Stereochemistry of Metal–Halogen Exchange-Initiated Intramolecular Conjugate Addition Reactions in the Construction of 5-Membered Carbocycles

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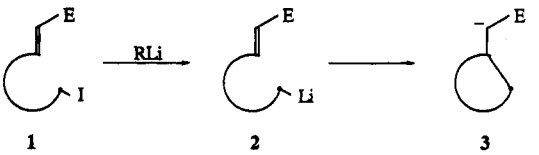
The stereochemistry of some lithium–iodine exchange-initiated cyclization reactions of model ω-iodo, γ-substituted activated olefins has been studied. The stereoselectivities of these anionic cyclization reactions have been found to be a function of the olefin activator employed, reaction conditions, Michael acceptor olefin geometry, the nature of the γ-substituent, and, in some cases, the presence of additives. Cyclization reactions of iodides possessing *E* olefin geometry give a moderate preference for trans cyclopentane formation while *Z* olefin geometry leads to extremely high (>300:1) trans product selectivity. Cyclization reactions of *E* olefins under radical conditions were found to be slightly more trans-selective than those observed under anionic conditions although *Z* olefin geometry again promotes very high trans product selectivity. The presence of the allylic methoxyl group in (*E*)-**7d** leads to cis selectivity under both anionic and radical conditions. Intramolecular complexation involving the reactive carbon center and the methoxyl group is suggested in both modes as a possible explanation for this cis product selectivity.

Introduction

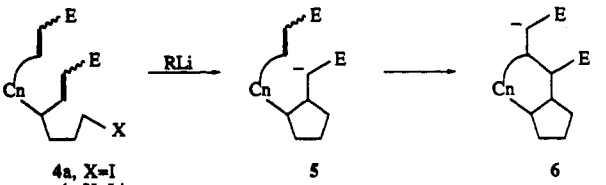
Intramolecular reactions of reactive carbon centers with carbon–carbon multiple bonds are of considerable importance in the construction of cyclic systems.[1] Cyclization reactions of carbocations[2] and radicals[3] have received greater attention than those involving electron-rich (carbanionic) centers. Studies of anionic cyclizations have centered largely on the intramolecular classical Michael reactions of enolates[4] and intramolecular carbometallation reactions of which the cyclization reactions of akenyl-[5] and alkynyllithium[6] derivatives are prominent.

We have shown that metal–halogen exchange reactions may be used to introduce internal nucleophilic centers which may then undergo intramolecular conjugate addition reactions leading to 3-, 4-, 5-, and 6-membered rings as shown in Scheme I.[7] Initial efforts[7a] centered on the use

Scheme I



Scheme II



of charge-protected olefin-activating groups such as acyl ylides (1, E = C(O)C(PPh_3)COOR) whose carbonyl groups, by virtue of proximal negative charge, are highly resistant to nucleophilic attack by either the metalating agent (RLi) or the internally generated lithiated carbon center. It became apparent that lithium–iodine exchange reactions of primary iodides are in many cases so rapid[8] that extraordinary protection of the Michael acceptor moiety often is not required and the use of simple unsaturated *tert*-butyl esters (1, E = $COOBu^t$) gives excellent results.[7b]

The intramolecular Michael addition approach offers a number of advantages over cyclization reactions of unactivated olefins. Lithium–iodine exchange-initiated cyclization reactions of substrates containing unactivated olefins are relatively slow, often requiring the presence of base-enhancing accelerating agents (e.g., TMEDA), leading to problems of adventitious quenching of highly basic intermediates and products[5] and are, in general, restricted to monosubstituted olefins. On the other hand, cyclizations involving activated olefins (Michael acceptors) are usually rapid, even at low temperatures (−100 °C), tolerate olefin substitution, and lead to relatively stable anionic products such as enolates which are useful in subsequent reactions.

We desired to extend the scope of these exchange-initiated conjugate addition reactions to systems involving sequential Michael reactions, thereby giving functionalized bicyclic ring systems as shown in Scheme II. Of crucial

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(2) (a) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, 265. (c) van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152. (d) Speckamp, N. *Recl. J. R. Neth. Chem. Soc.* **1981**, *100*, 345.
(3) (a) Julia, M. *Rec. Chem. Progr.* **1964**, *25*, 3. (b) Nonhebel, D. C.; Walton, J. *Free Radical Chemistry*; Cambridge University Press: Cambridge, 1974; Chapter 14. (c) Hart, D. *J. Science* **1984**, *223*, 883. (d) Giese, B. *Radicals in Organic Synthesis*; Pergamon: New York, 1986. (e) Neumann, W. P. *Synthesis* **1987**, 665. (f) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (g) Curran, D. P. *Synthesis* **1988**, *417*, 489.
(4) (a) General review: Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467. Recent samples intramolecular Michael reactions: (b) Stork, G.; Winkler, J. D.; Shiner, C. *J. Am. Chem. Soc.* **1982**, *104*, 3767. (c) Stork, G.; Winkler, S. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, *24*, 465. (d) Berthiaume, G.; Lavallee, J.-F.; DesLongchamps, P. *Ibid.* **1986**, *27*, 5451. (e) Marion, J. P.; Long, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 7916. (f) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *Ibid.* **1989**, *111*, 4533. (g) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 113.
(5) (a) Drozd, V. N.; Ustynyuk, Y. A.; Tseleva, M. A.; Dmitrievi, L. B. *J. Gen. Chem. U.S.S.R.* **1969**, *39*, 1951. (b) Smith, M. J.; Wilson, S. E. *Tetrahedron Lett.* **1981**, *22*, 4615. (c) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861, 1865. (d) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. J. *Am. Chem. Soc.* **1987**, *109*, 2442. (e) Chamberlin, A. R.; Bloom, S. H.; Ceruini, L. A.; Fotsch, C. H. *Ibid.* **1988**, *110*, 4788. (f) Broka, C. A.; Shen, T. *Ibid.* **1989**, *111*, 2981. (g) Paquette, L. A.; Gilday, J. P.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5044. (h) Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc.* **1989**, *111*, 765. (i) Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742.
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(7) (a) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381. (b) Cooke, M. P., Jr. *Ibid.* **1984**, *49*, 1144. (c) Organolithium intermediates are depicted throughout as monomers although they are likely aggregates: Wakerfield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: New York, 1974.
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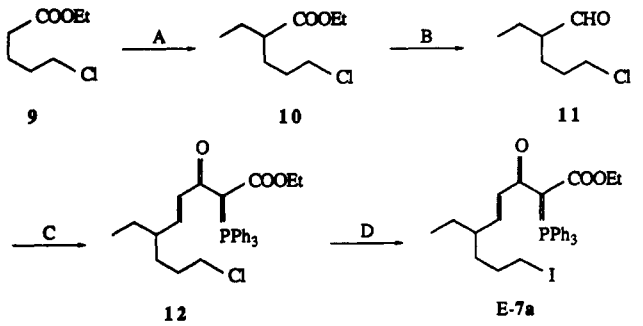
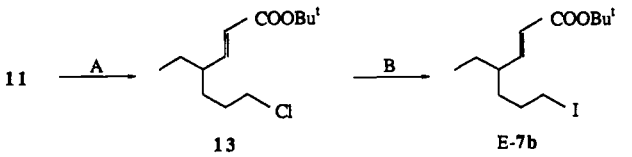
Scheme III[a]



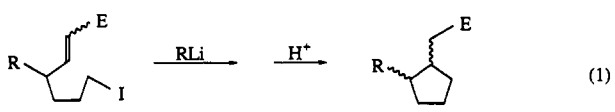
[a] (A) LDA, −78 °C then EtI (94%); (B) DIBAL, −78 °C (88%); (C) $(EtO)_2P(O)C(PPh_3)COOEt$, NaH, THF (94%); (D) NaI, acetone (93%).

Scheme IV[a]



[a] (A) $(EtO)_2P(O)CH_2COOBu^t$, NaH, THF (90%); (B) NaI, acetone (94%).

importance to this scheme is the stereochemistry of the ring junction-forming first addition step (**4b** → **5**). The analogous cyclization of (4-methyl-5-hexenyl)lithium to [(2-methylcyclopentyl)methyl]lithium occurs with encouragingly high stereoselective (t/c = 13.5)[5d] which led us to undertake a model study of exchange-initiated intramolecular conjugate addition reactions leading to 1,2-disubstituted cyclopentane derivatives (eq 1). We report



(1)

7 a E = C(O)C(PPh$_3$)COOEt, R = Et — 8
b E = COOBu^t, R = Et
c E = COOBu^t, R = t-Bu
d E = COOBu^t, R = OMe
e E = BMes$_2$, R = Et

herein the results of this study which examined the stereochemistry of this cyclization reaction as a function of the nature of the olefin activating group, *E*, reaction conditions, the stereochemistry of the acceptor olefin, and the nature of allylic substituents. The cyclization reactions of the same substrates under radical conditions (Bu_3SnH) also have been examined, and the results compared with those obtained under anionic cyclization conditions.

Results and Discussion

Acceptor Structure. The effect of acceptor structure on the stereochemical outcome of the reaction in eq 1 was examined using three olefin activators previously found by us to be effective in exchange-initiated cyclization reactions: a change-protected acyl phosphorane,[7a,9] (*E*)-**7a**, a *tert*-butoxycarbonyl group,[7b] (*E*)-**7b**, and a sterically encumbered boryl group,[10] (*E*)-**7e**. In each case a γ-ethyl group (**7**, R = Et) was employed as a reasonable model for

(9) (a) Cooke, M. P., Jr.; Goswami, R. *J. Am. Chem. Soc.* **1977**, *99*, 642. (b) Cooke, M. P., Jr. *Tetrahedron Lett.* **1979**, 2199. (c) Cooke, M. P., Jr.; Burman, D. L. *J. Org. Chem.* **1982**, *47*, 4955. (d) Cooke, M. P., Jr. *Ibid.* **1982**, *47*, 4963. (e) Cooke, M. P., Jr.; Jaw, J.-Y. *Ibid.* **1986**, *51*, 758.

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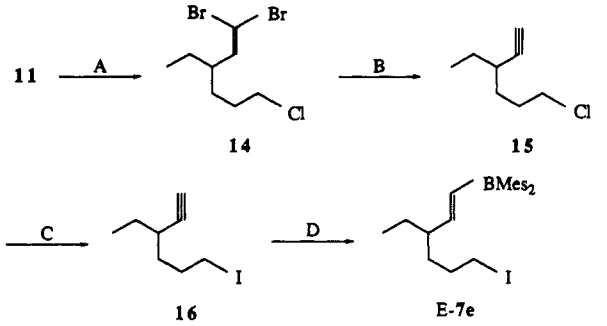
Scheme V[a]



[a] (A) CBr_4, Ph_3P, Zn (92%); (B) *n*-BuLi, THF, −78 °C then MeOH (100%); (C) NaI, acetone (80%); (D) Mes_2BH, THF (100%).

