Organometallics 1994, *13*, 1456–1464

Ring Formation through Intramolecular S_N' Displacement of an Allylic Methoxy Substituent

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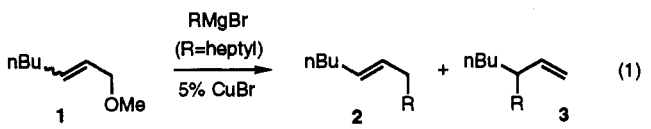
Received November 22, 1993®

Intramolecular S_N' displacement of an allylic methoxy substituent by an organomagnesium nucleophile selectively generated vinylcyclopentane and vinylcyclohexane products. This cyclization reaction was promoted by the addition of 5 mol % of CuI, CuBr, or CuBr·SMe_2. The Z isomer resulted in more efficient five-membered ring formation than did the *E* isomer, while the *E* isomer cyclized to a greater extent than the Z isomer for six-membered ring formation. Formation of five- and six-membered rings from organolithium intermediates were more efficient processes and did not show a significant dependence on olefin geometry. The selectivity obtained for cyclization of acyclic secondary allylic ethers was dependent on olefin geometry, and selective product formation was much greater for the organolithium cyclizations than for the Cu(I)-promoted reactions. Bicyclic ring products formed from a secondary allylic ether substrate were generated stereoselectively with cis ring fusion.

Introduction

Copper-catalyzed displacement reactions of organomagnesium and -lithium reagents with allylic ethers have enormous potential for the stereoselective formation of carbon–carbon bonds.[1] Allyl ether substrates are readily accessible functional groups that can be prepared with high enantioselectivity. Coupled with the *anti* displacement required for the allylic alkoxy substituent, these substrates can lead to the stereoselective synthesis of optically active products. A distinct advantage of the allylic ether functionality is the stability under most reaction conditions, which allows incorporation of this functionality early in an extended synthetic sequence.

The use of allylic ethers for intermolecular bond formation in organic synthesis has been limited due to the variable and incomplete regioselectivity of the reaction (S_N2 versus S_N2'). For example, while the reaction of (*E*)-1 with (*n*-heptyl)MgBr/5% CuBr gave a 99:1 ratio of **2** and **3**, respectively, the 87:13 product ratio obtained from (*Z*)-1 showed less selectivity (eq 1).[2] Under similar conditions,



(1)

(*E*)	65% Yield	99	:	1
(*Z*)	76% Yield	87	:	13

treatment of 3-methoxycyclohexene substrates produced only a 40:60 ratio of S_N2 to S_N2' products.[3] Hydroxyl functionality has been used to direct regioselective addition of the nucleophile to acyclic secondary allylic ethers.[4] Intermolecular reaction with *n*-BuLi has also resulted in the S_N2' displacement of a secondary methoxy substituent.[5] With the addition of a Cu(I) salt and a Lewis acid, the outcome of the reaction can be controlled by the nature of the reagents. The reaction of BuCu/LiX/BF_3 with 1-methoxy-2-decene primarily gave S_N2' displacement (13:87 6-tetradecene:3).[6] A reversed preference for the formation of 6-tetradecene:3 (98:2) was observed when Bu_2CuLi/BF_3 was used.

The regioselective S_N2' addition of organometallic species to allyl ethers has been controlled through intramolecular reaction (S_N').[7] Early evidence for successful cyclopentane formation from alkenyl–metal species was observed as a byproduct of an organocuprate reaction.[8] Subsequently, ring formation from a vinyllithium species was reported.[9] This strategy has also been used very successfully in the formation of tetrahydrofuran products from $ROCH_2Li$ species.[10]

On the basis of our interests in cyclization reactions of alkene substrates,[11] the intramolecular reaction of sp^3 alkyl–metal species of nonstabilized anions with allylic ethers was examined for the regio- and stereoselective formation of five- and six-membered carbocycles. In this study, the nature and utility of this reaction was probed

• Abstract published in *Advance ACS Abstracts*, March 1, 1994.

(1) For reviews in this area, see: (a) Normant, J. F. *Pure Appl. Chem.* **1978**, *50*, 709. (b) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (c) Erdik, E. *Tetrahedron* **1984**, *40*, 641.

(2) (a) Commercon, A.; Bourgain, M.; Delaumeny, M.; Normant, J. F.; Villieras, J. *Tetrahedron Lett.* **1975**, *44*, 3837. (b) Normant, J. F.; Commercon, A.; Gendreau, Y.; Bourgain, M.; Villieras, J. *Bull. Soc. Chim. Fr.* **1979**, 309.

(3) Gendreau, Y.; Normant, J. F. *Tetrahedron* **1979**, *35*, 1517.

(4) (a) Claesson, A.; Tämnefors, I.; Olsson, L.-I. *Tetrahedron Lett.* **1975**, 1509. (b) Claesson, A.; Olsson, L.-I. *J. Chem. Soc. Chem. Commun.* **1978**, 621.

(5) Kishi, N.; Imma, H.; Mikami, K.; Nakai, T. *Synlett* **1992**, 189.

(6) Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3079.

(7) For an excellent review on the intramolecular S_N' reaction, see: Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383.

(8) Katzenellenbogen, J.; Corey, E. J. *J. Org. Chem.* **1972**, *37*, 1441.

(9) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788.

(10) (a) Farnum, D. G.; Monego, T. *Tetrahedron Lett.* **1983**, *24*, 1361. (b) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336. (c) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981.

(11) (a) Rigollier, P.; Young, J. R.; Fowley, L. A.; Stille, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 9441. (b) Young, J. R.; Stille, J. R. *Organometallics* **1990**, *9*, 3022. (c) Young, J. R.; Stille, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 4936.

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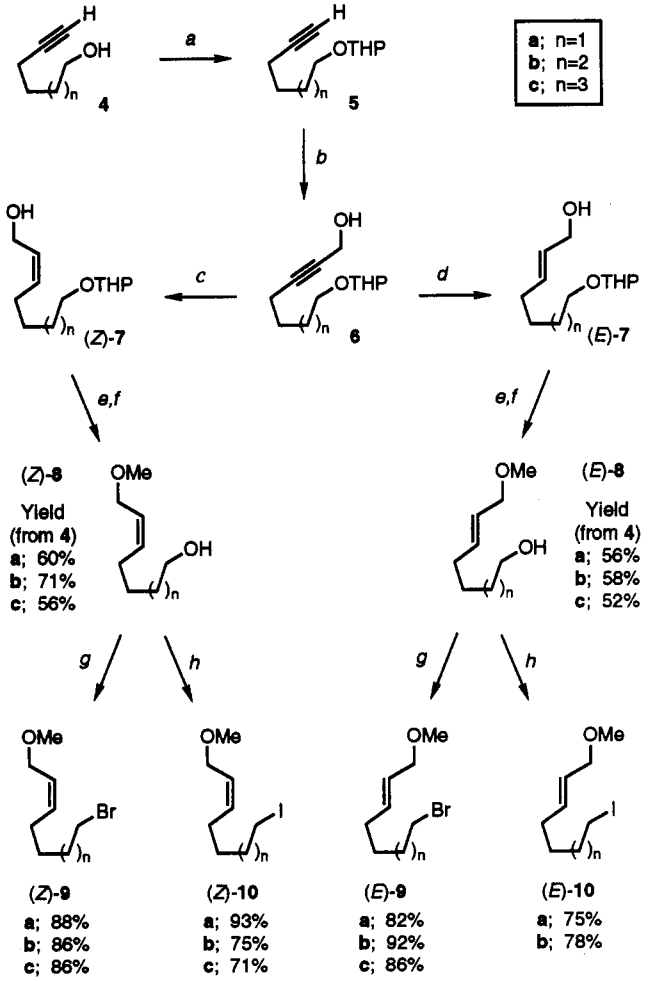
Scheme 1. Preparation of Cyclization Substrates 9 and 10[a]



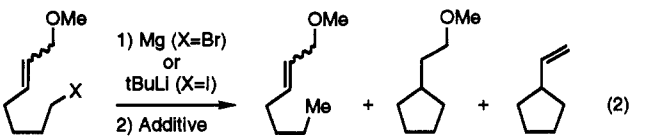
[a] Reagents and conditons: (a) DHP, PPTS; (b) *i.* *n*-BuLi, *ii.* $(CH_2O)n$; (c) H_2, NiB_2; (d) RedAl®; (e) NaH, MeI; (f) MeOH, PPTS; (g) NBS, PPh_3; (h) *i.* MsCl, NEt_3, *ii.* NaI.

through variation of substrate features such as olefin geometry, metal species, tether length, orientation of the allyl group, and the primary or secondary nature of the allylic substituent. The importance of these features are discussed with respect to conversion of substrate to cyclic product, reaction yield, and stereoselective alkene formation.

Results and Discussion

In order to address the characteristics of the S_N' reaction, a number of substrates were prepared through parallel routes that originated from the known hydroxyalkyne **4** (Scheme 1).[12] Protection of the alcohol as the THP ether **5**, followed by deprotonation of the terminal alkyne and reaction with paraformaldehyde, produced the homologated species **6**. Reduction of **6** with either H_2/NiB_2 or RedAl provided divergent routes to the isomeric alkenes (*Z*)-**7** and (*E*)-**7**.[13] Methylation of the allylic hydroxyl group and subsequent removal of the THP protection gave **8**. Overall, this five-step sequence generated **8** in 52–71% yields from **4**. From alcohol **8**, transformation to the corresponding halide provided routes to both **9** and **10**. An array of substrates, which differed in alkene geometry, alkyl halide, and tether length (**a**–**c**), were prepared through this sequence of reactions for use in these cyclization studies.

Table 1. Intramolecular Cyclopentane Formation from 9a and 10a



9a; X=Br
10a; X=I

11 **12** **13**

substrate[a]	additive[b]	product distribution[c] 11	13	yield (%)[d]
(*Z*)-**9a**		85	13	68
(*Z*)-**9a**	*e*	6	94	87
(*Z*)-**9a**	CuI	8	92	76
(*Z*)-**9a**	CuBr	7	93	81
(*Z*)-**9a**	$CuBr{\cdot}SMe_2$	9	91	74
(*Z*)-**10a**		4	96	88
(*Z*)-**10a**	CuI	13	87	73
(*Z*)-**10a**	TMEDA[f]	18	82	75
(*E*)-**9a**	*e*	12	87	85
(*E*)-**9a**	CuI	30	68	74
(*E*)-**9a**	CuBr	30	69	64
(*E*)-**9a**	$CuBr{\cdot}SMe_2$	31	67	67
(*E*)-**10a**		9	90	76

[a] Substrate **9a** was treated with 10.0 equiv of Mg, THF; substrate **10a** was treated with *t*-BuLi, Et_2O/hexane, −78 °C to room temperature. [b] 0.05 equiv of additive. [c] Reference 15. [d] GC yields.[14] [e] Reaction heated at 66 °C. [f] 1.0 equiv of TMEDA.

