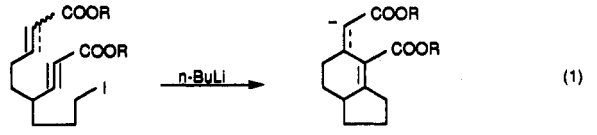
Tandem Metal-Halogen Exchange-Initiated Conjugate Addition Reactions of Conjugated Acetylenic Esters

Manning P. Cooke, Jr.,* and D. Gopal

Department of Chemistry, Washington State University, Pullman, Washington 99164

Received September 16, 1993

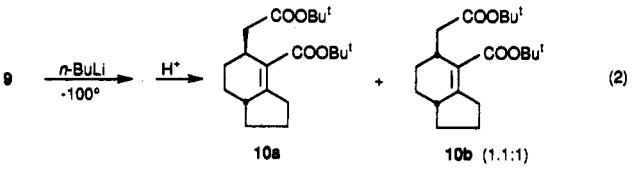
We have previously shown that rapid metal-halogen exchange reactions may be used to initiate cyclization reactions through the formation of highly nucleophilic centers which may then undergo intramolecular reactions with internal electrophilic centers.[1,2] Lithium-iodine exchange-initiated intramolecular conjugate addition reactions of ω-iodo-α,β-unsaturated esters have been especially successful and we have recently found that the enolates formed in such reactions may further undergo intramolecular cycloalkylation[1f] and Michael reactions[1g] leading to the stereoselective formation of bicyclic carbocycles. Conjugated acetylenic esters also undergo such metal-halogen exchange-initiated conjugate addition reactions, but intermediate allenoate anions generated in these addition reactions are more reactive and must be trapped immediately either intermolecularly by an already present electrophile or through an intramolecular cycloalkylation reaction.[2] We have now examined the use of internal activated olefinic or acetylenic units as electrophiles in such reactions (eq 1) and herein report the results of a model study.



(1)

We began our study with cyclization substrate **9** which was prepared as shown in Scheme 1. Alkylation of the enolate of ester **1** with 1-chloro-3-iodopropane gave chloro ester **2** in 53% yield. Reduction of **2** with diisobutylaluminum hydride (DIBAL) gave the corresponding aldehyde **3** (90%). This aldehyde was treated with the Wittig reagent prepared by the Corey-Fuchs protocol[3] (Ph_3P, CBr_4, Zn), giving dibromide **4** (81%). Treatment of this dibromide with 2 equiv of *n*-BuLi at -78 °C gave an intermediate lithium acetylide[3] which was acylated with di-*tert*-butyl dicarbonate (BOC_2O), giving acetylenic ester **5** in 89% yield. This ester as well as the other acetylenic esters reported herein was somewhat unstable, becoming viscous after several days. Decomposition could be markedly suppressed by the reconcentration of solutions in commercial diethyl ether (which contains a small amount of butylated hydroxytoluene as an inhibitor) and storing them at -20 °C. Hydrolysis of the acetal moiety in **5** (HCl-H_2O-THF) gave the corresponding aldehyde **6** (88%) which underwent Horner-Emmons-Wittig (HEW) olefination with the anion of phosphonate **7**, giving *E* ester **8** (89%). Halogen exchange (NaI, acetone) gave the desired cyclization substrate **9** in 89% yield.

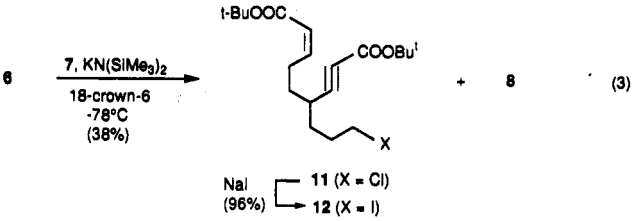
Treatment of **9** with *n*-BuLi at -100 °C in THF gave, after protonation of resulting enolates, a 1.1:1 mixture of two isomeric bicyclic esters, **10a** and **10b**, in a combined isolated yield of 61% (eq 2). These isomeric esters could



(2)

be separated by chromatography and the structure of the higher melting cis isomer **10b** was established by X-ray crystallographic analysis.[4] The lack of stereoselectivity in the second Michael addition ring-closure step led us to examine the cyclization of *Z* isomer **12** insomuch as we had previously observed that the stereoselectivity of an analogous ring-closure with a simple enolate (as opposed to an allenolate in the present case) was found to be markedly dependent on the stereochemistry of the terminal Michael acceptor.[1g]

