17d: mp 243 °C; MS, *m/e* (relative intensity) 337 (M^+, 2), 209 (90), 208 (100), 194 (21); ^1H NMR ($CDCl_3$) δ 2.28 (3 H, s), 4.31 (2 H, s), 7.40-7.80 (10 H, m).

Anal. Calcd for $C_{21}H_{15}N_5$: C, 74.76; H, 4.48; N, 20.76. Found: C, 75.14; H, 4.61; N, 20.83.

18d: ^1H NMR ($CDCl_3$) δ 2.31 (3 H, s), 5.22 (2 H, s), 7.40-7.80 (10 H, m).

Oxygenations and the [3 + 2] Cycloadditions of 1 and 6 in the Dark. The same oxygen-saturated solution exactly as described for the irradiation was stirred in the dark at room temperature. **1d** and **1e** were not oxygenated in acetonitrile and quantitatively recovered.

Tris(*p*-bromophenyl)aminium Hexachloroantimonate Catalyzed Oxygenations of 1a-1c and 6a-6e. A solution of **1** or **6** (0.1 mmol) and antimonate (0.025 mmol) in 3 mL of oxygen-saturated nitromethane was stirred at room temperature in the dark. **2a**, **2b**, and **2c** were isolated in 49%, 26%, and 71% yields, respectively, after 2 h of stirring. **7a-7e** were similarly isolated in 91%, 88%, 77%, 91%, and 22% yields, respectively, after 5 h of stirring in the dark.

Quenching Experiments. A solution of EDA complex with TCNE was irradiated or stirred in the dark in the presence of a quencher such as TMB or AN as described before. Neither cis-trans isomerization nor oxygenation of **8** was observed when a solution of **8** (0.10 mmol), TCNE (0.10 mmol), and TMB (0.10 mmol) in oxygen-saturated dichloromethane or nitromethane (3 mL) was irradiated for 3 h.

Thermal [3 + 2] Cycloadditions of 1 with TCNE. A solution of **1** (0.10 mmol) and TCNE (0.12 mmol) in 10 mL of dry toluene was heated under reflux in a nitrogen atmosphere.

Acknowledgment. Support from Kurata Foundation is gratefully acknowledged.

Registry No. 1a·TCNE, 107245-62-5; **1b**·TCNE, 107245-63-6; **1c**·TCNE, 107245-64-7; **1d**·TCNE, 107245-65-8; **1e**·TCNE, 107245-66-9; **2b**, 101810-64-4; **4a**, 107245-87-4; **4b**, 101810-66-6; **4c**, 101810-67-7; **4e**, 107245-88-5; **5a**, 101810-68-8; **5b**, 101810-69-9; **5c**, 101810-70-2; **5e**, 107245-89-6; **6a**·TCNE, 107245-67-0; **6b**-TCNE, 107245-69-2; **6c**·TCNE, 107245-70-5; **6d**·TCNE, 107269-61-4; **6e**·TCNE, 107245-72-7; **6f**·TCNE, 107245-73-8; **7a**, 107245-90-9; **7b**, 107299-76-3; **7c**, 107245-91-0; **7d**, 107245-92-1; **7e**, 107245-93-2; *trans*-**12a**·TCNE, 107245-74-9; *trans*-**12b**·TCNE, 107245-75-0; *cis*-**12c**·TCNE, 107245-76-1; *trans*-**12d**·TCNE, 107245-78-3; *trans*-**12e**·TCNE, 107245-79-4; *trans*-**12f**·TCNE, 107245-80-7; *trans*-**12g**·TCNE, 107245-81-8; *trans*-**12h**·TCNE, 107245-82-9; **13d**, 107245-94-3; **13f**, 107245-95-4; **13g**, 107245-96-5; **14a**, 107245-97-6; **14b**, 107245-99-8; **14c**, 107246-01-5; **14d**, 107246-03-7; **14g**, 107246-09-3; **14h**, 107246-11-7; **15a**, 107245-98-7; **15b**, 107246-00-4; **15c**, 107246-02-6; **15d**, 107246-08-2; **15g**, 107246-10-6; **15h**, 107246-12-8; *trans*-**16a**·TCNE, 107245-83-0; *cis*-**16b**·TCNE, 107245-84-1; *cis*-**16c**·TCNE, 107245-85-2; *cis*-**16d**·TCNE, 107245-86-3; **17a**, 107246-13-9; **17c**, 107246-05-9; **17d**, 107246-06-0; **18a**, 107246-04-8; **18c**, 107269-62-5; **18d**, 107246-07-1; tris(*p*-bromophenyl)aminium hexachloroantimonate, 40927-19-3; TMB, 95-93-2.

Cyclization of Diacetylenes to *E,E* Exocyclic Dienes. Complementary Procedures Based on Titanium and Zirconium Reagents†

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Abstract: The intramolecular cyclization of diacetylenes has been achieved by using either of the reagent combinations $Cp_2TiCl_2/PMePh_2/Na(Hg)$ or $Cp_2ZrCl_2/Mg/HgCl_2$ in solvent tetrahydrofuran. The procedures are compatible with a variety of saturated functionality (O, N, Si), and in each case, acid hydrolysis of the initially formed organometallic intermediate affords exclusively the *E,E* exocyclic diene. For synthesis of simple five- and six-membered-ring dienes, especially on a multigram scale, the titanium procedure is superior. The zirconium procedure is preferred for preparation of dienes containing bulky substituents or a four- or seven-membered ring. The mechanism of these transformations has been probed by extended Hückel molecular orbital calculations and X-ray crystal structures of the metallacyclic intermediates. The extreme facility of the cyclization is traced to the electronic structure of the intermediate d^2 acetylene complexes.

The selective formation of carbon-carbon bonds is frequently the most demanding step in organic synthesis. It is therefore not surprising that there is intense current interest in the development of new methodology in which the selectivity of C-C bond formation is controlled by a transition-metal template.[1] Although there are important exceptions, the substrates for such transition-metal-mediated reactions are typically organic molecules containing carbon-carbon unsaturations (e.g., alkenes, alkynes, arenes) rather than the carbonyl derivatives which serve as the basic building blocks of conventional synthesis. This represents both an advantage and a disadvantage to the synthesis chemist: On the one hand, such molecules (especially acetylenes) are readily prepared by simple, high-yield reactions. They are stable toward many reaction conditions (base, nucleophiles, reductions) required to assemble other portions of a complex organic molecule. On the other hand, with such molecules lacking the intrinsic polarization of carbonyl derivatives, the control of regiochemistry can be problematic.

This difficulty applies to the "oxidative coupling" reaction (eq 1) which has been observed by several workers[2] upon treating diphenylacetylene with various titanocene or zirconocene precursors. Notable among these procedures in terms of operational simplicity is that of Farona[2a] in which the source of the zirconocene equivalent consists of a mixture of commercially available bis(cyclopentadienyl)zirconium dichloride and magnesium turnings.[3] Cleaving the resultant metallacycle with acid releases exclusively

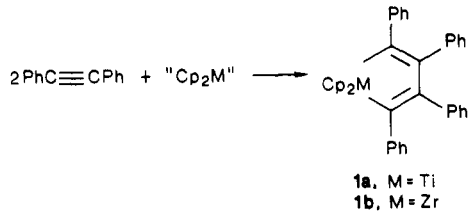
† Dedicated to Professor J. K. Kochi on the occasion of his 60th birthday.

(1) Pearson, A. J. *Metallo-organic Chemistry*; Wiley: Chichester, 1985. Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. *New Pathways for Organic Synthesis*; Plenum: New York, 1984.