Cyclopentane Formation. Optimum conditions for the formation of **13** were determined by varying reaction parameters for the cyclization of **9a** (Table 1, eq 2).[14] The slow addition of (*Z*)-**9a** to 10.0 equiv of Mg in THF at 0 °C generated the corresponding Grignard species, which produced an 85:2:13 mixture of **11**:**12**:**13** upon protonolysis.[15] As expected, the product of S_N' displacement, **13**, was formed from (*Z*)-**9a** without evidence of cycloheptene, the product of S_N displacement. Typically, the formation of **12**, either through proton abstraction by the intermediate anion prior to elimination or through radical intermediates, was found to be ≤2%.[16] When (*Z*)-**9a** was either added to the Mg in THF at reflux (66 °C), or added at 0 °C and then heated at 66 °C for 10 h after Grignard formation, a 6:94 ratio of **11** to **13** resulted after protonolysis.[17] Slightly lower conversion was observed when (*E*)-**9a** was used as the substrate for intramolecular displacement by the Grignard, but comparable yields resulted.

(12) Singer, R. D.; Hutzinger, M. W.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 4933.

(13) Stereoselective formation of each alkene isomer exceeded 95:5.

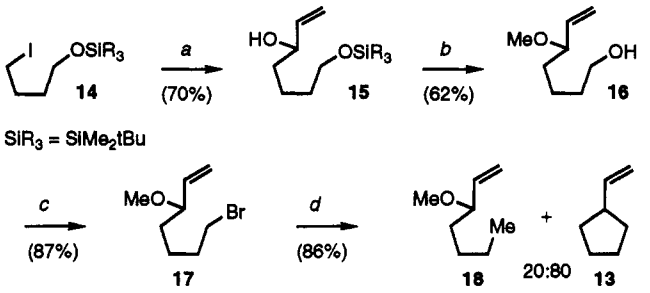
(14) Yields of these volatile compounds represent a combined yield for all products of the quenched reaction mixture (NH_4Cl/H_2O). Values were determined by capillary gas chromatographic analysis in comparison with *n*-heptane (substrate **a**) and *n*-octane (substrate **b**) as internal standards. Correction for detector response was made, and yields were based on the amounts of **9** and **10** used for formation of the organometallic intermediate.

(15) Relative product ratios were determined by capillary gas chromatographic analysis and were scaled to 100. In other cases, the balance of the reaction mixture (100% − [**11** + **13**]) consisted of byproducts (mostly **12**) contributing ≤2% each to the reaction mixture and were not included in these ratios.

(16) Radical cyclization of (*Z*)- and (*E*)-**9a** (0.01 M, $(n\text{-Bu})_3SnH$, AIBN, C_6H_6, 80 °C) resulted in complete conversion to **12** in 79% and 90% yields, respectively. For an analogous "S_N'-type" reaction of a free radical to an allyl phenyl thioether and subsequent elimination, see: (a) Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. *J. Org. Chem.* **1987**, *52*, 4072. (b) Cekovic, Z.; Saicic, R. *Tetrahedron Lett.* **1990**, *31*, 6085. (c) Boger, D. L.; Yun, W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 2873.

(17) Intramolecular S_N' displacement of allylic ethers with Grignard reagents has been reported for the formation of three-membered rings: Fischer, P. M.; Howden, M. E. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 475.

Scheme 2. Preparation and Cyclization of Substrate 17[a]



[a] Reagents and conditions: (a) *i.* *t*-BuLi, *ii.* acrolein; (b) *i.* NaH, MeI, *ii.* TBAF; (c) NBS, PPh_3; (d) Mg, CuI.

The same conversion of (*Z*)-**9a** to **13** was obtained in a more timely fashion by transfer of the Grignard solution to a suspension of 5 mol % of CuI, CuBr, or CuBr·SMe_2 in THF at −78 °C and then allowing the reaction to warm to 25 °C for 1 h. Alternatively, the catalytic amount of Cu(I) salts could be added directly to the reaction mixture of (*Z*)-**9a** and Mg, and **13** was produced without significant sacrifice in conversion or product yield. In each case, the reaction did not show a dependence on the nature of the Cu(I) salt used. If the same procedure was performed from (*E*)-**9a**, a lower yield of the product mixture resulted (64–68%), and conversion to **13** of greater than 68% could not be achieved. These results demonstrated a substantial effect of the alkene geometry on the efficiency of the reaction. Variation in the concentration of the Cu-promoted reaction mixture prepared from (*Z*)-**9a**, from 0.01 to 0.3 *M*, had little effect on the product distribution. The addition of 50 mol % of CuI did not alter the conversion to **13**.

An opposite approach, S_N displacement of the methoxy substituent, was also successful in formation of **13**, and the desired substrate **17** was prepared in an overall four-step sequence (Scheme 2). Formation of the alkyllithium species generated from **14**, followed by the addition of acrolein, resulted in generation of allylic alcohol **15**. Methylation and desilylation of **15** gave **16**, which was subsequently transformed to the corresponding bromide **17**. Treatment of **17** with Mg formed the Grignard species, and the addition of CuI promoted cyclization to give a 20:80 ratio of **18**:**13**.

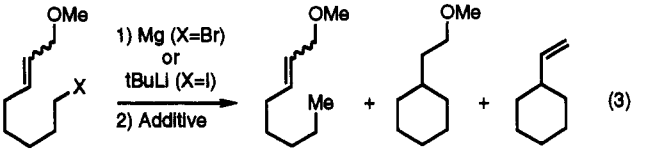
The study of organolithium species provided an interesting comparison to the Mg/Cu(I) systems. Generation of the corresponding organolithium species from **10a** was performed at −78 °C through standard methods.[18] Subsequent warming of the reaction mixture to 25 °C produced very high conversion to **13** (Table 1, eq 2). Interestingly, the addition of 5 mol % of CuI or 1.0 equiv of TMEDA to **10a** only served to reduce the efficiency of the reaction.[19] The intramolecular cyclization of the alkyllithium species was independent of alkene geometry.

Cyclohexane Formation. Formation of six-membered rings was also accomplished through this intramolecular S_N' approach. Generation of the Grignard reagent from either (*Z*)- or (*E*)-**9b**, followed by heating at reflux for 18 h, did not produce **21** in detectable amounts (Table 2, eq 3). However, the addition of Cu(I) salts to the Grignard

(18) (a) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442. (b) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404. (c) Bailey W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720 and references within.

(19) The use of copper acetylide in formation of the mixed cuprate, to conserve the active lithio species, was not examined.

Table 2. Intramolecular Cyclohexane Formation from 9b and 10b



9b; X=Br
10b; X=I

19 **20** **21**

substrate[a]	additive[b]	product distribution[c] 19	21	yield (%)[d]
(*Z*)-**9b**	*e*	100		76
(*Z*)-**9b**	CuI	12	84	74
(*Z*)-**9b**	CuBr	33	67	66
(*Z*)-**9b**	CuBr·SMe_2	30	70	67
(*Z*)-**10b**		9	85	82[f]
(*E*)-**9b**	*e*	100		66
(*E*)-**9b**	CuI	17	83	66
(*E*)-**9b**	CuBr	12	88	66
(*E*)-**9b**	CuBr·SMe_2	15	85	68
(*E*)-**9b**	CuCl	16	84	63
(*E*)-**9b**	CuCN	88	12	60
(*E*)-**10b**		17	83	88

[a] Substrate **9b** was treated with 10.0 equiv of Mg, THF; substrate **10b** was treated with *t*-BuLi, Et_2O/hexane, −78 °C to room temperature. [b] 0.05 equiv of additive. [c] Reference 15. [d] GC yields.[14] [e] Reaction heated at 66 °C. [f] Compound **20** contributed to 6% of the reaction mixture.

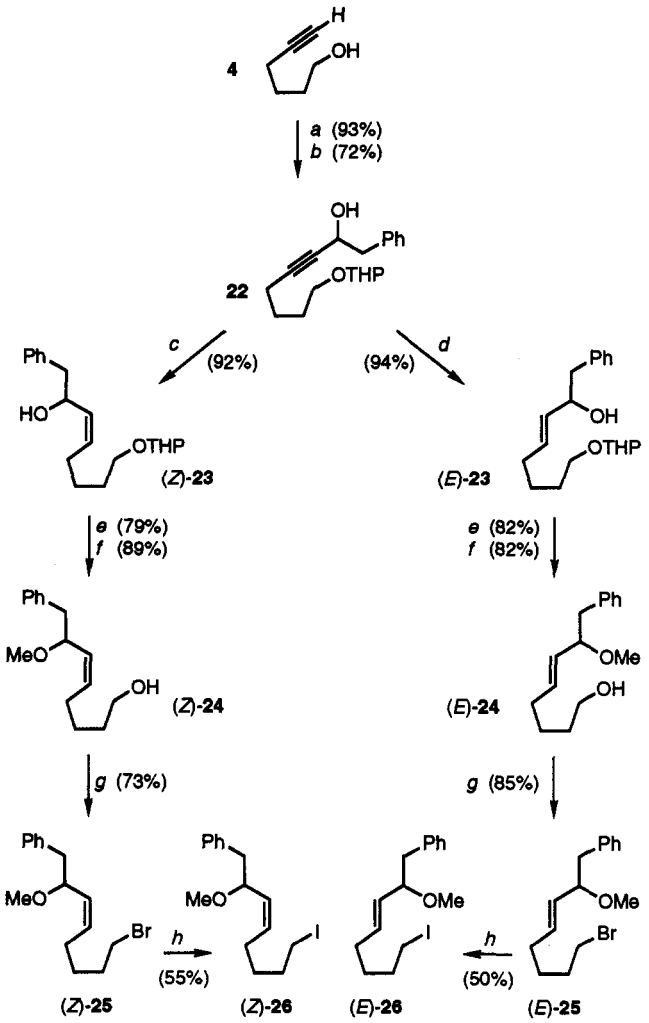
complex resulted in the formation of **21** as the major product. Upon examination of the products formed from (*Z*)-**9b**, a moderate dependence on the nature of the Cu(I) catalyst was found, in which the use of CuI resulted in greater conversion to **21**. For (*E*)-**9b**, conversion was more efficient than observed for (*Z*)-**9b**, and the reaction did not show a dependence on the nature of the Cu(I) species used. One exception, CuCN, produced poor conversion to **21**. In the case of **9a**, where the efficiency of the intramolecular S_N' displacement was affected by the alkene geometry, the *Z* isomer was more efficient in formation of five-membered rings than the *E* isomer. The opposite trend was observed for six-membered ring formation, in which conversion of the *E* isomer to cyclic product exceeded that of the *Z* isomer. Cyclization of the alkyllithium species generated from **10b** effectively produced **21**, but 6% of **20** was generated during the less efficient cyclization of the *Z* isomer.[20]

Extension of this methodology to the formation of seven-membered rings was unsuccessful. Generation of the Grignard reagent from (*E*)-**9c** or (*Z*)-**9c** under the standard reaction conditions, followed by the addition of Cu(I), did not produce formation of vinylcycloheptane. Even preparation of the corresponding alkyllithium from (*Z*)-**10c** did not result in seven-membered ring formation.