The *Z* isomer **12** was prepared from aldehyde **6** and phosphonate **7** (eq 3) using the HEW modification of Still[5] giving an approximately equal mixture of *Z* and *E* isomers **11** and **8**, respectively, which were chromatographically



(3)

separated. Halide exchange (NaI, acetone) gave the desired iodide **12** in 96% yield. Treatment of **12** with *n*-BuLi as described for the cyclization of **9** gave a 3.5:1 mixture of **10a** and **10b** in 65% yield. Thus modest stereoselectivity in the second Michael reaction is observed with *Z* olefin geometry. An explanation for this increased selectivity from an examination of molecular models is less than convincing insomuch as chelation effects[6] as well as conformational effects may be involved.

We also examined cyclization reactions of **17** in which both acceptors are activated acetylene units. Substrate **17** was prepared as shown in Scheme 2. Hydrolysis of **4** gave aldehyde **13** (93%) which gave tetrabromide **14** (71%) upon Wittig olefination. Treatment of **14** with 4 equiv of *n*-BuLi gave an intermediate bis-acetylide which was protonated in order to allow the purification of diyne **15** (87%). Reconversion of **15** into the bis-acetylide with 2 equiv of *n*-BuLi followed by acylation with BOC_2O gave diester **16** (72%). Halide exchange (NaI, acetone) gave the desired cyclization substrate **17** (83%).

(1) (a) Cooke, M. P., Jr. *J. Org. Chem.* **1984**, *49*, 1144. (b) Cooke, M. P., Jr.; Houpis, I. *Tetrahedron Lett.* **1985**, *26*, 3643. (c) Cooke, M. P., Jr.; Houpis, I. *Ibid.* **1985**, *26*, 4987. (d) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381. (e) Cooke, M. P., Jr. *Ibid.* **1992**, *57*, 1495. (f) Cooke, M. P., Jr. *Ibid.* **1993**, *58*, 2910. (g) Unpublished results with D. Gopal.

(2) Cooke, M. P., Jr. *J. Org. Chem.* **1993**, *58*, in press.

(3) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

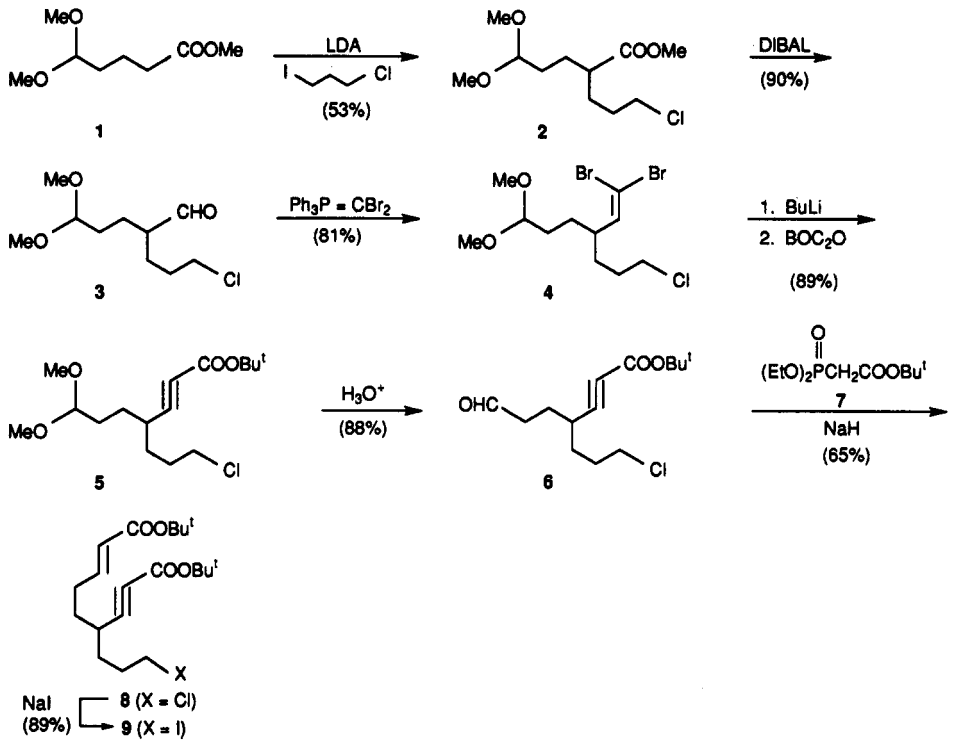
(4) The author has deposited atomic coordinates and other data for **10b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(5) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