(2) (a) Famili, A.; Farona, M. F.; Thanedar, S. *J. Chem. Soc., Chem. Commun.* **1983**, 435-436. (b) Shur, V. B.; Berkovich, E. G.; Vol'pin, M. E.; Lorenze, B.; Wahren, M. *J. Organomet. Chem.* **1982**, *228*, C36-C38. (c) Skibbe, V.; Erker, G. *Ibid.* **1983**, *241*, 15-26. (d) Yoshifuji, M.; Gell, K. I.; Schwartz, J. *Ibid.* **1978**, *153*, C15-C18. (e) Fachinetti, G.; Floriani, C. *J. Chem. Soc., Chem. Commun.* **1974**, 66-67. See also: Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568-2569.

(3) Another convenient zirconocene source for cyclic carbometallation reactions has recently been described: Negishi, E.; Cederbaum, F. E.; Tamotsu, T. *Tetrahedron Lett.* **1986**, *27*, 2829-2832.

0002-7863/87/1509-2788$01.50/0



(1)

1a, M = Ti
1b, M = Zr

the *E,E* isomer of 1,2,3,4-tetraphenylbutadiene. However, unsymmetrical acetylenes RC≡CR′ would presumably afford a mixture of three regioisomeric products; consequently, this system has been applied only to symmetrical acetylenes.

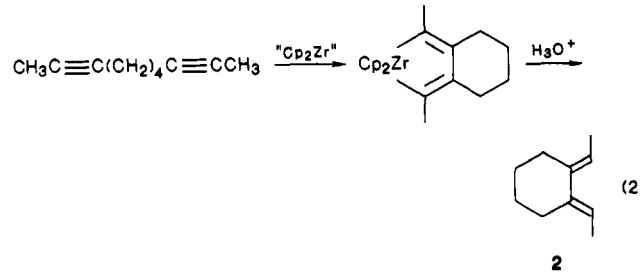
It occurred to us that the regiochemical problem could be circumvented when such a system was applied to the intramolecular cyclization of diacetylene. An ample precedent for this approach is found in the elegant studies of Vollhardt on the cobalt-catalyzed cyclotrimerization of acetylenes.[4] The regioselective cyclization of diacetylenes is a desirable goal since the products should be highly reactive in the Diels–Alder reaction, allowing their rapid, stereocontrolled elaboration into polycyclic structures. Moreover, the selective synthesis of these compounds has never been achieved by using conventional methodology.[5]

We have now demonstrated the viability of this approach. Initially the Farona system was adopted as the metallocene component in our studies, but we have subsequently developed a titanocene-based reagent which provides higher yields with many simple substrates.[6] The greater steric congestion of the titanium reagent has also proven advantageous for controlling diastereoselectivity in the cyclization of enynes, which we will report elsewhere.[7] In the current paper, we will describe the scope, limitations, and some mechanistic studies for these Ti- and Zr-mediated cyclizations of diynes. A noteworthy aspect of these studies is the sometimes striking differences in selectivity which are observed in comparing these nominally isoelectronic reagents which in principle differ only in the size of the transition-metal atom.

Results and Discussion

Development of Reagents. The procedure initially adopted was essentially that used by Farona[3a] for the intermolecular dimerization of symmetrical monoacetylenes. An excess of magnesium turnings in tetrahydrofuran was activated with mercuric chloride. A THF solution of 2,8-decadiyne and a 20% excess of bis(cyclopentadienyl)zirconium dichloride were added, and the mixture was stirred overnight at room temperature. When the mixture was quenched with 10% aqueous sulfuric acid, (*E,E*)-bis(ethylidene)cyclohexane (**2**) was produced in 70–72% yield (eq 2). The alternative *E,Z* product stereochemistry was ruled out on the basis of ^1H and ^{13}C NMR spectra. Exclusive formation of the *Z,Z* diene seemed unlikely given the strained nature of the product and the structure of the metallacyclic intermediate and now has been ruled out by the X-ray crystal structure of the Diels–Alder adduct of **2** with *N*-phenylmaleimide.[6]

Upon distillation of the product we noted that the pot residue consisted chiefly of oligomeric materials derived from the 2,8-decadiyne starting material. This suggested that the principal yield loss was due to a competing intermolecular C–C bond-forming process. It therefore appeared potentially advantageous to develop an alternative reagent which would permit the slow addition of the substrate to an excess of a prereduced metallocene equivalent.

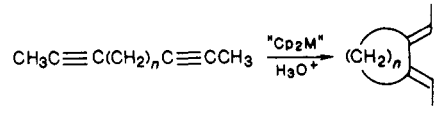


(2)

2

As the simplest approach to a prereduced titanocene reagent, we attempted reduction of bis(cyclopentadienyl)titanium dichloride in THF with sodium amalgam at −20 °C. However, dropwise addition of 2,8-decadiyne and an acid quench produced only small amounts of **2**. This was not unexpected in view of the known tendency of titanocene to decompose via intermolecular C–H insertion processes.[8] Accordingly, we modified the system to incorporate a donor phosphine ligand. Methyldiphenylphosphine appears to possess the ideal balance of steric and electronic properties in this regard. Dropwise addition of 2,8-decadiyne to a mixture of Cp_2TiCl_2, $PMePh_2$, and Na amalgam in an approximately 1:1:2 ratio at −20 °C afforded **2** in excellent yield (89% GLC, 76–80% isolated and distilled). In contrast, reaction was extremely slow with the more basic tributylphosphine while low yields, presumably reflecting reagent decomposition, were observed with the less basic and bulkier triphenylphosphine.

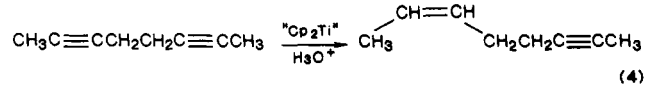
Scope and Limitations. We next compared the yields of cyclized products from these procedures as a function of ring size, substitution, and changes in functional groups under a set of standard conditions which had been optimized for the cyclization of 2,8-decadiyne. In the first of these studies, the terminal substituents on the diyne starting material were held constant as methyl groups while the number of methylene units in the carbon "spacer" was varied from 2 to 6 (eq 3). The results are reported in terms of



(3)

ring size ($n + 2$) in Table I. It is seen that, while the Ti-mediated cyclization is superior for the preparation of simple five- and six-membered-ring derivatives, the Zr-based reagent is better for seven-membered rings. Both cyclizations fail with eight-membered rings.

Most striking are the results for the case of the four-membered-ring compound. In this case the Zr-mediated cyclization affords the highest yield (89%) observed for any ring size while the Ti procedure fails completely. The discovery of this general route to cyclobutane derivatives **3** is of considerable synthetic interest. Although no general route to these compounds has previously been available, it has been demonstrated that such dienes, by virtue of their ability to add 2 equiv of dienophile in consecutive Diels–Alder reactions, are useful chemical "lynchpins", for example, in the construction of "ladder polymers".[9,10] Also noteworthy is the manner in which the Ti cyclization fails. Rather than affording the oligomer via intermolecular C–C bond formation, it apparently affords the corresponding *cis*-enyne according to eq 4. In support of eq 4 we have isolated the product from



(4)

(4) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–644. To our knowledge, this procedure has not been successfully applied to the synthesis of exocyclic dienes.