Secondary Allylic Ether Substrates. The intramolecular S_N' displacement of secondary allylic ethers **25** and **26** was examined, with respect to the relationship between the initial substrate alkene geometry and the product ratio of isomeric alkenes (Scheme 3). The substrates required for this study were prepared through a route which paralleled the preparation of the allyl ethers **9** and **10**. Protection of **4**, followed by addition of the acetylenic group to phenyl acetaldehyde, gave **22**, and selective reduction produced the *E* and *Z* isomers of the desired allylic alcohol species **23**. Methylation of the allylic

(20) Radical cyclization (0.01 M, $(n\text{-Bu})_3SnH$, AIBN, C_6H_6, 80 °C) for these substrates produced the following product distributions (**19**:**20**:**21**): (*Z*)-**9b**, 28:72:0 (81% combined yield); (*E*)-**9b**, 58:42:0 (82% combined yield).

Scheme 3. Preparation of Cyclization Substrates 25 and 26[a]



[a] Reagents and conditions: (a) DHP, PPTS; (b) *i.* *n*-BuLi, *ii.* $PhCH_2CHO$; (c) H_2, NiB_2; (d) RedAl®; (e) NaH, MeI; (f) MeOH, PPTS; (g) NBS, PPh_3; (h) KI, DMF.

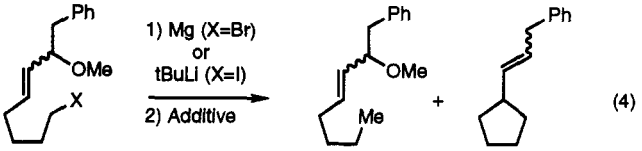
hydroxyl and deprotection of the terminal hydroxyl gave **24**, from which the corresponding isomeric bromides **25** were formed. Halide metathesis provided a route to the corresponding iodides **26**.[21]

Cyclization of **25** and **26** revealed a significant dependence on the alkene geometry and the method of cyclization (Table 3, eq 4). Treatment of (*Z*)-**25** with Mg produced the corresponding organometallic species, which resulted in 74% conversion to **28** upon heating for 40 h. The conversion and reaction yield were both improved substantially by the addition of 5 mol % of $CuBr{\cdot}SMe_2$, and even better results were observed for the generation of the organolithium species from (*Z*)-**26**. In each case, excellent *E*:*Z* product ratios (93:7 to 96:4) were obtained for the formation of **28**.

Similar effects on the conversion and product yields were observed for the reaction of (*E*)-**25**. The addition of 5 mol % of $CuBr{\cdot}SMe_2$ produced significant enhancement of the cyclization process for the Grignard complex prepared from (*E*)-**25**, and treatment of (*E*)-**26** with *t*-BuLi produced the optimum results with respect to reaction conversion, yield, and selectivity. Intramolecular S_N' displacement by the organolithium species generated **28** with excellent 98:2 *E*:*Z* selectivity. In comparison, the

(21) Albano, E. L.; Horton, D. *J. Org. Chem.* **1969**, *34*, 3515.

Table 3. Intramolecular Cyclopentane Formation from 25 and 26



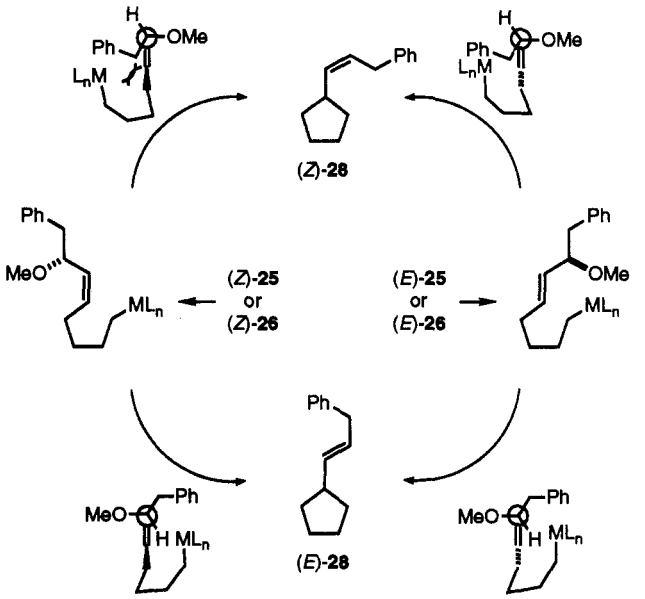
25; X=Br
26; X=I

27 **28**

substrate[a]	additive[b]	product distribution[c] 27	28 (*E*:*Z*)	yield (%)[d]
(*Z*)-**25**	*e*	26	74 (94:6)	65
(*Z*)-**25**	$CuBr{\cdot}SMe_2$	10	90 (93:7)	84
(*Z*)-**26**		1	99 (96:4)	91
(*E*)-**25**	*e*	24	76 (82:18)	63
(*E*)-**25**	$CuBr{\cdot}SMe_2$	9	91 (51:49)	84
(*E*)-**26**		6	94 (98:2)	90

[a] Substrate **25** was treated with 10.0 equiv of Mg, THF; substrate **26** was treated with *t*-BuLi, Et_2O/hexane, −78 °C to room temperature. [b] 0.05 equiv of additive. [c] Reference 15. [d] GC yields.[14] [e] Grignard reagents were generated at 66 °C and reactions heated at 66 °C for 40 h (*Z*-isomer) and 21.5 h (*E*-isomer).

Scheme 4. Possible Transition States for Formation of 28 through Intramolecular S_N' Displacement

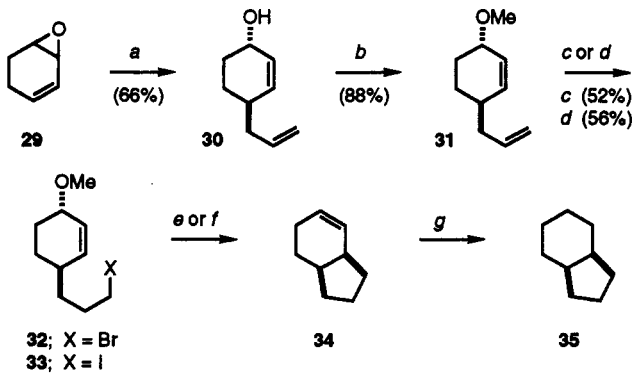


isomeric product ratio observed for cyclization of the corresponding Grignard reagent was somewhat lower (82:18), and the addition of $CuBr{\cdot}SMe_2$ to the organomagnesium species produced an equal mixture of the two isomers.

The selective formation of (*E*)-**28** was investigated through analysis of possible transition states, in which the anti-periplanar orientation necessary for displacement of the methoxy leaving group was maintained (Scheme 4).[22] By analysis of the intramolecular reaction of the organometallic species formed from (*Z*)-**25**, significant differences in transition state stability are rationalized through simple steric arguments. The geometry required for formation of (*Z*)-**28** from (*Z*)-**25** resulted in steric interaction of the benzyl substituent with the alkene and the *cis*-substituted alkyl tether, while the formation of (*E*)-**28** avoided these unfavorable interactions. In the case of the organolithium species formed from (*E*)-**26**, the

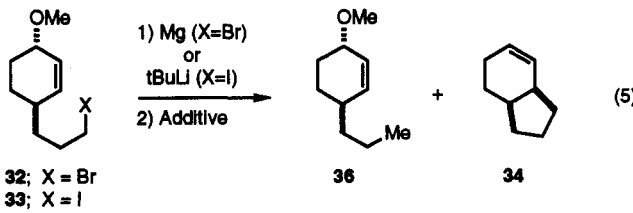
(22) Copper-catalyzed S_N2' carbon–carbon bond formation was found to proceed with *anti* selectivity.[3,4] See also: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

Scheme 5. Preparation and Cyclization of Substrate 33[a]



[a] Reagents and conditions: (a) Li, $PhOCH_2CH{=}CH_2$, CuCN; (b) NaH, MeI; (c) *i.* Cp_2ZrHCl, *ii.* NBS; (d) *i.* Cp_2ZrHCl, *ii.* I_2; (e) Mg, additive (X = Br); (f) *t*-BuLi (X = I); (g) H_2, PtO_2.

Table 4. Intramolecular Bicyclo[4.3.0]nonene Formation from 32 and 33



(5)

substrate[a]	additive[b]	product distribution[c] 36	34	yield (%)[d]
32	*e*	23	77	59
32	CuI	28	72	51
32	$CuBr{\cdot}SMe_2$	23	77	52
33		25	75	77

[a] Substrate 32 was treated with 10.0 equiv of Mg, THF; substrate 33 was treated with *t*-BuLi, Et_2O/hexane, −78 °C to room temperature. [b] 0.05 equiv of additive. [c] Reference 15. [d] GC yields.[14] [e] Reaction heated at 66 °C.

gauche interactions of the benzyl substituent with the (*E*)-alkene also favor the formation of (*E*)-**28**. These interactions produced excellent selectivity for the organolithium cyclization, possibly due to the low temperature at which the reaction was performed. Slightly reduced selectivity was observed for the corresponding Grignard cyclization, and interestingly, addition of the $CuBr{\cdot}SMe_2$ to the Grignard complex derived from (*Z*)-**25** produced and equal mixture of (*E*)- and (*Z*)-**28**.

In order to determine the stereoselectivity of this process for the intramolecular displacement of a cyclic allyl ether, substrates **32** and **33** were prepared (Scheme 5). The addition of allyl cuprate to **29** gave **30**,[23] and subsequent methylation of the allylic alcohol provided a route to **31**. Selective reaction of the terminal alkene with Cp_2ZrHCl,[24] followed by treatment with NBS, generated the desired substrate **32**. Similarly, the corresponding iodide was prepared by oxidative removal of the zirconium ligand with I_2 to give **33**, which was used in the lithium-mediated cyclization study.

