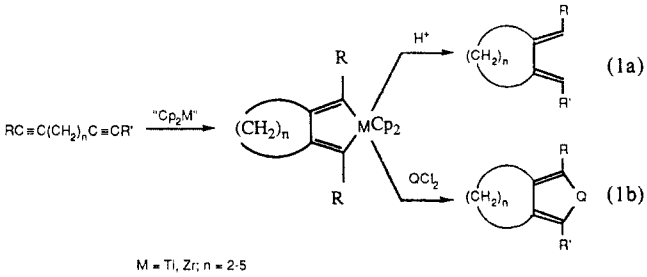
Stereoselective Cyclization of Enynes Mediated by Metallocene Reagents†

T. V. RajanBabu,* William A. Nugent,* Douglass F. Taber,[1] and Paul J. Fagan

Contribution from the Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898. *Received March 15, 1988*

Abstract: 1,6- and 1,7-enynes are efficiently cyclized to bicyclic metallacyclopentenes with titanocene or zirconocene reagents which are easily generated in situ. The metallacycles can be hydrolyzed to release the alkylidenecycloalkane or can be metathesized with main group halides such as S_2Cl_2, Se_2Cl_2, or Ph_2SnCl_2 to give heterocycles. The zirconium-mediated reaction is more effective for sterically demanding cases. The alkylidene moiety is introduced with 100% stereoselectivity for the *E*-diastereomer; this provides an excellent starting place for the elaboration of chiral side chains as illustrated by a formal synthesis of the ant pheromone invictolide. The cyclization is compatible with alkyl and silyl ether functionality. Sugar enynes, efficiently synthesized from readily available sugar lactones, undergo stereospecific cyclization to highly functional, enantiomerically pure carbocycles.

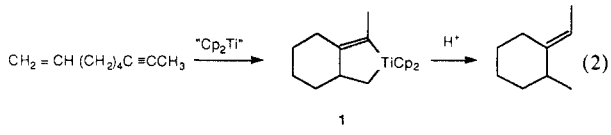
Transition-metal-mediated synthetic methods are bringing about a revolution in the manufacture of fine chemicals.[2] As a part of Du Pont's research effort in this area we have developed the stereoselective cyclization of diacetylenes mediated by titanocene and zirconocene reagents (eq 1). This reaction provides an efficient route to reactive *E,E*-exocyclic dienes (eq 1a)[3] and to a variety of heterocycles (eq 1b).[4]



M = Ti, Zr; n = 2-5

QCl_2 = SCl_2, $SOCl_2$, $PhSbCl_2$, $PhBCl_2$, $GeCl_4$, etc.

Several years ago we also communicated the first example of the cyclization of an enyne by using a group 4 metallocene reagent[5] (eq 2). Three features of this reaction appeared to be of special



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interest: (1) Metallacycles **1** should be useful nucleophiles comparable in reactivity to Grignard reagents.[6] We envisioned, for example, extending eq 1b to the synthesis of unusual heterocycles such as dihydroselenophenes. (2) Equation 2 proceeds with 100% control of the stereochemistry of the alkylidene moiety. This should provide an excellent starting place for the construction of carbocyclic targets with control of side-chain stereochemistry. (3) On the basis of our experience with the diyne cyclization, we expected eq 2 to be compatible with a range of functional groups. A particularly intriguing possibility was the use of eq 2 to directly convert carbohydrates to highly functional, enantiomerically pure carbocycles. We have investigated each of these possibilities and report our initial results.

An important development in the period since our initial report has been provided by Negishi and co-workers. These researchers have shown[7] that the combination of zirconocene dichloride with 2 molar equivalents of butyllithium provides a clean and convenient method for generating a "zirconocene" equivalent in situ. In our more recent studies we have frequently utilized this reagent combination in place of the older procedure[5,8] based on Cp_2ZrCl_2

† Contribution No. 4698.

Table I. GLC Yield (%) of Cycloalkanes from Enynes (eq 3)[a]

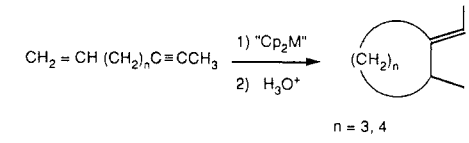
reagent/enyne	1-octen-6-yne (%)	1-nonen-7-yne (%)
$Cp_2TiCl_2/PMePh_2/Na(Hg)$	80	91
$Cp_2ZrCl_2/Mg(Hg)$	60	51
$Cp_2ZrCl_2/2BuLi$	82	89

[a] See Experimental Section for detailed reaction conditions.

and amalgamated magnesium metal. Of particular interest is the use of this reagent by Negishi et al. to effect the Pauson-Khand type carbonylation of C-silylated enynes to cyclopentenones.[9,10]

Results and Discussion

Comparison of Reagents. Initial studies on the cyclization of the simple enynes 1-octen-6-yne and 1-nonen-7-yne (eq 3) are summarized in Table I. Metallocenes were generated in situ by using the optimized reagent systems developed in our studies on diyne cyclization.[3] Cyclization of either substrate in eq 3 with



n = 3, 4

the reagent system $Cp_2TiCl_2/PMePh_2$/sodium amalgam followed by hydrolysis afforded the corresponding ethylidene cycloalkane in 80–90% yield by GLC analysis. Zirconocene generated in situ from $CpZrCl_2/Mg/HgCl_2$ also effected this cyclization but in somewhat lower yield. However, with the $Cp_2ZrCl_2/2BuLi$

(1) Du Pont Visiting Research Scientist, summer 1986; permanent address: Department of Chemistry, University of Delaware, DE 19716.

(2) For a series of reviews documenting the impact of this revolution on the manufacture of pharmaceuticals, agrichemicals, and other fine chemicals see: Parshall, G. W.; Nugent, W. A. *Chemtech* **1988**, *18*, 184–190; 314–320, 376–383.

(3) Nugent, W. A.; Thorn, D. L.; Harlow, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 2788–2796.

(4) Fagan, P. J.; Nugent, W. A. *J. Am. Chem. Soc.* **1988**, *110*, 2310–2312.

(5) Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422–6424. Nugent, W. A.; RajanBabu, T. V.; Thorn, D. L. *Abstract of Papers*, 190th National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society, Washington, DC, 1986; ORGN 78.

(6) Bertelo, C. A.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 228–230. Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333–1340.

(7) Negishi, E.-i.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829–2832.

(8) Famili, A.; Farona, M. F.; Thanedar, S. *J. Chem. Soc., Chem. Commun.* **1983**, 435–436.

(9) Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568–2569.

(10) Negishi, E.-i.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 917–920.

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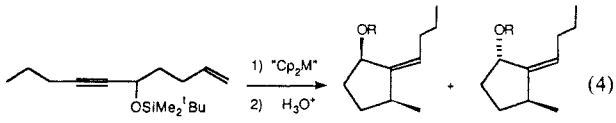
reagent,[8] yields comparable to those from the titanocene system could be achieved.

As a more realistic test of a substrate relevant to organic synthesis we then examined the cyclization of the readily available functional enyne **2**. This substrate contains a bulky α substituent. On the basis of our studies of sterically hindered diynes,[3] we anticipated that the zirconium reagents would prove superior under these circumstances. This expectation was borne out. Higher total yields of **3a** and **4a** were obtained (eq 4) when using the zirconium-based reagents (94%) as compared with 33% by the use of the titanium-based system.



(4)

2 3a-d 4a-d

3a, 4a R = $SiMe_2{}^tBu$

3b, 4b R = H

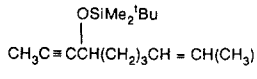
3c, 4c R = $^tBuC(O)$-

3d, 4d R = PhNHC(O)-

The stereochemistry of eq 4 is noteworthy. The major product from the zirconium-mediated cyclization has the siloxy and methyl substituents mutually cis. The cis/trans ratio **3a**:**4a** is 2.5:1. This selectivity is reversed in the case of titanium, the ratio **3a**:**4a** in this case is 1:7. Owing to the low overall yield of cyclopentanes in the titanium-mediated procedure, it seems unwise to propose a mechanistic rationale for this difference. (We cannot rule out the possibility that *cis*-titanacycle is being formed as the major product and then decomposes in a subsequent step.)

From a practical point of view, the formation of two diastereomers in eq 4 is not a problem. The isomeric silyl ethers **3a** and **4a** were remarkably well separated (0.3 R_f units) on silica and were easily isolated by flash chromatography.[11] This procedure was used to prepare multigram quantities of both **3a** and **4a**.

Extension of this procedure to enynes containing a substituted olefin component was briefly examined. The *Z*- and *E*-isomers of compound **5** were separately prepared, and cyclization of each



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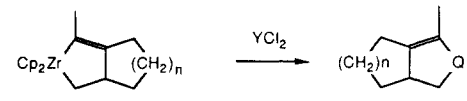
was attempted under our standard conditions. No cyclized products could be isolated.[12] The failure of nonterminal olefins to cyclize appears to represent the principal limitation on this procedure as a synthetic tool.[13]

Alternative Electrophiles. As shown in eq 1b, the cyclization of diynes with metallocene reagents provides a general one-pot synthesis of heterocycles incorporating a variety of main group elements. The procedure involves simply treating the metallacyclic intermediate with a main group compound containing at least two halogen atoms. We now report that this sequence can also be applied to the metallacycles derived from enynes. Yields for the three examples reported here are in the 40–50% range, possibly reflecting losses during chromatographic workup. However, this limitation appears to be offset by the simple one-pot procedures involved and the unavailability of alternative routes to the target heterocycles.