(5) The synthesis and Diels–Alder chemistry of the parent 1,2-dimethylenecycloalkanes are well-known: Bailey, W. J.; Golden, H. R. *J. Am. Chem. Soc.* **1953**, *75*, 4780–4782. Bailey, W. J.; Sorenson, W. R. *Ibid.* **1954**, *76*, 5421–5423. Van Straten, J. W.; Van Norden, J. J.; Van Schaik, T. A. M.; Franke, G. T.; De Wolf, W. H.; Bickelhaupt, F. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 105–106.

(6) A preliminary account of our titanium studies has appeared: Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422–6444.

(7) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F., manuscript in preparation.

(8) Wailes, P. C.; Coutts, R. S. P.; Weigold, H. *Organometallic Chemistry of Titanium, Zirconium and Hafnium*; Academic: New York, 1974; pp 229–237.

(9) Bailey, W. J. *Kinet. Mech. Polym.* **1972**, *3*, 279–232. See especially p 322.

(10) Minami, T.; Taniguchi, Y.; Hirao, I. *J. Chem. Soc., Chem. Commun.* **1984**, 1046–1047.

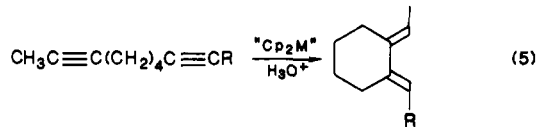
Table I. Effect of Ring Size on Yield of Bis(ethylidene)cycloalkanes via Equation 3

ring size[a]	% yield (Ti)[b]	% yield (Zr)[c]
4	0[d]	89
5	78	70
6	89	71
7	24	45
8	0	<2

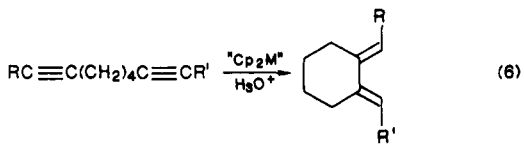
[a] Corresponds to $(n + 2)$ in eq 3. [b] GLC yield after 3 h at −20 °C; see Experimental Section. [c] GLC yield after 24 h at 25 °C; see Experimental Section. [d] (*Z*)-Oct-2-en-6-yne was formed in ca. 70% yield.

the attempted Ti-mediated cyclization of 5,9-tetradecadiyne and have shown it to be (5*Z*)-en-9-yne (see Experimental Section). This suggests that a titanium(II) acetylene complex is being formed (vide infra) but that the system is unable to "snap shut" to a metallacyclopentadiene structure.

For the experiments summarized in Table II, the carbon spacer in the diacetylene starting material was held constant at four methylene units while one (eq 5) or both (eq 6) of the terminal groups R and R′ were varied along the series methyl, ethyl, isopropyl, and *tert*-butyl.



(5)

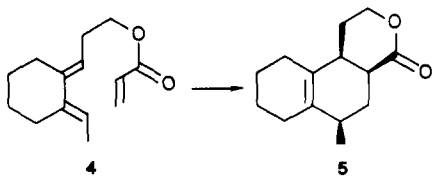


(6)

Particularly for the disubstituted derivatives, the yield from the Ti-mediated cyclization is seen to fall off sharply with increasing substitution.[11] In contrast, yields from zirconium show little variation in the disubstituted series. The somewhat more pronounced effect of a single *tert*-butyl substituent is not surprising since very dissimilar groups on the end of the diacetylene should favor intermolecular coupling of the less encumbered ends.

Finally, to probe the compatibility of this methodology with functional groups relevant to organic synthesis, we examined the cyclization of several heteroatom-containing diynes as summarized in Table III. It is seen that a variety of saturated oxygen, nitrogen, and silicon functionality can be accommodated by one or both of the reagents. In particular, an ether oxygen atom can be present as an exocyclic, endocyclic, vinylic, or side-chain substituent.

Of especial interest is the cyclization of 3,9-undecadiyn-1-ol (first entry, Table III) in that the product provides a simple entry to tricyclic structures via the intramolecular Diels–Alder reactions (e.g., eq 7). The analogous cyclization of *o*-xylylene derivatives



(7)

4 5

has proven broadly useful in the synthesis of steroids containing an aromatic A ring.[12] An unusual feature of the xylylene cyclizations is the fact that they often proceed with exo stereochemistry in apparent defiance of the Alder rules.[13] We felt it would be of interest to determine whether this unusual stereochemistry would also be observed with our simple exocyclic dienes as substrates. We therefore prepared **4** by straightforward esterification of the alcohol. Heating **4** (0.5% in toluene, reflux, 24 h) produced **5** in 65% yield, the remainder of the product apparently being that derived from an intermolecular Diels–Alder reaction of 2 equiv of **4**. The X-ray crystal structure of **5** (Figure 1) clearly shows it to be the product of normal endo cycloaddition. This then represents a revision of the tentative structure which we suggested earlier[6] based on NMR data.

Table II. Effect of Alkyl Substituents on Yield of Bis(alkylidene)cyclohexanes via Equation 5 or 6

R	R′	% yield (Ti)[a]	% yield (Zr)[b]
methyl	methyl	89	71
ethyl	ethyl	83	77
isopropyl	isopropyl	16	67
tert-butyl	*tert*-butyl	0[c]	65
methyl	isopropyl	56	69
methyl	*tert*-butyl	31	49

[a] GLC yield after 3 h at −20 °C; see Experimental Section. [b] GLC yield after 24 h at 25 °C; see Experimental Section. [c] Recovered 48% of unreacted starting material.

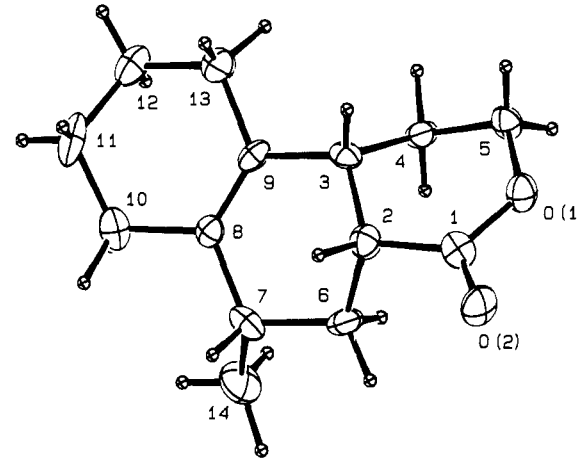


Figure 1. Structure of compound **5**.

One limitation on the use of these reagents is their anticipated incompatibility with unsaturated functionality such as nitrile and carbonyl groups. Preliminary experiments in which we have attempted to incorporate such functionality have been unsuccessful.[14] An additional limitation is the fact that terminal acetylenes cannot be cyclized with either reagent. This undoubtedly reflects the ready oxidative addition of the electron-rich metallocene to the acidic acetylenic hydrogen. This is a not a significant problem in terms of synthetic applications since silyl acetylenes can be cyclized and the silicon removed in a subsequent step.

Organometallic Intermediates. It seems certain that the cyclization reactions reported here proceed through the initial formation of an η^2-acetylene complex. Numerous examples of the formation of such species upon reduction of metallocene dihalides in the presence of monoacetylenes have been reported.[15] The eventual formation of a metallacyclopentadiene structure likewise seems secure. Hydrolysis of the organometallic intermediates from either the Ti- or the Zr-mediated cyclization of 2,8-decadiyne with 20% D_2SO_4/D_2O in each case affords **2** which is >90% dideuteriated in the vinylic position. Moreover, in several

(11) In the Ti-mediated cyclization where R = R′ = isopropyl most of the starting material is apparently converted to oligomeric side products. In contrast, when R = R′ = *tert*-butyl even the intermolecular reaction appears to be retarded. Thus the observed products are recovered starting material (48%) and a second C_{16} product tentatively identified as the *cis*-enyne (40%).