Intramolecular displacement of the organometallic species generated from **32** or **33** produced stereoselective formation of the cis-fused bicyclo[4.3.0]nonene ring system **34** (Table 4). This cyclization was accomplished through preparation of the corresponding Grignard complex from **32**, which underwent cyclization upon heating to generate **34** with 77% conversion. The addition of CuI or $CuBr{\cdot}SMe_2$ to the organomagnesium species led to comparable amounts of cyclization. Cyclization of the analogous organolithium intermediate prepared from **33** resulted in efficient formation of **34**. In each case, a single product of cyclization was obtained, and catalytic hydrogenation of the product mixtures with PtO_2 gave **35** (>95:5, cis:trans), which was compared to a commercially available standard. Interestingly, the allylic TBDMS ether analogous to **32** resulted in only 17% conversion to **34** upon Grignard formation and treatment with $CuBr{\cdot}SMe_2$.

Summary. There are a number of features that contribute to the attractiveness of the S_N' displacement as a method for carbocycle formation. The Cu(I)-promoted cyclization of organometallic species with allylic ether substrates was performed under relatively concentrated conditions (0.1–0.3 M), and this process was generally independent of the type and amount of catalyst species used as an additive. The stereoselectivity of this process, with respect to alkene geometry during ring formation and for the generation of bicyclic ring systems, is high in most cases and provides a useful tool for the strategic construction of complex organic molecules. Initial investigation of this methodology for the formation of bicyclic ring systems showed efficient ring formation with stereoselectively controlled ring fusion. Extension of this methodology to the selective formation of five- and six-membered rings onto existing ring systems would provide a powerful synthetic tool for the synthesis of a variety of cis and trans fused bicyclic ring systems.

The use of allylic ethers as trapping functionality has also expanded the versatility of existing organolithium cyclization methodology. Although intramolecular cyclization of disubstituted alkene substrates, such as 5-hepten-1-yllithium, did not occur,[9,18c] the lithium-mediated cyclization of the analogous species, **10**, was very efficient. Conversion of **10b** to **21** was also much greater than observed for cyclization of 6-hepten-1-yllithium (68%), which was optimum when TMEDA was added to facilitate cyclization.[18a] These metal-mediated displacement reactions with allylic ethers nicely complement free radical methodology in that ring formation selectively generated **13** or **21**, while free radical cyclization produced only **12** or **20**.[16,20]

Experimental Section

General Methods. The reactions were typically carried out performing standard inert-atmosphere techniques to exclude moisture and oxygen. Paraformaldehyde was dried under vacuum over anhydrous phosphorus pentoxide. Activation of Mg was performed by sequential washing of the metal with 5% aqueous HCl, H_2O, acetone, and Et_2O, followed by removal of residual solvent under vacuum; the Mg was heated under vacuum immediately prior to use. Unless otherwise stated, concentration of samples was performed by evaporation under a stream of N_2 or by rotary evaporation.

NMR spectra were obtained on a Varian Gemini or VXR-300 instrument with $CDCl_3$ as the solvent. ^1H NMR spectra data are reported as follows: chemical shifts relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, b = broad), coupling, and integration. ^{13}C signals are reported in ppm relative to $CDCl_3$ (77.0 ppm). Capillary gas chromatography was carried out either with an RSL-200 column (methyl 5% phenylsilicone) or an RTX-1 column.

Typical Procedure for Conversion of 5 to 6. To a solution of *n*-BuLi (32.7 mL, 65.4 mmol, 2.0 M in hexanes) in THF (100

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(24) Miller, J. A.; Negishi, E. *Isr. J. Chem.* **1984**, *24*, 76.

mL) at −78 °C was introduced **5b** (11.6 g, 59.4 mmol), and the reaction was stirred for 30 min at −78 °C. The reaction was warmed to 0 °C, and paraformaldehyde (4.0 g) was added. After being stored for 1 h at room temperature, and at 45–50 °C for an additional 1.5 h, the reaction mixture was poured into a mixture of saturated aqueous NH_4Cl (14 mL) and H_2O (125 mL). The aqueous layer was extracted with Et_2O (4 × 75 mL), and the organic layers were combined, dried ($MgSO_4$), and concentrated to give **6**, which was carried on without further purification.

Formation of 15. A solution 1-((*tert*-butyldimethylsilyl)oxy)-4-iodobutane[25] (9.2 g, 29.0 mmol) in hexane/Et_2O (130 mL/87 mL) at −78 °C was treated with *t*-BuLi (37.5 mL, 1.7 M in pentane). The reaction was stirred at −78 °C for 20 min, allowed to warm to −10 °C, and then cooled again to −78 °C. Acrolein (1.8 g, 32.0 mmol) was added, the mixture was stirred for 2 h at −78 °C, and was then warmed to room temperature. The reaction was quenched by the addition of 200 mL of 50% saturated aqueous NH_4Cl, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The crude product could be carried on without purification, or alternatively, chromatography (40:60, Et_2O/petroleum ether) provided **15** (5.0 g, 20.4 mmol) in 70% yield: ^1H NMR (300 MHz) δ 0.02 (s, 6 H), 0.84 (s, 9 H), 1.30–1.53 (m, 6 H), 1.83 (bs, 1 H), 3.57 (t, J = 6.4 Hz, 2 H), 4.06 (bq, J = 6.2 Hz, 1 H), 5.05 (dt, J = 10.5, 1.26 Hz, 2 H), 5.17 (dt, J = 17.6, 1.4 Hz, 1 H), 5.82 (ddd, J = 17.6, 10.5, 6.3 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −5.3, 18.3, 21.6, 25.9, 32.6, 36.7, 63.0, 73.1, 114.5, 141.2; IR (neat) 3600–3200, 3080, 2934, 2860, 1645, 920 cm^{-1}.

Preparation of 30. To a 500-mL round-bottom flask equipped with a pressure-equalizing addition funnel were added Li (4.2 g, 0.6 mol) and THF (50 mL). The flask was cooled to −15 °C, and allyl phenyl ether (6.7 g, 50.0 mmol) in Et_2O (25 mL) was added dropwise.[23] After the reaction was stirred at −15 °C for 45 min and at room temperature for 20 min, the dark red solution was cannula transferred to CuCN in Et_2O (10 mL) at −40 °C and then stirred at this temperature for 30 min. 3,4-Epoxycyclohex-1-ene (**29**, 2.4 g, 25.0 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction was quenched by the addition of H_2O (75 mL) and Et_2O (75 mL), and the aqueous layer was further extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with 10% aqueous NaOH (50 mL) and saturated aqueous NaCl (75 mL), dried ($MgSO_4$), and concentrated to yield a crude oil. Distillation (bp 75–80 °C, 1 mmHg) gave 2.3 g of product as a mixture of isomers. Major isomer, **30**: ^1H NMR (300 MHz) δ 1.23 (m, 1 H), 1.45 (m, 1 H), 1.80 (m, 1 H), 1.91–2.30 (m, 4 H), 2.18 (m, 1 H), 2.30 (bs, 1 H), 4.18 (m, 1 H), 4.95–5.05 (m, 2 H), 5.60–5.75 (m, 2 H), 5.72 (m, 1 H); ^{13}C NMR (75 MHz) δ 26.6, 31.6, 35.0, 40.0, 66.7, 116.1, 130.6, 133.4, 136.4; IR 3100–3600, 3076, 3020, 2932, 2858, 1641, 1448, 1060, 736 cm^{-1}.

Formation of 22. To a solution of *n*-BuLi (34 mL, 85 mmol, 2.5 M in hexanes) in THF (120 mL) at −78 °C was introduced **5a** (14.4 g, 79 mmol) over the period of 30 min, and the reaction was stirred for 30 min at −78 °C. The reaction was warmed to 0 °C, and a solution of freshly distilled phenylacetaldehyde (10.2 g, 85 mmol) in 40 mL of THF was added over 2.25 h. After being stirred at room temperature for 4 h, the reaction mixture was poured into a mixture of saturated aqueous NH_4Cl (20 mL) and H_2O (190 mL). The aqueous layer was extracted twice with Et_2O, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and 50% saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to give **22**. Purification was accomplished through silica gel chromatography (1:1, hexane:Et_2O) to give **22** (17.2 g, 56.7 mmol) in 72% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.45–1.89 (m, 10 H), 2.22 (td, J = 7.0, 1.9 Hz, 2 H), 2.62 (bs, 1 H), 2.95 (d, J = 6.4 Hz, 2 H), 3.38 (m, 1 H), 3.44 (m, 1 H), 3.71 (m, 1 H), 3.82 (m, 1 H), 4.47–4.59 (m, 2 H), 7.19–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.3, 19.3, 25.1, 25.2, 28.6, 30.5, 44.3, 62.0, 63.1, 66.8, 80.9, 85.8, 98.6, 126.4, 128.1, 129.6, 137.0; IR (neat) 3700–3200, 3028, 2943, 2868, 2210, 1495, 1454, 1033 cm^{-1}. HRMS: calcd for $C_{19}H_{26}O_3$, m/e 303.1916; obsd, m/e 303.1961.

Formation of (*E*)-23. To a solution of RedAl (20 mL, 3.4 M in toluene) in 20 mL of Et_2O was added dropwise a solution of **22** (7.00 g, 23.2 mmol) in 20 mL of Et_2O. After the mixture was stirred for 10 min at 0 °C, the ice bath was removed, and then the reaction mixture was stirred at room temperature for 12 h. The mixture was cooled to −5 °C and diluted with Et_2O, and 31 mL of 2 N H_2SO_4 was slowly added over 45 min. The resulting solids were removed by filtration and then washed three times with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated to give (*E*)-**23** (6.60 g, 21.8 mmol) in 94% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.38–1.90 (m, 11 H), 1.97 (bs, 1 H), 2.04 (q, J = 7 Hz, 2 H), 2.75–2.97 (m, 2 H), 3.36 (m, 1 H), 3.50 (m, 1 H), 3.72 (m, 1 H), 3.86 (m, 1 H), 4.37 (q, J = 6 Hz, 1 H), 4.57 (t, J = 2.5 Hz, 1 H), 5.46–5.66 (m, 2 H), 7.14–7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$ δ 19.5, 25.3, 25.6, 29.0, 30.6, 31.8, 44.0, 62.1, 67.2, 73.4, 98.6, 126.2, 128.2, 129.4, 131.7, 132.3, 138.0; IR (neat) 3700–3200, 3063, 3028, 2939, 2864, 1668, 1603, 1454, 1034, 972, 748, 700 cm^{-1}. HRMS: calcd for $C_{19}H_{28}O_3$, m/e 303.1916; obsd, m/e 303.1963.