Table I. Lithium–Iodine Exchange-Initiated Cyclization Reactions of Unsaturated Iodides 7

entry	substrate	RLi	*T* (°C)	additive	t/c-8	yield (%)[a]
1	(*E*)-**7a**	*n*-BuLi	−78	–	3.3[b]	88[g]
2		*n*-BuLi	−100	–	3.3[b]	90[g]
3		*t*-BuLi	−78	–	4.7[b]	93[g]
4		*n*-BuLi	−78	LiI[c]	7.6	
5		*n*-BuLi	−78	LiI[d]	6.3	
6		*n*-BuLi	−78	$BF_3{\cdot}Et_2O$[e]	4.4	
7	(*E*)-**7b**	*n*-BuLi	−78	–	3.0	88
8		*t*-BuLi	−78	–	3.9	88
9		*n*-BuLi	−100	LiI[c]	3.2	82
10		*n*-BuLi	−78	LiI[d]	3.2	91
11		*n*-BuLi	−78	$BF_3{\cdot}Et_2O$[e]	3.4	82
12		*n*-BuLi	−78	TMEDA[f]	2.6	87
13	(*E*)-**7e**	*t*-BuLi	−100	–	6.2[h]	90[g]
14	(*Z*)-**7b**	*n*-BuLi	−100	–	>300	
15	(*E*)-**7c**	*n*-BuLi	−100	–	5.8	80[g]
16	(*E*)-**7d**	*n*-BuLi	−100	–	0.6	46
17		*n*-BuLi	−100	LiI[i]	0.6	
18		*n*-BuLi	−100	TMEDA[j]	1.0	
19		*t*-BuLi	−100	–	1.0	

[a] Yields determined by gas chromatography unless noted. [b] Determined on the corresponding esters **8** (E = COOEt). [c] *n*-BuLi–LiI (5.7 equiv) solution added to **7**. [d] *n*-BuLi added to **7** containing 19 equiv of LiI. [e] $BF_3{\cdot}Et_2O$ (2.4 equiv) added to **7** prior to the addition of RLi. [f] TMEDA (4 equiv) present with **7**. [g] Isolated yield. [h] Determined on the corresponding alcohols, **8** (E = OH). [i] *n*-BuLi solution containing 3 equiv of LiI was added to **7**. [j] TMEDA (2.8 equiv) was present with **7**.

the pendant side chain necessary to execute the sequential cyclization reactions in Scheme II. The syntheses of these substrates are outlined in Schemes III–V, respectively.

Chloro aldehyde **11**, the intermediate common to the synthesis of all three *E* substrates, was prepared (Scheme III) by the low-temperature alkylation of the enolate of ester **9** with EtI followed by partial reduction of the ester moiety in **10** with diisobutylaluminum hydride (DIBAL). It is noteworthy that the lithium enolate of **9** is well behaved at low temperatures (<−30 °C) despite the presence of the internal chloromethyl group owing to the slow rate of 4-membered ring formation. Horner–Emmons–Wittig (HEW) olefination[11] of **11** gave chloro olefin **12** which was converted to the required iodo olefin, (*E*)-**7a**, by NaI. In a similar manner, HEW olefination of **11** with the sodium salt of diethyl [(*tert*-butoxycarbonyl)methyl]phosphonate gave, after chloride–iodine exchange (NaI), iodo olefin (*E*)-**7b** (Scheme IV).

The required boron-activated iodo olefin (*E*)-**7e** was prepared as shown in Scheme V. Olefination of **11** gave somewhat unstable vinylidene dibromide **14** which was

(11) Cooke, M. P., Jr.; Biciunas, K. P. *Synthesis* **1981**, 283.

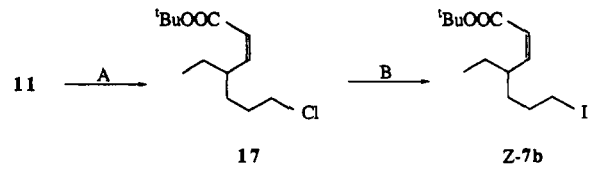
converted to acetylene **15** in nearly quantitative yield by the action of *n*-BuLi using the procedure of Corey and Fuchs.[12] Halogen exchange with NaI followed by hydroboration of the resulting iodoacetylene **16** with dimesitylborane[13] gave the desired vinyl borane, (*E*)-**7e**.

All three substrates cleanly cyclized in high yields (82–93% yield) when treated in THF with alkyllithium reagents at low temperatures (eq 1). Results of these cyclization experiments are shown in Table I. Trans/cis ratios of **8** were determined directly by capillary gas chromatography in the case of the *tert*-butyl esters, **8b**, but for analytical purposes it was necessary to convert nonvolatile ylides **8a** into the corresponding ethyl esters (**8**, E = COOEt) by heating the crude reaction products in acidic ethanol as previously described.[9a] Crude boranes **8e** were oxidized to the corresponding alcohols **8** (E = OH) with $NaOH-H_2O_2$[13] prior to analysis by capillary gas chromatography.

In all cases, the exchange and cyclization reactions were very fast. Rapid introduction of *n*-BuLi at −100 °C (<15 s) followed immediately (<10 s) by quenching with a proton source (MeOH) produced no detectable open-chain products resulting from interception (protonation) of the organolithium intermediate corresponding to **2** or any unreacted iodide **7**. Most notable is the poor cyclization stereoselectivity observed under standard conditions (Table I, entries 1, 7, and 13). Acyl ylide-activated iodo olefin (*E*)-**7a** and *tert*-butyl ester (*E*)-**7b** show only a moderate trans preference in the formation of **8** (t/c ≈ 3) while the trans selectivity with boron-activated (*E*)-**7e** is slightly higher (t/c = 6.2). This is in contrast with the 13.5 t/c ratio reported in the anionic cyclization of the analogous unactivated olefin, 1-iodo-4-methyl-5-hexene.[5d] The poorer selectivities with our activated olefins are likely the result of transition state changes brought about by the increased exothermicity of nucleophilic additions to olefins bearing carbanion-stabilizing groups and may be also a reflection of transition state structures that are significantly less restrictive than the concerted ones proposed for the carbolithiations of unactivated olefins.[5e,14] The higher trans selectivity observed in the case of (*E*)-**7e** may be the result of a steric effect induced by the presence of the large dimesitylboryl group or from a lower degree of olefin activation by the boryl group.

As can be seen in Table I, no significant improvement in selectivity results when cyclizations of (*E*)-**7a** and (*E*)-**7b** are conducted at even lower temperatures (−100 °C). The use of *tert*-butyllithium (entries 3 and 9) as metal–halogen exchange reagent resulted in a small improvement in trans selectivity, however, suggesting that variations in the detailed structure of the exchange-generated lithiated intermediate (**2**) might have an effect on the stereochemical outcome of the subsequent cyclization. Indeed, in the case of (*E*)-**7a**, the presence of LiI, added either to the *n*-BuLi solution or to the iodide solution (entries 4 and 5), resulted in a significant increase in cyclization selectivity (3.3 → 7.6, 3.3 → 6.3, respectively). This effect was absent in the case of *tert*-butyl ester (*E*)-**7b**, however. The highly polar oxygen of the acyl ylide moiety[15] may well be able to interact with lithium ions in a way which either affects the structure of the organolithium aggregate[7c] or which affects the structure and hence the reactivity of the acceptor moiety.

Scheme VI[a]



[a] (A) $(EtO)_2P(O)CH_2COOOBu^t$, $(Me_3Si)_2NK$, 18-crown-6, THF, −78 °C (36%); (B) NaI, acetone (84%).

To test the latter possibility, $BF_3{\cdot}Et_2O$ was added to (*E*)-**7a** prior to the addition of the metalating agent with the expectation that a strong Lewis acid–base interaction with the dipolar acyl ylide function would occur thereby increasing the reactivity of the olefin toward nucleophilic addition with a resulting lowering of selectivity. In the event (entry 6), a slight increase in selectivity was noted, however, while $BF_3{\cdot}Et_2O$ had essentially no effect in the case of the *tert*-butyl ester (*E*)-**7b**. A slight lowering in selectivity was noted in the case of (*E*)-**7b** when the cyclization was conducted in the presence of TMEDA (entry 12), but overall it is fair to say that the cyclization selectivity of this substrate is not significantly affected by any of the alterations described above.

Acceptor Stereochemistry. In order to examine the effect of acceptor olefin geometry on cyclization stereochemistry, (*Z*)-**7b** was prepared as outlined in Scheme VI. HEW phosphonate olefination of aldehyde **11** under conditions known to give *Z* selectivity (the use of $(Me_3Si)_2NK$ as base in the presence of 18-crown-6)[16] gave a 14:1 mixture of *Z*/*E* unsaturated ester **17**. Chlorine–iodine exchange with NaI gave the corresponding iodides which could be readily separated by PTLC ((*Z*)-**7b** and (*E*)-**7b**). Cyclization of (*Z*)-**7b** with *n*-BuLi at −100 °C gave nearly exclusively *trans*-**8b**. Capillary gas chromatography showed the presence of a very small component having the same retention time as authentic *cis*-**8b** (vide infra) from which we are able to calculate a t/c ratio of at least 300. This remarkably high trans selectivity is understood by noting the large difference in 1,3-allylic strain[17] present in the two rotamers, A and B, leading to *cis*- and *trans*-**8**, respectively. With *Z* olefin geometry, the considerable allylic strain present in conformer A leading to cis product greatly destabilies this rotomer relative to B, the one which leads to *trans*-**8**.

In order to confirm our stereochemical assignments in cyclization products **8**, authentic samples of cis isomers were prepared as outlined in Scheme VII. This was made necessary owing to difficulties in obtaining the crucial NMR coupling constants from 90- or 200-MHz NMR spectra and from a lack of confidence in stereochemical assignments based on small differences in coupling constants in such ring systems. Alkylation of the monolithiated intermediate[18] obtained from the low-temperature metal–halogen exchange reaction of dibromide **18** and *tert*-butyllithium with EtI gave unstable vinyl bromide **19**.