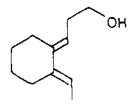
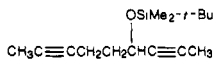
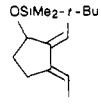
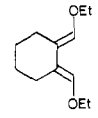
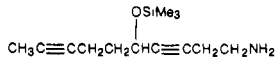
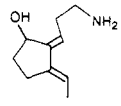
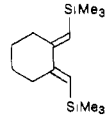
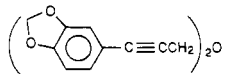
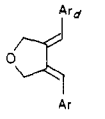
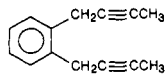
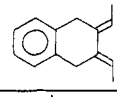
(12) Taub, D. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1984; Vol. 6, pp 16–37. Analogy can also be made to the intramolecular Diels–Alder reactions of acyclic precursors. Examples of both endo and exo addition are known: Taber, D. F. *Intramolecular Diels–Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 184. Ciganek, E. *Org. React. (N.Y.)* **1984**, *32*, 1–374.

(13) Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510–519.

(14) Substrates containing unsaturated functionality which we examined were 1-cyano-4-heptyne, 1-cyano-5-heptyne, and methyl-3-butynyl carbonate.

(15) See, for example: Shur, V. B.; Burlakov, V. V.; Yanovsky, A. I.; Petrovsky, P. V.; Struchkov, Yu. T.; Vol'pin, M. E. *J. Organomet. Chem.* **1985**, *297*, 51–59. Demerseman, B.; Mahe, R.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1394–1396.

Table III. Effect of Functionality on the Ti- and Zr-Mediated Cyclization of Diacetylenes

reactant	product	compd	% yield (Ti)[a]	% yield (Zr)[b]
$Ch_3C{\equiv}C(CH_2)_4C{\equiv}CCH_2CH_2OSiMe_3$		**10**	79	63
		**11**	19	82
$(CH_3C{\equiv}CCH_2)_2O$		**12**	72	
$(EtOC{\equiv}CCH_2CH_2{-})_2$		**13**	63	<16[c]
		**14**		41
$(Me_3SiC{\equiv}CCH_2CH_2{-})_2$		**15**	0	82
		**16**	67	55[e]
		**17**		60[f]

[a] Isolated yield after 3 h at −20 °C; see Experimental Section. [b] Isolated yield after 24 h at 25 °C (see Experimental Section) unless otherwise indicated. [c] Substantially impure by NMR. [d] Ar = 3,4-(methylenedioxy)phenyl. [e] After 72 h at 40 °C. [f] Contained 10–15% impurities by NMR; characterized as Diels–Alder adduct with naphthoquinone.

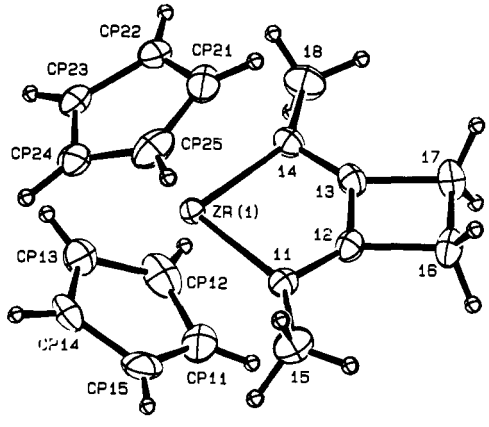
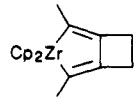
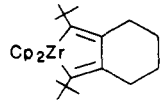


Figure 2. Structure of compound **6**.

cases we have actually isolated and characterized the metallacyclic intermediates from the zirconium-mediated cyclization. We felt that the structures of zirconacycles **6** and **7** were of especial interest since these are cases in which corresponding titanium complexes do not form. The molecular structures of **6** and **7** were therefore determined by X-ray crystallography.



6



7

The structures of these complexes are shown in Figures 2 and 3. The numbering system for compound **7** is shown in Figure

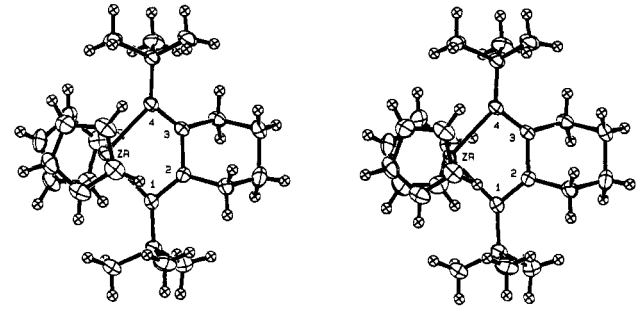


Figure 3. Stereoscopic view of compound **7**.

4. As summarized in Table IV, these compounds exhibit several structural similarities with one another and also with the structure of **1b**, which was previously reported.[16] In all three cases the vinyl C–Zr bond lengths fall in the range 2.20–2.26 Å. The cyclopentadienyl C–Zr bond lengths are likewise similar throughout this series. The constraint imposed by the fused carbocycle results in some necessary widening of the C–Zr–C angle from 77.5 (2)° in **1b** to 92.24 (8)° in **7** and 98.47 (7)° in **6**. Given this widening, the change in the angle between the centroids of the cyclopentadienyl ligands of **6** and **7** (130°) as compared with that in **1b** (134°) is in the expected direction.

In compound **6**, the metal and the diyne-derived carbocylic ligand are completely coplanar, and indeed one can envision the entire coordination and cyclization process as occurring in a single plane. One implication is that, if the failure of the Ti-mediated

(16) Hunter, W. E.; Atwood, J. L.; Fachinetti, G.; Floriani, C. *J. Organomet. Chem.* **1981**, *204*, 67–74.

Table IV. Comparison of the Structure of Three Zirconacyclopentadienes[a]

	1b[b]	6[c]	7
	Distances, Å		
Zr–Cl(α)	2.265 (6)	2.204 (2)	2.210 (2)
Zr–C(α′)	2.250 (5)	2.211 (2)	2.217 (2)
C(α)–C(β)	1.363 (7)	1.330 (3)	1.360 (3)
C(α′)–C(β′)	1.358 (8)	1.324 (3)	1.335 (3)
C(β)–C(β′)	1.500 (7)	1.565 (3)	1.547 (3)
Zr–C(Cp) (avg)	2.52 (2)	2.53 (1)	2.55 (1)
	Angles, deg		
C(α)–Zr–C(α′)	77.5 (2)	98.47 (7)	92.24 (8)
Zr–C(α)–C(β)	111.8 (4)	88.8 (1)	94.9 (1)
Zr–C(α′)–C(β′)	112.0 (4)	88.6 (1)	95.4 (1)
C(α)–C(β)–C(β′)	118.5 (5)	131.9 (2)	125.7 (2)
C(α′)–C(β′)–C(β)	119.4 (5)	132.2 (2)	126.2 (2)
Cp–Zr–Cp (centroids)	134.3	130.5	130.0

[a] C(α) and C(α′) are the zirconium-bound carbon atoms of the zirconacyclopentadiene ring. C(β) and C(β′) are the other ring carbon atoms. [b] From ref 16. [c] Data are for one of two inequivalent molecules in the asymmetric unit.