Formation of (*Z*)-23. To a mixture of $Ni(OAc)_2 \cdot 4H_2O$ (0.32 g, 4.3 mmol) and 16 mL of absolute EtOH was added $NaBH_4$ (0.16 g, 4 mmol) in portions (H_2 evolution). After the black mixture was stirred for 1 h at room temperature, ethylenediamine (0.18 mL) was added, followed by the addition of **22** (2.70 g, 8.9 mmol). The system was evacuated and placed under an atmosphere of H_2 for 3 h, and the hydrogen uptake was monitored with a gas buret. When disappearance of starting material was complete, the mixture was then filtered and evaporated. Further purification was performed by filtering the compound through silica gel, washing through with Et_2O/CH_2Cl_2, and removal of solvent to give (*Z*)-**23** (2.50 g, 8.2 mmol) in 92% yield: ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–2.10 (m, 11 H), 2.75 (dd, J = 13.2, 6.1 Hz, 1 H), 2.85 (dd, J = 13.2, 6.4 Hz, 1 H), 3.33 (m, 1 H), 3.48 (m, 1 H), 3.68 (m, 1 H), 3.84 (m, 1 H), 4.55 (m, 1 H), 4.65 (q, J = 7 Hz, 1 H), 5.40–5.50 (m, 2 H), 7.17–7.32 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.6, 25.4, 26.0, 27.3, 29.0, 30.6, 50.0, 62.2, 67.2, 68.7, 98.7, 98.8, 126.4, 128.3, 131.8, 132.0, 137.9; IR (neat) 3600–3200, 3026, 3005, 2941, 2866, 1603, 1497, 1454, 1030, 745, 700 cm^{-1}. HRMS: calcd for $C_{19}H_{27}O_3$, m/e 303.1916; obsd, m/e 303.2022.

General Procedure for Methylation of Alcohols. To a mixture of NaH (0.67 g, 28 mmol) in 19 mL of THF at 0 °C was added (*E*)-**23** (6.58 g, 21.6 mmol) in 6 mL of THF. The mixture was stirred for 1 h at room temperature before the dropwise addition of MeI (6.8 g, 44 mmol) was made. The mixture was stirred for 4 h at room temperature and at 50 °C for 1 h, and the reaction was quenched by the addition of 20 mL of Et_2O and 5 mL of H_2O. The aqueous layer was extracted three times with Et_2O, and the combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to give 5.84 g of methylated product.

(*E*)-Methyl ether (5.84 g, 18.3 mmol, 82% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.35–1.92 (m, 11 H), 2.07 (q, J = 7 Hz, 2 H), 2.73 (dd, J = 13.2, 6.1 Hz, 1 H), 2.92 (dd, J = 13.2, 6.4 Hz, 1 H), 3.25 (s, 3 H), 3.35 (m, 1 H), 3.51 (m, 1 H), 3.71 (m, 1 H), 3.86 (m, 1 H), 4.58 (t, J = 2.5 Hz, 1 H), 5.30 (dd, J = 15.1, 8.0 Hz, 1 H), 5.52 (dt, J = 15.4, 6.0 Hz, 1 H), 7.15–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.9, 24.7, 25.0, 28.3, 30.0, 31.1, 41.6, 55.2, 61.5, 66.6, 82.6, 98.0, 125.2, 127.2, 128.8, 129.2, 133.5, 137.8; IR (neat) 2940, 2866, 1667, 1603, 1454, 972, 748, 700 cm^{-1}. HRMS: calcd for $C_{20}H_{30}O_3$, m/e 319.2229; obsd, m/e 319.3291.

(*Z*)-Methyl ether (2.2 g, 6.9 mmol, 79% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 1.10–1.40 (m, 2 H), 1.40–1.64 (m, 6 H), 1.65–1.89 (m, 3 H), 1.90 (m, 1 H), 2.67 (dd, J = 13.4, 7.0 Hz, 1 H), 2.96 (dd, J = 13.4, 6.3 Hz, 1 H), 3.25 (s, 3 H), 3.32 (m, 1 H), 3.49 (m, 1 H), 3.66 (m, 1 H), 3.85 (m, 1 H), 4.16 (q, J = 7 Hz, 1 H), 4.55 (m, 1 H), 5.25 (m, 1 H), 5.55 (m, 1 H), 7.15–7.30 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.6, 25.6, 25.8, 29.1, 30.7, 31.9, 42.4, 56.0, 62.2, 67.3, 83.3, 98.8, 126.0, 128.0, 129.5, 123.0, 134.2, 138.5; IR (neat) 3028, 3005, 2941, 2870, 1604, 1496, 1454, 1033, 745, 700

(25) Nystrom, J.-E.; McCanna, T. D.; Helquist, P.; Amourox, R. *Synthesis* **1988**, 56.

cm^{-1}. HRMS: calcd for $C_{19}H_{27}O_3$, *m/e* 318.2195; obsd, *m/e* 318.2181.

31 (1.5 g, 10.0 mmol, 88% yield, bp 33–35 °C (1 mmHg)): ^{1}H NMR δ 1.18 (m, 1 H), 1.44 (m, 1 H), 1.82 (m, 1 H), 1.93–2.10 (m, 3 H), 2.16 (m, 1 H), 3.33 (s, 3 H), 3.75 (m, 1 H), 4.98 (d, *J* = 11.7 Hz, 1 H), 4.99 (dd, *J* = 17.0, 5.3 Hz, 1 H), 5.64–5.82 (m, 3 H); ^{13}C NMR δ 26.6, 27.7, 35.3, 40.2, 55.6, 75.4, 116.1, 128.1, 134.0, 136.5; IR (neat) 3076, 3024, 2978, 2930, 2862, 2818, 1641, 1103 cm^{-1}.

Conversion of 15 to 16. A solution of **15** (1.7 g, 32.5 mmol, crude) in THF (4.0 mL) was added dropwise to NaH (0.8 g, 35.8 mmol) in THF (32 mL). The reaction was stirred for 1 h and cooled to 0 °C, MeI (9.2 g, 65.0 mmol) was added, and the reaction was stirred for another 3 h. After the addition of 20 mL of Et_2O and 5 mL of H_2O, the aqueous layer was extracted three times with Et_2O, and the combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. After workup, the residue was added to a solution of TBAF (23 mL, 1.0 M in THF) at 0 °C. The desilylation reaciton was quenched by the addition of 50% saturated aqueous NaCl (20 mL) and subsequent extraction with Et_2O (5 × 20 mL). The concentrated organic layers were purified by chromatography (30:70, Et_2O/petroleum ether) to yield **16** (0.8 g, 5.5 mmol) in 62% yield: ^{1}H NMR (300 MHz) δ 1.30–1.62 (m, 6 H), 2.00 (bs, 1 H), 3.20 (s, 3 H), 3.46 (m, 1 H), 3.57 (t, *J* = 6.4 Hz, 2 H), 5.15 (ddd, *J* = 0.84, 1.9, 16.6 Hz, 1 H), 5.17 (dd, *J* = 1.0, 10.9 Hz, 1 H), 5.60 (ddd, *J* = 7.8, 10.9, 16.6 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4, 32.5, 34.9, 56.1 62.6, 83.0, 117.1, 138.6; IR (neat) 3600–3100, 3080, 2934, 2858, 1643, 1080, 925 cm^{-1}.

General Procedure for THP Deprotection. A mixture of the *E*-methylated THP ether (5.86 g, 18.4 mmol) and pyridinium *p*-toluenesulfonate (0.52 g, 2.0 mmol) in 29 mL of MeOH was stirred for 3 h at 50 °C and then at room temperature for 1 h. The mixture was concentrated and taken up in 50 mL of Et_2O, and 50 mL of saturated aqueous NaCl was added. The aqueous layer was extracted twice with Et_2O, and the combined organic layers were dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (50:50, hexanes:Et_2O) to give (*E*)-**24**.

(*E*)-**24** (3.55 g, 15.2 mmol, 82% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32–1.54 (m, 4 H), 1.90 (bs, 1 H), 2.02–2.10 (m, 2 H), 2.73 (dd, *J* = 13.7, 6.6 Hz, 1 H), 2.94 (dd, *J* = 13.7, 6.6 Hz, 1 H), 3.25 (s, 3 H), 3.57 (t, *J* = 6.2 Hz, 2 H), 3.73 (q, *J* = 7.1 Hz, 1 H), 5.30 (ddt, *J* = 15.4, 7.9, 1.0 Hz, 1 H), 5.50 (dt, *J* = 15.4, 6.6 Hz, 1 H), 7.15–7.32 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.1, 31.7, 31.9, 42.2, 55.9, 62.5, 83.3, 125.9, 128.0, 129.4, 130.0, 134.1, 138.4; IR (neat) 3700–3200, 3028, 2982, 2934, 1497, 1454, 1095, 987, 745, 700 cm^{-1}. HRMS: calcd for $C_{15}H_{22}O_2$, *m/e* 234.1620; obsd (M − 1), *m/e* 233.1553.

(*Z*)-**24** (1.4 g, 6.0 mmol, 89% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03–1.33 (m, 2 H), 1.35–1.48 (m, 2 H), 1.56 (bs, 1 H), 1.80 (m, 1 H), 1.93 (m, 1 H), 2.67 (dd, *J* = 13.4, 7.3 Hz, 1 H); 2.98 (dd, *J* = 13.4, 6.0 Hz, 1 H), 3.27 (s, 3 H), 3.53 (t, *J* = 6.5 Hz, 2 H), 4.15 (bq, *J* = 6 Hz, 1 H), 5.26 (m, 1 H), 5.56 (dt, *J* = 11.2, 7.4 Hz, 1 H), 7.15–7.31 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.1, 26.9, 31.7, 41.7, 55.5, 62.2, 77.3, 125.6, 127.7, 129.2, 129.4, 133.4, 137.8: IR (neat) 3600–3100, 3029, 2934, 2867, 1496, 1455, 1096, 745, 700 cm^{-1}. HRMS: calcd for $C_{15}H_{22}O_2$, *m/e* 234.1620; obsd (M − 2), *m/e* 232.1420.