(12) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(13) (a) Pelter, A.; Singaram, S.; Brown, H. C. *Tetrahedron Lett.* **1983**, *24*, 1433. (b) Pelter, A.; Williams, L.; Wilson, J. W. *Ibid.* **1983**, *24*, 627.
(14) (a) Dolzine, T. W.; Oliver, J. P. *J. Organomet. Chem.* **1974**, *78*, 165. (b) Hill, E. A. *Organomet. Chem.* **1975**, *91*, 123.
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(16) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(17) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
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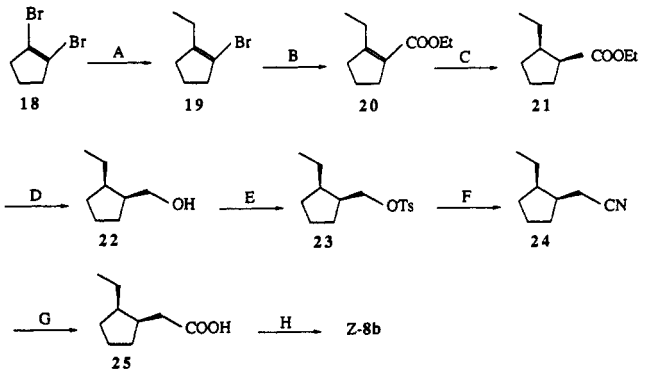
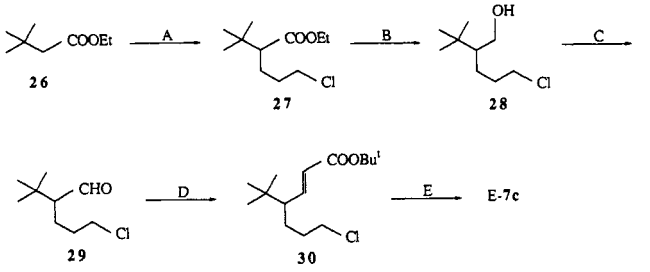
Scheme VII[a]



[a] (A) 2 equiv of *t*-BuLi, THF, −78 °C then EtI (80%); (B) 2 equiv of *t*-BuLi, THF, −78 °C then ClCOOEt (85%); (C) H_2, Rh–C, EtOAc, 100 °C, 85 psi (80%); (D) $LiAlH_4$ (93%); (E) TsCl, py (64%); (F) NaCN, DMSO (92%); (G) NaOH, 100 °C then HCl (84%); (H) $SOCl_2$ then *t*-BuOH, $PhNMe_2$ (59%).

Scheme VIII[a]



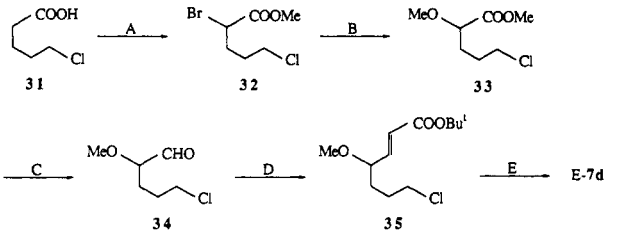
[a] (A) LDA, THF, −78 °C then $ICH_2CH_2CH_2Cl$, HMPA (91%); (B) DIBAL (89%); (C) DMSO, $(COCl)_2$ then Et_3N (90%); (D) $(EtO)_2P(O)CH_2COOBu^t$, NaH (93%); (E) NaI, acetone (95%).

Exchange of the remaining bromine with *tert*-butyllithium followed by acylation of the resulting vinyllithium intermediate with ethyl chloroformate gave unsaturated ester **20**. Catalytic hydrogenation of **20** (Rh/C, EtOAc, 85 psi of H_2, 100 °C) gave cis ester **21**[19] along with small amounts of the trans isomer (c/t = 7–12:1). Reduction of **21** with $LiAlH_4$ gave authentic cis alcohol **22**, the minor product from the cyclization–oxidation sequence of boron-activated (*E*)-**7e**. Treatment of **23**, the tosylate ester of **22**, with NaCN gave nitrile **24** which upon hydrolysis provided cis carboxylic acid **25**. Fisher esterification of **25** gave an authentic sample of the cis ethyl ester (**8**, R = Et, E = COOEt) obtained as the minor isomer in the cyclization of acyl ylide-activated (*E*)-**7a** while the authentic cis *tert*-butyl ester **8b** was obtained by converting **25** into its acid chloride followed by alcoholysis with tert-butanol.

Allylic Substituents. Although it was clear that the use of *Z* olefin stereochemistry would allow the excellent control of cyclization stereochemistry desired in the execution of Scheme II, we were curious as to the effect of the nature of the allylic substituent on cyclization stereoselectivity. Two additional models were therefore examined: (*E*)-**7c** in which the γ-substituent is a sterically demanding *tert*-butyl group and methoxy ether (*E*)-**7d** which contains a potential lithium-coordinating oxygen atom for probing the possible effects of intramolecular complexation. The syntheses of these two substrates are outlined in Schemes VIII and IX, respectively.

Alkylation of the enolate of **26** with 1-chloro-3-iodopropane gave chloro ester **27** in high yield (91%). At-

Scheme IX[a]



[a] (A) $SOCl_2$ then *N*-bromosuccimide then MeOH (60%); (B) NaOMe, MeOH (62%); (C) DIBAL, −78 °C (73%); (D) $(EtO)_2P(O)CH_2COOBu^t$, NaH, THF (91%); (E) NaI, acetone (68%).

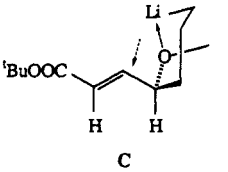
tempted partial reduction of ester **27** with 1 equiv of DIBAL at −78 °C gave an equal mixture of alcohol **28** and starting material (**27**) with only traces of aldehyde **29**. Apparently the tetrahedral aluminate adduct formed upon addition of DIBAL to the ester carbonyl group is destabilized by the presence of the bulky α-*tert*-butyl group and collapses prematurely to aldehyde which is quickly reduced. Reduction of **27** with excess DIBAL cleanly gave alcohol **28** which efficiently underwent Swern oxidation to aldehyde **29**. HEW carboxyolefination gave unsaturated chloro ester **30** and then (*E*)-**7c** after chlorine–iodine exchange.

An attempt to alkylate the enolate of methyl 2-methoxylacetate with 1-chloro-3-iodopropane failed to give desired ester **32**, but its synthesis was achieved as shown in Scheme IX. α-Bromination of 5-chlorovaleric acid (**31**) via its acid chloride[20] followed by methanolysis gave α-bromo ester **32** which in turn provided **33** upon treatment with NaOMe. Partial reduction of the ester moiety in **33** with DIBAL provided **34** which upon HEW olefination gave unsaturated ester **35**. Halogen exchange using NaI provided the desired iodide (*E*)-**7d**.

Cyclization of (*E*)-**7c** with *n*-BuLi at −100 °C (Table I, entry 15) gave **8c** in 80% yield as a mixture of isomers (t/c = 5.8). Thus the presence of the bulky *tert*-butyl group promotes a modest improvement in trans selectivity (cf. t/c = 3.3 in the cyclization of the ethyl analogue (*E*)-**7a** (Table I, entry 2)).

On the other hand, cyclization of methoxy ether (*E*)-**7d** with *n*-BuLi at −100 °C (entry 16) gave a cis-rich mixture (t/c = 0.6) of **8d** in diminished yield (46%). The presence of LiI (entry 17) did not alter this outcome, but the presence of TMEDA (entry 18) did increase the relative proportion of *trans*-**8d** (t/c = 1.0). A similar result was obtained with (*E*)-**7d** was cyclized with *t*-BuLi (entry 19, t/c = 1.0). The configurations of **8c** and **8d** were assigned on the basis of gas chromatographic retention times[21] and downfield ^1H NMR shifts of the substituent R in **8** in each cis isomer.

These results suggest that the exchange-generated organolithium intermediate from (*E*)-**7d** may be engaged in intramolecular Li–O complexation leading to conformers such as C which would enhance *cis*-**8** production. A sim-



C

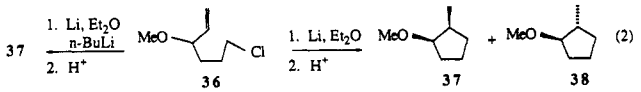
ilar phenomenum has been observed by Smith and Wil-

(19) An increase in the amount of trans isomer was observed upon heating with NaOMe in MeOH as further proof of the stereochemical assignment.

(20) Gleason, J. W.; Harpp, P. N. *Tetrahedron Lett.* **1970**, 343.

(21) In all cases, we observed the retention time of the cis isomer (**8**) to be greater than that of the trans isomer.

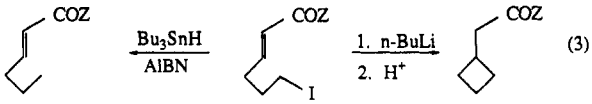
son[22] in the cyclization reactions of 6-chloro-3-methoxy-1-hexene with lithium metal (eq 2) where equal amounts of *cis*- (**37**) and *trans*-1-methoxy-2-methylcyclopentane (**38**) were formed—the cis isomer being formed exclusively (apparently) in the presence of added *n*-BuLi.



Radical Cyclizations. For comparison purposes we also examined the cyclization of each of our unsaturated iodides under radical conditions (Bu_3SnH, benzene, AIBN, 80 °C). The results of these experiments along with comparisons of the anionic and radical modes of cyclization are shown in Table II. In general, with *E* ethyl-substituted substrates ((*E*)-**7**, R = Et) selectives for trans-substituted cyclopentane formation are higher (t/c ≈ 7–9) in the radical cyclization mode than in the corresponding anionic cyclization mode (entries 1–3), and they are slightly greater than the selectivity observed in the radical cyclization of 6-bromo-3-methyl-1-hexene (t/c = 4.8).[23] As in the anionic case, *Z* olefin stereochemistry in (*Z*)-**7b** results in very high trans selectivity (entry 4, t/c >280). A study of the intramolecular radical cyclization reactions of variously substituted ω-bromo-α,β-unsaturated esters leading to cyclohexane derivatives has recently been reported.[24] While γ-substituents were not examined and trans selectivities were typically low (t/c ≈ 2–3) with more remotely located substituents, in one case, *Z* olefin geometry resulted in a moderate increase in trans product selectivity (t/c 3 → 9). Interestingly, substitution of the bulky *tert*-butyl group for the ethyl group leads in (*E*)-**7c** (entry 5) to a much greater increase in trans selectivity (t/c 8.8 → 88) than was observed in the anionic cyclization (t/c 3 → 5.8).

Most surprisingly, the cis selectivity observed in the anionic cyclization of methoxy-substituted (*E*)-**7d** (t/c = 0.6) is also observed under radical cyclization conditions (Table II, entry 6, t/c = 0.9). The reason for this cis preference in the radical cyclization mode is not clear. It should be noted that while it has been suggested that the exchange-initiated cyclizations of 5-hexenyl halides might occur by a radical pathway[25] stronger evidence suggests that no significant radical pathway is present under our reaction conditions when primary iodides are substrates.[26] Indeed, the significant differences in trans–cis product ratios observed under the two differing reaction conditions in Table II (entries 1, 2, and 5) support this notion as does our observation[27] that **36** undergoes cyclobutane formation under anionic conditions but as is characteristic of radical reactions,[28] fails to undergo cyclobutane formation under radical conditions and is simply reduced (eq 3). It does not appear likely, therefore, that the similar selectivities observed in Table II, entry 6, under the two differing sets of reaction conditions are a result of the cyclization of a common intermediate.