Treatment of the metallacycle in eq 5 with sulfur monochloride afforded the dihydrothiophene **6a** in 48% isolated yield.[14] Treating



(5)

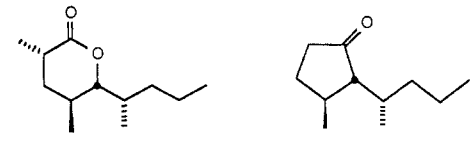
6a n = 2, $YCl_2 = S_2Cl_2$, Q = S

6b n = 2, $YCl_2 = Ph_2SnCl_2$, Q = $SnPh_2$

7 n = 1, $YCl_2 = Se_2Cl_2$, Q = Se

the same metallacycle with diphenyltin dichloride gave the corresponding stannacycle **6b** (40%). Thus, as is true in eq 1b, this transformation is not limited to highly electronegative electrophiles. Also in eq 5 a zirconacycle fused to a five-membered carbocyclic ring was converted to **7** (46% isolated), an example of the rare[15] 2,3-dihydroselenophene ring system. Full delineation of the scope of this reaction will be the subject of future studies.

Application to Stereocontrolled Construction of Side Chains. Trost[16] has recently stressed the abundance of important natural products containing both a carbocyclic ring system and chiral side-chains. Our ability to affix alkylidene substituents to carbocycles with 100% stereochemical control should facilitate the construction of such side-chains. Local interest in invictolide, **8**, the queen pheromone of the imported fire ant,[17] provided a relevant testing ground. Cyclopentanone **9**, an intermediate in the invictolide synthesis reported by Tumlinson and co-workers,[17,18] was adopted as a synthetic target.



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Many procedures can be considered for the transfer of chirality from the hydroxyl substituent of compounds **3b** and **4b** to the side-chain.[19] Of these, the S_N2' chemistry of organocuprates developed by Goering and by Gallina and co-workers[20] appeared especially appropriate to our interests. Depending on the nature of the leaving group and organocopper reagent this transformation can be effected with either syn or anti stereochemistry. Therefore both of the epimeric alcohols from eq 4 could potentially be converted into the desired **9**.

To this end, samples of **3a** and of **4a** were converted to the corresponding pivalates (**3c** and **4c**) and to the phenyl carbamate derivatives **3d** and **4d**. As shown in eq 6 and 7, treatment of either

(11) We note that the free alcohols were much less cleanly separable.

(12) Negishi and co-workers[10] have also noted that trimethylsilylalkynes containing a methyl-substituted alkenyl group fail to undergo Zr-mediated bicyclization.

(13) As in the case of the diyne cyclization[3] enynes containing a terminal acetylene fail to cyclize presumably reflecting the acidity of the acetylenic hydrogen. By analogy to the diyne cyclization we also expect that the cyclization of substrates containing unsaturated heterofunctionality (e.g., carbonyl, cyano) will also be excluded because of competing reductive side reactions.

(14) We have been informed by Dr. Stephen Buchwald[14a] (MIT) that significantly higher yields can be obtained in related reactions[14b] by replacing the S_2Cl_2 used here by sulfur dichloride provided that extreme care is taken in purifying the SCl_2. (a) Buchwald, S. L., personal communication. (b) Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137–7141.

(15) Simple 2,3-dihydroselenophenes have been isolated from mixtures of hydrogen selenide and organic matter after heating to 300 °C in the presence of zeolites: Mamedov, E. Sh.; Babakhanov, R. A.; Akhverdieva, R. Ya.; Veinberg, A. K.; Mishiev, R. D.; Nasibov, Sh. S.; Lidak, M. Yu. *Khim. Geterotsikl Soedin.* **1986**, 1478–1480. See, also: Konstantinova, T. G.; Gul'tyai, V. P.; Vitninov, V. P.; Shteinshneider, A. Ya.; Daeva, E. D.; Moiseenkov, A. M. *Izv. Akad. Nauk SSSR, Ser. Khim* **1983**, 944–947.

(16) Schmuff, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404–1412.

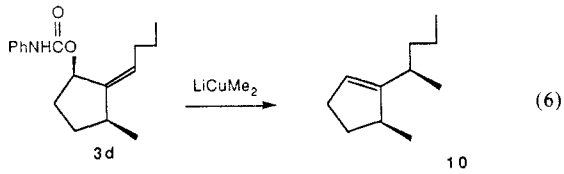
(17) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, *24*, 1893–1896.

(18) For other syntheses of invictolide, see: Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738–2739. Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303–5305. Ziegler, F. E.; Stirchak, E. P.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1229–1232. Yamamoto, Y.; Taniguchi, K.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1429–1431. Mori, K.; Nakazomo, Y. *Tetrahedron* **1986**, *42*, 6459–6464.

(19) For other procedures for chirality transfer in allyl alcohol systems, see: Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products through Pericyclic Reactions*; American Chemical Society: Washington, DC, 1983. Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885–902.

(20) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035–1036. Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422–426.

carbamate with lithium dimethyl cuprate[20] resulted in clean syn delivery of the methyl group.



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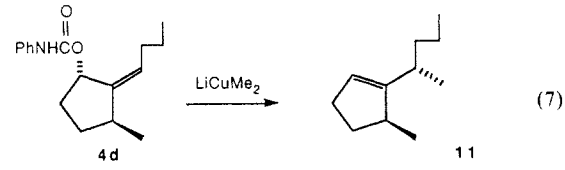
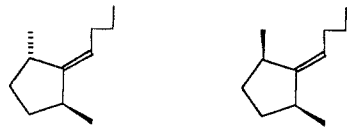
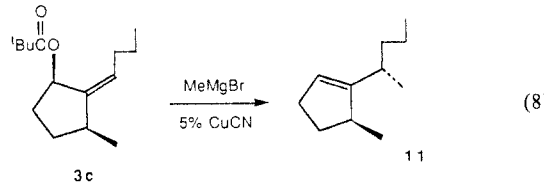


(7)

In contrast, the S_N2' product from treating the pivalates with $LiCuMe_2$ was exclusively that from backside (anti) attack. However, in this case, S_N2 displacement of the pivalate to afford compounds **12a** or **12b** was a significant side-reaction. Some 24% of the hydrocarbon product **12a** from **3c** and 45% of **12b** from **4c** arose by this pathway.

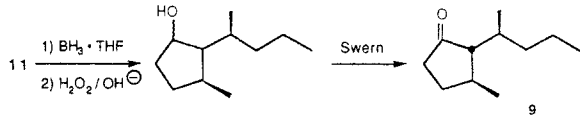


This problem was circumvented by application of a more recent procedure developed by the Goering group.[21] The modified procedure utilizes methylmagnesium bromide as the nucleophile, and the reaction is carried out in the presence of a catalytic amount of copper cyanide as shown in eq 8. By using this approach pivalate **3c** derived from the major isomer **3a** could be converted to cyclopentene **11** in 74% yield with formation of only 4% of S_N2 product **12a**.



(8)

Hydroboration/oxidation of **11** with BH_3·THF followed by Swern oxidation afforded a cyclopentanone with a ^{13}C spectrum identical with that reported[17] by Rocca, Tumlinson, and co-workers for **9**. This transformation is shown in eq 9. The hydroboration



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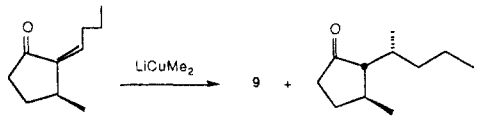
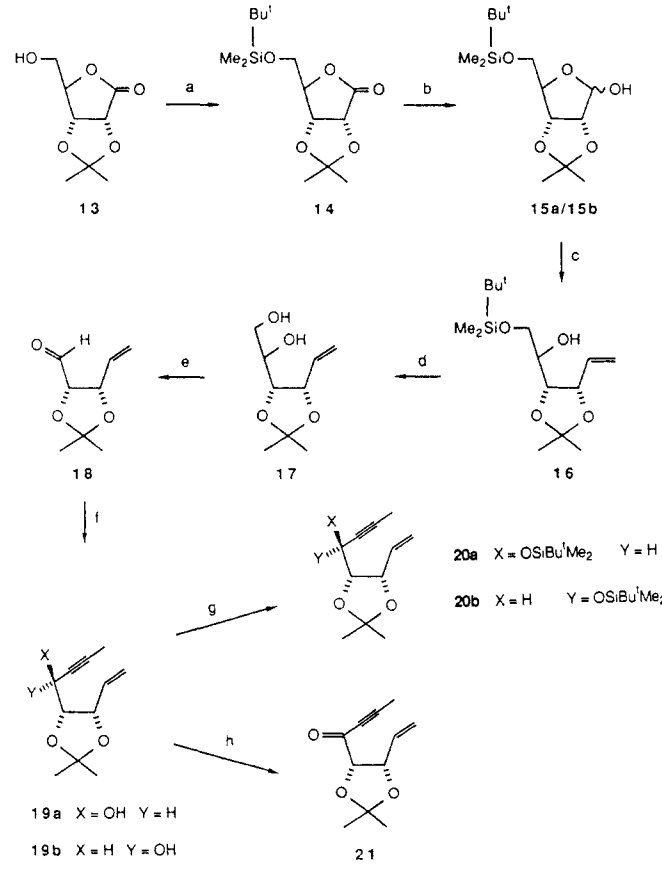


(10)

proceeds remarkably sluggishly—presumably for steric reasons—requiring a 72-h reaction to achieve a 50% conversion. However, the yield of intermediate alcohol based on recovered **11** was high (ca. 80%).[22] For comparison, a sample of **3b** was oxidized to the α,β-unsaturated cyclopentanone and treated with lithium dimethyl cuprate. As indicated in eq 10, this procedure afforded a 55:45 mixture of **9** and its methyl epimer.

