Metal-Halogen Exchange-Initiated Intramolecular Conjugate Addition Reactions of Conjugated Acetylenic Esters

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The lithium-iodine exchange-initiated intramolecular conjugate addition reactions of some model γ-iodo-α,β-acetylenic esters have been examined. Product mixtures arising from proton abstraction reactions were observed in reactions leading to 5-membered ring formation. More efficient cyclizations resulted when reactions were conducted in the presence of trimethylsilyl chloride to trap intermediate allenolate ions. Allenolate ion trapping by an internal electrophilic center in **26** resulted in the highly efficient formation of bicyclic ester **27**.

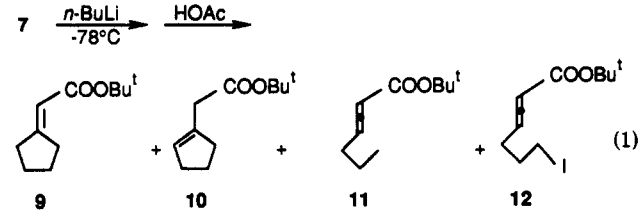
Introduction

The intramolecular addition of nucleophilic carbon centers to polarized carbon-carbon π-systems constitutes an important class of ring-forming reactions.[1] Intramolecular conjugate addition or Michael-type reactions[2] usually employ stabilized carbanions insomuch as methods for the introduction of highly reactive unstabilized nucleophilic centers are usually not compatible with the functional groups commonly employed to predispose olefinic or acetylenic centers to nucleophilic attack. We have shown that extremely rapid lithium-iodine exchange reactions may be used to introduce such centers in compounds containing activated olefins.[3] Intermediate alkyllithium derivatives may then undergo rapid intramolecular conjugate addition reactions forming cyclic enolate ions which may be further elaborated upon reaction with electrophiles.

Recent interest in the cyclization reactions of simple acetylenic lithium derivatives[4] prompted us to examine the metal-halogen exchange-initiated reactions of ω-iodo-α,β-acetylenic esters as shown in Scheme I. In contrast to the relatively slow cyclization reactions of unactivated acetylenes,[4e] our studies with α,β-unsaturated esters suggested that activated acetylenes might also undergo rapid anionic ring closure reactions, thereby circumventing problems which attend persistent alkyllithium intermediates such as proton abstraction reactions and reactions with other internal electrophilic centers. Additionally, interesting but infrequently studied[5] allenolates[6] **3** (allenyl enolates) would result from such conjugate addition reactions. We now report the results of our study of this scheme.

Results and Discussion

We began our investigation of exchange-initiated cyclization reactions of acetylenic esters with simple iodo ester **7** which was prepared as shown in Scheme II. The lithium acetylide formed upon treatment of 6-chloro-1-hexyne with *n*-BuLi readily gave the desired *tert*-butyl ester **5** upon acylation with di-*tert*-butyl dicarbonate (BOC_2O). Iodine-chlorine exchange (NaI, acetone) provided iodide **7**. Treatment of **7** with *n*-BuLi in THF at −78 °C gave a mixture containing approximately equal amounts of anticipated carbocyclic ester **9**, its unconjugated isomer **10**, and allenes **11** and **12** (eq 1). No



(1)

improvement resulted when the reaction was conducted at −100 °C or when *tert*-butyllithium was employed as the metalating agent.

The presence of β,γ-unsaturated ester **10** is apparently the result of the isomerization of **9** which we intially believed occurred during workup. We were unable, however, to eliminate its formation using a variety of quenching techniques. Similar isomerizations have been observed in the course of Emmons-Wadsworth phospho-

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(6) For a discussion of the allenolate vs [α-(alkoxycarbonyl)vinyl]metal structure of such intermediates, see ref 5d. For examples of cyclic anions which are structurally prevented from possessing an allenolate structure, see: (a) Carpenter, T. A.; Jenner, P. J.; Leeper, F. J.; Staunton, J. *J. Chem. Soc. Chem. Commun.* **1980**, 1227. (b) Clemo, N. G.; Pattenden, G. *Tetrahedron Lett.* **1982**, *23*, 581.