Two possibilities remain. First, for reasons not obvious, methoxy-substituted (*E*)-**7d** may prefer a conformation which leads to cis cyclization product. This would mean that the internal chelation hypothesis invoked earlier in the anionic cyclization of (*E*)-**7d** might be invalid and



36, (Z = C(PPh3)COOEt

cis-richness under anionic conditions could also follow from conformational considerations. Alternately, an intramolecular interaction (complexation) of the radical center with the heteratom[29f] (methoxyl oxygen lone pair) might, as in the anionic case, also introduce cis-product bias. While we are not aware of any strong precedent for such an interaction with carbon radicals, radical–lone electron pair interactions have been invoked in radical relay reactions involving chlorine atom–iodine electron lone pairs,[29a,b] chlorine atom–sulfur lone pairs,[29b,c] chlorine atom–pyridine lone pairs,[29d] and chlorine atom–*N*-oxide pyridine oxygen lone pairs.[29e] It must be said, however, that while such speculation is fascinating, the true cause of these cis preferences remains to be firmly established.

Summary

Lithium–iodide exchange initiated (anionic) cyclization reactions of γ-substituted activated ω-iodo olefins (**7**) give a modest preference for trans cyclopentane formation when the acceptor olefin possesses *E* geometry while *Z* olefin geometry leads to very high trans product selectivity. In the case of acyl ylide olefin activation ((*E*)-**7a**), cyclization product stereochemistry is a function of the alkyllithium reagent employed in the exchange reaction and is altered by the presence of LiI or $BF_3{\cdot}Et_2O$ while *tert*-butoxycarbonyl-activated olefin (*E*)-**7b** is relatively insensitive to such effects. The nature of the γ-(allylic)-substituent has been found to have an effect on cyclization stereochemistry: the presence of an α-*tert*-butyl group causes a moderate increase in trans product selectivity while the presence of a methoxyl group in the γ-position results in cis product selectivity. Cyclizations under radical conditions with *E* olefins were found to be slightly more trans-selective than those observed under anionic conditions while the *Z* isomer stereochemistry in (*Z*)-**7b**, again promoted very high trans product selectivity. The presence of the allylic *tert*-butyl group in (*E*)-**7c** effected a much larger increase in trans selectivity under radical conditions than under anionic cyclization conditions while the presence of the allylic methoxy substituent in (*E*)-**7d** also gave a sizable increase in cis product formation under radical cyclization conditions, although the effect is not so large as is observed under anionic cyclization conditions. Novel intramolecular radical–lone pair complexation is suggested as a possible explanation for this surprising cis selectivity.

Experimental Section

NMR spectra were recorded in $CDCl_3$ at 90 MHz (^1H) and at 22.5 MHz (^{13}C). Operations involving solvent removal under reduced pressure or concentration of mixtures refer to the use of a Buchii 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

(22) Smith, J. J.; Wilson, S. E. *Tetrahedron Lett.* **1981**, *22*, 4615.
(23) Beckwith, A. L. J.; Schiessen, C. H. *Tetrahedron* **1985**, *41*, 3925.
(24) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859.
(25) Ashby, E. C.; Pham, T. N.; Park, B. *Tetrahedron Lett.* **1985**, *26*, 4691.
(26) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861.
(27) Unpublished results by the author.
(28) Reference 3d, p 143.
(29) (a) Breslow, R.; Wife, R. L.; Presant, D. *Tetrahedron Lett.* **1976**, 1925. (b) Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045. (c) Breslow, R. *Advances in Enzymology and Related Areas of Molecular Biology*; Meister, A., Ed.; Wiley: New York, 1986; Vol. 58, pp 1–60. (d) Breslow, R.; Brandl, M.; Hunger, J.; Turro, N.; Cassidy, K.; Krogh-Jespersen, K.; Westbrook, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 7204. (e) Breslow, R.; Adams, A.; Brandl, M.; Guo, T.; Hunger, J. *Lect. Heterocycl. Chem.* **1987**, *9*, 43. (f) Abu-Raqabah, A.; Symons, M. C. R. *J. Am. Chem. Soc.* **1990**, *112*, 8614.

Table II. Cyclization of Unsaturated Iodides 7

entry	iodide	t/c-8 radical mode[a]	t/c-8 anionic mode[b]
1	(*E*)-7a	7.4 (7.2)[c]	3.3
2	(*E*)-7b	8.8	3.0
3	(*E*)-7e	7.3	6.2
4	(*Z*)-7b	>280	>300
5	(*E*)-7c	88	5.8
6	(*E*)-7d	0.9	0.6

[a] *n*-Bu_3SnH, AIBN, refluxing benzene. [b] Standard conditions (−100 or −78 °C, *n*-BuLi, THF) from Table I. [c] Ethylene dichloride as solvent.

for column (flash) chromatography. Gas chromatography was performed using a 12-m cross-linked methyl silicone capillary column. Bulb-to-bulb distillations of the Kugelrohr type were conducted at the air oven temperatures and pressures cited. Melting points and boiling points are unconnected. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

All reactions involving air-sensitive materials were conducted under an argon atmosphere. For reactions said to be conducted at −78 °C, a dry ice–acetone bath was employed while those conducted at −100 °C used a MeOH liquid–solid bath cooled with liquid N_2. Alkyllithium reagents were obtained from Aldrich Chemical Co. and titrated[30] prior to use. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl prior to use.

Ethyl 5-Chloro-2-ethylpentanoate (10). To a stirred solution containing 8.0 mL (57 mmol) of diisopropylamine in 100 mL of THF at −78 °C was added 30 mL (48 mmol) of 1.6 N *n*-BuLi in hexane. After 5 min, 5.6 mL (35 mmol) of ethyl 5-chloropentanoate (**9**) was added dropwise over 4 min, and stirring was continued for 20 min. HMPA (12 mL) was added[31] followed by 12 mL (150 mmol) of EtI, and the mixture was stirred at −78 °C for 14 h and then at 0 °C for 0.5 h whereupon 1.5 mL of HOAc was added. Solvent was removed under reduced pressure, and the residue was dissolved in pentane and washed with water. Concentration of the dried extract (Na_2SO_4) followed by distillation gave 6.34 g (94%) of **10**: bp 121–123 °C (26 mm); ^{1}H NMR δ 0.90 (t, *J* = 7.1 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.4–1.8 (m, 6 H), 2.1–2.4 (m, 1 H), 3.52 (m, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H); ^{13}C NMR δ 11.7, 14.4, 25.5, 29.2, 30.5, 44.6, 46.5, 60.1, 175.6. Anal. Calcd for $C_9H_{17}ClO_2$: C, 56.10; H, 8.90. Found: C, 55.88; H, 8.53.

5-Chloro-2-ethylpentanal (11). A solution containing 2.85 g (14.8 mmol) of **10** in 36 mL of toluene was stirred at −78 °C and treated with 18.5 mL (18.5 mmol) of 1 M DIBAL in hexanes added dropwise over 5 min with vigorous stirring. Stirring was continued for 5 min whereupon 750 μL of MeOH was added. After 2 min, 2 mL of 1:1 MeOH–H_2O was added, the mixture was stirred at 20 °C for 5 min and then treated with 3 mL of 4 N NaOH, and stirring was continued for 5 min. A small amount of Na_2SO_4 was added to aid in the separation of the solution phase by filtration from gelatinous aluminum salts. The salts were extracted with pentane, and concentration of the combined extracts followed by distillation gave 1.95 g (88%) of **11**: bp 121–123 °C (26 mm); ^{1}H NMR δ 0.94 (t, *J* = 7.2 Hz, 3 H), 1.1–1.9 (b, 6 H), 2.0–2.4 (m, 1 H), 3.54 (t, *J* = 6.0 Hz, 2 H), 9.60 (d, *J* = 2.3 Hz, 1 H); ^{13}C NMR δ 11.3, 21.9, 25.4, 30.0, 44.7, 52.6, 204.5. 2,4-DNP: mp 111–113 °C. Anal. Calcd for $C_{13}H_{16}ClN_4O_4$: C, 47.49; H, 5.21; N, 17.04. Found: C, 47.69; H, 5.18; N, 17.12.

Ethyl 6-Ethyl-9-chloro-3-oxo-2-(triphenylphosphoranylidene)-4(*E*)-nonenoate (12). NaH (300 mg (7.5 mmol), 60% in mineral oil) was washed three times with small portions of pentane and then covered with 15 mL of THF. To this stirred mixture were added 2.18 g (4.1 mmol) of diethyl [2,4-dioxo-4-ethoxy-3-(triphenylphosphoranylidene)butyl]-phosphonate[11] and 40 μL of MeOH. Stirring was continued until the evolution of H_2 ceased (10 min) whereupon 500 mg (3.37 mmol) of **11** was added. After 15 min, the mixture was concentrated under reduced pressure, treated with H_2O, and extracted with CH_2Cl_2. Concentration of the dried (Na_2SO_4) extracts gave an oil which, upon chromatography on a 20-cm column of silica gel (15:1 CH_2Cl_2–EtOAc), gave 1.64 g (94%) of **12** as a glass: ^{1}H NMR δ 0.65 (t, *J* = 7.1 Hz, 3 H), 0.85 (t, *J* = 6.8 Hz, 3 H), 1.1–1.9 (b, 6 H), 1.9–2.3 (b, 1 H), 3.46 (t, *J* = 6.3 Hz, 2 H), 3.72 (q, *J* = 7.1 Hz, 2 H), 6.41 (dd, *J* = 15.4, 8.6 Hz, 1 H), 7.2–7.8 (m, 16 H); ^{13}C NMR δ 11.7, 13.7, 27.5, 30.4, 31.5, 43.4, 45.2, 58.4, 71.6 (d, *J* = 111.5 Hz), 127.0 (d, ^1J = 94.0 Hz), 128.5 (d, ^2J = 12.0 Hz), 131.5 (d, ^4J = 2.7 Hz), 133.0 (d, ^3J = 9.4 Hz), 144.2, 167.6 (d, ^2J = 14.8 Hz), 186.4 (d, ^2J = 4.0 Hz).