Scheme I.[a] A General Synthesis of Sugar Enynes



[a] a. Bu^tSiMe_2Cl, DMF, imidazole; b. Dibal-H; c. $Ph_3P^+CH_2^-$; d. Bu_3^nNF; e. $NaIO_4$, Bu^tOH, H_2O; f. Me-≡-M; g. Bu^tSiMe_2Cl, DMF, imidazole; h. $(CF_3CO)_2O$, DMSO, Pr^iNEt_2.

Preparation of Substrates for Sugar Cyclizations. A general and operationally simple synthesis of enynes starting with readily available sugar lactones is shown in Scheme I. The dimethyl-*tert*-butylsilyl derivative **14** was reduced with diisobutylaluminum hydride giving a mixture of anomers, **15a** and **15b** in 97% yield. Upon reaction with 2 equiv of methylene triphenylphosphorane, **15** gives a moderate yield of the enol **16** which is further converted into the diol **17** by desilylation with tetrabutylammonium fluoride. The diol was oxidatively degraded with $NaIO_4$ in *tert*-butyl alcohol, THF, and water. The product aldehyde **18** was treated with various propynyl organometallic reagents[23] to get mixtures of **19a** and **19b**. The best results were obtained with propynyllithium in THF at −20 °C. Under these conditions a ratio of 76:24 for the major to minor product is observed. Attempts to improve the ratio in favor of the major isomer were unsuccessful (see Experimental Section).

Although the major isomer from the above procedure could be separated by careful column chromatography, an alternate route involving oxidation and reduction was developed to provide larger amounts of material and to assign the structure of the diastereomers. Thus the mixture of isomeric alcohols was readily oxidized under the Swern reaction conditions[24] to give a 96% yield of ketone **21**. Reduction of the ketone with (*R*)-alpine borane[25a] gives a single isomer **19a**, identical with the major product from

(21) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884–2891. Tseng, C. C.; Yen, S.-J.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2892–2895.

(22) As an alternative, cyclopentene **11** underwent $Mo(CO)_6$-catalyzed epoxidation by *tert*-butyl hydroperoxide to afford a mixture of two epoxides in 84% combined yield. Treatment of the mixed epoxides with BF_3 etherate at −40 °C afforded **9**, but the isolated yield for this rearrangement was only 23%.

(23) For a discussion of stereochemistry of such additions, see: (a) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031–1034. (b) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843–2846. (c) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422–424, and references cited therein.

(24) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(25) (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867–869. (b) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1984**, *25*, 5981–5984.

Table II. NMR Spectra of Cyclized Products

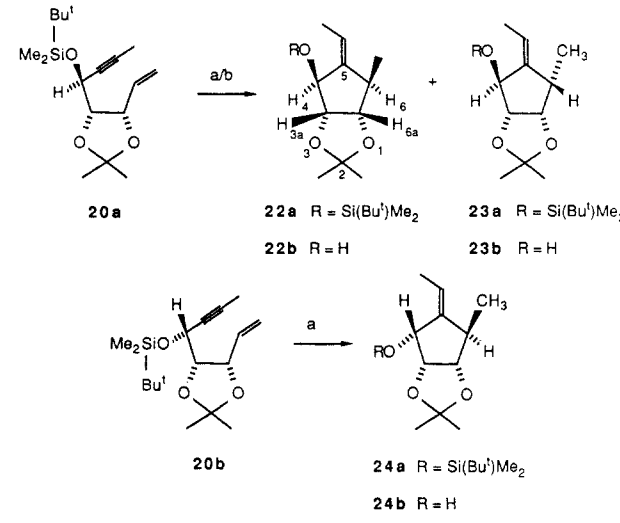
compd	H_6	H_{6a}	H_{3a}	H_4	=CH	$J_{6,6a}$	$J_{3a,6a}$	$J_{3a,4}$	C_6-CH_3
22a	2.55	4.35	4.45	4.58	5.50	0	6	0	
	(q, 7)	(d, 6)	(d, 6)	(s)	(q, 7)				
22b	2.66	4.37	4.58	4.64	5.62	1	6	0	14.41
	(q, 8)	(dd, 6, 1)	(d, 6)	(s)	(q, 7)				
23a	2.74	4.56	4.34	4.50	5.27	6	6	0	
	(m)	(t, 6)	(d, 6)	(s)	(qm, 7)				
23b	2.79	4.61	4.46	4.59	5.43	5	5	0	10.51
	(m)	(t, 5)	(d, 5)	(s)	(qdd, 7, 3, 1)				
24a	2.75	4.03	4.31	4.64	5.26	6	8	6	
	(m)	(dd, 8, 6)	(dd, 8, 6)	(d, 6)	(qdd, 7, 3, 1)				
24b	2.70	4.16	4.51	4.61	5.46	4	6	6	13.83
	(m)	(dd, 6, 4)	(dd, 6, 6)	(dd, 6, 4)	(qt, 7, 2)				

propynyllithium additions. Reduction of the acetylenic ketone with (*S*)-alpine borane gives a mixture of alcohols **19a** and **19b** in a ratio of 40:60.[25] Confirmation of the structures of **19a** and **19b** comes from NOE studies (vide infra) of the cyclized products **22b**, **23b**, and **24b** where the relationship between H_{3a} and H_4 can be unambiguously established. Since the relative stereochemistry of H_{3a} and H_4 remains unaltered during the course of the intervening transformations (i.e., **19a** → **22**, **23**; **19b** → **24**), this provides a direct proof of structure of **19a** and **19b**.

Cyclization of Sugar Enynes. The zirconocene-mediated cyclization of the isomerically pure enyne **20a** gives a mixture of two allylic ethers, **22a** and **23a**, in a ratio of 62:8 as judged by GLC of the crude product. The analysis of the isomers is best done after desilylation to give the allylic alcohols **22b** and **23b**. High field proton and carbon NMR of these compounds and the subsequent reduction products are characteristic of the assigned structures (see Table II). In **22b**, strong NOE's are observed on the signals due to H_6,H_{6a} and the vinyl proton upon irradiation of the C_6-methyl protons (see structure **22** for numbering). A weak NOE of H_{3a} is also noticed. Irradiation of H_{6a} has the expected effect on the signal intensities of C_6–CH_3 and H_{3a}. In **23b**, irradiation of the C_6-methyl signal causes NOE's on H_6 and the vinyl proton and *significantly* no change on the intensity of the H_{6a} signal. The irradiation of H_6 results in the enhancement of the H_{6a} signal. The coupling constants $J_{3a,4}$ and $J_{3a,6a}$ as well as $J_{6,6a}$ are also in accordance with suggested structures. In both **22b** and **23b**, $J_{3a,4}$ is nearly zero suggesting a 90° dihedral angle between the protons. This is possible only in a trans relationship between these two centers. Since C_{3a} configuration is invariant under the reaction conditions, this relationship also confirms the sense of the Alpine borane reduction. By similar argument one can arrive at a trans relationship between H_6 and H_{6a} (J = 1 Hz) in **22b** and a cis relationship (J = 5 Hz) in **23b**. As expected, $J_{3a,6a}$ for the cis protons is near 6 Hz in both the compounds. This analysis can also be applied to the respective silyl derivatives **22a** and **23a**. Finally in the ^{13}C spectra of **22b** and **23b** the relative shifts of the C_6-methyl carbon (14.41 and 10.51, respectively) clearly suggest a more sterically compressed situation in the latter compound.[27]

The titanocene-mediated reaction gives only a 32% yield of the two products. A significant amount of the starting material is recovered under these conditions. Depending on the conditions, ratios of **22a** and **23a** ranging from 4:1 to 2:1 are observed in this rather poor reaction.

Scheme II.[a] Cyclization of Sugar Enynes



[a] a. Cp_2ZrCl_2, Mg, $HgCl_2$; b. Cp_2TiCl_2, $PMePh_2$, Na(Hg).

Since we have been unable to prepare the isomerically pure **19b** or its silyl ether, a mixture of the substrates **20a** and **20b** (72/28) was used to evaluate the effect of the C_4 configuration on the cyclization. Knowing the products from the pure isomer **20a**, we hoped to analyze the products from **20b** without difficulty. Indeed, only one new product is formed in the Zr-mediated cyclization reaction, and its structure is readily established as **24a** by the methods outlined earlier. The coupling constants $J_{3a,4}$ (6 Hz) and $J_{3a,6a}$ (6 Hz) in **24b** are consistent with the relative orientations of attached groups even though a value of 4 Hz for $J_{6,6a}$ appears anomalous. However, the NOE and ^{13}C data clearly support the assigned structures. In the difference NOE spectrum of the desilylation product **24b** irradiation of C_6–CH_3 resulted in enhancements due to H_6,H_{6a} and the vinyl proton. Irradiation of H_{3a} has a similar effect on the intensity of H_4 and H_{6a}. Irradiation of H_{6a} increases the amplitude of H_{3a},C_6–CH_3 and one of the acetonide CH_3's. The C_6–CH_3 carbon appears at 13.83 clearly suggesting a sterically uncongested environment for the methyl group like that in the structure **22b** (14.41 ppm). Recall that due to the considerable steric shielding the corresponding signal in **23b** appears at 10.51 ppm.