(*E*)-**8a** (1.2 g, 8.3 mmol, 56% yield from **4a**): bp 85–90 °C (1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.55 (m, 4 H), 2.01 (q, *J* = 6.7 Hz, 2 H), 2.30 (bs, 1 H), 3.24 (s, 3 H), 3.55 (t, *J* = 6.4 Hz, 2 H), 3.80 (dd, *J* = 0.8, 6.1 Hz, 2 H), 5.42–5.70 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 32.0, 32.1, 57.3, 62.2, 73.0, 126.0, 134.2; IR (neat) 3600–3100, 2940, 2870, 1660 cm^{-1}. HRMS: calcd for $C_8H_{16}O_2$, *m/e* 144.1150; obsd (M − 1), *m/e* 143.1011.

(*Z*)-**8a** (1.2 g, 8.3 mmol, 60% yield from **4a**): bp 75–80 °C (1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37–1.47 (m 2 H), 1.50 (m, 1 H), 1.53–1.67 (m, 2 H), 2.08 (q, *J* = 6.7 Hz, 2 H), 3.29 (s, 3 H), 3.61 (t, *J* = 6.4 Hz, 2 H), 3.95 (d, *J* = 5.0 Hz, 2 H), 5.47–5.61 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 27.2, 32.2, 57.9, 62.6, 68.0, 126.2, 133.3; IR (neat) 3600–3200, 3020, 2940, 2860, 2820, 1620, 1200 cm^{-1}. HRMS: calcd for $C_8H_{16}O_2$, *m/e* 144.1150; obsd, *m/e* 144.1183.

(*E*)-**8b** (5.5 g, 34.8 mmol, 58% yield from **4b**): bp 105–109 °C (1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.40 (m, 4 H), 1.49 (quint, *J* = 6.8 Hz, 2 H), 2.00 (q, *J* = 6.6 Hz, 2 H), 2.24 (bs, 1 H), 3.23 (s, 3 H), 3.54 (t, *J* = 6.6 Hz, 2 H), 3.79 (d, *J* = 6.1 Hz, 2 H), 5.50 (m, 1 H), 5.61 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 28.7, 31.9, 32.3, 57.3, 62.2, 73.0, 125.9, 134.2; IR (neat) 3600–3100, 3010, 2920, 2870, 1670, 1080 cm^{-1}. HRMS: calcd for $C_9H_{18}O_2$, *m/e* 158.1307; obsd, *m/e* 158.1300.

(*Z*)-**8b** (4.4 g, 27.8 mmol, 71% yield from **4b**): bp 100–103 °C (1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (m, 4 H), 1.49 (quint, *J* = 6.7 Hz, 2 H), 2.02 (q, *J* = 6.7 Hz, 2 H), 2.28 (bs, 1 H), 3.25 (s, 3 H), 3.54 (t, *J* = 6.6 Hz, 2 H), 3.91 (d, *J* = 5.9 Hz, 2 H), 5.40–5.56 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 27.1, 29.0, 32.2, 57.7, 62.2, 68.0, 125.8, 133.3; IR (neat) 3020, 2920, 2860, 2810, 1650, 1110 cm^{-1}. HRMS: calcd for $C_9H_{18}O_2$, *m/e* 158.1307; obsd, *m/e* 158.1324.

(*E*)-**8c** (1.9 g, 5.7 mmol, 52% yield from **4c**): bp 113–115 °C (<1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.40 (m, 6 H), 1.44 (quint, *J* = 6.6 Hz, 2 H), 1.99 (q, *J* = 6.7 Hz, 2 H), 2.22 (bs, 1 H), 3.25 (s, 3 H), 3.55 (t, *J* = 6.6 Hz, 2 H), 3.80 (d, *J* = 6.1 Hz, 2 H), 5.49 (m, 1 H), 5.63 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 28.7, 28.8, 32.0, 32.3, 57.3, 62.2, 73.2, 126.0, 134.6; IR (neat) 3600–3100, 3010, 2920, 2870, 1610 cm^{-1}.

(*Z*)-**8c** (2.9 g, 16.8 mmol, 56% yield from **4c**): bp 110–115 °C (<1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.40 (m, 6 H), 1.50 (quint, *J* = 6.6 Hz, 2 H), 2.06 (q, *J* = 6.7 Hz, 2 H), 2.20 (bs, 1 H), 3.26 (s, 3 H), 3.55 (t, *J* = 6.6 Hz, 2 H), 3.91 (d, *J* = 5.6 Hz, 2 H), 5.40–5.59 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 27.1, 28.7, 29.0, 32.3, 57.6, 62.4, 68.0, 125.7, 131.8; IR (neat) 3600–3200, 3070, 2930, 2870, 1610, 1200 cm^{-1}.

Typical Procedure for Conversion of 8 to 9. A solution of (*E*)-**8c** (1.1 g, 6.3 mmol) and PPh_3 (1.8 g, 7.0 mmol) in 6 mL of CH_2Cl_2 was cooled to 0 °C, and *N*-bromosuccinimide (1.2 g, 7.0 mmol) was added over a 15-min period. The mixture was stirred at 0 °C for 1 h, warmed to ambient temperature for 2 h, and then concentrated. The slush was suspended in 2 mL of CH_2Cl_2, petroleum ether (12 mL) was added, and the reacton was stirred vigorously. After the solids were removed by filtration, they were washed with petroleum ether (2 × 7 mL). This filtration procedure was repeated, and the solvent was removed until the mixture reached a volume of 3–4 mL. The residue was filtered through a plug of basic alumina, rinsed through with petroleum ether (10 mL), and concentrated. Kugelrohr distillation gave (*E*)-**9c**.

(*E*)-**9a** (1.0 g, 5.0 mmol, 82% yield) (oven temperature 80–90 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (quint, *J* = 7.5 Hz, 2 H), 1.82 (quint, *J* = 7.2 Hz, 2 H), 2.03 (q, *J* = 7.1 Hz, 2 H), 3.24 (s, 3 H), 3.38 (t, *J* = 6.8 Hz, 2 H), 3.81 (dd, *J* = 1.1, 5.8 Hz, 2 H), 5.47 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4, 31.2, 32.1, 33.6, 57.7, 73.0, 126.7, 133.6; IR (neat) 2920, 2850, 1720, 1680, 1110 cm^{-1}. HRMS: calcd for $C_8H_{15}BrO$, *m/e* 206.0306 (^{79}Br); obsd, *m/e* 206.0267.

(*Z*)-**9a** (1.0 g, 4.8 mmol, 88% yield) (oven temperature 50–53 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (quint, *J* = 7.2 Hz, 2 H), 1.83 (quint, *J* = 7.2, 2 H), 2.08 (q, *J* = 6.7 Hz, 2 H), 3.32 (s, 3 H), 3.40 (t, *J* = 6.7 Hz, 2 H), 3.94 (d, *J* = 4.5 Hz, 2 H), 5.53 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.9, 32.1, 33.4, 57.9, 68.0, 126.6, 132.6; IR (neat) 3020, 2930, 2890, 2860, 2820, 1110, 1450 cm^{-1}. HRMS: calcd for $C_8H_{15}BrO$, *m/e* 208.0286 (^{81}Br); obsd, *m/e* 208.0198.

(*E*)-**9b** (2.3 g, 11.1 mmol, 92% yield) (oven temperature 84–95 °C, 1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (m, 4 H), 1.80 (quint, *J* = 6.8 Hz, 2 H), 2.03 (q, *J* = 6.5 Hz, 2 H), 3.27 (s, 3 H), 3.36 (t, *J* = 6.8 Hz, 2 H), 3.82 (dd, *J* = 1.0, 6.0 Hz, 2 H), 5.53 (m, 1 H), 5.62 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 28.1, 31.9, 32.6, 33.6, 57.6, 73.1, 126.5, 134.1; IR (neat) 3010, 2930, 2860, 1620, 1110 cm^{-1}. HRMS: calcd for $C_9H_{17}BrO$, *m/e* 220.0463; obsd, *m/e* 220.0451.

(*Z*)-**9b** (1.3 g, 5.9 mmol, 86% yield) (oven temperature 75–90 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32–1.60 (m, 4 H), 1.83 (quint, *J* = 7.0 Hz, 2 H), 2.00 (q, *J* = 6.3 Hz, 2 H), 3.30 (*s*, 3 H), 3.37 (t, *J* = 6.8 Hz, 2 H), 3.94 (d, *J* = 5.3 Hz, 2 H), 5.53 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1, 27.4, 28.6, 32.5, 33.6, 57.8,

68.0, 126.1, 133.0; IR (neat) 3020, 2920, 2860, 2810, 1650, 1110 cm^{-1}. HRMS: calcd for $C_9H_{17}BrO$, *m/e* 220.0463; obsd, *m/e* 220.0307.

(*E*)-**9c** (1.2 g, 5.4 mmol, 86% yield) (oven temp 72–80 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.45 (m, 6 H), 2.10 (q, *J* = 6.6 Hz, 2 H), 3.28 (s, 3 H), 3.36 (t, *J* = 6.7 Hz, 2 H), 3.81 (dd, *J* = 1.0, 5.0 Hz, 2 H), 5.45–5.55 (m, 1 H), 5.60–5.71 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 28.2, 28.8, 32.1, 32.6, 33.9, 57.6, 73.2, 126.2, 134.5; IR (neat) 3020, 2930, 2850, 1600, 1100, 760 cm^{-1}. HRMS: calcd for $C_{10}H_{19}BrO$, *m/e* 234.0620; obsd, *m/e* 234.0621.

(*Z*)-**9c** (1.2 g, 5.1 mmol, 86% yield) (oven temperature 75–90 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.47 (m, 6 H), 1.82 (quint, *J* = 7.0, 2 H), 2.05 (q, *J* = 6.4 Hz, 2 H), 3.31 (s, 3 H); 3.38 (t, *J* = 6.8 Hz, 2 H), 3.94 (d, *J* = 5.0 Hz, 2 H), 5.46–5.60 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4, 27.9, 28.2, 29.2, 32.7, 33.9, 58.0, 68.0, 126.1, 143.4; IR (neat) 3010, 2930, 2850, 1600, 1500, 1100 cm^{-1}. HRMS: calcd for $C_{10}H_{19}BrO$, *m/e* 234.0620; obsd, *m/e* 234.0631.

17 (0.7 g, 3.4 mmol, 87% yield) (oven temperature 32–35 °C, 4 mmHg): ^{1}H NMR (300 MHz) δ 1.40–1.62 (m, 4 H), 1.75–1.90 (m, 2 H), 3.22 (s, 3 H), 3.36 (t, *J* = 6.8 Hz, 2 H), 3.46 (m, 1 H), 5.15 (ddd, *J* = 0.84, 1.6, 16.6 Hz, 1 H), 5.17 (dd, *J* = 0.86, 10.6 Hz, 1 H), 5.60 (ddd, *J* = 7.8, 10.6, 16.6 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.0, 32.7, 33.6, 34.4, 56.1, 82.6, 117.3, 138.5; IR (neat) 3078, 2980, 2938, 2820, 1643, 1101, 927 cm^{-1}.