Ethyl 6-Ethyl-9-iodo-3-oxo-2-(triphenylphosphoranylidene)-4(*E*)-nonenoate [(*E*)-7a]. A mixture containing 4.5 g of NaI, 25 mL of acetone, and 1.34 g (2.6 mmol) of **12** was heated under reflux for 24 h. The solvent was removed under reduced pressure, and the resulting residue was treated with water and extracted with CH_2Cl_2 (pentane extraction was used in all other preparations (vide infra) citing this procedure). The extracts were washed with water (2×), 5% $NaHSO_3$, water, and brine and then dried (Na_2SO_4). Concentration gave 1.46 g (93%) of (*E*)-**7a** as a thick oil: ^{1}H NMR δ 0.65 (t, *J* = 7.1 Hz, 3 H), 0.86 (t, *J* = 6.8 Hz, 3 H), 1.2–1.9 (b, 6 H), 1.9–2.3 (m, 1 H), 3.13 (t, *J* = 6.7 Hz, 2 H), 3.72 (q, *J* = 7.1 Hz, 2 H), 6.40 (dd, *J* = 15.4, 8.8 Hz, 1 H), 7.3–7.9 (m, 16 H); ^{13}C NMR δ 7.4, 11.6, 13.6, 27.4, 31.2, 35.1, 43.1, 58.3, 71.5 (d, ^1J = 111.5 Hz), 126.9 (d, ^1J = 94.0 Hz), 128.4 (d, ^2J = 12.1 Hz), 131.4 (d, ^4J = 2.7 Hz), 132.9 (d, ^3J = 9.4 Hz), 144.2, 167.5 (d, ^2J = 14.8 Hz), 186.3 (d, ^2J = 2.7 Hz). This iodide was reconcentrated from benzene solution prior to use to remove any traces of protic solvents.

Anionic Cyclization of (*E*)-7a. Illustrating a typical procedure (Table I, entry 1), 330 mg (0.54 mmol) of (*E*)-**7a** (reconcentrated from benzene solution and vacuum dried) was dissolved in 6 mL of THF and cooled to −78 °C. With vigorous stirring 0.5 mL (0.75 mmol) of 1.5 N *n*-BuLi solution was added over 6 min followed by stirring for 3 min. MeOH (250 μL) was added, and the mixture was warmed to 20 °C and concentrated under reduced pressure giving 260 mg (99%) of crude product. PTLC (silica gel, 12:1 CH_2Cl_2–EtOHc) gave 230 mg (88%) of pure **8a** (thick oil) as a 3.3:1 mixture of t/c isomers (vide infra): ^{1}H NMR δ 0.64 (t, *J* = 7.1 Hz, 3 H), 0.80 (m, 3 H), 1.0–2.2 (b, 10 H), 2.75 (cis isomer) and 2.90 (trans isomer) (m, 2 H), 3.71 (q, 2 H), 7.2–7.9 (b, 15 H); ^{13}C NMR (trans isomer) δ 12.9, 13.7, 23.7, 27.4, 31.5, 32.4, 42.3, 45.3, 47.7, 58.2, 71.5 (d, ^1J = 110.1 Hz), 127.3 (d, ^1J = 94.0 Hz), 128.3 (d, ^2J = 14.8 Hz), 197.8 (d, ^2J = 4.0 Hz). The cis isomer had distinguishable peaks at δ 13.1, 22.9, 22.8, 30.7, 39.2, 44.6, 45.1, and 45.3.

For accurate isomer ratio determination, crude reaction products were converted to the corresponding ethyl esters[7a] (**8**, R = Et, Et = COOEt) as follows: the residue obtained after concentrating a reaction mixture (200–400 mg) was dissolved in 8–10 mL of EtOH, treated with 20 drops of H_2SO_4, and heated under reflux for 48–72 h. The mixture was cooled, diluted with 4 N HCl, and twice extracted with pentane, and the extracts were analyzed by capillary gas chromatography. Both the minor (cis) isomer and the major (trans) isomer were identical by GC and ^{13}C NMR to authentic compounds (vide infra).

Variations of the general cyclization procedure are detailed in Table I. In entry 4, a 3 M solution of LiI in THF (5.7 equiv) was added to the *n*-BuLi solution prior to its addition to the solution containing (*E*)-**7a**. In entry 5, 19 equiv of LiI in THF (1 M) was added to the solution containing (*E*)-**7a** prior to the addition of *n*-BuLi.

Radical Cyclization of (*E*)-7a. A solution containing 280 mg (0.46 mmol) of (*E*)-**7a**, 150 μL (0.55 mmol) of (*n*-Bu)$_3$SnH, and 26 mg of AIBN in 7 mL of benzene was heated under reflux for 0.5 h. Concentration of the mixture gave a residue which was dissolved in CH_2Cl_2 and washed with water and then saturated $NaHCO_3$ solution. Solvent removal followed by PTLC (silica gel, 12:1 CH_2Cl_2–EtOAc) gave 210 mg (95%) of isomers **8a** which were converted to the ethyl esters as above.

***tert*-Butyl 7-Chloro-4-ethyl-2(*E*)-heptenoate (13).** NaH (525 mg (12.3 mmol), 56% in oil) was freed of oil by twice washing with pentane and then suspended in 25 mL of THF. With vigorous stirring, 1.93 g (7.6 mmol) of *tert*-butyl diethylphosphonoacetate[32] was added over 2 min and stirring was con-

(30) Watson, S. C.; Eastham, S. F. *Organomet. Chem.* **1967**, *9*, 165.
(31) Cregge, R. J.; Herrman, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2425.
(32) Griffiths, G. F.; Kenner, G. W.; McCombie, S. W.; Smith, K. M.; Sutton, M. J. *Tetrahedron* **1976**, *32*, 275.

tinued until the evolution of H_2 ceased and the mixture was homogeneous (5 min). Aldehyde **11** (1.15 g (7.7 mmol)) in a small amount of THF was added over 1 min, and stirring was continued for 15 min. The mixture was concentrated under reduced pressure, and the residue was treated with H_2O and extracted with several portions of pentane. Concentration of the extracts followed by bulb-to-bulb distillation (160 °C (0.5 mm)) gave 1.71 g (90%) of **13**: ^{1}H NMR δ 0.87 (t, J = 6.8 Hz, 3 H), 1.2–1.8 (b, 6 H), 1.48 (s, 9 H), 1.9–2.2 (m, 1 H), 3.50 (t, J = 6.1 Hz, 2 H), 5.71 (dd, J = 15.6, 0.7 Hz, 1 H), 6.61 (dd, J = 15.6, 8.8 Hz, 1 H); ^{13}C NMR δ 11.6, 27.2, 28.2, 30.3, 31.3, 43.5, 44.8, 80.0, 123.5, 150.9, 165.7. Anal. Calcd for $C_{13}H_{23}Cl_2$: C, 63.27; H, 9.39. Found: C, 63.04; H, 9.55.

***tert*-Butyl 7-Iodo-4-ethyl-2(*E*)-heptenoate [(*E*)-7b].** In the manner described for the preparation of (*E*)-**7a**, 320 mg (1.3 mmol) of **13** gave, after bulb-to-bulb distillation (190 °C, 0.25 mm) 413 mg (94%) of (*E*)-**7b** as an oil: ^{1}H NMR δ 0.87 (t, J = 6.8 Hz, 3 H), 1.3–1.6 (b, 6 H), 1.48 (s, 9 H), 1.7–1.9 (m, 1 H), 3.16 (t, J = 6.6 Hz, 2 H), 5.70 (dd, J = 15.6, 0.7 Hz, 1 H), 6.62 (dd, J = 15.6, 9.0 Hz, 1 H); ^{13}C NMR δ 6.5, 11.6, 27.2, 28.1, 31.1, 34.8, 43.1, 80.0, 123.4, 150.9, 165.7. Anal. Calcd for $C_{13}H_{23}IO_3$: C, 46.16; H, 6.85. Found: C, 46.04; H, 6.92. This ester was prone to decomposition (loss of isobutylene) when heated unless glassware had been previously washed with alkali.

Anionic Cyclization of (*E*)-7b. In a typical experiment (Table I, entry 7) 188 mg (0.56 mmol) of (*E*)-**7b** in 3–4 mL of THF was treated at −78 °C with 0.45 mL (0.72 mmol) of 1.6 M *n*-BuLi added dropwise over 2 min. After 6 min, the mixture was treated with 200 μL of EtOH followed by 60 μL of HOAc, warmed to 20 °C and concentrated under reduced pressure ($T \leq 20$ °C). The crude products were taken up in pentane and washed with water, and the extract was analyzed by capillary gas chromatography after the addition of an internal standard (dodecane). In a preparative run concentration of the pentane extracts followed by bubl-to-bulb distillation (160 °C, 5 mm) gave isomeric **8b** containing NMR peaks corresponding to those of the pure trans isomer obtained from (*Z*)-**7b** (vide infra) and an authentic sample of the cis isomer (vide infra): ^{13}C NMR (trans isomer) δ 12.7, 23.6, 27.4, 28.2, 31.5, 32.3, 41.2, 42.3, 47.5, 79.9, 172.9; (cis isomer) δ 13.1, 22.5, 22.8, 29.7, 30.8, 36.2, 39.2, 44.5. Variations of cyclization conditions are detailed in Table I.

Radical Cyclization of (*E*)-7b. Cyclization of (*E*)-**7b** with *n*-Bu_3SnH was conducted in a manner similar to the procedure described above for the radical cyclization of (*E*)-**7a** (see Table II).

1,1-Dibromo-6-chloro-3-ethyl-1-hexene (14). Using the method of Corey and Fuchs,[12] 6.62 g (20 mmol) of CBr_4 was added with stirring at 0 °C to 10.5 g (40 mmol) of Ph_3P in 40 mL of CH_2Cl_2 (dried over 4-Å molecular sieve). After 5 min, 1.48 g (10 mmol) of **11** was added, and stirring was continued for 10 min whereupon 1 mL of MeOH was added. The mixture was concentrated under reduced pressure, and the residue was dissolved in a small volume of CH_2Cl_2 and reprecipitated by the addition of pentane. Concentration of the pentane extracts followed by bulb-to-bulb distillation (200 °C, 20 mm) gave 2.8 g (92%) of **14** as an oil: ^{1}H NMR δ 0.91 (t, J = 6.8 Hz, 3 H), 1.0–2.0 (b, 6 H), 2.0–2.5 (m, 1 H), 3.53 (t, J = 6.1 Hz, 2 H), 6.13 (d, J = 9.8 Hz, 1 H); ^{13}C NMR δ 11.5, 27.4, 30.2, 31.3, 44.8, 44.9, 88.7, 142.5 This compound decomposed upon standing and was immediately used.

6-Chloro-3-ethyl-1-hexyne (15). Dibromide **14** (910 mg (3 mmol)) was placed in 20 mL of THF, cooled to −78 °C and treated, with stirring, with 7.0 mL (11.2 mmol) of 1.6 N *n*-BuLi solution added over 2 min. The solution was stirred for 30 min and then treated with 100 μL of MeOH followed by 200 μL of water. The mixture was concentrated under reduced pressure ($T \leq 20$ °C), and the residue was treated with water and extracted with pentane. The extracts were washed with water and concentrated, giving 445 mg (103%) of **15**: ^{1}H NMR δ 1.01 (t, J = 6.6 Hz, 3 H), 1.20–1.75 (m, 4 H), 1.75–2.20 (m, 2 H), 2.07 (d, J = 2.4 Hz, 1 H), 2.2–2.4 (m, 1 H), 3.57 (t, J = 6.3 Hz, 2 H); ^{13}C NMR δ 11.6, 28.0, 30.4, 31.8, 32.7, 44.9, 69.8, 87.0.