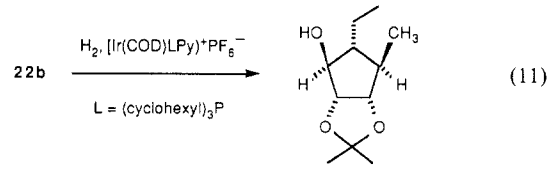
Further proof of the stereochemistry of **22b** and **23b** comes from hydrogenation of the double bond with the complex [Ir(COD)-Lpy]$^+PF_6^-$ (L = tricyclohexylphosphine). By using this catalyst, the delivery of hydrogen from the intermediate iridium hydride is known to be controlled by the configuration of the allylic center.[28] The only products obtained from hydrogenation of **22b**

(26) As has been observed earlier,[25b] the rate of reduction is considerably slower than with the *R*-borane reduction. Under identical conditions about 30% of the starting ketone was recovered from reductions with *S*-alpine-borane. The effect of an α-chiral center in asymmetric reductions of acetylenic ketones has been observed earlier in some steroidal substrates. The observed rate difference and selectivity can be rationalized by examination of the model cyclic transition states[25] proposed for these reductions. It is clear from such models that the ketone **21** and *R*-alpine-borane constitute a "matching pair" of reagents giving maximum asymmetric induction. Serious nonbonded interactions are clearly evident in the diastereomeric transition states from **21** and *S*-alpine-borane. Coincidently the relative rates of reactions, diastereoselectivity, and the sense of α-chirality are the same as in the other example[25b] where similar effects have been noticed.

(27) (a) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; Verlag Chemie: Weinheim, Federal Republic Of Germany, 1987. (b) Schneider, H.-J.; Ngeyun-ba, N.; Thomas, F. *Tetrahedron* **1982**, *38*, 2327–2337. (c) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.

(28) (a) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072–1073. (b) Schultz, A. G.; McCloskey, P. J. *J. Org. Chem.* **1985**, *50*, 5905–5907. (c) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661. (d) For a review, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203.

and **23b** were assigned the structures **25** and **26** by NMR and mass spectrometry data (eq 11 and 12). The chemical shifts of the two methyl carbons, the methylene carbon, and the 5 and 6 carbons appear at higher field in **26** as compared to those in the sterically less crowded **25**.



(11)

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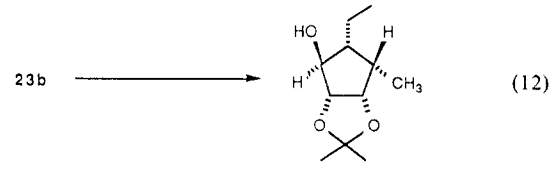

(12)

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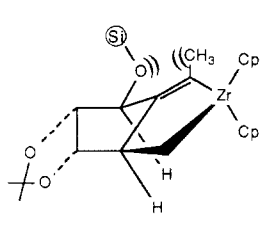
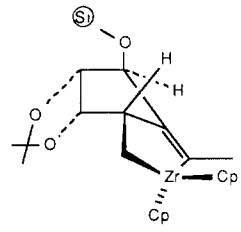
One approach to rationalizing the stereochemical outcome of the Zr-mediated reactions of **2**, **20a**, and **20b** follows. We assume that the formation of the metallacycle is reversible[29] and the Zr–C(sp^2) and Zr–C(sp^3) are long enough (i.e., 2.3–2.4 Å) to permit the incipient 2,5-methylenecyclopentane to assume its most favorable conformation. In this conformation (for example, structure **27**) the CH_2–Zr and the OSi(Me_2)-*t*-Bu will be in



27



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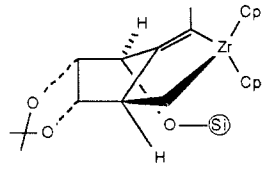

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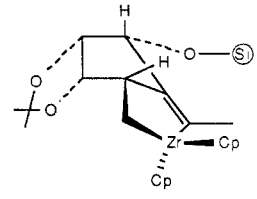

30

diequatorial orientation leading to the major 2,5-cis-product, **22a**. The isomeric metallacycle **28** will have at least one of the above groups in a quasi-axial orientation because of its trans-2,5-disubstituted 1-methylenecyclopentane structure. One of the unfavorable interactions still present in the structure **27** is the allylic (1,3) strain between the OSiMe_2-*t*-Bu and the vinyl methyl group. This interaction is absent in the metallacycle **29** formed from **20b**, and this may explain the formation of a single product from this substrate. If so, one must conclude that under thermodynamic conditions the above mentioned allylic strain causes the equilibration between **27** and **28**. In addition, the endo methylene(Zr) intermediate **30** which would lead to the cis isomer of **24a** has two severe eclipsing interactions in its concave face. Thus this cis-2,5-diequatorial methylenecyclopentane cannot assume its most favorable conformation without some steric crowding. For these reasons the reaction of **20b** is stereospecific. (Alternatively, kinetic arguments may be applied.) Interpretation of the stereochemical results in the titanium-mediated cyclization of **20a** does not seem prudent given the poor material balance.

(29) There is ample precedent for such reversibility, see: Erker, G.; Dort, U.; Rheingold, A. L. *Organometallics* **1988**, *7*, 138–143, and references therein.

Conclusion

We have shown that both titanocene- and zirconocene-based reagents are effective for the cyclization of simple 1,6- and 1,7-enynes to the corresponding carbocycles. It appears that the zirconocene-based systems are superior in the case of sterically demanding substrates. Our enyne cyclization can be regarded as a part of a body of emerging methodology based on intramolecular carbometalation. Related reactions include intramolecular carbalkylation–carbonylation with stoichiometric cobalt complexes (the "Pauson–Khand reaction")[30] and the palladium-catalyzed reductive enyne cyclization developed by Trost and co-workers.[31] It is becoming evident that these reactions are complementary in many regards. For example, the Co- and Pd-based reactions differ from our Ti- and Zr-mediated chemistry in that the former are compatible with terminal acetylenes and with unsaturated heterofunctionality such as the carbonyl moiety. *A particular strength of the early transition-metal approach is that the metallacyclic intermediates are themselves nucleophilic organometallic species which are amenable to further elaboration.* In the present report we have begun to explore this feature in the synthesis of heterocycles **6a**, **6b**, and **7**.

Another strength of the Ti- and Zr-mediated cyclizations is the fact that the exocyclic alkylidene group is formed with 100% stereoselectivity. We have utilized this feature in our synthesis of **9**. Furthermore, we have shown that with appropriate choice of substrates, as in the case of our sugar enynes, the absolute stereochemistry of the alkyl group in the product carbocycle can likewise be controlled. Both of these control elements should prove extremely valuable in future synthetic applications. Perhaps the most exciting feature of our results is the compatibility of the reagents with highly functional substrates as illustrated by the sugar enyne derivatives **20a** and **20b**. Because of the ready availability of carbohydrates as chiral building blocks there has been an explosive growth in their use for the synthesis of various biologically active compounds.[32] Indeed, we have previously reported a series of short and versatile transformations of readily available sugars to carbocycles via free-radical chemistry.[33] However, most of the carbohydrate to carbocyclic transformations reported to date involve torturous protocols and several steps. In this context, we believe that new, stereochemically well-defined transformations like the ones reported in this paper will have practical value.

Experimental Section

General Methods. The model enynes 1-nonen-7-yne and 1-octen-6-yne were prepared by straightforward displacement reactions described in detail by Brandsma.[34] GLC yields were determined relative to a hydrocarbon internal standard on a 50-ft cross-linked methylsilicone fused-silica capillary column. Response factors were determined by using purified compounds prepared in separate runs from which the internal standard was omitted. Solvent tetrahydrofuran was freshly distilled from benzophenone radical anion. All cyclization reactions were carried out under an atmosphere of dry nitrogen. The 80, 90, and 300 MHz ^1H NMR spectra were determined, respectively, on an IBM NR80, Varian EM390, or General Electric QE300 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in parts per million downfield from internal reference tetramethylsilane. Couplings (J) are in hertz. Flash chromatography was carried out on 230–400 mesh silica (EM Reagents) following the procedure of Still.[35] Bis(cyclopentadienyl)titanium di-

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(31) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161–3163. See, also: Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268–5270.

(32) (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: Oxford, 1983. (b) Inch, T. D. *Tetrahedron* **1984**, *40*, 3161–3213. (c) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984.

(33) (a) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609. (b) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S., *J. Am. Chem. Soc.*, in press. (c) See, also: Wilcox, C. S.; Gaudino, J. *J. Am. Chem. Soc.* **1986**, *108*, 3102 and references cited therein.

(34) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1971.

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

chloride and -zirconium dichloride (ALFA) and all other materials were reagent grade chemicals and were used as received.

Typical GLC Run (Ti). A round-bottomed flask was charged with bis(cyclopentadienyl)titanium dichloride (2.28 g, 9.16 mmol), methyldiphenylphosphine (2.20 g, 11.0 mmol), and tetrahydrofuran (100 mL). An addition funnel was charged with 0.5% sodium amalgam (8 mL, 110 g, 23.9 mmol), 1-nonen-7-yne (0.87 g, 7.15 mmol), nonane internal standard (0.87 g), and tetrahydrofuran (100 mL). The flask was cooled to −45 °C, and the amalgam only was added to the stirred solution. The mixture was allowed to warm to −25 °C at which temperature it was maintained for 15 min. The THF solution was then added dropwise over 1 h, and the mixture was stirred an additional 3 h at −25 °C. The reaction was quenched by rapid addition of 10% H_2SO_4 (100 mL). After warming to room temperature, the mixture was extracted with ether (3 × 100 mL), and the ether phase was washed with 5% sodium bicarbonate (50 mL). The yield of (*E*)-1-ethylidene-2-methylcyclohexane was determined by duplicate GLC injections.