General Procedure for Formation of 25. To a solution of (*E*)-**24** (0.13 g, 0.55 mmol) and PPh_3 (0.16 g, 0.61 mmol) in 0.5 mL of CH_2Cl_2 at 0 °C was added *N*-bromosuccinimide (0.11 g, 0.26 mmol) in two portions over 3 min. The mixture was kept at 0 °C for 1 h and was then stirred at room temperature for 2.5 h. The solvent was removed, and the remaining solids were washed with 3 × 5 mL of petroleum ether. After concentration of the combined soluble fractions, the organic material was loaded onto a short column of basic alumina and eluted through with 7 mL of petroleum ether: Et_2O (85:15). Further purification was performed with silica gel chromatography (85:15, petroleum ether: Et_2O) to give (*E*)-**25** (0.14 g, 0.40 mmol) in 85% yield after Kugelrohr distillation (bp 98–100 °C, 0.2 mmHg).

(*E*)-**25** (0.14 g, 0.40 mmol, 85% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (quint, *J* = 7.3 Hz, 2 H), 1.78 (quint, *J* = 7.2 Hz, 2 H), 2.06 (qd, *J* = 6.8, 2.9 Hz, 2 H), 2.76 (dd, *J* = 13.6, 6.8 Hz, 1 H), 2.96 (dd, *J* = 13.6, 6.3 Hz, 1 H), 3.27 (s, 3 H), 3.38 (t, *J* = 6.8 Hz, 2 H), 3.75 (q, *J* = 7.0 Hz, 1 H), 5.33 (dd, *J* = 15.1, 7.8 Hz, 1 H), 5.50 (dt, *J* = 15.1, 6.6 Hz, 1 H), 7.16–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.1, 30.8, 31.5, 33.2, 41.9, 55.7, 82.9, 125.7, 127.7, 129.2, 130.1, 133.2, 138.0; IR (neat) 3061, 3029, 2982, 2932, 1497, 1455, 1437, 1094, 970, 747, 700 cm^{-1}. HRMS: calcd for $C_{15}H_{21}BrO$, *m/e* 296.0776; obsd (M − 1), *m/e* 295.0746.

(*Z*)-**25** (1.9 g, 6.4 mmol, 73% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14–1.42 (m, 2 H), 1.69 (quint, *J* = 7.2 Hz, 2 H), 1.75–2.05 (m, 2 H), 2.69 (dd, *J* = 13.2, 7.4 Hz, 1 H), 3.01 (dd, *J* = 13.2, 6.0 Hz, 1 H), 3.29 (s, 3 H), 3.30 (t, *J* = 6.7 Hz, 2 H), 4.15 (m, 1 H), 5.30 (m, 1 H), 5.56 (dt, *J* = 11, 7 Hz, 1 H), 7.17–7.33 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.2, 27.4, 31.7, 33.1, 41.7, 55.6, 77.3, 125.7, 127.7, 129.2, 129.9, 132.8, 137.7; IR (neat) 3029, 3005, 2936, 1497, 1455, 1100, 966, 747, 700 cm^{-1}. HRMS: calcd for $C_{15}H_{21}BrO$, *m/e* 296.0776; obsd (M − 1), *m/e* 295.0636.

Typical Procedure for Conversion of an Alcohol to the Corresponding Iodide. A −10 °C solution of (*E*)-**8a** (0.7 g, 4.8 mmol) and NEt_3 (1 mL, 7.2 mmol) in CH_2Cl_2 (20 mL) was treated dropwise with methanesulfonyl chloride (0.6 g, 5.3 mmol). After 15 min at −10 °C, the reaction was diluted with CH_2Cl_2 (18 mL), and the mixture was washed with 10% aqueous HCl (1 mL), saturated aqueous $NaHCO_3$ (9 mL), and saturated aqueous NaCl (1 mL). The organic layer was dried ($MgSO_4$), concentrated, and added to a solution of NaI (1.4 g, 9.7 mmol) in THF (12 mL) at 0 °C. The reaction was warmed to room temperature and stirred until reaction was complete. The mixture was diluted with Et_2O (35 mL), washed with saturated aqueous $NaHCO_3$ (2 × 65 mL), washed with saturated aqueous NaCl (6 mL), dried ($MgSO_4$), and concentrated. Kugelrohr distillation gave (*E*)-**10a**.

(*E*)-**10a** (0.9 g, 3.5 mmol, 75% yield) (oven temperature 54–70 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (quint, *J* = 7.5 Hz, 2 H), 1.80 (quint, *J* = 7.2 Hz, 2 H), 2.05 (q, *J* = 6.8 Hz, 2 H), 3.16 (t, *J* = 7.0 Hz, 2 H), 3.29 (s, 3 H), 3.83 (dd, *J* = 0.8, 5.8 Hz, 2 H), 5.43–5.71 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.6, 29.7, 31.0, 33.0, 57.8, 73.0, 126.8, 133.8; IR (neat) 3010, 2930, 2850, 1670, 1110 cm^{-1}.

(*Z*)-**10a** (1.8 g, 7.1 mmol, 93% yield) (oven temperature 64–70 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (quint, *J* = 7.4 Hz, 2 H), 1.80 (quint, *J* = 7.3 Hz, 2 H), 2.07 (q, *J* = 6.7 Hz, 2 H), 3.17 (t, *J* = 6.8 Hz, 2 H), 3.29 (s, 3 H), 3.93 (d, *J* = 4.5 Hz, 2 H), 5.50–5.56 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.4, 26.4, 30.2, 32.9, 57.9, 68.0, 126.7, 132.6. HRMS: calcd for $C_8H_{15}IO$, *m/e* 254.0168; obsd, *m/e* 254.0170.

(*E*)-**10b** (2.2 g, 8.2 mmol, 78% yield) (oven temperature 70–90 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34–1.47 (m, 4 H), 1.76–1.87 (m, 2 H), 2.30 (dq, *J* = 0.84, 6.1 Hz, 2 H), 3.17 (t, *J* = 7.0 Hz, 2 H), 3.30 (s, 3 H), 3.83 (dd, *J* = 0.84, 5.8 Hz, 2 H), 5.57 (m, 1 H), 5.65 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.6, 28.0, 30.0, 32.0, 33.4, 57.8, 72.6, 126.3, 134.2; IR (neat) 3010, 2920, 2860, 1600, 1110 cm^{-1}.

(*Z*)-**10b** (0.90 g, 3.3 mmol, 75% yield) (oven temperature 70–85 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32–1.40 (m, 2 H), 1.72–1.84 (m, 2 H), 2.00–2.10 (m, 2 H), 3.15 (t, *J* = 7.0 Hz, 2 H), 3.29 (s, 3 H), 3.93 (d, *J* = 5.3 Hz, 2 H), 5.44–5.56 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.8, 27.2, 28.3, 30.0, 33.3, 57.8, 68.0, 126.2, 133.1; IR (neat) 2990, 2930, 2850, 1650, 1480, 1200 cm^{-1}. HRMS: calcd for $C_9H_{17}IO$, *m/e* 268.0325; obsd, *m/e* 268.0377.

(*Z*)-**10c** (1.5 g, 5.3 mmol, 71% yield) (oven temperature 80–95 °C, 1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.41 (m, 6 H), 1.79 (quint, *J* = 7.3 Hz, 2 H), 2.02 (q, *J* = 6.4 Hz, 2 H), 3.28 (s, 3 H), 3.57 (t, *J* = 7.0 Hz, 2 H), 3.82 (dd, *J* = 1.0, 6.1 Hz, 2 H), 5.43–5.60 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.0, 27.3, 27.9, 29.2, 30.2, 33.3, 57.8, 68.0, 126.0, 133.3; IR (neat) 3010, 2930, 2850, 1670, 1500, 1100 cm^{-1}.

General Procedure for Formation of 26. A mixture of (*E*)-**25** (0.43 g, 1.4 mmol) and KI (2.4 g, 14 mmol) in 4.5 mL of dry DMF was stirred for 22 h at 50 °C. The mixture was cooled to room temperature, 15 mL of H_2O and 15 mL CH_2Cl_2 were added, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were sequentially washed with H_2O and saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The crude product was purified by silica gel chromatography (85:15, hexane: Et_2O) to give (*E*)-**26**.

(*E*)-**26** (0.25 g, 0.70 mmol, 50% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (quint, *J* = 7.3 Hz, 2 H), 1.69 (quint, *J* = 7.3 Hz, 2 H), 2.01 (qd, *J* = 6.8, 2.0 Hz, 2 H), 2.71 (dd, *J* = 13.6, 6.4 Hz, 1 H), 2.92 (dd, *J* = 13.6, 6.3 Hz, 1 H), 3.10 (t, *J* = 7.1 Hz, 2 H), 3.22 (s, 3 H), 3.70 (q, *J* = 7.2 Hz, 1 H), 5.28 (bdd, *J* = 15.6, 7.8 Hz, 1 H), 5.45 (dt, *J* = 15.6, 6.6 Hz, 1 H), 7.15–7.30 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.8, 29.7, 30.8, 32.5, 42.2, 56.0, 83.1, 125.9, 127.9, 129.4, 130.4, 133.4, 138.3; IR (neat) 3027, 2980, 2930, 1454, 1094, 970, 748, 700 cm^{-1}. HRMS: calcd for $C_{15}H_{21}IO$, *m/e* 344.0638; obsd, *m/e* 344.0575.

(*Z*)-**26** (0.90 g, 2.6 mmol, 55% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (m, 1 H), 1.28 (m, 1 H), 1.64 (quint, *J* = 7.2 Hz, 2 H), 1.79 (m, 1 H), 1.92 (m, 1 H), 2.67 (dd, *J* = 13.2, 7.3 Hz, 1 H), 3.00 (dd, *J* = 13.2, 5.9 Hz, 1 H), 3.08 (t, *J* = 7.1 Hz, 2 H), 3.28 (s, 3 H), 4.13 (q, *J* = 7.5 Hz, 1 H), 5.28 (m, 1 H), 5.54 (dt, *J* = 11.1, 7.6 Hz, 1 H), 7.08–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.6, 26.4, 30.0, 32.7, 42.0, 56.0, 77.6, 126.1, 128.0, 129.6, 130.2, 133.1, 138.0; IR (neat) 2976, 2932, 1495, 1454, 1098, 745, 700 cm^{-1}. HRMS: calcd for $C_{15}H_{21}IO$, *m/e* 344.0688; obsd (M − 1), *m/e* 343.0575.