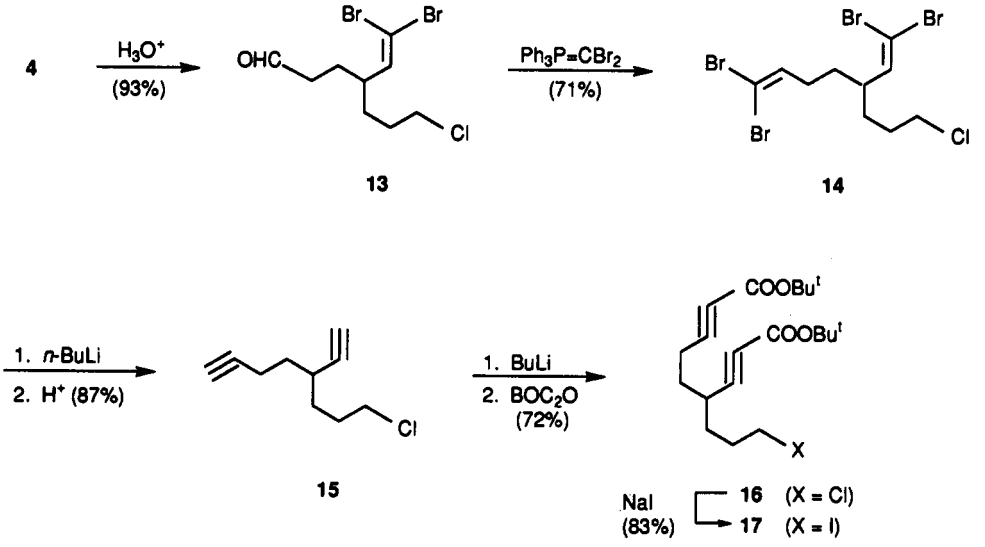
(6) (a), Oare, D. A.; Heathcock, C. H. *Topics in Stereochemistry*, Vol. 19, J. Wiley and Sons, New York, 1989, pp 227-407. (b) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132. (c) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157. (d) Viteva, L.; Stefanousky, Y. *Tetrahedron Lett.* **1990**, *31*, 5649.

0022-3263/94/1959-0260$04.50/0

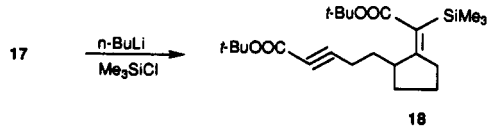
Scheme I



Scheme II



Treatment of diyne 17 with *n*-BuLi at −100 °C using the standard procedure resulted in a complex mixture of products which we were unable to resolve. In light of our previous experience,[2] it seems likely that the desired bicyclic allenolate (or perhaps the allenolate resulting from the first conjugate addition step) engages in side reactions in the absence of a trapping agent. We therefore conducted the cyclization reaction in the presence of 4 equiv of Me_3SiCl in hopes of C-silylating[7] the desired bicyclic allenolate. In the event (eq 4), a less complex mixture was obtained



(4)

from which the major product, monocyclic derivative 18, was isolated in approximately 30% yield (85% pure) by preparative thin-layer chromatography. The structure of 18 was deduced from its ^{13}C NMR spectrum and those of model compounds.[2] Peaks at δ 82.3 and 86.5 (conjugated acetylene), 152.8 and 77.2 (acetylenic ester), 164.6 (cyclopentyidene), 171.4 (carbonyl carbon of the silylated ethylenic ester), and −0.2 (TMS) strongly support this structure. Unfortunately, the trapping agent, Me_3SiCl, intercepted the initial allenolate resulting from the first conjugate addition reaction, preventing the execution of the second Michael addition reaction. A less reactive electrophile can perhaps be found which will permit the second conjugate addition reaction to occur while ultimately trapping the final allenolate anion before undesired side reactions occur.