6-Iodo-3-ethyl-1-hexyne (16). In the manner described for the preparation of (*E*)-**7a**, 270 mg (1.87 mmol) of **15** was heated for 16 h with excess NaI in acetone giving, after bulb-to-bulb distillation (160 °C, 20 mm), 340 mg (80% from **14**) of **16** as an oil: ^{1}H NMR δ 1.01 (t, J = 6.3 Hz, 3 H), 1.3–1.7 (m, 4 H), 1.7–2.1 (m, 2 H), 2.07 (d, J = 2.4 Hz, 1 H), 2.1–2.4 (m, 1 H), 3.21 (t, J = 6.8 Hz, 2 H); ^{13}C NMR δ 6.6, 11.6, 27.9, 31.2, 32.3, 35.2, 69.8, 86.9. Anal. Calcd for $C_8H_{13}I$: C, 40.70; H, 5.55. Found: C, 41.11; H, 5.89.

3-Ethyl-6-iodo-1-(dimesitylboryl)-1(*E*)-hexene [(*E*)-7c]. To a solution containing 135 mg (0.57 mmol) of **16** in 2 mL of THF was added 170 mg (0.68 mmol) of Mes_2BH (Aldrich). The solution was stirred for 3 h and then concentrated under reduced pressure giving a residue which, upon PTLC (5:1 hexane–CH_2Cl_2), gave 277 g (100%) of an oil [(*E*)-**7e**] which slowly solidified: ^{1}H NMR δ 0.85 (t, J = 6.9 Hz, 3 H), 1.2–1.9 (b, 6 H), 2.1–2.3 (b, 1 H), 2.17 (s, 12 H), 2.26 (s, 6 H), 3.12 (t, J = 7.1 Hz, 2 H), 6.0–6.7 (m, 2 H), 6.78 (s, 4 H); ^{13}C NMR δ 6.6, 12.0, 21.0, 23.2, 27.4, 31.5, 35.0, 47.2, 128.1, 138.1, 140.2, 162.4.

Anionic Cyclization of (*E*)-7e (Table I, Entry 13). A solution containing 277 mg (0.57 mmol) of (*E*)-**7e** in 5 mL of THF was cooled to −100 °C, and with stirring 0.65 mL (1.1 mmol) of 1.7 M *t*-BuLi in pentane was added over 1 min. After 10 min, the yellow solution was allowed to warm to −78 °C, whereupon 100 μL HOAc was added. The mixture was warmed to 20 °C, concentrated, treated with water, and extracted with pentane. The residue (222 mg) obtained upon concentration of the extracts were purified by PTLC (silica gel, 6:1 hexane–CH_2Cl_2), giving 184 mg (90%) of **8e** as a mixture of isomers: ^{13}C NMR (major (trans)isomer) δ 13.0, 21.0, 22.8, 27.0, 30.8, 34.6, 43.9, 50.1, 128.4, 137.8, 138.6, 142.7. Additional peaks assignable to the minor (cis) isomer: δ 13.2, 23.2, 29.6, 33.3, 40.3, 45.9.

The above boranes (180 mg, 0.5 mmol) were placed in 4 mL of THF and treated with 375 μL of 4N NaOH, 1 mL of 30% H_2O_2, and 1.5 mL of MeOH. The mixture was vigorously stirred for 1 h whereupon additional H_2O_2 (360 μL) and NaOH (350 μL) were added. The mixture was then heated under reflux for 0.5 h, cooled, concentrated, treated with water, and extracted with pentane. The alcohol **8** (E = OH, R = Et) isomer ratio (t/c = 6.2) was determined by capillary GC analysis of this extract. The minor isomer was identical by GC and ^{13}C NMR with authentic *cis*-**22** (vide infra), and the major (trans) isomer corresponded to the minor isomer of **22** generated in Scheme VII.

Radical Cyclization of (*E*)-7e. Cyclization of (*E*)-**7e** under radical cyclization conditions similar to those described for (*E*)-**7a** gave, after oxidation of product boranes (as above), alcohols **8** (R = Et, E = OH) in 73% GC yield (t/c = 7.3).

***tert*-Butyl 7-Iodo-4-ethyl-2(*Z*)-heptenoate [(*Z*)-7b].** A solution containing 1.32 g (5 mmol) of 18-crown-6 and 320 mg (1.27 mmol) of *tert*-butyl(diethylphosphono)acetate[32] in 12 mL of THF was cooled to −78 °C, and with stirring, 2.2 mL (1.1 mmol) of 0.5 M $(Me_3Si)_2NK$ in toluene was added. After 5 min, 164 mg (1.1 mmol) of **11** in 4 mL of THF was added, and stirring was continued for 40 min. Saturated NH_4Cl solution (10 mL) was added, and the mixture was twice extracted with pentane. The extracts were concentrated, and the residue was treated with water and extracted again with pentane. After washing with water, the pentane extracts were concentrated giving 165 mg (61%) of crude **17** as a 1.4:1 mixture of *Z* and *E* isomers. The chlorides were converted into the corresponding iodides with NaI in acetone as described in the preparation of (*E*)-**7a**. PTLC (1:1 hexane-CH_2Cl_2) gave 111 mg (84% base on (*Z*)-**17**) of pure (*Z*)-**7b** (R_f = 0.5; *E* isomer: R_f = 0.4) as an oil: ^{1}H NMR δ 0.86 (t, J = 7.2 Hz, 3 H), 1.1–1.6 (b, 4 H), 1.77 (q, J = 7.2 Hz, 2 H), 3.18 (t, J = 6.6 Hz, 2 H), 3.2–3.5 (m, 1 H), 5.74 (m, 2 H); ^{13}C NMR δ 7.0, 11.5, 28.1, 28.2, 31.2, 35.6, 38.1, 80.1, 122.4, 151.6, 165.8; HRMS (CI) m/z 339.0834 (MH^+), calcd for $C_{13}H_{24}IO_2$ 339.0821.

Anionic Cyclization of (*Z*)-7b. In a manner similar to that described for the anionic cyclization of (*E*)-**7b**, (*Z*)-**7b** upon treatment with *n*-BuLi at −100 °C gave nearly exclusively *trans*-**8b**. GC analysis showed the presence of a trace component (t/c >300) with a retention time corresponding to the authentic cis isomer prepared as outlined in Scheme VII (vide infra); ^{1}H NMR (*trans*-**8b**) δ 0.86 (m, 3 H), 1.0–2.0 (b, 10 H), 1.44 (s, 9 H), 2.0–2.5 (m, 2 H); ^{13}C NMR (*trans*-**8b**) δ 12.6, 23.5, 27.4, 28.1, 31.5, 32.3, 41.2, 42.3, 47.4, 79.9, 172.9. An analytical sample was prepared by bulb-to-bulb distillation (160 °C, 5 mm). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.75; H, 11.41.

Radical Cyclization of (*Z*)-7b. Conditions similar to those described for the radical cyclization of (*E*)-**7a** were employed: t/c > 280 for **8b** by capillary GC analysis.

1-Bromo-2-ethyl-1-cyclopentene (19). A stirred solution containing 6.78 g (30 mmol) of 18[33] in 100 mL of THF was cooled to −78 °C and treated[18] with 35 mL (60 mmol) of 1.7 M *t*-BuLi solution (in pentane) added over several minutes. The solution became yellow at the endpoint. The solution was stirred for 0.5 h and then treated with 5.0 mL (62 mmol) of EtI. The cooling bath was removed and the mixture was warmed to 20 °C over approximately 5 min, whereupon the mixture was concentrated under reduced pressure and the residue was treated with water and extracted with pentane. Concentration of the extracts and distillation of the residue gave 4.2 g (80%) of **19** as an oil which rapidly discolored: bp 73–74 °C (21 mm); ^{1}H NMR δ 0.99 (t, *J* = 7.3 Hz, 3 H), 1.93 (q, 2 H), 2.0–2.5 (m, 4 H), 2.5–2.7 (m, 2 H); ^{13}C NMR δ 11.7, 21.8, 23.2, 33.3, 40.0, 114.6, 142.2.

Ethyl 2-Ethyl-1-cyclopentenecarboxylate (20). A solution containing 5.25 g (30 mmol) of **19** in 40 mL of THF was cooled to −78 °C, and with stirring there was added 35 mL (60 mmol) of 1.7 M *t*-BuLi solution over several minutes. The mixture was stirred for 20 min and then treated over 10 min with 5.0 mL (52 mmol) of ethyl chloroformate in 85 mL of THF. The mixture was warmed to 20 °C, concentrated under reduced pressure, treated with water, and extracted with pentane. The extracts were washed with saturated $NaHCO_3$ solution and then with water and concentrated. Distillation gave 4.3 g (85%) of **20** as an oil: bp 115–120 °C (30 mm); ^{1}H NMR δ 1.05 (t, *J* = 7.5 Hz, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.82 (q, 2 H), 2.0–2.8 (b, 6 H), 4.18 (q, 2 H); ^{13}C NMR δ 12.5, 14.4, 21.5, 23.2, 33.8, 37.8, 59.5, 126.7, 161.0, 166.2. Transesterification of a sample of **20** (NaOMe, MeOH, 50 °C) gave the methyl ester which was identical to an authentic sample.[34]

Ethyl *cis*-2-Ethylcyclopentanecarboxylate (21). A solution containing 1.5 g (9 mmol) of **20** and 150 mg of 5% Rh/C in 4 mL of EtOAc was stirred under H_2 (85 psi) at 100 °C overnight. The catalyst was removed by filtration, and the solvent was removed under reduced pressure, giving 1.2 g (80%) of **21** containing a small (variable) amount of the trans isomer (c/t = 7.5–11.5):[35] ^{1}H NMR δ 0.90 (t, *J* = 6.8 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.1–2.0 (b, 7 H), 2.7–2.9 (m, 1 H), 4.11 (q, 4 H); ^{13}C NMR δ 13.2, 14.4, 24.0, 24.2, 28.6, 30.9, 45.9, 47.7, 59.8, 175.6. An analytical sample was obtained by bulb-to-bulb distillation (160 °C, 5 mm). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.46; H, 10.75.