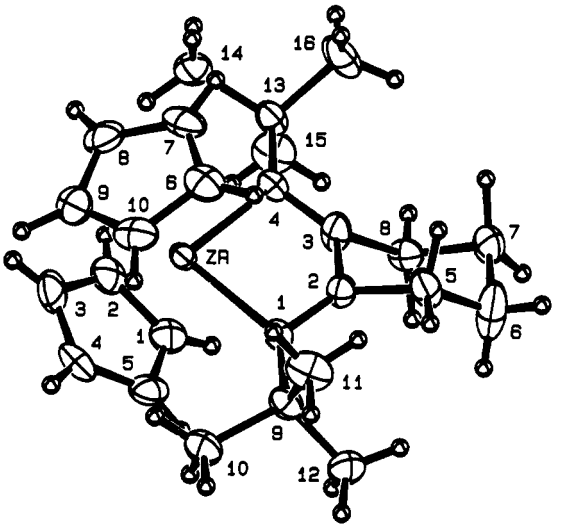


Figure 4. Alternative view of **7** showing the numbering system.

cyclization of 2,6-octadiyne is ascribed to steric problems, any prohibitive interaction must occur at the rear of the cavity between the cyclopentadienyl ligands. However, another factor must be considered. The Zr–C(1)–C(2) angle of 89° is indicative of considerable strain at this sp^2 center. Moreover, by using the Ti–C bond length data for compound **1a**[17] we can predict that this angle would be further constricted to ca. 85° in the titanium analogue of **6**. Thus, the considerably greater reducing power of Zr(II) vs. Ti(II) may be critical in overcoming the significant strain energy involved in this cyclization.

The structure of **7** is somewhat complicated by disorder at C(7) and C(8) as the cyclohexyl ring flips between two nearly equivalent twist-boat conformations. Nevertheless, it can be clearly seen that the "cog wheels" of the *tert*-butyl groups can be rotated in the zirconium complex such that the shortest H(methyl)–H(cyclopentadienyl) distances are 2.26 and 2.34 Å, well beyond the sum of the van der Waals radii of approximately 2.0 Å. A further indication of the lack of steric constraints in the zirconium series is the observation that 4,4-dimethyl-2-pentyne was exclusively cyclized to **8** with none of the regioisomer **9** being detected.

8 **9**

(17) Atwood, J. L.; Hunter, W. E.; Alt, H.; Rausch, M. D. *J. Am. Chem. Soc.* **1976**, *98*, 2454–2459.

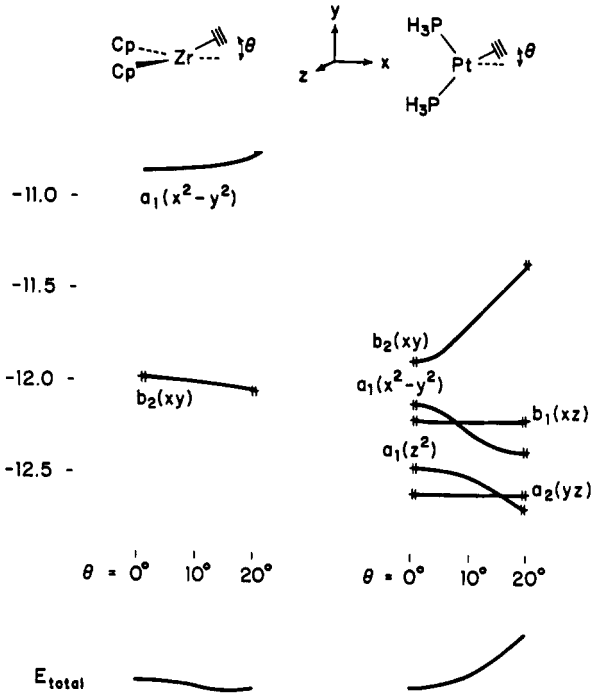


Figure 5. Walsh diagram for moving the acetylene off the symmetry axis, for Cp_2Zr(acetylene) [left] and $Pt(PH_3)_2$(acetylene) [right]. Orbitals are labeled according to their symmetries in C_{2v} (θ = 0°) and their dominant d-orbital components.

Again, we can combine the structural data for **7** with those for **1a** to generate a molecular model for the titanium analogue of **7**. Such a model indicates that the shortest H(methyl)–H(cyclopentadienyl) distance would be 2.08 Å, still somewhat beyond the van der Waals radii. However, it must be noted that steric buttressing between the Ti-coordinated diyne and the cyclopentadienyl ligands is expected to be considerably more pronounced in the transition state for C–C bond formation. This will reflect both the lesser extent to which the acetylenic moiety is "bent back" (e.g., C(2)–C(1)–C(9) is more nearly linear) and the fact that the *tert*-butyl moiety is thrust further back into the cyclopentadienyl cavity prior to C–C bond formation. On this basis the failure of eq 5 with Ti when R = R′ = *tert*-butyl appears entirely reasonable.

Molecular Orbital Calculations. We have shown that diacetylenes are readily cyclized even at −20 °C with our metallocene reagents. In order to understand the remarkable facility with which these cyclizations occur we have carried out a series of extended Hückel calculations on an appropriate model complex, (acetylene)bis(cyclopentadienyl)zirconium(II).

An initial geometry optimization indicated that, as expected, the acetylene greatly prefers (62 kcal/mol) to be oriented parallel to (rather than perpendicular to) the plane of the cyclopentadienyl ligands. Interestingly, in the optimized geometry, the acetylene ligand is not symmetrically disposed about the central plane of the molecule but rather moves back into the cavity of the cyclopentadienyl ligands. Our calculations indicate that moving the acetylene back 20° in this manner is favorable to the extent of 0.7 kcal/mol. The effect of this distortion on the frontier orbitals of the system is shown in the Walsh diagram, Figure 5. Also in Figure 5 we contrast the situation for a typical group VIII (group 10)[36] acetylene complex, (acetylene)bis(phosphine)platinum(0). In this case moving the acetylene back by 20° is found to be disfavored by 10 kcal/mol.

Much more significant than the calculated energy values, which are approximate at best, is the observation that this distortion entails little or no barrier in the Cp_2Zr system, relative to the much greater barrier in the PtL_2 system. The reason for this difference is evident from Figure 5. In each case the distortion results in second-order Jahn–Teller mixing between a_1 and b_2 levels. But in the platinum case the upper level, initially b_2, is filled, and the