(7) We have found that allenolates of acetylenic *tert*-butyl esters undergo C-silylation with TMSCl.[2] Also see: Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841.

In summary, we have demonstrated the feasibility of constructing bicyclic derivatives through tandem metal–halogen exchange-initiated conjugate addition reactions in which allenolate anions resulting from the intramolecular conjugate addition of highly nucleophilic centers to an activated carbon–carbon triple bond participate in further conjugate addition reactions with internal activated ethylenic units. The stereoselectivity of the intramolecular Michael addition reaction of an allenolate with an internal α,β-unsaturated ester has been found to be a function of acceptor olefin stereochemistry. Attempts to prepare a bicyclic derivative through tandem Michael reactions of a substrate containing two activated acetylenic units were not successful, owing to the reactivity of the product allenolate anion produced.

Experimental Section

NMR spectra were recorded in $CDCl_3$ at 90 MHz (^1H) and at 22.5 MHz (^{13}C) unless otherwise noted. Operations involving solvent removal under reduced pressure or concentration refer to the use of a Buchi rotoevaporator operated at water aspirator pressure. Preparative thick-layer chromatography (PTLC) was performed on 20- × 20-cm glass plates coated with a 1–2-mm layer of Merck 60 PF-254 silica gel. Baker 60–200-mesh silica powder was used for column (flash) chromatography. Gas chromatography employed a 12-m cross-linked methyl silicone capillary column. Bulb-to-bulb distillations of the Kugelrohr type were conducted at the air at oven temperatures and pressures cited. Melting points and boiling points are uncorrected. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or Desert Analytics, Tucson, AZ.

All reactions involving air-sensitive materials were conducted under an argon atmosphere. Reactions said to be conducted at −78 °C employed a dry ice–acetone bath and those said to be conducted at −100 °C used a MeOH liquid–solid bath cooled with liquid N_2. Alkyllithium reagents were obtained from Aldrich Chemical Co. Tetrahydrofuran (THF) was distilled from sodium–benzophenone prior to use.

Methyl 2-(3-Chloropropyl)-5,5-dimethoxypentanoate (2). A solution containing 4.2 mL (30 mmol) of diisopropylamine in 60 mL of THF was cooled to -78 °C and with stirring treated with 14.0 mL (24 mmol) of 1.6 N *n*-BuLi (hexane). After 10 min, 3.42 g (20 mmol) of methyl 5,5-dimethoxypentanoate (1)[8] was added dropwise and stirring was continued for 12 min. 1-Chloro-3-iodopropane (2.6 mL, 24 mmol) was added followed by 4 mL of HMPA and stirring was continued for 1.3 h whereupon the cooling bath was removed. After 10 min, 200 μL of HOAc was added and the mixture was concentrated in vacuo. The residue was treated with water and extracted with pentane. Distillation gave 2.70 g (53%) of 2: bp 107–109 °C (0.2 mm); ^1H NMR δ 1.4–1.9 (b, 8 H), 2.3 (b, 1 H), 3.30 (d, 6 H), 3.52 (t, J = 6.2 Hz, 2 H), 3.68 (s, 3 H), 4.33 (t, J = 5.1 Hz, 1 H); ^{13}C NMR δ 27.2, 29.6, 30.3 (2C), 44.5, 51.5, 52.6, 53.0, 104.2, 175.9. Anal. Calcd for $C_{11}H_{21}ClO_4$: C, 52.27; H, 8.38. Found: C, 52.66; H, 8.47.

2-(3-Chloropropyl)-5,5-dimethoxypentanal (3). A solution containing 1.26 g (5.0 mmol) of 2 in 18 mL of toluene was cooled to −78 °C and 6.6 mL (6.6 mmol) of 1 M DIBAL (in hexane) was added over 5 min with vigorous stirring. After 1 h, 250 μL of MeOH was added and stirring was continued for 5 min whereupon 1 mL of 1:1 MeOH–H_2O was added and the mixture was stirred at 20 °C for 10 min. Sodium hydroxide solution (1 mL, 4 N) was then added and after 10 min several grams of Na_2SO_4 was added to coaggulate the gelatinous aqueous phase. The organic phase was separated and concentrated and the residue purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2–EtOAc), giving 1.00 g (90%) of 3: ^1H NMR δ 1.5–1.9 (b, 8 H), 2.28 (b, 1 H), 3.31 (s, 6 H), 3.55 (m, 2 H), 4.35 (m, 1 H), 9.60 (d, J = 2.4 Hz, 1 H); ^{13}C NMR δ 23.5, 25.9, 29.9, 44.6, 50.7, 52.9, 53.0, 104.3, 204.0.