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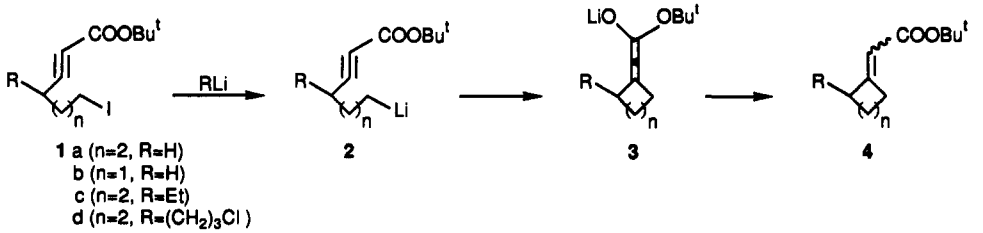
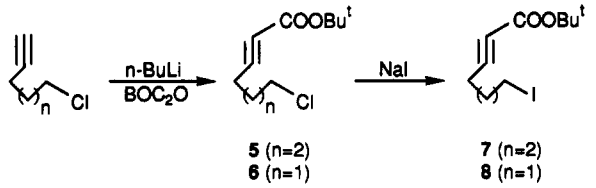
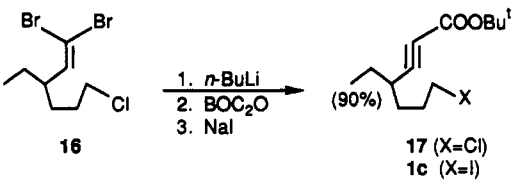
Scheme I



Scheme II

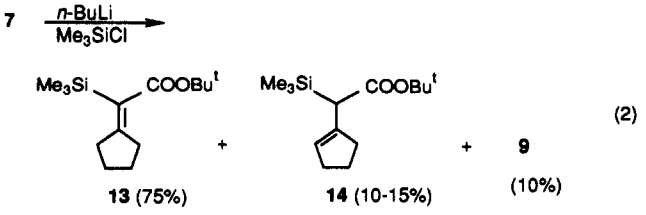


Scheme III



nate olefinations of cyclopentanone derivatives.[7] Allenic products **11** and **12** apparently arise from γ-hydrogen loss from acetylenic esters. Indeed, authentic samples of **11** and **12** were prepared in 66% and 75% yields, respectively, by the deprotonation of *tert*-butyl 2-heptynoate and **5**, respectively, with LDA followed by reprotonation of the corresponding enolates with HOAc.[8] While **11** may arise from an intramolecular proton transfer in the lithiated cyclization precursor **2a**, the presence of iodine-containing allenic ester **12** clearly points to the presence of an intermolecular process as well. It is noteworthy that treatment of *tert*-butyl 2-heptynoate with *n*-BuLi under similar conditions gives only 1,2-addition products suggesting that alkyllithium intermediates are not the deprotonating agents. It is thought more likely that allenolate **3a**, formed in the cyclization process, is the base involved. This would explain our inability to minimize the formation of unconjugated ester **10** insomuch as this pathway allows for the formation and isomerization of **9** prior to a protic quench.

These deprotonation pathways leading to allenes and isomerized carbocycle would appear to seriously limit the utility of the desired cyclization process. We reasoned, however, that if the intermediate allenolate **3** formed in the cyclization reaction could be rapidly trapped, the undesired deprotonation pathways might be suppressed. Indeed, when **7** was treated with *n*-BuLi at −78 °C in the presence of 5 equiv of Me_3SiCl (which is known to react relatively slowly with tetrahedral alkyllithium intermediates[9]), a mixture containing approximately 75% of silylated ester **13** resulted (eq 2). While rapid allenolate

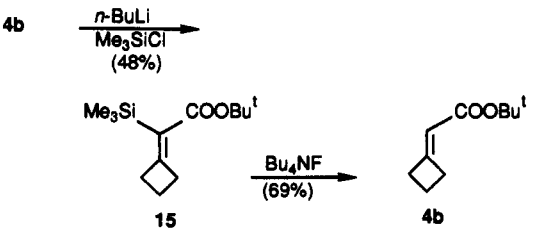


(2)

trapping considerably simplifies the reaction mixture, it is noteworthy that predominately C-silylation occurs.[5c,6] A small amount of unconjugated product **14** is also formed along with **9** which may arise from O-silylation with subsequent hydrolysis of the labile silyl enol ether during the aqueous workup. The mixture of silylated esters **13** and **14**, easily separated from **9** by chromatography, could be readily desilylated by treatment with Bu_4NF in moist THF (eq 3) but a less favorable mixture of conjugated (**9**) and unconjugated ester (**10**) results (**9**/**10** = 2.3, cf. **13**/**14** ≈ 7).

$$13 + 14 \xrightarrow[\text{THF-H}_2\text{O}]{\text{Bu}_4\text{NF}} 9 + \underset{(2.3:1)}{10} \qquad (3)$$

Insomuch as it seemed probable that facile double-bond isomerization was peculiar to cyclopentylidene derivatives, we investigated cyclization reactions of homolog **8** which would give cyclobutylidene ester **4b**. Treatment of **8** (from Scheme II) with *n*-BuLi at −78 °C gave a complex mixture of products containing only 11% of the desired carbocycle **4b**. When the reaction was conducted in the presence of excess TMSCl, however, silylated ester **15** was clearly produced in 48% yield (eq 4). This ester was readily desilylated upon brief treatment with Bu_4NF giving **4b** in 69% yield.