Typical GLC Run (Zr/Mg). A round-bottomed flask was charged with magnesium turnings (0.91 g, 37 mmol), mercury(II) chloride (1.03 g, 3.79 mmol), and tetrahydrofuran (50 mL). The mixture was stirred 15 min whereupon a solution of 1-nonen-7-yne (0.70 g, 5.74 mmol), nonane internal standard (0.70 g), and bis(cyclopentadienyl)zirconium dichloride (2.02 g, 6.91 mmol) in tetrahydrofuran (50 mL) was added dropwise. The solution was stirred for 24 h and was then decanted from unreacted magnesium; the reaction was rapidly quenched with 10% H_2SO_4 (100 mL). The mixture was extracted with hexane (3 × 100 mL), and the organic phase was washed with 5% sodium bicarbonate (50 mL) and dried ($MgSO_4$). The yield of (*E*)-1-ethylidene-2-methylcyclohexane was determined by duplicate GLC injections.

Typical GLC Run (Zr/BuLi). A round-bottomed flask with septum-covered side arm was charged with bis(cyclopentadienyl)zirconium dichloride (1.17 g, 4.0 mmol) in tetrahydrofuran (25 mL). An addition funnel[36] was charged with 1-nonen-7-yne (0.49 g, 4.0 mmol), nonane internal standard (0.49 g), and tetrahydrofuran (25 mL). The flask was cooled to −78 °C, and 1.6 M butyllithium in hexane (5.0 mL, 8.0 mmol) was added via hypodermic syringe. The mixture was stirred for 1 h at −78 °C whereupon the substrate solution was added, the mixture was allowed to warm to room temperature, and stirring was continued overnight. The solution was quenched and analyzed as in the preceding example.

Preparation of Dihydrothiophene 6a. A 300-mL, round-bottomed flask was fitted with an additional funnel capped with N_2 inlet and septum-covered side arm. The flask was charged with bis(cyclopentadienyl)-zirconium dichloride (2.34 g, 8.0 mmol) and 1-nonen-7-yne (0.98 g, 8 mmol) in THF (100 mL). The addition funnel was charged with sulfur monochloride (1.08 g, 8.0 mmol) in hexane (15 mL). After having been flushed with nitrogen, the flask was cooled to −78 °C, and 1.6 M butyllithium (10.0 mL, 16 mmol) was added via hypodermic syringe. After having been stirred 1 h, the mixture was allowed to warm to room temperature and stirred an additional 1 h. The contents of the addition funnel were added dropwise at 0 °C followed by 15 min stirring at room temperature. The reaction was quenched with 10% sulfuric acid (100 mL) and extracted with ether (3 × 100 mL). The ether extracts were washed with saturated sodium bicarbonate and dried ($MgSO_4$), and the solvent was removed at reduced pressure. The residue was purified by flash chromatography with hexane/toluene (85:15) as eluant to afford **6a** (0.59 grams, 48%) as a yellow liquid: HRMS 154.0799 (M^+; calcd for $C_9H_{14}S$ 154.0816); Anal. C, H, S; ^1H NMR δ 1.1–1.4 (m, 3 H), 1.60 (m, 1 H), 1.70–1.82 (s + m, 5 H total), 1.95 (m, 1 H), 2.50 (d, J = 15 Hz, 1 H), 2.75 (t, J = 10 Hz, 1 H), 2.88 (m, 1 H), 3.26 (dd, J = 11,12 Hz, 1 H); ^{13}C NMR δ 13.16, 25.33, 26.05, 27.00, 34.71, 36.15, 50.25, 124.43, 130.17.

Stannacycle 6b. The previous procedure was followed except that diphenyltin dichloride (2.75 g, 8 mmol) was used as electrophile, and the reaction mixture was heated at reflux for 3 days to ensure complete reaction. Flash chromatography (hexane/toluene 90:10) afforded **6b** (1.25 g, 40%) as a viscous, colorless oil: HRMS 396.0921 (M^+; calcd 396.0900); ^{13}C NMR ($CDCl_3$) δ 12.86 (^{119}Sn satellites $J_{^{119}Sn^{13}C}$ = 353.84 Hz) 17.99, 27.42, 28.04, 29.67, 40.83, 47.86, 127.24, 128.46 (meta), 128.49 (meta), 128.72 (para), 136.85 (ortho), 136.94 (ortho), 140.14, 140.42, 159.32; ^{119}Sn NMR ($CDCl_3$ versus tetramethyltin) δ 17.10. Anal. Calcd for $C_{21}H_{24}Sn$: C, 63.84; H, 6.12. Found: C, 64.12; H, 6.14.

Dihydroselenophene 7. The procedure for **6a** was followed substituting 1-octen-6-yne (0.87 g, 8 mmol) as enyne component and selenium monochloride (1.83 g, 8 mmol) as electrophile. Flash chromatography (hexane/toluene 90:10) afforded **7** (0.69 g, 46%) as an orange liquid: HRMS 188.0919 (M^+; calcd for $C_8H_{12}Se$ 188.0104); Anal. C, H; ^{13}C NMR ($CDCl_3$) δ 16.86, 24.50, 30.56, 31.08, 32.12, 59.34, 118.20, 144.98.

5-(*tert*-Butyldimethylsiloxy)-1-decen-6-yne, 2. Butyllithium (1.6 M, 35 mL, 55.8 mmol) was added dropwise to a solution of 1-pentyne (4.43 g, 65.0 mmol) in THF (150 mL) at 0 °C. The solution was warmed to room temperature, whereupon 5-pentenal (4.47 g, 53.1 mmol) in THF (75 mL) was added dropwise. After 15 min *tert*-butyldimethylchlorosilane (8.41 g, 55.8 mmol) was added, and the mixture was heated at reflux overnight.[37] The cooled mixture was quenched with 200 mL of half-saturated ammonium chloride and extracted with hexane (100 mL) and ether (2 × 100 mL). Removal of solvent followed by flash chromatography (10% toluene/90% hexane) afforded **2** (5.87 g, 41%) as a colorless liquid: ^1H NMR δ 0.10 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 9 H), 0.98 (t, J = 7, 3 H), 1.45 (m, 2 H), 1.77 (m, 2 H), 2.20 (m, 4 H), 3.84 (tt, J = 7,2, 1 H), 4.9–5.1 (m, 2 H), 5.82 (m, 1 H); Anal. ($C_{16}H_{30}OSi$) C, H.

Cyclization of 2. Butyllithium (1.6 M, 42.2 mL, 67.5 mmol) was added dropwise to a solution of bis(cyclopentadienyl)zirconium dichloride (9.87 g, 33.8 mmol) in THF (400 mL) at −78 °C. After 1 h a solution of **2** (9.00 g, 33.8 mmol) in THF (25 mL) was added, and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with 5% H_2SO_4 (400 mL) at 0 °C, was extracted with ether, washed with saturated sodium bicarbonate, and dried ($MgSO_4$). After removal of solvent, the residue was purified by flash chromatography (hexane for 15 cuts then 95:5 hexane/toluene for 20 cuts) to afford **3a** (5.16 g, 57%) as high R_f component and **4a** (3.35 g, 37%) as low R_f component. 90 MHz ^1H NMR for **3a**: δ 0.07 (s, 6 H), 0.87 (s, 9 H), 1.09 (d, J = 7, 3 H), 0.8–2.5 (m, 12 H), 4.62 (br s, 1 H), 5.22 (tt, J = 7, 2, 1 H); Anal. ($C_{16}H_{32}OSi$) C, H. 90 MHz ^1H NMR for **4a**: δ 0.10 (s, 6 H), 0.91 (s, 9 H), 0.99 (d, J = 7, 3 H), 0.8–2.6 (m, 12 H), 4.69 (t, J = 6, 1 H), 5.21 (tt, J = 7, 2, 1 H); Anal. ($C_{16}H_{32}OSi$) C, H.

Desilylation of 3a and 4a. The silyl ether (2.60 g, 9.68 mmol) was dissolved in a 1 M solution of anhydrous tetrabutylammonium fluoride in THF (20 mL, 20 mmol). After having stood overnight, the mixture was added to 100 mL of water and extracted with ether (3 × 50 mL). The ether layer was washed with water (50 mL) and dried (K_2CO_3). After removal of solvent the crude product alcohol (ca. 2.15 g) was azeotropically dried with toluene (50 mL). The alcohols were not further purified but were directly converted to the pivalate or phenylcarbamate as described below following the general procedures of Trost and coworkers.[16]

Preparation of Pivalate 3c. To the crude alcohol **3b** (2.15 g, 13.9 mmol) in methylene chloride (25 mL) was added (*p*-dimethylamino)-pyridine (0.13 g, 1.1 mmol), triethylamine (3.10 g, 31 mmol), and trimethylacetyl chloride (2.18 g, 18.1 mmol). After stirring overnight the reaction was diluted with ether (200 mL) and extracted with 1N HCl (100 mL), saturated sodium bicarbonate (50 mL), and water. After drying ($MgSO_4$), the solvent was removed, and flash chromatography of the residue (95:5 hexane/ethyl acetate) afforded **3c** (2.33 g, 70%): 80 MHz ^1H NMR δ 0.88 (t, J = 7, 3 H), 1.13 (d, J = 7, 3 H), 1.17 (s, 9 H), 1.2–2.7 (m, 9 H), 5.39 (td, J = 7, 2, 1 H), 5.64 (br s, 1 H); Anal. ($C_{15}H_{26}O_2$) C, H.

Preparation of Pivalate 4c. Treatment of crude alcohol **4b** according to the previous procedure afforded **4c** in 65% yield: 80 MHz ^1H NMR δ 0.88 (t, J = 7, 3 H), 1.04 (d, J = 7, 3 H), 1.17 (s, 9 H), 1.2–2.8 (m, 9 H), 5.35 (dt, J = 7, 2, 1 H), 5.61 (t, J = 6, 1 H); Anal. ($C_{15}H_{26}O_2$) C, H.