4-(2,2-Dibromovinyl)-7-chloro-1,1-dimethoxyheptane (4). A mixture containing 10.6 g (32 mmol) of CBr_4, 8.4g (32 mmol) of triphenylphosphine, and 2.1 g (32 mmol) of Zn dust in 90 mL of dry CH_2Cl_2 was vigorously stirred for 24 h whereupon 1.68 g (7.5 mmol) of 3 in 10 mL of CH_2Cl_2 was added.[3] After 1 h, 90 mL of hexane was added and the mixture was filtered. Concentration of the filtrate and flash chromatography (CH_2Cl_2) gave 2.33 g (81%) of 4 as an oil: ^1H NMR δ 1.3–2.0 (m, 9 H), 3.32 (s, 6 H), 3.53 (t, J = 5.8 Hz, 2 H), 4.34 (t, J = 5.1 Hz, 1 H), 6.12 (d, J = 9.7 Hz, 1 H); ^{13}C NMR δ 29.3, 30.0, 31.6, 43.0, 44.8, 52.8, 53.0, 89.2, 104.3, 162.3. Anal. Calcd for $C_{11}H_{19}Br_2ClO_2$: C, 34.90; H, 5.06. Found: C, 34.85; H, 5.06.

***tert*-Butyl 4-(3-Chloropropyl)-7,7-dimethoxy-2-heptynoate (5).** A stirred solution containing 2.0 g (5.3 mmol) of 4 in 60 mL of THF was treated at −78 °C with 7.0 mL (11.0 mmol) of 1.6 N *n*-BuLi added over 2 min. After 30 min, a solution containing 2.4 g (11.0 mmol) of BOC_2O in 6 mL of THF was added. The mixture was warmed to 20 °C and stirred for 1 h. Solvent was removed under reduced pressure and the residue was treated with water and extracted with pentane. The extracts were washed with water, dried (Na_2SO_4), and concentrated. Chromatography (SiO_2, CH_2Cl_2 then 30:1 CH_2Cl_2–EtOAc) gave 1.50 g (89%) of 5 as an oil: ^1H NMR δ 1.3–2.0 (m, 9 H), 1.48 (s, 9 H), 3.32 (s, 6 H), 3.56 (t, J = 6.1 Hz, 2 H), 4.37 (t, J = 5.6 Hz, 1 H); ^{13}C NMR δ 28.1, 29.1, 30.2, 30.9, 31.5, 44.6, 52.7, 53.1, 76.3, 83.1, 88.2, 104.2, 152.8; HRMS(CI) MH^+ calcd for $C_{16}H_{28}ClO_4$ 319.1676, obsd 319.1679.

***tert*-Butyl 4-(3-Chloropropyl)-7-oxo-2-heptynoate (6).** To a solution containing 1.40 g (4.4 mmol) of 5 in 25 mL of THF was added 4 N HCl until turbidity (phase separation) occurred. The mixture was stirred for 0.5 h with periodic addition of 4 N HCl to keep the mixture near saturation. THF was removed under reduced pressure at 20 °C and the aqueous phase was extracted with pentane. The extracts were washed with H_2O and 10% $NaHCO_3$ solution, dried, and concentrated ,giving 1.17 g (98%) of 6 as an unstable oil: ^1H NMR δ 1.48 (s, 9 H), 1.5–2.1 (b, 6 H), 2.4–2.8 (m, 3 H), 3.57 (t, J = 6.3 Hz, 2 H), 9.80 (t, J = 1.2 Hz, 1 H); ^{13}C NMR δ 28.0, 26.4, 30.1, 30.5, 31.5, 41.5, 44.5, 76.8, 83.2, 87.2, 152.6, 201.1.