(4)

Encouraged by this result, we examined γ-substituted iodide **1c** in hopes that γ-alkyl substitution would retard the deprotonation reactions responsible for the problems encountered in cyclopentylidene ester formation as well as allow an investigation of the stereochemical aspects of the formation of **4c**. Cyclization substrate **1c** was prepared as shown in Scheme III. Treatment of known[3c] vinylidene dibromide **16** with *n*-BuLi following the Corey–Fuchs protocol[10] gave the corresponding acetylenic ester **17** in 96% yield upon acylation of the intermediate lithium acetylide with BOC_2O as previously described.

Treatment of **1c** with *n*-BuLi at −78 °C in THF followed by an HOAc quench gave a mixture of isomeric esters (**18**, **19**, and **20**) in 43% yield (eq 5). Gas chromatographic

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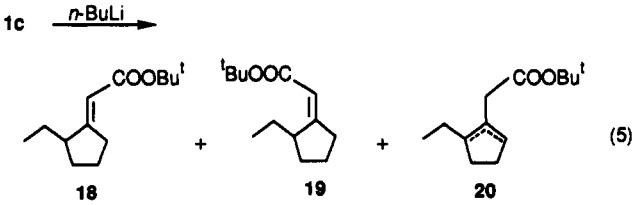
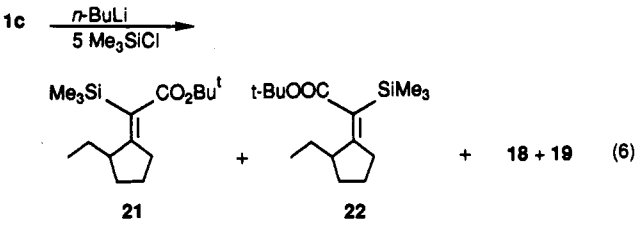


analysis indicated that conjugated esters **18** and **19** constituted 88% of the mixture (E/Z = 1.25) in addition to a small amount (12%) of what is believed to be an unconjugated isomer **20**. This inseparable mixture was reduced (H_2, Pd–C) to the known[3c] cis and trans isomers of *tert*-butyl (2-ethylcyclopentyl)acetate. Cyclization of **1c** in the presence of excess Me_3SiCl resulted in the formation of a mixture of conjugated silylated and unsilylated esters (**21**:**22**:**18**:**19** = 0.7:2.5:1:1) (eq 6). The



significant quantity of unsilylated esters **18** and **19** (approximately 40%) may be due to an increased O-silylation of the more hindered intermediate allenolate with subsequent hydrolysis of the labile silyl enol ether during workup.

NMR data obtained on chromatographically enriched fractions allowed stereochemical assignments of reaction products. Of the isomeric silylated esters, the major isomer **22** has for its ethyl group the lower field methyl resonance in its 500 MHz ^1H NMR spectrum (δ 0.93 vs 0.85 in **21**) and in its ^{13}C NMR spectrum (δ 12.5 vs 12.3 in **22**). The stereochemical assignments for **18** and **19**, previously produced in eq 5, are based on observation that isomer **19** contains the less shielded vinyl hydrogen (δ 5.66 vs 5.62 in **18**) in its ^1H NMR spectrum and a compressional strain-induced higher field ethyl methylene carbon (δ 22.6 vs 24.2 in **18**) in its ^{13}C NMR spectrum. Additionally, the trans isomer **18** gave an 18% NOE enhancement of its vinyl hydrogen signal upon ethyl methylene group irradiation. These assignments also find support in the observation that **1c** cyclizes under radical conditions (Bu_3SnH, AIBN, refluxing benzene) to give equal amounts of **18** and **19** at short reaction times but predominately **18**, presumably the more stable isomer, after several hours (E/Z = **18**/**19** = 5:1) (eq 7). Thermodynamic equilibration under these reaction conditions in similar systems has been recently reported.[11]

$$\mathbf{1c} \xrightarrow[\text{AIBN, PhH}]{Bu_3SnH} \mathbf{18} + \mathbf{19} \qquad (7)$$

It is interesting to note that while allenolate trapping by Me_3SiCl occurs with some stereoselectively (**22**:**21** = 3.6), as would be anticipated by reactant approach to the least hindered face of the relevant π-bond (Figure 1), this selectivity is not high. This is in contrast to the reported alkylations of allenolates containing bulky β-substituents where high facial selectivity was observed.[5a] In our case, the more remote substituent exercises less control over subsequent reactions with electrophiles. In the previously