Preparation of Phenylcarbamate 3d. The crude alcohol **3b** (0.93 g, 6.0 mmol) in methylene chloride (40 mL) was treated overnight with phenyl isocyanate (0.72 g, 6.0 mmol), triethylamine (1.02 g, 10.0 mmol), and (*p*-dimethylamino)pyridine (0.13 g, 1.1 mmol). The reaction was quenched with 10% HCl (100 mL) and extracted with ether (3 × 50 mL). The ether phase was washed with saturated sodium bicarbonate (25 mL) and water (25 mL), and the solvent was removed at reduced pressure. Flash chromatography (75:25 toluene/methylene chloride) afforded the desired product (1.16 g, 70%) as well as a low R_f side product which was shown by ^1H NMR to be derived from 2 equiv of phenyl isocyanate per alcohol moiety: mp 78–80 °C; 90 MHz ^1H NMR δ 0.88 (t, J = 7, 3 H), 1.05 (d, J = 7, 3 H), 1.0–2.8 (m, 9 H), 5.38 (td, J = 7, 2, 1 H), 5.68 (m, 1 H), 6.58 (br s, 1 H), 6.9–7.5 (m, 5 H); Anal. ($C_{17}H_{23}O_2N$) C, H, N.

Preparation of Phenylcarbamate 4d. Treatment of the crude alcohol **4b** according to the previous procedure afforded **4d** in 82% yield. Formation of a 2:1 adduct was also observed but in considerably lesser amounts than in the previous example. The observed melting point of

(36) For cyclization of enynes containing the trimethylsilylacetylene moiety, Negishi[10] has advised the dropwise addition of the substrate to a pregenerated dibutyl zirconocene species. Presumably this prevents transmetalation of the silicon. Although we have likewise followed a dropwise regimen here, subsequent studies indicate that this is not required for simple substrates such as 1-octen-6-yne and 1-nonen-7-yne. Essentially identical yields are obtained by adding butyllithium to a mixture of Cp_2ZrCl_2 and the enyne (1 h at −78 °C then 1 h at 25 °C).

4d at 78–80 °C was the same as for **3d**, but a 1:1 mixture of **3d** and **4d** melted at 75–77 °C: 90 MHz ^{1}H NMR δ 0.88 (t, J = 7, 3 H), 1.16 (d, J = 7, 3 H), 1.0–2.6 (m, 9 H), 5.47 (dt, J = 7, 2, 1 H), 5.71 (br s, 1 H), 6.55 (br s, 1 H), 6.9–7.6 (m, 5 H); Anal. ($C_{17}H_{23}O_2N$) C, H, N.

Conversion of Phenylcarbamate 3d to 10. A solution of 1.5 M methyllithium in ether (36 mL, 54 mmol) was added dropwise to a stirred suspension of copper(I) iodide (5.20 g, 27.3 mmol) in ether (70 mL) at 0 °C. Phenylcarbamate **3d** (1.95 g, 7.13 mmol) in ether (70 mL) was added dropwise, and the mixture was maintained at 0 °C overnight. The reaction was quenched with saturated ammonium chloride (125 mL), extracted with ether (2 × 100 mL), washed with 1 N HCl, saturated sodium bicarbonate, and water (100 mL each), and was dried ($MgSO_4$). Careful removal of the solvent afforded **10** (0.88 g, 81%) as a colorless liquid which was shown by GLC analysis to contain ca. 1% of the S_N2 product as the only volatile impurity: 300 MHz ^{1}H NMR δ 0.88 (t, J = 7, 3 H), 1.00 (d, J = 7, 3 H), 1.05 (d, J = 7, 3 H), 1.1–1.5 (m, 5 H), 2.0–2.3 (m, 4 H), 2.64 (apparent q, J = 7, 1 H), 5.29 (br s, 1 H); Anal. ($C_{11}H_{20}$) C, H.

Conversion of Phenylcarbamate 4d to 11. Treatment of **4d** with lithium dimethyl cuprate as in the preceding procedure afforded **11** in 84% yield. The colorless liquid contained 5% of the S_N2 product by GLC: 300 MHz ^{1}H NMR δ 0.89 (t, J = 7, 3 H), 0.94 (d, J = 7, 3 H), 1.00 (d, J = 7, 3 H), 1.1–1.6 (m, 5 H), 2.0–2.4 (m, 4 H), 2.65 (apparent q, J = 7, 1 H), 5.27 (br s, 1 H); ^{13}C NMR δ 14.32, 19.57, 20.21, 20.79, 30.49, 32.48, 33.08, 37.77, 40.27, 120.80, 154.28; HRMS 152.1548 (M^+; calcd for $C_{11}H_{20}$ 152.1565); Anal. C, H. A sample of neat **11** stored under air at room temperature became viscous within days and contained only ca. 10% of unchanged **11** by GLC. However, a separate sample stored under nitrogen at −25 °C was unchanged after 14 months.

Reactions of Pivalates 3c and 4c with $LiCuMe_2$. Treatment of pivalates **3c** and **4c** with lithium dimethyl cuprate was carried out on a 1 mmol scale and otherwise under identical conditions to the preceding examples; in each case the isolated yield of hydrocarbon product was 60%. The product from **3c** was shown by GLC to contain 74% of **11** and 24% of the S_N2 product **12a**; that from **4c** contained 55% of **10** and 45% of S_N2 product **12b**.

Conversion of Pivalate 3c to 11. A mixture of pivalate **3c** (2.38 g, 10 mmol) and copper(I) cyanide (0.04 g, 0.5 mmol) in ether (70 mL) was cooled to 0 °C. A solution of 2.7 M methylmagnesium bromide in ether (7.4 mL, 20 mmol) was added dropwise. The usual workup afforded **11** as a colorless liquid (1.12 g, 74%) which was shown by GLC to contain 3% of the S_N2 product. The ^{1}H and ^{13}C NMR were identical with that of **11** prepared by the phenylcarbamate route.

Synthesis of Cyclopentanone 9. Cyclopentene **11** (0.76 g, 5.0 mmol) was treated with a 1 M solution of borane in THF (10 mL, 10 mmol) overnight. Half-saturated sodium bicarbonate (25 mL) was added followed by 30% hydrogen peroxide (5 mL) at 0 °C. After 0.5 h the temperature was raised to 25 °C for 2 h and 45 °C for 2 h. After extractive workup, flash chromatography (80:20 hexane/ethyl acetate) afforded in addition to 0.50 g of recovered **11** some 0.23 g (78% based on recovered starting material) of a pair of epimeric alcohols. Oxidation of the mixed alcohols (0.20 grams) according to the standard procedure of Swern[24] afforded **9** (0.12 g, 61%) as a colorless oil which was homogeneous by TLC and GLC: 300 MHz ^{1}H NMR δ 0.88 (t, J = 7, 3 H), 0.92 (d, J = 7, 3 H), 1.14 (d, J = 6, 3 H), 1.2–1.4 (m, 5 H), 1.63 (dt, J = 11, 1, 1 H), 1.90 (m, 1 H), 2.00–2.15 (m, 3 H), 2.23–2.34 (m, 1 H); ^{13}C NMR δ 14.01, 16.84, 20.38, 20.77, 29.66, 31.82, 34.24, 36.56, 39.18, 61.08, 220.93. Anal. ($C_{11}H_{20}O$) C, H.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-di-*O*-isopropylidene-D-ribono-1,4-lactone (14). To 9.04 g (50 mmol) of 2,3-di-*O*-isopropylidene-1,4-ribonolactone[38] dissolved in 50 mL of anhydrous DMF was added 9.04 g (60 mmol) of *tert*-butyldimethylchlorosilane and 4.08 g of imidazole. The mixture was stirred for 4 h and was subsequently added to 200 mL of 1:1 ether/hexane and 100 mL of water. The organic layer was separated, and the aqueous layer was extracted repeatedly with ether. The combined ether layer was washed with saturated sodium dihydrogen phosphate and dried. Concentration and evaporation of the volatiles gave 13.85 g (93%) of the desired product which was used for the subsequent step: ^{1}H NMR δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.85 (s, 9 H), 1.36 (s, 3 H), 1.45 (s, 3 H), 3.82 (ABX, J_{AB} = 13 Hz, J_{AX} = 3 Hz, J_{BX} = 2 Hz, 2 H) 4.57 (m, 1 H), 4.70 (m, 2 H).

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-di-*O*-isopropylidene-D-ribofuranose (15). A flame-dried three-necked flask fitted with a thermocouple, dropping funnel, and a serum stopper was charged with 13.85 g (45.70 mmol) of **14** and 120 mL of dry toluene. The mixture was cooled to −40 °C, and from the dropping funnel was added 50 mL of a 1 M solution of diisobutylaluminum hydride. The mixture was stirred at −40 °C for 90 min at which time TLC showed that all the starting material had disappeared. Three hundred mL of saturated sodium–potassium tartrate was added, and the cold bath was removed. The mixture was brought to room temperature, and the solution was transferred into a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with 1:1 ether/hexanes. The combined organic layers were washed and dried. Purification yielded 13.61 g of product identified as a mixture of anomers (**15a** and **15b**) by ^{1}H NMR: δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.82 and 0.87 (2 s, together 9 H), 1.26 (s), 1.34 (s) together 3 H, 1.42 (s), 1.50 (s) together 3 H, 3.70 (dABq, J = 2 Hz, J_{AB} = 11 Hz, 2 H), 4.30 (s, br, OH), 4.44 (d, J = 6 Hz), 4.48 (dd, J = 6 Hz, 4 Hz) together 1 H, 4.63–4.72 (m, 2 H), 5.25 (d, J = 12 Hz, 1 H); FABMS 287.31 (M^+ − OH; calcd 305.18).