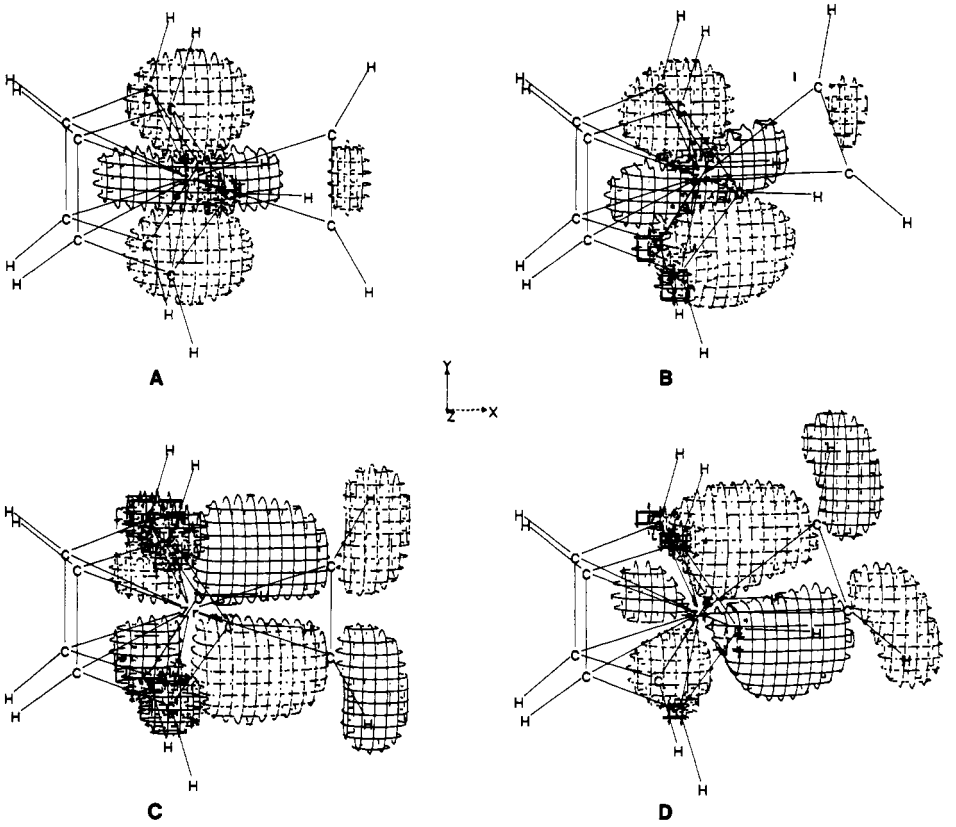


Figure 6. Orbital diagrams showing the LUMO before (A) and after (B) and the HOMO before (C) and after (D) a second-order Jahn–Teller distortion of 20°.

overall effect is to destabilize the complex. In the zirconium case the upper level is empty, resulting in a slight stabilization (at this level of theory).

The effect of this distortion on the reactivity of the complex is best seen in the orbital plots of Figure 6.[18] Moving the acetylene not only provides a site physically capable of binding the second acetylene but also exposes a HOMO and a LUMO which are perfectly suited (π-donor, σ-acceptor) to capture the incoming second acetylene.

Once the second acetylene has entered the coordination sphere the coupling process is symmetry allowed, which can be seen from the schematic orbital correlation diagram (Figure 7). It happens that this correlation scheme is appropriate for the d^4 halo–oxo–bis(acetylene)rhenium compounds of Mayer.[19] Adding two electrons to Figure 7 results in a symmetry-forbidden process for acetylene coupling, consistent with Mayer's observation that the acetylenes do not couple even at elevated temperature. However, this correlation scheme is not appropriate for acetylene coupling in other bis(alkyne)metal complexes, for instance, bis(alkyne)-cyclopentadienylcobalt systems. Correlation diagrams for cobalt-mediated coupling were presented in a earlier study,[20] where the authors showed that acetylene coupling in coplanar geometry is symmetry forbidden and proposed an "upright" geometry for a symmetry-allowed mechanism.

Conclusion

We have described two procedures for the intramolecular cyclization of diacetylenes to *E,E* exocyclic dienes. These procedures have in several instances proven complementary to one another. Several natural products are known which contain the *E,E* exocyclic diene substructure.[21,22] However, we feel that the principal utility of this methodology will be in the synthesis of diene intermediates which can be elaborated into more complex polycyclic structures via the Diels–Alder reaction. In this regard, our studies have demonstrated that these reactions can accommodate a

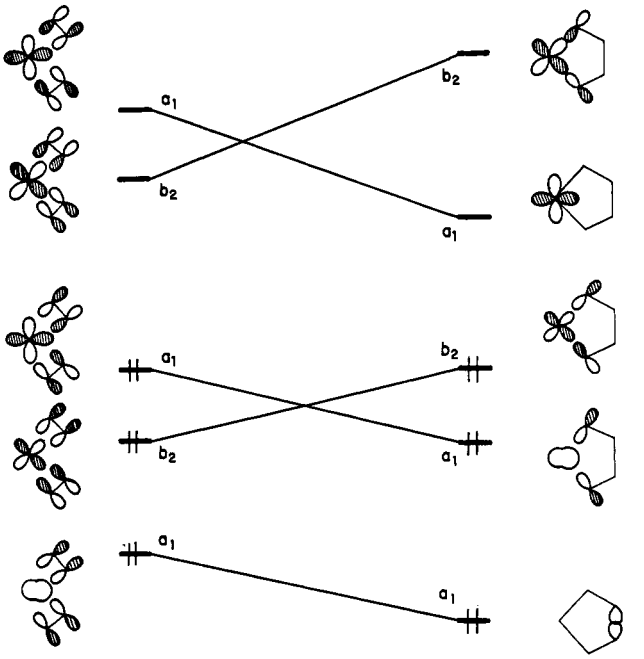


Figure 7. Schematic correlation diagram for coupling two acetylenes on Cp_2Zr. The highest filled orbitals of the bis(acetylene) compound (left) are derived from bonding combinations of the incoming acetylene π-orbital with orbital "B" of Figure 6 and the incoming acetylene π^*-orbital with orbital "D" of Figure 6. The out-of-plane acetylene π-orbitals correlate smoothly with metallacycle π-orbitals and are omitted for clarity.

(18) The importance of "olefin slippage" in promoting *nucleophilic* attack on coordinated olefins has been noted. Eisenstein, O.; Hoffmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4308–4320.

(19) Mayer, J. M.; Thorn, D. L.; Tulip, T. H. *J. Am. Chem. Soc.* **1985**, *107*, 7454–7462.

(20) Wakatsuki, Y.; Nomura, O.; Kitaura, K.; Morokuma, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 1907–1912.

(21) Kozikowski, A. P.; Park, P.-u. *J. Am. Chem. Soc.* **1985**, *107*, 1763–1765.

(22) Swoboda, G. A.; Wang, K.-T.; Weinstein, B. *J. Chem. Soc., Chem. Commun.* **1967**, 161–162.

considerable range of organic substituents and heterofunctionality.

Beyond this, we feel that the theoretical and structural studies reported herein provide a degree of insight into the steric and electronic factors which control the selectivity of these reagents. Hopefully others will now apply more sophisticated techniques such as molecular mechanics to these systems. Meanwhile, the present results have proven immensely valuable in developing the stereoselective cyclization of enynes, which we will report soon.[7]

Experimental Section

General. Most of the diacetylenes used in this study were either commercially available from Farchan Labs, Inc., or were prepared by straightforward displacement reactions described in detail by Brandsma.[23] Two exceptions were the precursors for compounds **14** and **16** that are given below. 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-, 300-, and 360-MHz NMR spectra were determined respectively on an IBM NR80, Varian EM390, General Electric QE300, and a Nicolet NT 360WB 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.[24] Bis(cyclopentadienyl)titanium and -zirconium dichloride (ALFA) and all other materials were reagent grade chemicals used as received.

Typical GLC Run (Ti). A round-bottom 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), 2,8-decadiyne (0.96 g, 7.15 mmol), decane internal standard (0.96 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% aqueous sodium bicarbonate (50 mL). The yield of (*E*,*E*)-1,2-bis(ethylidene)cyclohexane was determined by duplicate GLC injections.

Typical GLC Run (Zr). A round-bottom flask was charged with magnesium turnings (0.91 g, 37 mmol), mercuric chloride (1.03 g, 3.79 mmol), and tetrahydrofuran (50 mL). The mixture was stirred 15 min whereupon a solution of 2,8-decadiyne (0.77 g, 5.74 mmol), decane internal standard (0.77 g), and bis(cyclopentadienyl)zirconium dichloride (2.02 g, 6.91 mmol) in tetrahydrofuran (50 mL) was added rapidly dropwise. The solution was stirred for 24 h and was then decanted from the unreacted magnesium; the reaction was rapidly quenched with 100 mL of 10% H_2SO_4. The mixture was extracted with hexane (3 × 100 mL), and the organic phase was washed with 5% aqueous sodium bicarbonate (50 mL) and dried ($MgSO_4$). The yield of (*E*,*E*)-1,2-bis(ethylidene)cyclohexane was determined by duplicate GLC injections.