***cis*-(2-Ethylcyclopent-1-yl)methanol (22).** A solution of 1.14 g (6.7 mmol) of **21** in 5 mL of Et_2O was added dropwise to a stirred mixture containing 460 mg (12.1 mmol) of $LiAlH_4$ in 30 mL of Et_2O. The mixture was stirred for 0.5 h, and then the excess hydride was destroyed by the dropwise addition of water followed by the addition of 1 mL of 4 N NaOH. After briefly stirring, a small amount of Na_2SO_4 was added to aid in the coagulation of the aluminum salts, and the solution phase was removed and concentrated. The residue was taken up in pentane and washed twice with water. Concentration of the pentane solution gave 800 mg (93%) of **22** as an oil: ^{1}H NMR δ 0.92 (m, 3 H), 1.0–2.2 (b, 10 H), 2.32 (s, 1 H), 3.2–3.8 (m, 2 H); ^{13}C NMR δ 13.2, 22.6, 22.9, 28.1, 30.5, 43.7, 44.6, 63.1. An analytical sample was obtained by bulb-to-bulb distillation (150 °C, 20 mm). Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.90; H, 12.51.

***cis*-(2-Ethyl-1-cyclopentyl)methyl *p*-Toluenesulfonate (23).** A solution containing 650 mg (5.1 mmol) of **22** and 650 μL (8 mmol) of pyridine in 25 mL of CH_2Cl_2 was stirred at 0 °C, and 1.16 g (6.1 mmol) of *p*-toluenesulfonyl chloride was added. The mixture was stirred for 20 h at 20 °C and then concentrated under reduced pressure. The residue was dissolved in pentane and washed sequentially with water, 4 N NaOH, water, dilute HCl, and water. The residue obtained after concentration was dissolved in 10 mL of THF and treated with 1 mL of concd NH_3 to destroy excess *p*-TsCl. After 5 min, the mixture was diluted with water and extracted with pentane. The extracts were washed with 4 N NaOH, water, and 4 N HCl, dried (Na_2SO_4), and concentrated giving 1.06 g of crude **23**. Chromatography on silica gel (13 cm, CH_2Cl_2) gave 920 mg (64%) of **23** as an oil: ^{1}H NMR δ 0.82 (t, 3 H), 1.0–1.9 (b, 10 H), 2.44 (s, 3 H), 3.92 (dd, *J* = 8.1, 7.3 Hz, 2 H), 7.2–7.9 (m, 4 H); ^{13}C NMR δ 13.0, 21.6, 22.4, 22.6, 28.1, 30.2, 41.1, 43.5, 71.4, 127.8, 129.8, 133.4, 144.6.

***cis*-(2-Ethylcyclopent-1-yl)acetonitrile (24).** A solution containing 820 mg (2.9 mmol) of **23** and 186 mg (3.8 mmol) of NaCN in 4 mL of DMSO was stirred at 20 °C for 18 h. Additional NaCN (600 mg) was added, and the mixture was heated on a water bath for 0.5 h. The mixture was poured into water and twice extracted with pentane. The extracts were washed with water and concentrated under reduced pressure giving 365 mg (92%) of **24** as an oil: ^{1}H NMR δ 0.91 (m, 3 H), 1.0–2.0 (b, 10 H), 2.22 (m, 2 H); ^{13}C NMR δ 12.9, 17.9, 22.3, 22.7, 29.4, 30.9, 39.2, 44.4, 120.0. An analytical sample was obtained by bulb-to-bulb distillation (150 °C, 20 mm). Anal. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 78.66; H, 11.04; N, 9.88.

(*cis*-2-Ethylcyclopent-1-yl)acetic Acid (25). A solution of 300 mg (2.2 mmol) of **24** in 1.2 mL of EtOH was added to a solution containing 350 mg (8.4 mmol) of NaOH in 0.4 mL of water. The mixture was heated in a 110 °C bath for 24 h, cooled, treated with 5 mL of water, and extracted (2×) with pentane. The aqueous layer was acidified with concd HCl and extracted with 1:1 pentane–Et_2O. Concentration of the extracts gave 290 mg (84%) of **25** as an oil: ^{1}H NMR δ 0.89 (t, *J* = 6.1 Hz, 3 H), 1.0–1.9 (b, 10 H), 2.0–2.5 (m, 2 H), 15.07 (s, 1 H); ^{13}C NMR δ 12.9, 22.4, 22.8, 29.7, 30.9, 34.7, 38.8, 44.5, 180.9. An analytical sample was obtained by bulb-to-bulb distillation (160 °C, 2 mm). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.31; H, 10.50.

***tert*-Butyl (*cis*-2-Ethylcyclopent-1-yl)acetate [(*Z*)-8b].** A mixture containing 100 mg (0.64 mmol) of **25** and 2 mL of $SOCl_2$ was heated under reflux for 1.5 h and then concentrated under reduced pressure. The residue was treated with 1.5 mL of *tert*-butyl alcohol and 0.5 mL of $PhNMe_2$ and allowed to stand for 20 h. The mixture was diluted with water and extracted with pentane. The extracts were washed with water, 4 N HCl (3×), 4 N NaOH (2×), and water. Concentration gave 125 mg (93%) of crude (*Z*)-**8b** which upon bulb-to-bulb distillation (150 °C, 3 mm) gave 80 mg (59%) of pure (*Z*)-**8b** as an oil: ^{1}H NMR δ 0.87 (t, *J* = 6.1 Hz, 3 H), 1.0–1.85 (b, 10 H), 1.44 (s, 9 H), 1.85–2.4 (m, 2 H); ^{13}C NMR δ 13.0, 22.5, 22.8, 28.1, 29.7, 30.8, 36.2, 39.2, 44.5, 79.8, 173.2. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.57; H, 11.16.

Ethyl 2-*tert*-Butyl-5-chloropentanoate (27). A solution containing 3.7 mL (26 mmol) of diisopropyl amine in 50 mL of THF was cooled to −78 °C, and with stirring there was added 14.0 mL (24 mmol) of 1.7 N *n*-BuLi. After 10 min, 3.4 mL (20 mmol) of ethyl 3,3-dimethylbutanoate was added dropwise, and stirring was continued for 20 min. HMPA (4 mL) and then 2.4 mL (22.4 mmol) of 1-chloro-3-iodopropane were added, and stirring was continued for 3.5 h. The mixture was allowed to warm to −60 °C over 0.5 h and then warmed to 0 °C. Acetic acid (1 mL) was added, and the mixture was concentrated under reduced pressure. The residue was treated with water and extracted with pentane. The extracts were washed with 2 N HCl, 2 N NaOH, and water and after drying (Na_2SO_4) were concentrated. Distillation gave 4.0 g (91%) of **27** as an oil: bp 126 °C (18 mm); ^{1}H NMR δ 0.97 (s, 9 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.6–1.8 (b, 4 H), 2.0–2.2 (m, 1 H), 3.52 (m, 2 H), 4.14 (q, 2 H); ^{13}C NMR δ 14.4, 25.0, 27.8, 31.3, 33.0, 44.5, 55.6, 59.8, 174.9. An analytical sample was prepared by chromatography (SiO_2, CH_2Cl_2) and bulb-to-bulb distillation (170 °C, 20 mm). Anal. Calcd for $C_{11}H_{21}ClO_2$: C, 59.85; H, 9.59. Found: C, 59.71; H, 9.70.

2-*tert*-Butyl-5-chloro-1-pentanol (28). A solution containing 3.0 g (13.6 mmol) of **27** in 50 mL of CH_2Cl_2 was cooled to −78 °C, and with stirring 30 mL (30 mmol) of 1 M DIBAL in hexane was added over 2 min. After 50 min, 2 mL of MeOH was added followed by 10 mL of H_2O and 30 mL of 4 N HCl. After stirring at 20 °C for 5 min, the organic phase was separated, washed with water, dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation (150 °C, 1 mm) gave 2.18 g (89%) of **28** as an oil: ^{1}H NMR δ 0.93 (s, 9 H), 1.0–1.7 (m, 4 H), 1.7–2.0 (m, 1 H), 2.70 (s, 1 H), 3.56 (t, *J* = 6.1 Hz, 2 H), 3.65 (m, 2 H); ^{13}C NMR δ 25.4, 28.2, 32.5, 33.0, 45.5, 50.3, 63.5. Anal. Calcd for $C_9H_{19}ClO$: C, 60.49; H, 10.72. Found: C, 60.46; H, 10.74.

2-*tert*-Butyl-5-chloropentanal (29). By use of the method of Swern,[36] 1.1 mL (12.6 mmol) of $(COCl)_2$ in 35 mL of dry (4-Å

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(35) Heating with NaOEt in EtOH resulted in an increase in the amount of trans isomer.

molecular sieves) CH_2Cl_2 was cooled to −60 °C, and 1.8 mL (25.4 mmol) of DMSO was added with stirring. After 2 min, 1.78 g (10 mmol) of **28** in 10 mL of CH_2Cl_2 was added, and stirring was continued for 15 min. Triethylamine (7 mL) was added, after 5 min 10 mL of CH_2Cl_2 was added, and the mixture was warmed to 20 °C and treated with water. The organic phase was washed with water (2×), dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation (180 °C, 6 mm) gave 1.6 g (90%) of **29** as an oil: ^1H NMR δ 1.02 (s, 9 H), 1.5–1.8 (b, 4 H), 1.8–2.0 (b, 1 H), 3.53 (m, 2 H), 9.72 (d, J = 3.9 Hz, 1 H); ^{13}C NMR δ 21.8, 27.9, 30.9, 33.3, 44.6, 61.1, 205.8. 2,4-DNP derivative: mp 171.5–173.0 °C (EtOH). Anal. Calcd for $C_{15}H_{20}ClN_4O_4$: C, 50.49; H, 5.93; N, 15.70. Found: C, 50.50; H, 5.89; N, 15.66.

***tert*-Butyl 4-*tert*-Butyl-7-chloro-2(*E*)-heptenoate (30).** In the manner described for the preparation of **13**, 1.6 g (9 mmol) of **29** gave, after bulb-to-bulb distillation (180 °C, <0.2 mm), 2.3 g (93%) of **30** as an oil: ^1H NMR δ 0.90 (s, 9 H), 1.2–1.9 (m, 5 H), 3.50 (t, J = 6.1 Hz, 2 H), 5.68 (d, J = 15.6 Hz, 1 H), 6.67 (dd, J = 15.4, 10.0 Hz, 1 H); ^{13}C NMR δ 25.9, 27.7, 28.2, 31.3, 33.3, 44.7, 52.8, 79.9, 124.8, 149.0, 165.4. Anal. Calcd for $C_{15}H_{27}ClO_2$: C, 65.55; H, 9.90. Found: C, 65.61; H, 10.05.

***tert*-Butyl 4-*tert*-Butyl-7-iodo-2(*E*)-heptenoate [(*E*)-7c].** In the manner described for the preparation of (*E*)-**7b**, 1.0 g (3.64 mmol) of **30** gave, after bulb-to-bulb distillation (200 °C, <0.2 mm), 1.27 g (95%) of (*E*)-**7c** as an oil: ^1H NMR δ 0.90 (s, 9 H), 1.49 (s, 9 H), 1.2–2.0 (b, 5 H), 3.15 (t, J = 6.3 Hz, 2 H), 5.66 (dd, J = 15.4, 0.5 Hz, 1 H), 6.66 (dd, J = 15.4, 10.0 Hz, 1 H); ^{13}C NMR δ 6.6, 27.7, 28.1, 29.5, 31.9, 33.1, 52.4, 79.9, 124.6, 148.9, 165.4. Anal. Calcd for $C_{15}H_{29}IO_2$: C, 49.18; H, 7.43. Found: C, 49.17; H, 7.46.

