl chlorides are not ordinarily good substrates for radical addition and are generally avoided on that account.[7] The dichlorocyclobutanone cycloaddition in the examples above is successful because the chlorides involved are $\alpha$ to the carbonyl and to a second chloro substituent, and they are more reactive than normal alkyl chlorides.[8-10] Like the 5-hexenyl radical,[11]

(1) For free radical based cyclobutanone ring expansions, see: Dowd, P.; Zhang, W. *J. Am. Chem. Soc.* **1991**, *113*, 9875. Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 3285.

(2) For cycloaddition of dichloroketene to olefins, see: Mehta, G.; Rao, H. S. P. *Synth. Commun.* **1985**, *15*, 991. Brady, W. T. *Tetrahedron* **1981**, *37*, 2949. Ghosez, L.; Montaigne, R.; Roussel, A.; Vanlierde, H.; Mollet, P. *Tetrahedron* **1971**, *27*, 615. Brady, W. T.; Roe, R., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 1662.

(3) For recent reviews of synthetic applications of free radical chemistry, see: Curran, D. P. In *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.1, 4.2. Thebtararnonth, C.; Thebtararnonth, Y. *Tetrahedron* **1990**, *46*, 1385. Curran, D. P. *Synthesis* **1988**, *417*, 489. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986.

(4) For representative studies on free radical addition to alkenes, see: Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429. Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5442. Keck, G. E.; Tafesh, A. M. *J. Org. Chem.* **1989**, *54*, 5845. Keck, G. E.; Burrett, D. A. *J. Org. Chem.* **1987**, *52*, 2958. Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079. Keck, G. E.; Byers, J. H. *J. Org. Chem.* **1985**, *50*, 5442. Keck, G. E.; Tafesh, A. M. *J. Org. Chem.* **1985**, *50*, 5442. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. Curran, D. P.; van Elberg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501. Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6785. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. Stork, G.; Sher, P. M.; Chen, H. L. *J. Am. Chem. Soc.* **1986**, *108*, 6384. See also ref 11.

(5) If 1 equiv of tin hydride is employed, the monochloride adduct can be isolated.

(6) Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1980**, *21*, 2639.

(7) Neumann, W. P. *Synthesis* **1987**, 665.

(8) Nagashima, H.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1984**, 652. Takano, S.; Nishizawa, S.; Akiyama, M.; Ogasawara, K. *Synthesis* **1984**, 949.

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