6-(Trimethylsiloxy)-10-amino-2,7-decadiyne (Precursor for 14). To a suspension of propynyllithium (12.7 g, 276 mmol) in THF (500 mL) was added 2-(2-bromoethyl)-1,3-dioxolane (25 g, 138 mmol), and the mixture was heated at reflux for 72 h. The reaction was quenched with saturated NH_4Cl (1 L) and extracted with 2 × 250 mL of ether. Most of the solvent was removed in vacuo, and the crude residue was added to 2500 mL of H_2O, acidified with 25 mL of 0.1 M HCl, and heated to reflux for 1 h. Sodium chloride (200 g) was added to the cooled product, which was extracted with 3 × 100 mL of ether, washed with 5% $NaHCO_3$ and H_2O, and dried ($MgSO_4$). After distillation of the solvent, the residue was distilled under N_2 to afford 4-hexynal (6.42 g, 49%, bp 145–149 °C). To a suspension of 4-aminobutyne hydrochloride[25] (1.69 g, 16 mmol) in 75 mL of THF was added 1.6 M butyllithium (20 mL, 32 mmol). A solution of 4-hexynal (1.54 g, 16 mmol) in THF (20 mL) was added dropwise and the mixture stirred overnight. *tert*-Butyldimethylchlorosilane (2.41 g, 16 mmol) was added, and the mixture was stirred for 72 h. The solvent was removed, and the residue was purified by flash chromatography (85% CH_2Cl_2, 13% MeOH, 2% concentrated NH_4OH) to afford a product in cuts 19–27 which was not the silyl ether but 10-amino-2,7-decadiyn-6-ol (0.59 g, 22%): ^1H NMR (80 MHz) δ 1.7–2.0 (m, 5 H), 2.2–2.5 (m, 7 H), 2.81 (t, J = 7 Hz, 2 H), 4.45 (tt, J = 7, 2 Hz, 1 H). Anal. ($C_{10}H_{15}NO$) C, H, N. This material was silylated in situ with (dimethylamino)trimethylsilane prior to cyclization.

3,3′-Bis[3,4-(methylenedioxy)phenyl]propargyl Ether (Precursor for 16). 3,4-(Methylenedioxy)iodobenzene[26] (3.12 g, 12.6 mmol), triethylamine (1.90 g, 18.8 mmol), propargyl alcohol (0.85 g, 15.2 mmol), toluene·(15 mL), (dimethylamino)trimethylsilane (1.78 g, 15.2 mmol), tetrakis(triphenylphosphine)palladium (0.15 g, 0.13 mmol), and copper(I) iodide (0.05 g, 0.26 mmol) were heated for 1 h at 60 °C.[27] The mixture was filtered, the solvent was removed in vacuo, and the residue was stirred overnight in 5% potassium fluoride in methanol (50 mL). To this mixture was added water (200 mL), and the product was extracted with ether (3 × 100 mL). After removal of solvent, flash chromatography (40% ethyl acetate/60% hexane) afforded from cuts 12–24 [3,4-(methylenedioxy)phenyl]propargyl alcohol (1.86 g, 84%) as a yellow solid, mp 75.5–76.0 °C. To this alcohol (9.59 g, 54.4 mmol) in THF (200 mL) was added potassium hydride (2.18 g, 54.3 mmol) a little at a time. Methanesulfonyl chloride (3.12 g, 27.2 mmol) in methylene chloride (25 mL) was added dropwise followed by HMPA (20 mL). After 2 h the mixture was added to half-saturated ammonium chloride (500 mL), extracted with ether (3 × 150 mL), and dried ($MgSO_4$). The solvent was removed and the product was subjected to flash chromatography (hexane) to afford the product in cuts 10–15 whereupon the eluant was changed to ethyl acetate to afford 2.53 g of recovered alcohol. The product was a pale-yellow solid (3.64 g, 54% based on recovered starting material): mp 98–100 °C; ^1H NMR (90 MHz) δ 4.51 (s, 4 H), 5.99 (s, 4 H), 6.6–7.2 (m, 6 H). Anal. ($C_{20}H_{14}O_5$) C, H.

Typical Preparative Run (Ti). (*E*,*E*)-1,2-Bis(ethylidene)cyclohexane. To a stirred suspension of bis(cyclopentadienyl)titanium dichloride (9.3 g, 37.3 mmol) and methyldiphenylphosphine (9.0 g, 45.0 mmol) in THF (400 mL) at −45 °C was added rapidly dropwise 0.5% sodium amalgam (33 mL, 450 g, 97.9 mmol). The temperature was allowed to rise to −25 °C where it was maintained for 15 min. A solution of 2,8-decadiyne (3.9 g, 29.1 mmol) in THF (100 mL) was added dropwise, and the temperature was maintained at −25 °C for another 3 h. The reaction was rapidly[28] quenched with 20% H_2SO_4 (200 mL), the solution was extracted with ether (2 × 250 mL) and dried ($MgSO_4$), and the solvent was removed at reduced pressure. Distillation of the residue afforded the product (3.16 g, 80%) as a colorless liquid: bp 67–69 °C (12 torr); ^1H NMR (360 MHz) δ 1.59 (d, J = 7 Hz, 6 H), 1.59 (m, 4 H), 2.10 (m, 4 H), 5.38 (q, J = 7 Hz, 2 H). Anal. ($C_{10}H_{16}$) C, H. *N*-Phenylmaleimide derivative: mp 138.0–138.5 °C. For some higher boiling products it proved expedient to separate the product from phosphine by flash chromatography prior to distillation.

Typical Preparative Run (Zr). (*E*,*E*)-1,2-Bis[(trimethylsilyl)methylene]cyclohexane (15). A suspension of magnesium turnings (1.61 g, 66.2 mmol) and mercuric chloride (1.82 g, 6.70 mmol) in THF (100 mL) was stirred for 15 min. A solution of bis(cyclopentadienyl)zirconium dichloride (3.57 g, 12.2 mmol) and 1,8-bis(trimethylsilyl)-1,8-octadiyne (2.55 g, 10.2 mmol) in THF (100 mL) was added rapidly dropwise, and the mixture was stirred overnight. The product was decanted from the unreacted magnesium, rapidly quenched with 10% sulfuric acid (100 mL), extracted with hexane (3 × 100 mL), washed with saturated sodium bicarbonate (50 mL), and dried ($MgSO_4$). The solvent was removed at reduced pressure to afford a crude product which was purified by flash chromatography (hexane). The product was obtained from cuts 6–10 as a colorless liquid (2.12 g, 82%): ^1H NMR (90 MHz) δ 0.13 (s, 18 H), 1.65 (m, 4 H), 2.36 (m, 4 H), 5.49 (s, 2 H). Anal. ($C_{14}H_{28}Si_2$) C, H. *N*-Phenylmaleimide derivative: mp 189–190 °C.

In a similar manner we additionally prepared the following:

(*E*,*E*)-1,2-Bis(ethylidene)cyclobutane: ^1H NMR (300 MHz) δ 1.56 (d, J = 7 Hz, 6 H), 2.53 (s, 4 H), 5.50 (q, J = 7 Hz, 2 H). Anal. (C_8H_{12}) C, H.