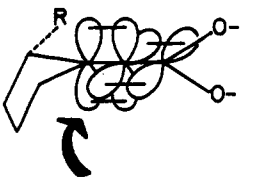
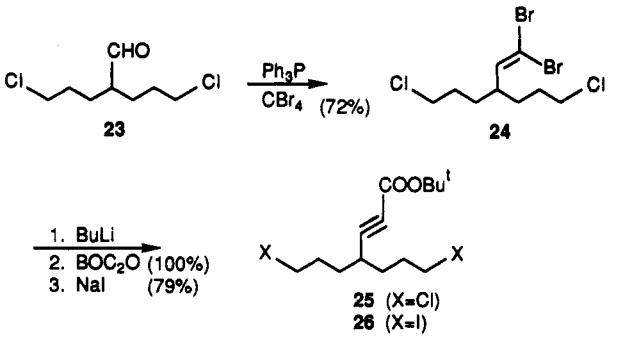


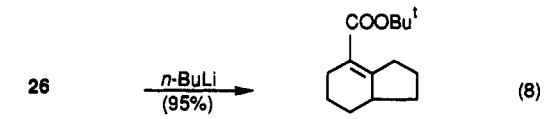
Figure 1.

Scheme IV



cited radical cyclization of **1c** (eq 7), one would also expect considerable cis-product selectivity as a result of hydrogen atom delivery by Bu_3SnH to the least hindered face of the orbital associated the carbon radical formed in the cyclization, but in this case the ongoing isomerization to more stable **18** obscures the fact.

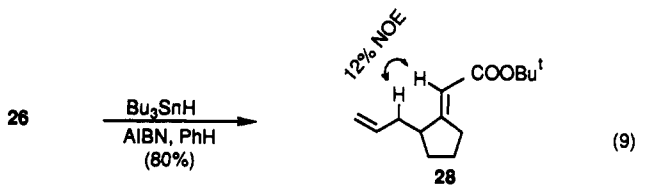
If the allenolate formed upon intramolecular anionic cyclization were to contain an appropriately tethered electrophilic center, stereoselectivity could be forced through structural constraints and the increased rate of intermediate allenolate capture owing to the intramolecularity of the reaction might preclude the forementioned problems arising from allenolate side reactions. To this end we prepared for study symmetrical diiodide **26** as shown in Scheme IV. Known dichloride **23**[3d] gave through the Corey–Fuchs protocol vinylidene dibromide **24** which afforded upon treatment with BuLi the corresponding lithium acetylide which was acylated with BOC_2O as previously described. Treatment of **26** with *n*-BuLi at −78 °C cleanly gave bicyclic ester **27** in 95% yield (eq 8).



Several features of this very efficient cyclization are noteworthy. Unlike the simple models previously discussed, double bond migration did not occur as evidenced by the absence of ^1H NMR peaks characteristic of allylic protons ≤3 ppm, the lower field ^{13}C NMR carbonyl resonance at 167.7 ppm typical of conjugated esters (cf ~170 ppm for comparable nonconjugated esters) and a vinyl carbon resonance at 158.9 ppm likewise typical of a conjugated olefin. It should also be noted that the cyclization substrate **26** contains two exchangeable iodide atoms and after the initial exchange-initiated cyclization step, an iodide remains which must either undergo a very rapid cycloalkylation reaction with the nucleophilic carbon of the allenoate or face rapid lithium–iodine exchange in the presence of *n*-BuLi. While we have previously observed that cycloalkylations of similar enolates forming saturated

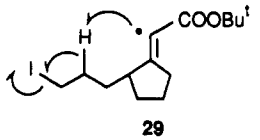
6-membered rings are slow relative to lithium–iodine exchange,[3b] the rate of cycloalkylation with the more constrained and likely more reactive allenoate center is probably considerably faster. In any event, the rapidly reversible nature of the lithium-iodine exchange reaction[3d] would be expected to allow the reformation of the electrophilic center required for the final ring closure.

As a sidelight, we also subjected diiodide **26** to radical cyclization conditions (Bu_3SnH, AIBN, refluxing benzene) with the expectation that two sequential radical cyclizations would lead to the [3.3.0]bicyclooctane ring system. To our surprise, monocyclic ester **28** was formed in good yield (eq 9). A minor product with a slightly shorter GLC



(9)

retention time may well be the cis isomer, but it was not characterized. Olefin stereochemistry was established by ^1H NMR spectroscopy (300 MHz) where a 12% NOE enhancement of the vinyl proton resonance upon allyic proton irradiation was observed as indicated. This stereochemical outcome supports the suggestion that vinyl radical **29** formed in the initial cyclization intramolecularly



abstracts a hydrogen atom β to the iodine-containing center with subsequent loss of an iodine atom in a process which is analogous to the classic polar E-2 elimination process. However, as previously noted, the trans stereochemistry may merely be the result of the previously cited equilibration known to occur under these reaction conditions.[11] Indeed, if the uncharacterized coproduct is the cis isomer, it is noteworthy that the trans–cis ratio (~4:1) would be similar to that observed for **18** and **19** (5:1) produced under similar equilibrating conditions (vide supra).