Di-*tert*-butyl 4-(3-Chloropropyl)non-2-yn-(*E*)-7-enedioate (8). NaH (250 mg, 56%, 6.0 mmol) was freed of oil by washing with pentane and then suspended in 25 mL of THF. To this stirred slurry was added over 3 min 1.1 g (4.4 mmol) of *tert*-butyl diethylphosphonoacetate (7).[9] After 15 min, the mixture was cooled with an ice bath and 1.0 g (3.7 mmol) of 6 in 5 mL of THF was added over 1 min. After 3 min, the bath was removed and stirring was continued at 20 °C for 0.5 h. Solvent was removed under reduced pressure and the residue was treated with water and extracted with pentane. The dried (Na_2SO_4) extracts were concentrated and the crude product purified by chromatography (SiO_2, CH_2Cl_2), giving 880 mg (65%) of 8 as an oil: ^1H NMR δ 1.2–2.0 (b, 6 H), 1.48 (s, 9 H), 1.50 (s, 9 H), 2.1–2.6 (m, 3 H), 3.57 (t, J = 6.3 Hz, 2 H), 5.77 (dt, J = 15.6, 1.5 Hz, 1 H), 6.82 (dt, J = 15.6, 6.6 Hz, 1 H); ^{13}C NMR δ 28.0, 28.1, 29.6, 30.1, 30.6, 31.4, 32.6, 44.5, 76.6, 80.2, 83.1, 87.6, 124.0, 146.1, 152.7, 165.8.

Di-*tert*-butyl 4-(3-Iodopropyl)non-2-yn-(*E*)-7-enedioate (9). In a dry 50-mL flask, previously washed with 4 N NaOH and then with water, were placed 880 mg (2.4 mmol) of 8, 10 g of NaI, and 20 mL of acetone. The mixture was heated at reflux for 22 h, cooled, and then concentrated in vacuo. The residue was treated with water and twice extracted with pentane. The extracts were washed with water, dried (Na_2SO_4), and concentrated, giving 980 mg (89%) of 9 as an oil: ^1H NMR δ 1.2–2.0 (b, 6 H), 1.48 (s, 9 H), 1.50 (s, 9 H), 2.1–2.6 (b, 3 H), 3.21 (t, J = 6.6 Hz, 2 H), 5.78 (dt, J = 15.6, 1.4 Hz, 1 H), 6.83 (dt, J = 15.6, 6.8 Hz, 1 H); ^{13}C NMR δ 5.9, 28.0, 28.1, 29.6, 30.3, 30.8, 32.5, 34.8, 76.6, 80.2, 83.1, 87.6, 124.0, 146.0, 152.7, 165.7. Anal. Calcd for $C_{20}H_{31}IO_4$: C, 51.95; H, 6.76. Found: C, 51.91; H, 6.80.

Cyclization of 9. A stirred solution containing 225 mg (0.48 mmol) of 9 in 4 mL of THF was treated at −100 °C with 0.35 mL (0.56 mmol) of 1.6 N *n*-BuLi added over 30 s. The solution was allowed to warm to −70 °C over 15 min whereupon 100 μL of HOAc was added. Solvents were removed under reduced pressure and the residue was treated with water and extracted with pentane. The extracts were washed with water then aqueous

(8) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

(9) Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M.; Sutton, M. J. *Tetrahedron* **1976**, *32*, 275.

$NaHCO_3$ and after drying over Na_2SO_4 they were concentrated. Capillary GLPC indicated the presence of **10a** and **10b** in a ratio of 1.1:1. Flash chromatography (SiO_2, CH_2Cl_2) gave a mixture (100 mg, 61%) of **10a** and **10b**, which were separated by PTLC (CH_2Cl_2, two developments). **10b** (higher R_f and t_R): mp 70–72 °C; ^1H NMR (300 MHz) δ 1.00–1.30 (m, 2 H), 1.35–1.70 (b, 3 H), 1.45 (s, 9 H), 1.49 (s, 9 H), 1.75–1.87 (m, 2 H), 1.87–2.0 (m, 1 H), 2.04 (dd, J = 15.2, 10.9 Hz, 1 H), 2.12–2.25 (b, 1 H), 2.52 (ddd, J = 15.2, 2.5, 1.5 Hz, 1 H), 2.62–2.88 (m, 2 H), 2.97–3.07 (m, 1 H); ^{13}C NMR δ 23.0 23.8, 27.1, 28.2, 28.4, 31.3, 32.5, 32.9, 40.9, 45.6, 79.8, 79.9, 124.3, 160.8, 166.7, 172.3. Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.16; H, 9.51. The structure of **10b** was confirmed by X-ray crystallographic analysis.[4] **10a** (lower R_f, shorter t_R) mp 47–49 °C; ^1H NMR (300 MHz) δ 0.80–1.83 (b, 5 H), 1.42 (s, 9 H), 1.50 (s, 9 H), 1.87–2.28 (m, 5 H), 2.38–2.59 (m, 2 H), 2.70–2.87 (m, 1 H), 2.87–3.03 (m, 1 H); ^{13}C NMR δ 23.9, 27.9, 28.2, 28.4, 29.2, 32.5, 33.2, 33.9, 41.4, 44.1, 80.0 (2C), 125.7, 158.9, 167.3, 172.2.