Anionic Cyclization of (*E*)-7c. In a manner similar to that previously described for the anionic cyclization of (*E*)-**7b**, (*E*)-**7c** cyclized at −100 °C upon treatment with *n*-BuLi to give **8d** as a mixture of isomers (t/c = 5.8) which were purified by PTLC (silica gel, 1:1 CH_2Cl_2–hexane, 80%): ^1H NMR (trans isomer) δ 0.87 (s, 3 H), 1.0–1.6 (b, 8 H), 1.44 (s, 9 H), 1.95–2.25 (b, 2 H); (cis isomer) δ 0.95 (s, 3 H), 2.25–2.40 (b, 2 H); ^{13}C NMR (trans isomer) δ 25.6, 27.8, 28.2, 28.9, 29.4, 33.4, 36.9, 43.9, 55.7, 79.7, 172.7; (cis isomer) δ 21.2, 23.7, 31.9, 33.2, 36.5, 38.1, 54.6. An analytical sample was prepared by bulb-to-bulb distillation (150 °C, 2 mm). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.82; H, 11.78.

Radical Cyclization of (*E*)-7c. Cyclization under radical conditions similar to those previously described for (*E*)-**7a** gave **8c** in 96% GC yield (t/c = 88).

Methyl 2-Bromo-5-chloropentanoate (32). A mixture containing 13.7 g (100 mmol) of 5-chloropentanoic acid, 10 mL of CCl_4, and 29 mL (400 mmol) of $SOCl_2$ was heated at 65 °C for 0.5 h, whereupon 21.4 g (120 mmol) of *N*-bromosuccinimide was added followed by 50 mL of CCl_4 and 7 drops of 48% HBr.[20] The mixture was heated at 70 °C for 10 min and then at 85–90 °C for 3 h. After cooling (ice bath) the mixture was filtered to remove succinimide, the filtrate was concentrated under reduced pressure (15 mm), the residue was treated with water and extracted with pentane. The extracts were washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. Distillation of the residue gave 13.7 g (60%) of **32** as an oil: bp 108 °C (6 mm); ^1H NMR δ 1.7–2.4 (m, 4 H), 3.58 (t, J = 6.1 Hz, 2 H), 3.79 (s, 3 H), 4.30 (dd, J = 7.5, 6.3 Hz, 1 H); ^{13}C NMR δ 30.1, 32.1, 43.8, 44.8, 53.0, 169.4. Anal. Calcd for $C_6H_{10}BrClO_2$: C, 31.40; H, 4.39. Found: C, 31.43; H, 4.39.

Methyl 5-Chloro-2-methoxypentanoate (33). A stirred solution containing 8.6 g (37 mmol) of **32** in 100 mL of MeOH was treated with 2.16 g (40 mmol) of solid NaOMe and heated under reflux for 0.5 h. Portions of NaOMe were added (≈0.5 g) until the starting material had been consumed, whereupon the mixture was cooled, concentrated, treated with water, and extracted with pentane. The aqueous layer was saturated with NaCl and again extracted with pentane, and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated. Distillation gave 4.15 g (62%) of **33** as an oil: bp 90 °C (4 mm); ^1H NMR δ 1.91 (m, 4 H), 3.39 (s, 3 H), 3.56 (m, 2 H), 3.79 (s, 3 H), 3.7–3.9 (m, 1 H). An analytical sample was obtained by PTLC (SiO_2, CH_2Cl_2) and bulb-to-bulb distillation. Anal. Calcd for $C_7H_{13}Cl_3$: C, 46.54; H, 7.25. Found: C, 46.50; H, 7.21.

5-Chloro-2-methoxypentanal (34). A solution containing 1.81 g (10 mmol) of **33** in 12 mL of toluene was stirred at −78 °C and treated with 6.5 mL (6.5 mmol) of 1 M DIBAL in hexane over 2 min. After stirring for 1.25 h, 500 μL of MeOH was added and after 5 min 1 mL of 1:1 MeOH–H_2O was added, and the mixture was vigorously stirred at 20 °C for 10 min. To this mixture was added 1 mL of 4 N NaOH, after 5 min Na_2SO_4 was added to coagulate salts, and the solution phase was collected and concentrated giving an oil which was chromatographed on a short column (10 cm) of silica gel (CH_2Cl_2), giving 1.1 g (73%) of **34** as an oil: ^1H NMR δ 1.85 (m, 4 H), 3.46 (s, 3 H), 3.57 (m, 2 H), 3.4–3.8 (b, 1 H), 9.67 (d, J = 1.7 Hz, 1 H); ^{13}C NMR δ 27.0, 27.8, 44.6, 58.2, 85.0, 203.2. This compound decomposed upon attempted distillation at <0.1 mm.

***tert*-Butyl 7-Chloro-4-methoxy-2(*E*)-heptenoate (35).** In the manner described for the preparation of **13**, 1.0 g (6.6 mmol) of **34** gave, after chromatography on silica gel (5 cm, CH_2Cl_2), 1.50 g (91%) of **35** as an oil: ^1H NMR δ 1.49 (s, 3 H), 1.4–2.0 (b, 2 H), 3.30 (s, 3 H), 3.55 (t, J = 6.2 Hz, 2 H), 3.6–3.8 (m, 1 H), 5.90 (dd, J = 15.8, 0.7 Hz, 1 H), 6.68 (dd, J = 15.8, 6.6 Hz, 1 H); ^{13}C NMR δ 28.1, 28.2, 32.1, 44.8, 57.0, 79.8, 80.5, 124.2, 146.2, 165.3. An analytical sample was obtained by bulb-to-bulb distillation (180 °C, 0.2 mm). Anal. Calcd for $C_{12}H_{21}ClO_3$: C, 57.94; H, 8.51. Found: C, 57.71; H, 8.56.

***tert*-Butyl 7-Iodo-4-methoxy-2(*E*)-heptenoate [(*E*)-7d].** As described in the preparation of (*E*)-**7a**, **35** (540 mg, 2.17 mmol) was converted by excess NaI into crude **36** which was purified by chromatography on a short plug of silica gel (CH_2Cl_2), giving 504 mg (68%) of (*E*)-**7d** as an oil: ^1H NMR δ 1.49 (s, 3 H), 1.4–2.1 (m, 4 H), 3.19 (t, J = 6.6 Hz, 2 H), 3.30 (s, 3 H), 3.74 (m, 1 H), 5.90 (dd, J = 15.6, 1.1 Hz, 1 H), 6.67 (dd, J = 15.6, 6.3 Hz, 1 H); ^{13}C NMR δ 6.3, 28.1, 29.1, 35.6, 57.0, 79.4, 80.5, 124.2, 146.1, 165.2. An analytical sample was obtained by bulb-to-bulb distillation (190 °C, <0.1 mm). Anal. Calcd for $C_{12}H_{21}IO_3$: C, 42.36; H, 6.22. Found: C, 42.32; H, 6.26. This compound was found to discolor over several days at 20 °C and was best stored at −100 °C.

Anionic Cyclization of (*E*)-7d. Cyclization of (*E*)-**7d** at −100 °C (Table I, entry 16) in a manner similar to that described for (*E*)-**7b** gave **8d** (46%) as a mixture of isomers (c/t = 1.7): ^1H NMR (cis isomer) δ 1.45 (s, 9 H), 1.0–1.8 (b, 7 H), 2.0–2.5 (b, 2 H), 3.30 (s, 3 H), 3.5–3.7 (b, 1 H); the trans isomer has its methoxyl peak at 3.25; ^{13}C NMR (cis isomer) δ 22.2, 28.1, 29.8, 30.6, 39.9, 42.0, 56.8, 80.0, 87.2, 172.2 or 173.1; trans isomer δ 21.8, (28.1), 29.3, 30.0, 35.3, 40.8, 56.6, 79.7, 83.4, 172.2, or 173.1. An analytical sample was obtained from the run described in entry 19, Table I, by bulb-to-bulb distillation (140 °C, 2 mm). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.38; H, 10.68. Variations in cyclization conditions are noted in Table I.

Radical Cyclization of (*E*)-7d. Conditions similar to those previously described for the cyclization of (*E*)-**7a** were employed giving **8d** (c/t = 1.1).

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Registry No. 7a, 138541-81-8; (*E*)-**7b**, 138541-82-9; (*Z*)-**7b**, 138541-83-0; **7c**, 138541-84-1; **7d**, 138541-85-2; **7e**, 138541-86-3; *cis*-**8a**, 138541-87-4; *trans*-**8a**, 138541-88-5; *trans*-**8b**, 138541-89-6; *cis*-**8b**, 138541-90-9; *cis*-**8d**, 138541-91-0; *trans*-**8d**, 138541-92-1; *trans*-**8e**, 138541-93-2; *cis*-**8e**, 138541-94-3; *cis*-**8** (R = Et, E = COOEt), 138541-95-4; *trans*-**8** (R = Et, E = COOEt), 138541-96-5; *trans*-**8** (R = Et, E = OH), 36258-08-9; *cis*-**8** (R = Et, E = OH), 36258-09-0; **9**, 2323-81-1; **10**, 33020-11-0; **11**, 62498-23-1; **12**, 138541-97-6; **13**, 138542-02-6; **14**, 138541-98-7; **15**, 138541-99-8; **16**, 138542-00-4; (*Z*)-**17**, 138542-01-5; (*E*)-**17**, 138542-02-6; **18**, 75415-78-0; **19**, 138542-03-7; **20**, 138542-04-8; **21**, 5183-34-6; **22**, 36258-09-0; **23**, 138542-05-9; **24**, 138542-06-0; **25**, 82167-97-3; **26**, 5340-78-3; **27**, 138542-07-1; **28**, 138542-08-2; **29**, 138542-09-3; **30**, 138542-10-6; **31**, 1119-46-6; **32**, 138542-11-7; **33**, 138542-12-8; **34**, 138542-13-9; **35**, 138542-14-0; $(EtO)_2P(O)C(PPh_3)COOEt$, 138542-15-1; $(EtO)_2P(O)CH_2COOBu$-*t*, 27784-76-5; CBr_4, 558-13-4; Mes_2BH, 51458-06-1; 1-chloro-3-iodopropane, 6940-76-7.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of **12**, (*E*)-**7a**, **8a**, **8b**, **14**, **15**, (*E*)-**7e**, **8e**, (*Z*)-**7b**, **23**, **29**, and **34** (24 pages). Ordering information is given on any current masthead page.

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