Summary

Lithium–iodine exchange-initiated intramolecular conjugate addition reactions of acetylenic esters leading to 5-membered carbocycles were found to give mixtures of products resulting from proton transfer reactions. Low stereoselectivity was observed in the silylation of intermediate allenolates, which gives rise to isomeric olefins. Considerable improvements were observed, especially in 4-membered ring formation, when cyclization reactions were conducted in the presence of Me_3SiCl which traps reactive intermediate allenoates. A very efficient ring-forming process which employs an internal electrophic center to trap the initially formed allenoate results in the cyclization of **26**. Thus, in certain cases, intramolecular conjugate addition reactions of very reactive nucleophic centers with activated acetylenes offer a viable approach to carbocycle formation.[12]

(11) Lowinger, T. B.; Weiler, L. *J. Org. Chem.* **1992**, *57*, 6099.
(12) See ref 3c for general experimental details.

Experimental Section

***tert*-Butyl 7-Chloro-2-butynoate (5).** To a solution containing 3.5 g (30 mmol) of 6-chloro-1-butyne in 50 mL of THF at −78 °C was added over 2 min 18 mL (29 mmol) of 1.6 N *n*-BuLi (hexane). After 15 min, a solution containing 6.1 g (28 mmol) of BOC_2O in 10 mL of THF was added and the cooling bath was removed. The mixture was stirred 1.25 h at 20 °C, concentrated, treated with water, and extracted with pentane. Concentration of the extracts gave 6.0 g (99%) of nearly pure **5** as an oil which was reconcentrated from Et_2O solution (to add some inhibitor present in anhydrous ether) and stored at −20 °C: ^1H NMR δ 1.49 (s, 9 H), 1.4–2.0 (m, 4 H), 2.36 (t, J = 6.1 Hz, 2 H), 3.56 (t, J = 6.1 Hz, 2 H); ^{13}C NMR δ 18.0, 24.8, 28.1, 31.5, 44.2, 75.1, 83.0, 85.7, 152.8. An analytical sample was prepared by PTLC (1:1 hexane–CH_2Cl_2) followed by bulb-to-bulb distillation (160 °C, 0.1 mm). Anal. Calcd for $C_{11}H_{17}ClO_2$: C, 60.96; H, 7.91. Found: C, 61.28; H, 7.93.

***tert*-Butyl 7-Iodo-2-butynoate (7).** A mixture containing 2.35 g (1.8 mmol) of **5**, 5 g of NaI, and 20 mL of acetone was heated under reflux for 18 h. The mixture was concentrated, treated with water, and twice extracted with pentane. The extracts were washed with dilute $NaHCO_3$ solution and then water. Concentration of the dried pentane solution gave 2.66 g of crude **7**, which upon flash chromatography (1:1 hexane–CH_2Cl_2) gave 2.4 g (72%) of pure **7** as an oil: ^1H NMR δ 1.49 (s, 9 H), 1.5–2.1 (m, 4 H), 2.35 (t, J = 6.2 Hz, 2 H), 3.20 (t, J = 6.4 Hz, 2 H); ^{13}C NMR 5.4, 17.6, 28.0, 28.3, 32.2, 75.0, 83.0, 85.6, 152.7. Bulb-to-bulb distillation (160 °C, 0.1 mm) gave an analytical sample. Anal. Calcd for $C_{11}H_{17}IO_2$: C, 42.87; H, 5.56. Found: C, 42.81; H, 5.42.

Cyclization of 7. A solution containing 308 mg (1.0 mmol) of **5** in 7 mL of THF was treated with 0.75 mL (1.2 mmol) of 1.6 N *n*-BuLi at −78 °C over 2 min. After an additional 2.5 min, 100 μL of HOAc was added and the mixture was warmed to 20 °C, concentrated, treated with water, and twice extracted with pentane. GC analysis showed the mixture to contain approximately equal amounts of **9**, **10**, **11**, and **12**. Concentration of the dried extracts followed by bulb-to-bulb distillation (140 °C, 15 mm) gave 78 mg of the above mixture. Cyclic products **9** and **10** were obtained nearly pure by PTLC (1:1 hexane–CH_2Cl_2). **10**: ^1H NMR δ 1.45 (s, 9 H), 1.30–2.05 (m, 2 H), 2.10–2.45 (m, 4 H), 3.02 (bs, 2 H), 5.51 (bs, 1 H); ^{13}C NMR δ 23.5, 28.1, 32.5, 35.2, 38.4, 80.4, 127.7, 137.3, 170.9. **9** was identified by comparison with its literature ^1H NMR spectrum[13] and an authentic sample obtained upon treatment of **5** with Bu_3SnH (AIBN, refluxing PhH). Allenes **11** and **12** were identical to authentic samples (vide infra).