Di-*tert*-butyl 4-(3-Chloropropyl)non-2-yn-(*Z*)-7-enedioate (11). Using the method of Still,[5] a solution containing 388 mg (1.54 mmol) of *tert*-butyl diethylphosphonoacetate and 2.0 g of 18-crown-6 was treated dropwise with 3.1 mL (1.55 mmol) of 0.5 N $KN(SiMe_3)_2$ (in PhMe) at −78 °C. After 5 min, 420 mg (1.54 mmol) of **6** in 2 mL of THF was added dropwise and stirring continued for 2 h at −78 °C. The mixture was allowed to come to 20 °C whereupon the solvents were removed under reduced pressure. The residue was treated with water and twice extracted with hexane. The extracts were washed with water and dried (Na_2SO_4) and the crude product obtained upon concentration gave, upon PTLC (CH_2Cl_2) 128 mg (22%) of **8** (lower R_f) and 92 mg (16%) of **11** as an oil: ^1H NMR δ 0.8–3.0 (m, 9 H), 1.49 (s, 18 H), 3.56 (t, J = 6.3 Hz, 2 H), 5.70 (dt, J = 11.5, 1.5 Hz, 1 H), 6.10 (dt, J = 11.5, 6.3 Hz, 1 H); ^{13}C NMR δ 26.6, 28.1, 28.3, 30.2, 30.9, 31.2, 33.6, 44.6, 76.5, 80.3, 83.1, 88.1, 122.6, 146.7, 152.9, 165.8.

Di-*tert*-butyl 4-(3-Iodopropyl)non-2-yn-(Z)-7-enedioate (12). In the manner described above for the preparation of **9**, 92 mg (0.25 mmol) of **11** gave 110 mg (96%) of **12** as an oil: ^1H NMR δ 0.8–3.0 (m, 9 H), 1.49 (s, 18 H), 3.20 (t, J = 6.6 Hz, 2 H), 5.70 (dt, J = 11.5, 1.5 Hz, 1 H), 6.10 (dt, J = 11.5, 7.1 Hz, 1 H); ^{13}C NMR δ 5.9, 28.0, 28.3, 26.6, 30.6, 30.9, 33.6, 34.7, 76.3, 80.2, 83.0, 88.1, 122.5, 146.7, 152.7, 165.7.

Cyclization of 12. In the manner described above for the cyclization of **9**, 125 mg (0.27 mmol) of **12** gave 59 mg (65%) of a 7:2 mixture of **10a** and **10b**.

1,1,7,7-Tetrabromo-3-(3-chloropropyl)-1,6-heptadiene (14). In the manner described above for the preparation of **6**, hydrolysis of 1.05 g (2.8 mmol) of **4** gave 870 mg (93%) of unstable aldehyde **13** which was immediately added to Wittig reagent prepared from 6.64 g of CBr_4, 5.24 g of Ph_3P and 1.31 g Zn in 50 mL of CH_2Cl_2 as described in the preparation of **4**. Workup and chromatography (SiO_2, hexane) gave 956 mg (71%) of **14** as an oil: ^1H NMR δ 1.0–2.6 (b, 9 H), 3.54 (t, J = 6.1 Hz, 2 H), 6.13 (d, J = 9.8 Hz, 1 H), 6.38 (t, J = 7.3 Hz, 1 H); ^{13}C NMR δ 29.9, 30.6, 31.4, 32.3, 42.6, 44.8, 89.6, 89.8, 137.6, 141.5.

