glycosidation reaction (β-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** (4α-epimer, major) and its 4β-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 4β-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 ($\mathbf{12} \rightarrow \mathbf{13}$, 90% yield); (ii) $TsOH \cdot H_2O$ ($\mathbf{13} \rightarrow \mathbf{14}$, 70% yield); and (iii) Et_2NH ($\mathbf{14} \rightarrow \mathbf{1}$, 90% yield) furnished calicheamicin γ_1^I (**1**). Synthetic calicheamicin γ_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 γ_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.

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[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 α-anomer, thermodynamic product) is apparently undergoing stereoselective glycosidation to afford the β-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 γ_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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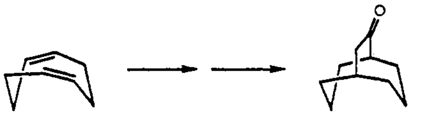
We have discovered an unusual reaction sequence that interpolates the elements of ketene into a 1,5-diene and forms a new seven-membered-ring ketone, as illustrated for 1,5-cyclooctadiene (eq 1). Since we are unaware of any comparable sequence in the literature, our findings are reported here.



(1)

71%

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 α 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]

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[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.

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[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.

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[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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Scheme I

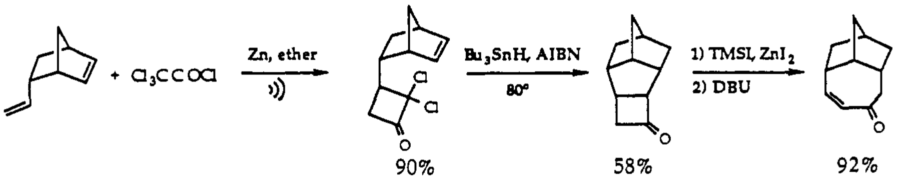
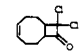
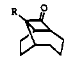
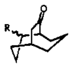
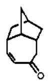
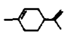
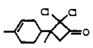
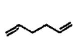
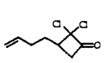
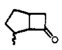
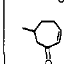
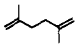
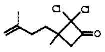
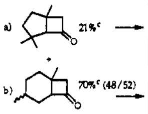
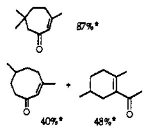
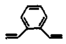
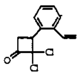
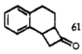
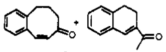


Table I. Bicyclic and Medium Ring Systems from Dichlorocyclobutanone Free Radical Annulation

entry	1,5-diene	ketene adduct[a]	radical-cyclization product	ring-opening product
1			 R=Cl, 91%[b] R=H, 85%[c]	 R=I, 87%[d] (35/65) R=H, 84%[e,f]
2	 75/25 (endo/exo)		 58%[c] based on endo	 92%[e]
3			 51%[c] (87/13)	 94%[e]
4			 85%[c] (84/16)	 90%[e,g]
5			 a) 21%[c] b) 70%[c] (48/52)	 87%[e] 40%[e] + 48%[e]
6			 61%[c]	 trace[e] + 83%[e]

[a] 1.2–1.5 equiv of Cl_3CCOCl, 2.0 equiv of zinc dust, ether, sonication. Yields: 69–95%. [b] 1.1 equiv of Bu_3SnH (170 mM) with AIBN, benzene, reflux. [c] 2.2–2.5 equiv of Bu_3SnH (70–170 mM) with AIBN, benzene, reflux. [d] 1.5 equiv of TMSI, 0.24 equiv of anhydrous ZnI_2, CH_2Cl_2, 25 °C, then 1.2 equiv of Bu_3SnH with AIBN, benzene, reflux. [e] 1.5 equiv of TMSI, 0.24 equiv of anhydrous ZnI_2, CH_2Cl_2, 25 °C, then 10% DBU, ether, 25 °C. [f] Bingham, R. C.; Schleyer, P. v. R. *J. Org. Chem.* **1971**, *36*, 1198. Coll, J. C.; Crist, D. R.; Barrio, M. d. C. G.; Leonard, N. J. *J. Am. Chem. Soc.* **1972**, *94*, 7092. [g] Heathcock, C. H.; Germroth, T. C.; Graham, S. L. *J. Org. Chem.* **1979**, *44*, 4481.

radicals generated from dichlorocyclobutanones prefer 5-exo ring closure (Table I, entries 1–4), but substitution at the 5-position causes a preference for 6-endo closure (Table I, entry 5). Entry 6 also shows endo ring closure since a stabilized benzyl radical is formed. For 5,4-fused cyclobutanones, TMSI selectively opens the fused bond of cyclobutanones to give the seven-membered ring (Table I, entries 1–5a). However, for 6,4-fused cyclobutanones, ring opening to give the six-membered ring is the major process (Table I, entries 5b and 6).

In summary, we have discovered a new free radical annulation reaction that promises to become a powerful method for assembling fused and bridged ring systems of some complexity. The synthetic sequence employs 1,5-dienes; many are at hand, having been developed in the context of the Cope rearrangement.[12] The new method also takes advantage of the ready synthesis of dichlorocyclobutanones from alkenes.[2]

Acknowledgment. This research was generously supported by the Institute of General Medical Sciences of the National Institutes of Health under Grant 39825.

Supplementary Material Available: Listings of experimental procedures and spectral data for the cyclization and ring-opened products (7 pages). Ordering information is given on any current masthead page.

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Measurement of Electric Fields at Rough Metal Surfaces by Electrochromism of Fluorescent Probe Molecules Embedded in Self-Assembled Monolayers

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We describe here a new experimental strategy for measurement of electric field strengths at charged surfaces which employs a surface-immobilized, oriented fluorescent dye as probe. The method takes advantage of interactions of dipolar ground and excited states of the dye with the interfacial electric field which lead to shifts in the absorption and emission spectra, referred to as the electronic Stark effect or the electrochromic effect. This strategy has been used previously to measure electric fields in both model and biological membranes,[1,2] but has not to our knowledge been applied to the measurement of electric fields at charged solid surfaces. The electric field at a charged interface has enormous impact on interfacial chemistry and physics. While interest in interfacial electric fields has a long history[3] and several mathematical models of interfacial electric fields have been developed and applied in attempts to explain interfacial phenomena,[3-5] there have been only a very few actual measurements of interfacial field strengths or potential differences.[6-10]

We have chosen an (aminostyryl)pyridinium derivative (also referred to as a hemicyanine or stilbazolium derivative) as the probe molecule because the extent of charge displacement during its optical transition is both large and well studied[2a] and because its structure allows relatively simple synthetic elaboration[2b] to

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