***tert*-Butyl 2,3-Heptadienoate (11).** A solution containing 182 mg (1.0 mmol) of *tert*-butyl 2-heptynoate in 1 mL of THF was added by cannula to a stirred solution of LDA (1.2 mmol, from 180 μL *i*-Pr_2NH, 0.75 mL (1.2 mmol) of 1.6 N *n*-BuLi, 5 mL of THF) at −78 °C over 2 min. The mixture was stirred for 5 min and then the reaction was quenched with 200 μL of HOAc. The mixture was concentrated, treated with water, and extracted with pentane. The extracts were washed with water, dilute HCl, and dilute $NaHCO_3$ and dried. Concentration and bulb-to-bulb distillation (150 °C, 15 mm) gave 120 mg (66%) of **11** as a slightly impure oil: ^1H NMR δ 0.96 (t, J = 6.4 Hz, 3 H), 1.3–1.6 (b, 2 H), 1.95–2.25 (m, 2 H), 5.4–5.7 (m, 2 H); ^{13}C NMR δ 13.5, 22.1, 28.1, 29.6, 80.6, 89.7, 94.8, 165.5, 211.9.

***tert*-Butyl 7-Iodo-2,3-heptadienoate (12).** In the manner described above 100 mg (0.32 mmol) of **7** gave 75 mg (75%) of **12** as an oil: ^1H NMR δ 1.48 (s, 9 H), 1.8-2.1 (m, 2 H), 2.1–2.4 (m, 2 H), 3.28 (t, J = 6.3 Hz, 2 H), 5.4–5.6 (m, 2 H); ^{13}C NMR δ 5.5, 28.0, 28.1, 32.1, 80.9, 90.5, 93.1, 165.1, 211.8. Anal. Calcd for $C_{11}H_{17}O_2$: C, 42.87; H, 5.56. Found: C, 43.26; H, 5.68.

Cyclization of 7 with TMSCl Present. A solution containing 228 mg (0.74 mmol) of **7** and 450 μL (3.7 mmol) of freshly distilled Me_3SiCl in 5 mL of THF was treated with 0.6 mL (0.9 mmol) of 1.6 N *n*-BuLi added over 3.5 min. Stirring was continued for 2.5 min, whereupon the mixture was allowed to warm to 20 °C. The residue obtained upon concentration was treated with water and extracted with pentane. Concentration of this extract and PTLC

(13) Inoue, S.; Sato, Y. *J. Org. Chem.* **1991**, *56*, 347.

(1:1 hexane–CH_2Cl_2) gave 161 mg (86%) of **13** and **14** in addition to a small amount of **9** (~10%). Careful PTLC (7:3 hexane–CH_2Cl_2, 2×) allowed isolation of pure **13** as an oil: ^{1}H NMR δ 0.19 (s, 9 H), 1.2–1.8 (b, 4 H), 1.49 (s, 9 H), 2.2–2.6 (m, 4 H); ^{13}C NMR δ –0.12, 25.7, 26.5, 28.4, 33.7, 34.0, 80.0, 128.2, 163.6, 171.7. Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 66.08; H, 10.30. Found: C, 66.49; H, 10.37. A mixture of **13** and **14** was dissolved in moist 1 M Bu_4NF in THF and allowed to stand overnight. Concentration and treatment with water followed by pentane extraction gave a 2.3:1 mixture of **9** and **10** upon GC analysis.

***tert*-Butyl 6-Chloro-2-hexynoate (6).** In the manner described for the preparation of **5**, 3.1 g (30 mmol) of 5-chloro-1-pentyne (Aldrich) gave 5.26 g (87%) of **6** as an oil: ^{1}H NMR δ 1.49 (s, 9 H), 1.8–2.2 (m, 2 H), 2.51 (t, J = 6.5 Hz, 2 H), 3.64 (t, J = 6.1 Hz, 2 H); ^{13}C NMR δ 16.1, 28.1, 30.5, 44.3, 75.3, 83.2, 84.6, 152.7. Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.46. Found: C, 59.47; H, 7.57.

***tert*-Butyl 6-Iodo-2-hexynoate (8).** In the manner described for the preparation of **7**, 2.0 g (9.8 mmol) of **6** gave 1.6 g (55%) of **8** as an oil; ^{1}H NMR δ 1.49 (s, 9 H), 1.9-2.2 (m, 2 H), 2.47 (t, J = 6.1 Hz, 2 H), 3.28 (t, J = 6.6 Hz, 2 H); ^{13}C NMR δ 4.5, 19.7, 28.0, 31.1, 75.3, 83.1, 84.3, 152.6. Anal. Calcd for $C_{10}H_{15}IO_2$: C, 40.83; H, 5.14. Found: C, 40.98; H, 5.22.