1,2-Dideoxy-3,4-di-*O*-isopropylidene-6-*O*-(*tert*-butyldimethylsilyl)-D-ribohex-1-enitol (16). A flame-dried three-necked flask fitted with thermocouple adapter, serum stopper, and an addition funnel was charged with 70.25 g (0.191 mol) of dry methyl triphenylphosphonium bromide and 600 mL of THF. The dropping funnel was charged with 120 mL of 1.6 M *n*-butyllithium. The contents of the flask were cooled to −20 °C, and the butyllithium solution was carefully added. During this time the temperature was maintained between −20 °C and −10 °C. At the end of the addition the dropping funnel was washed down with 20 mL of THF. The reaction mixture was stirred at −20 °C to room temperature during which time all the solid went into solution. The dropping funnel was charged with 25.97 g (0.0851 mol) of **15** in 100 mL of THF. The reaction flask was cooled to −20 °C, the contents of the dropping funnel were added, and, at the end of addition, the dropping funnel was washed with 20 mL of THF to assure complete transfer of **15**. The reaction was warmed to room temperature with the bath in place, and the mixture was stirred for 48 h. It was then added to 1800 mL of 1:1 ether/hexanes, and the solid that precipitated was filtered off with the aid of Celite. The Celite bed was washed with excess ether, and then the organic layer was washed with three portions of bicarbonate, sodium chloride, and water. Drying, concentration, and column chromatography yielded 12.404 g (48%) of **16**: ^{1}H NMR δ 0.75 (2 s separated by 2 Hz, 6 H), 0.90 (s, 9 H), 1.35 (s, 3 H), 1.45 (s, 3 H), 2.51 (d, J = 5 Hz, -OH), 3.65 (m, 2 H), 3.80 (m, 2 H), 4.05 (dd, J = 9 Hz, 6 Hz, 1 H), 4.67 (dd, J = 6 Hz, 6 Hz, 1 H), 5.26 (d, br, J = 10 Hz, 1 H), 5.40 (dm, J = 16 Hz, 1 H), 6.04 (ddd, J = 16 Hz, 10 Hz, 6 Hz, 1 H); FABMS 303.26 (M + H; calcd for $C_{15}H_{30}O_4Si$ (M^+) 302.19), 287.25 (M − CH_3, calcd 287.17).

1,2-Dideoxy-3,4-di-*O*-isopropylidene-D-ribohex-1-enitol (17). To a solution of 6.35 g of **16** in 40 mL of THF was added 30 mL of 1 M tetrabutylammonium fluoride, and the mixture was stirred at room temperature for 90 min. After adding 40 mL of water, the THF was evaporated on the rotary, and the product was extracted into CH_2Cl_2. The usual workup followed by column chromatography yielded 3.007 g (76%) of **17**: ^{1}H NMR δ 1.31 (s, 3 H), 1.42 (s, 3 H), 3.20 (s, br, 2 H, exchange D20), 3.62 (m, 2 H), 3.75 (m, 1 H), 4.05 (m, 1 H), 4.65 (t, J = 6 Hz, 1 H), 5.26 (d, J = 11 Hz, 1 H), 5.41 (dm, J = 17 Hz, 1 H), 5.96 (ddd, J = 17 Hz, 11 Hz, 6 Hz, 1 H).

Addition of Propynyllithium to 18. A mixture of 3.007 g of **17**, 5.20 g of $NaIO_4$, 10 mL of *tert*-butyl alcohol, and 6 mL of water was stirred at room temperature for 24 h. An excess (250 mL) of ether was added and the precipitated solid was filtered off. The solid is washed with excess ether, and the combined ether solution was washed with $NaHCO_3$ and NaCl solutions. The organic layer was dried and concentrated. (The product is volatile; appropriate care was exercised to minimize the losses.) Finally the aldehyde **18** was dried by carefully azeotroping any water present with benzene (bath temperature below 35 °C) before reacting with propynyl reagents: ^{1}H NMR δ 1.45 (s, 3 H), 1.64 (s, 3 H), 4.41 (dd, J = 7 Hz, 3 Hz, 1 H), 4.86 (t, J = 7 Hz, 1 H), 5.32 (dm, J = 10 Hz, 1 H), 5.48 (dm, J = 17 Hz, 1 H), 5.78 (ddd, J = 17 Hz, 10 Hz, 8 Hz, 1 H), 9.55 (d, J = 3 Hz, 1 H).

The aldehyde prepared in the above experiment was added to 1.20 g of propynyllithium suspended in 30 mL of anhydrous THF at −20 °C, and the mixture was stirred for 90 min during which time the temperature of the bath rose to 25 °C. Ten milliliters of saturated NaH_2PO_4 was added, and the product was extracted into ether. Analysis by GLC and ^{1}H NMR indicated that the product consisted of a mixture of isomeric alcohols **19a** and **19b** in a ratio of 76:24. Yield from **17**:2.298 g (73%).

The major product, **19a**, can be separated by careful column chromatography on silica gel with either acetone/hexane or ether/hexane as the solvent system. To circumvent this problem several attempts were made to increase the diastereoselection of the addition. The following ratios of **19a**:**19b** were obtained under conditions listed: propynyl magnesium bromide/THF 45:55; propynyl lithium/THF 76:24; propynyl

(37) Attempts to isolate the alcohol and carry out the silylation in a separate step resulted in significantly lower yields. Apparently the chlorosilane has a beneficial effect in promoting addition of the acetylide to the aldehyde.

(38) Hough, L.; Jones, J. K. N.; Mitchell, D. L. *Can. J. Chem.* **1958**, *36*, 1720–1726.

lithium/ether 44:56; propynyl lithium/ether/TMEDA 58:42; propynyl lithium/THF/BF_3 45:55. These ratios are easily determined by integration of the propargyl methyl signals. They were further confirmed by GLC of the dimethyl-*tert*-butylsilyl ethers. **19a**: see below for physical data; **19b**: 1.40 (s, 3 H), 1.55 (s, 3 H), 1.87 (d, J = 2 Hz, 3 H), 2.40 (d, J = 6 Hz, br, OH), 4.20 (m, 1 H), 4.32 (m, 1 H), 4.70 (t, J = 7 Hz, 1 H), 5.31 (dm, J = 10 Hz, 1 H), 5.45 (dm, J = 16 Hz, 1 H), 6.11 (ddd, J = 16 Hz, 10 Hz, 7 Hz, 1 H); HRMS 181.0858 ($M^+ - CH_3$; calcd for $C_{10}H_{13}O_3$ 181.0864).

Preparation of 20a. An azeotropically dried sample of 793 mg of the alcohol **19a** was dissolved in 10 mL of anhydrous DMF, and the solution was treated with 344 mg (1.25 equiv) of imidazole and 780 mg of dimethyl-*tert*-butylchlorosilane at room temperature. The mixture was stirred overnight under nitrogen, and the product was isolated by extraction into 1:1 ether/hexanes. The organic layer was washed with water, saturated NaH_2PO_4, and brine. Concentration and column chromatography on silica gel using 5% ethyl acetate/hexane as solvent gave 900 mg of the product. Analysis by GLC indicated it to be greater than 98% pure. GLC and ^1H NMR also show that the product is the same as the major product obtained from the addition of propynyllithium to the aldehyde **18**: ^1H NMR 0.11 (s, 3 H), 0.14 (s, 3 H), 0.90 (s, 9 H), 1.36 (s, 3 H), 1.51 (s, 3 H), 1.81 (d, J = 2 Hz, 3 H), 4.15 (t, J = 6 Hz, 1 H), 4.28 (dq, J = 6 Hz, 2 Hz, 1 H), 4.60 (t, J = 7 Hz, 1 H), 5.24 (dm, J = 9 Hz, 1 H), 5.34 (dm, J = 16 Hz, 1 H), 6.06 (ddd, J = 16 Hz, 9 Hz, 7 Hz, 1 H).

Starting from a mixture of alcohols identical procedure yielded a mixture of enynes **20a** and **20b**.

Preparation of (5*S*,6*S*)-5,6-*O*-isopropylidene-oct-7-ene-2-yn-4-one (21) by Swern Oxidation of 19a/19b. A 50-mL, three-necked flask fitted with a magnetic stirrer, dropping funnel, and thermocouple was flame dried and was charged with 1.35 mL (19 mmol) of distilled DMSO and 15 mL of dry methylene chloride. The dropping funnel was charged with 1.34 mL (9.51 mmol) of distilled trifluoroacetic anhydride in 5 mL of methylene chloride. The contents of the flask were cooled to −78 °C, and the TFAA was dripped in. At the end of the addition the dropping funnel was washed with 5 mL more methylene chloride. The mixture was stirred for 10 min, and 612 mg (3.17 mmol) of the alcohol mixture in 10 mL of CH_2Cl_2 was added dropwise at −78 °C. Stirring was continued at −78 to −40 °C for 1 h and 2.20 mL (12.68 mmol) of diisopropylethylamine was added slowly at −78 °C. The cold bath was removed, and the solution was warmed to room temperature. Saturated sodium bicarbonate (40 mL) was added, and the product was extracted into methylene chloride. The combined methylene chloride layer was washed with NaH_2PO_4, dried, and concentrated. Column chromatography on silica using 30% ethyl acetate/hexane as solvent gave pure **21** (yield 96%): IR (neat 3080, 2990, 2940, 2210, 1685, 1670, 1090, 1380, 1375 cm^{-1}; ^1H NMR δ 1.41 (s, 3 H), 1.66 (s, 3 H), 2.05 (s, 3 H), 4.61 (t, J = 8 Hz, 1 H), 4.86 (t, J = 8 Hz, 1 H), 5.30 (dt, J = 10 Hz, 1 Hz, 1 H), 5.43 (dt, J = 17 Hz, 1 Hz, 1 H), 5.79 (ddd, J = 17 Hz, 10 Hz, 8 Hz, 1 H); HRMS 194.0939 (M^+; calcd for $C_{11}H_{14}O_3$ 194.0943).