Transformation of 31 to 32 and 33. Diene **31** (3.2 g, 12.9 mmol) was added to a slurry of Cp_2ZrHCl (3.6 g, 13.8 mmol) in 1,2-dichloroethane (20 mL) at 0 °C.[24] The mixture was stirred at 0 °C for 2 h and at room temperature until the reaction was complete. After the mixture was cooled to 0 °C, NBS (2.4 g, 13.8 mmol) or I_2 (1.4 equiv) was added, and the reaction was stirred at room temperature and stirred for 5 h. Petroleum ether (60 mL) was added, the suspension was filtered through silica gel, and the product was eluted with petroleum ether. The organic

layers were concentrated and chromatographed (90:10, petroleum ether:Et_2O) to yield **32** or **33**.

32 (1.2 g, 5.1 mmol, 52% yield): ^1H NMR (300 MHz) δ 1.16 (m, 1 H), 1.26–1.50 (m, 4 H), 1.85 (quint, J = 7.4 Hz, 2 H), 1.98–2.16 (m, 2 H), 3.32 (s, 3 H), 3.36 (t, J = 6.8 Hz, 2 H), 3.74 (m, 1 H), 5.60–5.75 (m, 2 H); ^{13}C NMR δ (75 MHz) 26.6, 27.6, 30.0, 33.7, 34.3, 34.8, 55.5, 75.3, 128.2, 133.9; IR (neat) 3022, 2932, 2858, 2818, 1651, 1450, 1103 cm^{-1}.

33 (1.0 g, 3.6 mmol, 56% yield): ^1H NMR (300 MHz) δ 1.10–1.50 (m, 6 H), 1.85 (quint, J = 7.4 Hz, 2 H), 2.05 (m, 1 H), 3.13 (t, J = 6.8 Hz, 2 H), 3.32 (s, 3 H), 3.74 (m, 1 H), 5.60–5.75 (m, 2 H); ^{13}C NMR δ (75 MHz) 6.8, 26.7, 27.6, 30.8, 34.7, 36.7, 55.6, 75.3, 128.2, 133.9; IR (neat) 3022, 2932, 2858, 2818, 1649, 1450, 1103 cm^{-1}.

General Procedure for Grignard Formation. A Schlenk flask, equipped with a magnetic stirring bar and activated magnesium (0.246 g, 10.0 mmol), was placed under vacuum, heated for 5 min with a heat gun, and then placed under an atmosphere of argon. At the desired temperature, two drops of the bromide were used to initiate Grignard formation. Tetrahydrofuran (10 mL) was then added followed by slow addition of the corresponding bromide (1.0 mmol) over 60 min. The reaction was stirred at the desired temperature until Grignard formation was complete.

(*E*)-**27**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7 Hz, 3 H), 1.18–1.35 (m, 4 H), 2.97 (bq, J = 7.4 Hz, 2 H), 2.78 (dd, J = 13.7, 6.4 Hz, 1 H), 2.87 (dd, J = 13.7, 6.9 Hz, 1 H), 3.28 (s, 3 H), 3.44 (q, J = 7 Hz, 2 H), 5.23 (m, 1 H), 5.46 (dt, J = 15.6, 6.6 Hz, 1 H), 7.21–7.70 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 22.0, 31.2, 31.8, 42.4, 55.9, 83.4, 126.0, 128.0, 129.5, 129.6, 134.7, 138.6; IR (neat) 3028, 2957, 2928, 1496, 1454, 1099, 970, 748, 698 cm^{-1}. HRMS: calcd for $C_{15}H_{22}O$, m/e 218.1672; obsd, m/e 218.1601.

(*Z*)-**27**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J = 7 Hz, 3 H), 0.95–1.35 (m, 4 H), 1.62–2.00 (m, 2 H), 2.59 (dd, J = 13.4, 6.5 Hz, 1 H), 2.83 (dd, J = 13, 6 Hz, 1 H), 3.38 (s, 3 H), 4.20 (m, 1 H), 5.25 (m, 1 H), 5.60 (m, 1 H), 7.26–7.76 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 27.2, 27.4, 31.4, 42.1, 55.8, 77.5, 125.9, 127.9, 129.1, 129.4, 129.5, 134.1; IR (neat) 3028, 2955, 2928, 1497, 1454, 1098, 745, 698 cm^{-1}. HRMS: calcd for $C_{15}H_{22}O$, m/e 218.1672; obsd, m/e 218.1591.

Cu(I)-Facilitated Cyclization Studies. A solution of the organomagnesium bromide, prepared as stated above, was treated with 0.05 equiv of the Cu(I) salt (see tables) at −78 °C by direct addition of the Cu(I) salt to the Grignard solution. The cold bath was removed after 10 min, and the reaction was stirred at room temperature until reaction was complete. An aliquot was quenched by addition to a cooled saturated aqueous NH_4Cl solution and analyzed by gas chromatography. Yields were determined with the use of an internal standard; *n*-heptane was used for the five-membered ring products, and *n*-octane was used for the six-membered ring products (see tables).

Cu(I)-Facilitated Cyclization. A Schlenk flask, equipped with a magnetic stirring bar and activated magnesium (0.123 g, 5.0 mmol), was evacuated, heated with a heat gun for 5 min, and then placed under an atmosphere of argon. At the desired temperature, 1 mL of THF was added, and three drops of the bromide were used to initiate the Grignard formation. After 30 min, 4 mL of THF were added followed by the slow addition of the remaining bromide (0.5 mmol) over 45 min. The reaction was heated at reflux until Grignard formation was complete by gas chromatographic analysis.

A solution of the organomagnesium bromide was cooled to −78 °C and treated with $CuBr{\cdot}SMe_2$ (7 mg, 0.03 mmol) by direct addition of the Cu(I) salt to the Grignard solution. The cold bath was removed after 10 min, and the reaction was stirred at room temperature for 4.5 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with 20 mL of Et_2O, and the organic layer was washed with saturated aqueous $NaHCO_3$ and NaCl and dried ($MgSO_4$). Removal of solvent and purification with silica gel chromatography (85:15, hexanes, Et_2O) gave **28** in 84% yield (93:7, *E*:*Z*) from (*Z*)-**25** and **28** in 84% yield (51:49, *E*:*Z*) from (*E*)-**25**.

(*E*)-**28**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.23–1.36 (m, 2 H), 1.50–1.74 (m, 4 H), 1.73–1.85 (m, 2 H), 2.43 (m, 1 H), 3.35 (d, J = 5.4 Hz, 2 H), 5.51–5.59 (m, 2 H), 7.16–7.55 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.0, 33.2, 39.0, 43.2, 125.8, 126.7, 127.2, 128.3, 128.4, 128.7, 136.7, 141.2; IR (neat) 968, 737, 698 cm^{-1}. HRMS: calcd for $C_{14}H_{18}$, m/e 186.1409; obsd (M − 1), m/e 185.1352.

Wittig Preparation of 28. To prepare the necessary phosphonium salt, a mixture of (2-bromoethyl)benzene (5.55 g, 30 mmol) and PPh_3 (9.17 g, 35 mmol) in 18 mL of benzene was heated at 70 °C for 14 h. Partial removal of solvent *in vacuo* resulted in the formation of white crystalline material, which was isolated by filtration with nitrogen pressure. The hygroscopic crystalline material was dried at 80 °C at 1 mmHg for 11 h prior to use.

A solution of *n*-BuLi (1.4 mL, 2.5 M in hexanes, 3.9 mmol) was added dropwise to 4 mL of DMSO, and the resulting mixture was stirred for 30 min at room temperature. A solution of the phosphonium salt (1.6 g, 3.5 mmol) in 4 mL of DMSO was then added to the mixture dropwise at room temperature. After the mixture was stirred for 30 min, cyclopentanecarbaldehyde (0.5 g, 5 mmol) in 2 mL of DMSO was added, and the mixture was stirred for 10 h at room temperature. The reaction was quenched by the addition to 20 mL of ice water, and the aqueous layer was extracted twice with 40 mL of hexane. The product was eluted on silica gel (80:20, hexanes:Et_2O) to give **28** (0.42 g, 2.2 mmol, 65% yield). Further purification could be made by Kugelrohr distillation (oven temperature 90–95 °C, 1 mmHg). (*Z*)-**28**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.23–1.37 (m, 2 H), 1.50–1.95 (m, 6 H), 2.88 (sext, J = 8 Hz, 1 H), 3.47 (d, J = 5.8 Hz, 2 H), 5.45–5.60 (m, 2 H), 7.16–7.35 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.0, 33.1, 38.9, 43.2, 125.8, 126.7, 127.2, 128.4, 128.7, 136.7; IR (neat) 3028, 2953, 2908, 1495, 1453, 1603, 1653, 739, 696 cm^{-1}. HRMS: calcd for $C_{14}H_{18}$, m/e 186.1409; obsd, m/e 186.1408.

Typical Procedure for Lithium-Facilitated Cyclization. A solution of **26** (0.120 g, 0.355 mmol) in Et_2O/hexane (3:2 by volume, 5 mL) was cooled to −78 °C, and a solution of *t*-BuLi (1.7 *M* in pentane, 0.45 mL, 0.76 mmol) was added dropwise. After addition, the reaction was stirred at −78 °C for 15 min, the dry ice–acetone bath was then removed, and the reaction was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl (4 mL) and extracted twice with 10 mL of Et_2O, and the combined organic layers were washed with saturated aqueous NaCl and dried ($MgSO_4$). Removal of solvent gave **28** in 84% yield (96:4, *E*:*Z*) from (*Z*)-**26** and **28** in 84% yield (98:2, *E*:*Z*) from (*E*)-**26**.

Acknowledgment. Support from the National Institutes of Health (Grant G44163) is gratefully acknowledged. Spectral product characterization was performed on NMR instrumentation purchased in part with funds from NIH Grant 1-S10-RR04750 and from NSF Grant CHE-88-00770. Mass spectral data were obtained at the Michigan State University Mass Spectrometry Facility, which is supported, in part, by a grant (DDR-00480) from the Biotechnology Resources Branch, Division of Research Resources, National Institutes of Health. Intellectually stimulating conversations with Professor Paul Knochel (Phillips-Universitat Marburg) were invaluable.

Supplementary Material Available: Figures of ^1H NMR spectra of key compounds (**9a**, **10a**, **17**, **25**, **26**, **27**, **28**, **31**, **32**, **33**) reported in the Experimental Section (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the Journal, and can be ordered from the American Chemical Society; ordering information is given on any current masthead page.

OM9307895