***tert*-Butyl (Trimethylsilyl)cyclobutylideneacetate (15).** In the manner described above for the cyclization of **7** with TMSCl present, 294 mg (1.0 mmol) of **8** gave 114 mg (48%) of **15** as an oil: ^{1}H NMR δ 0.15 (s, 9 H), 1.47 (s, 9 H), 1.8–2.6 (m, 2 H), 2.7–3.2 (m, 4 H); ^{13}C NMR δ 0.1, 17.2, 28.4, 34.4, 36.4, 79.8, 127.1, 127.3, 171.3. Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.94; H, 10.06. Found: C, 65.26; H, 10.14.

***tert*-Butyl Cyclobutylideneacetate (4b).** A solution containing 23 mg (0.1 mmol) of **15** in 1 mL of 1 M Bu_4NF in THF (Aldrich) was allowed to stand for 5 min and then was concentrated under reduced pressure. The residue was treated with water and extracted with pentane. The extracts were washed successively with water, dilute HCl, and $NaHCO_3$ solution and then dried (Na_2SO_4). Solvent removal gave 11 mg (69%) of **4b** as an oil: ^{1}H NMR δ 1.46 (s, 9 H), 1.8–2.3 (m, 2 H), 2.80 (m, 2 H), 3.09 (m, 2 H), 5.48 (m, 1 H); ^{13}C NMR δ 17.8, 28.4, 32.2, 33.7, 79.6, 114.3, 165.8, 166.1. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.66.

***tert*-Butyl 4-Ethyl-7-iodo-2-heptynoate (1c).** A solution containing 330 mg (1.08 mmol) of **16**[3c] in 4 mL of THF was treated at –78 °C with 1.4 mL (2.24 mM) of 1.6 N *n*-BuLi added over 2 min. After 50 min at –78 °C, a solution containing 436 mg (2 mmol) of BOC_2O (Fluka) in 2 mL of THF was added and the mixture was allowed to warm to 20 °C. After 1 h at 20 °C, 200 μL of water was added and stirring was continued for 30 min. The residue obtained after solvent removal was treated with water and extracted with pentane. The extracts were washed with water, dried and concentrated. Chromatography of the residue (SiO_2, 1:1 hexane–CH_2Cl_2) gave 253 mg (96%) of **17** as an oil: ^{13}C NMR δ 11.7, 27.4, 28.1, 30.3, 31.0, 32.8, 44.7, 76.2, 83.0, 88.8, 153.0. A portion of this material (225 mg, 0.92 mmol) gave upon reaction with NaI as previously described in the preparation of **7**, 270 mg (87%) of **1c** as an oil: ^{1}H NMR δ 1.02 (t, J = 6.8 Hz, 3 H), 1.49 (s, 9 H), 1.2–2.1 (b, 6 H), 2.2-2.6 (m, 1 H), 3.21 (t, J = 6.6 Hz, 2 H); ^{13}C NMR δ 6.1, 11.7, 27.2, 28.0, 31.0, 32.4, 34.4, 76.1, 82.9, 88.7, 152.9; [M^+ – 1] calcd 335.0508, found 335.0485.

Anionic Cyclization of 1c. In the manner described above for the cyclization of **7**, 193 mg (0.57 mmol) of **1c** gave, after PTLC (SiO_2, CH_2Cl_2), 51 mg (43%) of **18**, **19**, and **20** (3.8:3.3:1 by GLC analysis). Conjugated esters **18** and **19** were shown to be identical to those produced by the radical cyclization of **1c** (vide infra).

Radical Cyclization of 1c. A solution containing 125 mg (0.37 mmol) of **1c**, 200 μL (0.75 mmol) of Bu_3SnH, and 20 mg of AIBN in 5 mL of benzene was heated at reflux under argon for 2.5 h. The residue obtained after solvent removal was treated with saturated $NaHCO_3$ solution and pentane with stirring over 10 min. Concentration of the pentane extract followed by PTLC (SiO_2, 1:1 CH_2Cl_2–hexane) gave 60 mg (77%) of a mixture of **18** and **19** (4.8:1). **18**: ^{13}C NMR δ 11.9, 24.2, 26.3, 28.3, 31.0, 32.9, 48.3, 79.3, 113.2, 166.7, 170.2; additional peaks assignable to **19** δ 12.3, 22.6, 30.6, 35.1, 43.6, 113.8, 166.0, 170.4; ^{1}H NMR (300 MHz), vinyl H multiplet at 5.622 in **18**, 5.657 in **19**; HRMS M^+ (C.I.) calcd 210.1620, found 210.1614.