***R*-Alpine-Borane Reduction of 21.** A solution of 852 mg (4.39 mmol) of the ketone **21** in 10 mL of THF was treated with 18 mL of a 0.5 M solution of *R*-alpine-borane (Aldrich). The mixture was stirred in a stoppered flask for 4 days. Excess acetaldehyde (0.8 mL) was added, and stirring was continued for 15 min. The low boiling solvents were removed on the rotary evaporator, and the residue was dissolved in 40 mL of ether. The solution was cooled to −10 °C, and 0.66 mL of ethanolamine was added, and the mixture was stirred at 0 °C for 10 min. The solid was filtered with the aid of Celite, and the Celite bed was washed with 10 mL of ice-cold ether. The organic layer was washed with saturated sodium chloride and then concentrated. The product, **19a**, was isolated by column chromatography using 20–30% ethyl acetate/hexane as the solvent: yield 794 mg (93%). GLC indicated complete absence of the isomeric alcohol **19b**. **19a**: ^1H NMR δ 1.41 (s, 3 H), 1.52 (s, 3 H), 1.82 (d, J = 2 Hz, 3 H), 2.41 (d, J = 5 Hz, 1 H), 4.20 (dd, J = 10 Hz, 7 Hz, 1 H, H5), 4.25 (m, 1 H, H4), 4.68 (t, J = 7 Hz, 1 H, H6), 5.30 (dm, J = 10 Hz, 1 H), 5.40 (dm, J = 17 Hz, 1 H), 5.99 (ddd, J = 17 Hz, 10 Hz, 7 Hz, 1 H); HRMS 181.0858 ($M^+ - CH_3$; calcd for $C_{10}H_{13}O_3$ 181.0864).

***S*-Alpine-Borane Reduction of 21.** The above experiment was repeated with *S*-alpine-borane as reducing agent. The resulting product(s) were identified as a mixture of isomeric alcohols **19a** and **19b** now obtained in a ratio of 40:60 as judged by GLC. The latter peak was identified as the same product obtained by the *R*-alpine-borane reduction.

Cyclization of (4*S*5*R*,5*R*6*S*)-4-(Dimethyl-*tert*-butylsiloxy)-5,6-*O*-isopropylideneoct-7-en-2-yne (20a). (a) Zirconium-Mediated Cyclization. A mixture of magnesium turnings (0.32 g, 13 mmol) and mercury(II) chloride (0.36 g, 1.3 mmol) in THF (15 mL) was stirred for 15 min. A solution of bis(cyclopentadienyl)zirconium dichloride (0.71 g, 2.43 mmol) and **20a** (160 mg, 0.52 mmol) in THF (20 mL) was added dropwise. After the mixture was stirred overnight, unreacted magnesium was filtered off under N_2, and the mixture was quenched with 10% sulfuric acid (30 mL). The mixture was extracted with ether (2 × 25 mL), washed with sodium bicarbonate (25 mL), and dried ($MgSO_4$), and the solvent was removed at reduced pressure. Flash chromatography (95:5 hexane/ethyl acetate) afforded the product (114 mg, 71%) as a 92:8 mixture of **22a** and **23a** by GLC.

(b) Titanium-Mediated Cyclization. To a mixture of bis(cyclopentadienyl)titanium dichloride (0.32 g, 1.29 mmol) and methyldiphenylphosphine (0.31 g, 1.55 mmol) in THF (25 mL) at −40 °C was added 0.5% sodium amalgam (15 g, 3.26 mmol). The solution was allowed to warm to −25 °C where it was maintained for 15 min. A solution of **20a** (310 mg, 1.0 mmol) in THF (15 mL) was added dropwise, and stirring was continued for 3 h at −25 °C. The mixture was quenched with 10% sulfuric acid (20 mL) and was extracted with ether (2 × 25 mL). The ether extracts were washed with saturated sodium bicarbonate (50 mL) and dried ($MgSO_4$), and the solvent was removed at reduced pressure. Flash chromatography (95:5 hexane/ethyl acetate) afforded the product (98 mg, 32%) as a 2:1 mixture of **22a** and **23a** by ^1H NMR.

Cyclization of Mixed (4*S*5*R*,5*R*6*S*) and (4*R*5*R*,5*R*6*S*) of 4-(Dimethyl-*tert*-butylsiloxy)-5,6-*O*-isopropylideneoct-7-en-2-yne: Preparation of [(3a*S*)-(3aα,4β,6β,6aα)]Tetrahydro-4-(*tert*-butyldimethylsiloxy)-2,2-dimethyl-5-(*Z*)-ethylidene-6-methylcyclopenta-1,3-dioxole (22a). A mixture of **20a** and **20b** (ratio 74/26 by GLC) was subjected to the reaction conditions described above to get a mixture of three compounds. Chromatography on silica gel with ethyl acetate/hexane as solvent system gave two fractions. The first fraction consisted of two compounds roughly in a ratio of 15:2. These were identified as products **22a** and **23a** arising from the cyclization of the major isomer **20a** by comparison of ^1H NMR and GLC with the authentic samples derived from the cyclization of isomerically pure starting enyne (vide supra). The second fraction was a homogeneous compound identified as arising from the minor enyne **20b** via cyclization. The structure **24a** was assigned to this product based on its ^1H NMR and further transformation described below. The separation among **22a**, **23a**, and **24a** is easier upon desilylation. The ratio of **24a**:**22a** + **23a** is, within experimental error, the same as the isomer ratio of the starting material. The overall yield from the acyclic starting material to the desilylated product was 60–65% in several runs. ^1H NMR data for **22a**, **23a**, and **24a** are in Table II.

Ti-Mediated Reactions. Under conditions described earlier, the cyclization of a mixture of enynes (72/28) gave only a 29% yield of the products **22a**, **23a**, and **24a**. The most significant difference from the Zr-mediated reaction is the relative amounts of **22a** and **23a** formed under these reaction conditions. Analysis of the crude ^1H NMR indicates that the ratio of **22a** to **23a** is now in the range of 2:1. Analysis of the desilylated materials also indicated the presence of the expected product **24a** derived from the minor isomer **20b**.

Desilylation of the Cyclization Products 22a, 23a, and 24a. Extensive analysis of the structure and relative amounts of the various products were carried out after desilylation of the cyclization products. The following products were obtained by desilylation of the cyclized materials by tetrabutylammonium fluoride.

22b: ^1H NMR (see Table II) ^{13}C NMR 14.41, 20.98, 24.84, 26.95, 45.86, 75.50, 86.02, 87.33, 110.05, 123.79, 146.75; HRMS 183.1038 ($M^+ - CH_3$; calcd for $C_{10}H_{15}O_3$ 183.1022).

23b: ^1H NMR (see Table II) ^{13}C NMR 10.51, 14.13, 24.73, 26.51, 39.45, 74.58, 81.96, 85.44, 110.06, 120.77, 145.00.

24b: ^1H NMR (see Table II) ^{13}C NMR 13.83, 16.73, 25.10, 26.61, 41996, 68.40, 78.82, 86.03, 112.83, 121.98, 145.50; FABMS 199.40 (M + H; calcd for $C_{11}H_{18}O_3$(M) 198.13).

Ir^+-Catalyzed Reductions of Cyclization Products 22b and 23b. To a solution of 50 mg of the allyl alcohol **22b** in 3 mL of methylene chloride was added 3 mg of $[Ir(COD)(Cy_3P)Py]^+PF_6^-$, and the solution was vigorously stirred under hydrogen in a balloon. After the starting material had disappeared (as judged by TLC; 20% ethyl acetate/hexanes), the solvent was removed, and the product **25** was isolated by preparative TLC and identified by ^1H and ^{13}C NMR and HRMS. Compound **26** was similarly prepared in near quantitative yields from **23b**.

25: ^1H NMR δ 0.95 (t, J = 7 Hz, 3 H), 1.10 (d, J = 6 Hz, 3 H), 1.30 (s, 3 H), 1.50 (s, 3 H), 1.45–1.60 (m, 4 H), 2.20 (s, br, 1 H), 3.85 (ddm, J = 4 Hz, 3 Hz, 1 H), 4.16 (dd, J = 8 Hz, 6 Hz, 1 H), 4.37 (dd, J = 8 Hz, 4 Hz, 1 H); ^{13}C NMR δ 10.54, 17.37, 22.66, 24.95, 27.23, 41.90, 53.05, 80.90, 85.20, 86.65, 112.42; FABMS 201.38 (M + H; calcd for $C_{11}H_{20}O_3$(M) 200.14).

26: ^1H NMR δ 0.94 (t, J = 8 Hz, 3 H), 1.00 (d, J = 7 Hz, 3 H), 1.30 (s, 3 H), 1.45 (s, 3 H), 1.40–1.70 (m, 4 H), 2.42 (m, 1 H), 4.04 (d, br, J = 3 Hz, 1 H), 4.40 (d, br, 1 H), 4.60 (t, J = 6 Hz, 1 H); ^{13}C NMR δ 9.83, 13.14, 20.12, 23.74, 25.72, 37.46, 52.84, 79.08, 81.96, 87.48, 111.01.