3-(3-Chloropropyl)-1,6-heptadiyne (15). A solution containing 950 mg (1.94 mmol) of **14** in 30 mL of THF was cooled to −78 °C and with stirring treated with 5.0 mL (8.0 mmol) of 1.6 N *n*-BuLi over 3 min. After 1.5 h, 200 μL of AcOH was added and the mixture was warmed to 20 °C. Solvent was removed in vacuo and the residue treated with water and extracted twice with pentane. The extracts were washed sequentially with water, aqueous $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. Chromatography (SiO_2, 9:1 hexane–Et_2O) gave 282 mg (87%) of **15** as an oil: ^1H NMR δ 0.7–2.7 (b, 11 H), 3.57 (t, J = 6.5 Hz, 2 H); ^{13}C NMR δ 16.4, 30.0, 30.2, 31.8, 33.7, 44.7, 68.8, 70.6, 83.5, 85.8. Anal. Calcd for $C_{10}H_{13}Cl$: C, 71.21; H, 7.77. Found: C, 71.14; H, 7.97.

Di-*tert*-butyl 4-(3-Chloropropyl)-2,7-nonadiynoate (16). A solution of 324 mg (1.9 mmol) of **15** in 25 mL of THF was treated at −78 °C with 2.5 mL (4.0 mmol) of 1.6 N *n*-BuLi added dropwise. After 15 min, a solution containing 880 mg (4.0 mmol) of BOC_2O in 5 mL of THF was added and stirring was continued for 0.5 h. The mixture was stirred at 20 °C for 3 h whereupon 0.2 mL of HOAc was added and the solvent removed under reduced pressure. The residue was treated with water and extracted with hexane. The extracts were washed successively with water, aqueous $NaHCO_3$, and water and then dried (Na_2SO_4). Concentration gave 510 mg (72%) of **16** as an oil: ^1H NMR δ 1.0–2.3 (b, 6 H), 1.49 (s, 18 H), 2.4–2.8 (m, 3 H), 3.57 (t, J = 6.2 Hz, 2 H); ^{13}C NMR δ 16.7, 28.0 (6C), 30.1, 30.3, 31.7, 32.2, 44.4, 75.2, 76.9, 83.1, 83.2, 85.0, 86.7, 152.6 (2 C=O).

Di-*tert*-butyl 4-(3-Iodopropyl)-2,7-nonadiynoate (17). In the manner described above for the preparation of **9**, 550 mg (1.5 mmol) of **16** gave 570 mg (83%) of **17** after chromatography (SiO_2, 7:3 CH_2Cl_2–hexane): ^1H NMR δ 1.1–2.2 (b, 6 H), 1.50 (s, 18 H), 2.3–2.8 (m, 3 H), 3.22 (t, J = 6.6 Hz, 2 H); ^{13}C NMR δ 5.7, 16.7, 28.0 (6 CH3), 30.0, 30.7, 32.1, 34.6, 75.2, 76.8, 83.1, 83.2, 85.0, 86.7, 152.5 (2 C=O).

Cyclization of 17 in the Presence of Me_3SiCl. A solution containing 184 mg (0.4 mmol) of **17** and 200 μL (1.6 mmol) of Me_3SiCl was stirred at −78 °C and 0.3 mL (0.48 mmol) of 1.6 N *n*-BuLi was added over 40 s. After 3 min, the cooling bath was removed and the mixture was allowed to warm to 20 °C. Solvent was removed under reduced pressure and the residue was treated with water and extracted with pentane. The extracts were washed with H_2O, aqueous $NaHCO_3$ and H_2O and dried (Na_2SO_4). Concentration gave a mixture containing **18** (58% of the volatiles by GC analysis) and a number of minor components. The major product (**18**) was obtained in approximately 30% yield, 85% pure, by PTLC (9:1 hexane–Et_2O) and contained ^{13}C NMR peaks at δ 17.3, 23.4, 28.0, 28.3, 29.8, 31.9, 32.6, 43.7, 77.2, 80.5, 82.8, 86.5, 152.8, 164.6, 171.4.

Acknowledgment. We thank the National Science Foundation for support of this work.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for **3**, **5**, **6**, **8**, **11**–**14**, and **16**–**18** (20 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. X-ray data for **10b** is also available.[4]