1,1-Dibromo-6-chloro-3-(3-chloropropyl)-1-hexene (24). A solution containing 2.4 g (7.2 mmol) of CBr_4 in 15 mL of dry CH_2Cl_2 was stirred at 0 °C and treated with 3.78 g (14.4 mmol) of triphenylphosphine.[10] The resulting red solution was stirred for 5 min, whereupon a solution containing 700 mg (3.55 mmol) of **23**[3d] in 1 mL of CH_2Cl_2 was added. After 10 min, 40 drops of MeOH were added and the mixture was concentrated under reduced pressure. The residue was extracted with pentane and then twice dissolved in a small amount of CH_2Cl_2 and reprecipitated by the addition of more pentane. The pentane extracts gave, upon concentration, an oil which upon flash chromatography (SiO_2, 4:1 hexane–CH_2Cl_2) gave 900 mg (72%) of **24** as an oil: ^{1}H NMR δ 1.0–2.0 (b, 8 H), 2.1–2.7 (m, 1 H), 3.54 (t, J = 6.3 Hz, 4 H), 6.13 (d, J = 9.8 Hz, 1 H); ^{13}C NMR δ 30.0, 31.6, 42.5, 44.8, 89.3, 141.9. Anal. Calcd for $C_9H_{14}Br_2Cl_2$: C, 30.63; H, 4.00. Found: C, 30.86; H, 4.07.

***tert*-Butyl 7-Iodo-4-(3-iodopropyl)-2-heptynoate (26).** A solution containing 706 mg (2.0 mmol) of **24** in 8 mL of THF with stirring at –78 °C was treated with 2.55 mL (4.08 mmol) of 1.6 N *n*-BuLi over 2 min. After 50 min, 436 mg (2.0 mmol) of BOC_2O in 2 mL of THF was added and the mixture was allowed to warm to 20 °C. The mixture was stirred for an additional 2 h, whereupon the solvent was removed and the residue treated with water and extracted with pentane. Concentration of the dried extracts gave 580 mg (99%) of crude **25**. In the manner described for the preparation of **7**, 480 mg (1.64 mmol) of crude **25** was heated with NaI in acetone (19 h), giving, after chromatography (SiO_2, 4:1 hexane–CH_2Cl_2), 614 mg (79%) of **26** as an oil: ^{1}H NMR δ 1.49 (s, 9 H), 1.4–2.2 (m, 8 H), 2.3–2.7 (m, 1 H), 3.21 (t, J = 6.3 Hz, 4 H); ^{13}C NMR δ 6.0, 28.0, 29.9, 30.9, 34.9, 76.5, 83.2, 87.7, 152.7.

Anionic Cyclization of 26. A rapidly stirred solution containing 260 mg (0.54 mmol) of **26** in 7 mL of THF was treated at –78 °C with 0.41 mL (0.65 mmol) of 1.6 N *n*-BuLi added dropwise over 5 min. The mixture was stirred for 50 min and the bath temperature was allowed to rise to –60 °C. The mixture then was allowed to come to 20 °C over 15 min, whereupon the solvent was removed under reduced pressure. The residue was treated with water and extracted with pentane. Concentration and PTLC (SiO_2, 3:2 hexane–CH_2Cl_2) gave 115 mg (95%) of pure **27** as an oil: ^{1}H NMR δ 0.7–2.1 (b), 1.49 (s, 9 H), 2.5–2.8 (b); ^{13}C NMR δ 22.7, 23.8, 25.7, 27.9, 28.4, 32.5, 33.1, 44.7, 79.6, 122.0, 158.9, 167.7. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.25; H, 10.05.

Radical Cyclization of 26. A solution containing 47 mg (0.1 mmol) of **26**, 84 μL (0.3 mmol) of Bu_3SnH, and 20 mg of AIBN in 4 mL of benzene was heated under reflux (argon) for 1 h. An additional 85 μL of Bu_3SnH was added and heating was continued for 2 h. The residue obtained after solvent removal was treated with saturated $NaHCO_3$ solution and pentane and stirred for 10 min. Concentration of the pentane extract and PTLC (SiO_2, 4:1 hexane–CH_2Cl_2, 3X development) gave 18 mg (80%) of **28** as an oil: ^{1}H NMR (300 MHz) δ 1.32 (m, 1 H), 1.482 (s, 9 H), 1.58 (m, 1 H), 1.82 (m, 2 H), 2.08 (m, 1 H), 2.38 (m, 1 H), 2.52 (m, 1 H), 2.68 (m, 1 H), 2.91 (m, 1 H), 5.03 (m, 2 H), 5.68 (m, 1 H); ^{13}C NMR δ 24.1, 28.4, 31.2, 32.9, 38.0, 46.1, 79.4, 113.6, 116.1, 136.6, 166.7, 169.4. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H.9.98. Found: C, 75.97; H, 10.10.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **1c**, **10**, and **26** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.