(*E*,*E*)-1,2-Bis(ethylidene)cyclopentane: ^1H NMR (80 MHz) δ 1.67 (d, J = 7 Hz, 6 H), 1.67 (d, J = 7 Hz, 6 H), 1.67 (m, 2 H), 2.36 (m, 4 H), 5.76 (q, J = 7 Hz, 2 H). Anal. (C_9H_{14}) C, H. *N*-Phenylmaleimide derivative: mp 98 °C.

(*E*,*E*)-1,2-Bis(ethylidene)cycloheptane: ^1H NMR (300 MHz) δ 1.53 (m, 6 H), 1.60 (d, J = 7 Hz, 6 H), 2.24 (m, 4 H), 5.39 (q, J = 7 Hz, 2 H). Anal. ($C_{11}H_{18}$) C, H. *N*-Phenylmaleimide derivative: mp 77–78 °C.

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(*E*,*E*)-1,2-Bis(propylidene)cyclohexane: ^{1}H NMR (300 MHz) δ 0.97 (t, J = 6 Hz, 6 H), 1.60 (m, 4 H), 2.03 (dq, J = 7, 7 Hz, 4 H), 2.19 (m, 4 H), 5.31 (t, J = 7 Hz, 2 H). Anal. ($C_{12}H_{20}$) C, H. *N*-Phenylmaleimide derivative: mp 150–151 °C.

(*E*,*E*)-1,2-Bis(isobutylidene)cyclohexane: ^{1}H NMR (360 MHz) δ 0.95 (d, J = 7 Hz, 6 H), 1.58 (m, 4 H), 2.20 (m, 4 H), 2.44–2.58 (m, 2 H), 5.12 (d, J = 9 Hz, 2 H). Anal. ($C_{14}H_{24}$) C, H. *N*-Phenylmaleimide derivative: mp 146–148 °C.

(*E*,*E*)-1,2-Bis(neopentylidene)cyclohexane: ^{1}H NMR (80 MHz) δ 1.13 (s, 18 H), 1.61 (m, 4 H), 5.34 (s, 2 H). Anal. ($C_{16}H_{28}$) C, H. *N*-Phenylmaleimide derivative: mp 179–180 °C.

(1*E*,2*E*)-1-Ethylidene-2-isobutylidenecyclohexane: ^{1}H NMR (300 MHz) δ 0.94 (d, J = 7 Hz, 6 H), 1.60 (d, J = 7 Hz superimposed on m, 7 H total), 2.20 (m, 4 H), 2.51 (m, 1 H), 5.13 (d, J = 7 Hz, 1 H), 5.37 (q, J = 7 Hz, 1 H). Anal. ($C_{12}H_{20}$) C, H. Maleic anhydride derivative: mp 96 °C.

(1*E*,2*E*)-1-Ethylidene-2-neopentylidenecyclohexane: ^{1}H NMR (300 MHz) δ 1.11 (s, 9 H), 1.58 (d, J = 7 Hz superimposed on m, 7 H total), 2.21 (m, 2 H), 2.34 (m, 2 H), 5.32 (s, 1 H), 5.34 (q, J = 7 Hz, 1 H). Anal. ($C_{13}H_{22}$) C, H.

Compound 8: ^{1}H NMR (360 MHz) δ 1.13 (s, 18 H), 1.83 (d, J = 1.5 Hz, 6 H), 5.44 (q, J = 1.5 Hz, 2 H); ^{13}C NMR (75.6 MHz) δ 15.86, 31.20, 32.01, 135.38, 138.29.

Compound 10: ^{1}H NMR (90 MHz) δ 1.61 (d, J = 7 Hz, 3 H), 1.61 (m, 4 H), 2.1–2.5 (m, 6 H), 3.62 (t, J = 7 Hz, 2 H), 5.2–5.6 (m, 2 H). Anal. ($C_{11}H_{18}O$) C, H. *N*-Phenylmaleimide derivative: mp 53–55 °C.

Compound 11: ^{1}H NMR (360 MHz) δ 0.10 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 1.70 (d, J = 8 Hz, 3 H), 1.70–1.77 (m, 2 H), 1.82 (d, J = 8 Hz, 3 H), 2.26–2.40 (m, 1 H), 2.41–2.57 (m, 1 H), 4.83 (m, 1 H), 5.75 (m, 1 H), 5.84 (q, J = 8 Hz, 1 H). Anal. ($C_{15}H_{28}OSi$) C, H. *N*-Phenylmaleimide derivative: mp 105–106 °C.

Compound 12: ^{1}H NMR (300 MHz) δ 1.69 (d, J = 7 Hz, 6 H), 4.79 (s, 4 H), 5.74 (q, J = 7 Hz, 2 H). Anal. ($C_8H_{12}O$) C, H. Naphthoquinone derivative: mp 155 °C.

Compound 13: ^{1}H NMR (80 MHz) δ 1.21 (t, J = 7 Hz, 6 H), 1.55 (m, 4 H), 2.17 (m, 4 H), 3.75 (q, J = 7 Hz, 4 H), 5.93 (s, 2 H). Anal. ($C_{12}H_{20}O_2$) C, H. Naphthoquinone derivative: mp 133–136 °C.

Compound 14: ^{1}H NMR (80 MHz) δ 1.69 (d, J = 6 Hz, 3 H), 1.8–2.7 (m, 8 H), 2.66 (s, 3 H), 4.88 (d, J = 5 Hz, 1 H), 5.5–6.0 (m, 2 H). Anal. ($C_{10}H_{17}NO$) C, H, N.

Compound 16: ^{1}H NMR (80 MHz) δ 4.86 (d, J = 2 Hz, 4 H), 6.07 (s, 4 H), 6.73–7.00 (m, 8 H). Anal. ($C_{20}H_{16}O_5$) C, H.

Compound 17: ^{1}H NMR (90 MHz) δ 1.69 (d, J = 7 Hz, 6 H), 3.48 (s, 4 H), 5.66 (q, J = 7 Hz, 2 H), 7.08 (s, 4 H), but product also showed resonances due to 10–15% hydrocarbon impurities. Anal. ($C_{14}H_{16}$) Calcd: C, 91.25; H, 8.75. Found: C, 90.59; H, 9.31. Naphthoquinone derivative: mp 95–101 °C dec. Anal. ($C_{24}H_{22}O_2$) C, H.

Compound 5. To a solution of **10** (1.66 g, 10 mmol) and triethylamine (1.10 g) in ether (25 mL) at 0 °C was added dropwise a solution of acryloyl chloride (0.93 g, 10 mmol) in ether (10 mL). After 15 min the mixture was filtered and after removal of solvent was purified by flash chromatography (10% ethyl acetate/90% hexane); fractions 7–14 afforded **4** (1.36 g, 62%). A portion (0.51 g) of this material was dissolved in toluene (100 mL) and heated at reflux for 24 h. Removal of the solvent and flash chromatography (40% ethyl acetate/60% hexane) afforded 5 (0.31 g, 65%): mp 92.5–93.0 °C; ^{1}H NMR (360 MHz) δ 0.98 (d, J = 7 Hz, 3 H), 1.46 (m, 2 H), 1.54 (m, 2 H), 1.63–2.29 (m, 10 H), 2.77 (ddd, J = 13, 5, 4 Hz, 1 H), 4.25 (td, J = 11, 3 Hz, 1 H), 4.43 (ddd, J = 11, 5, 2 Hz, 1 H). Anal. ($C_{14}H_{20}O_2$) C, H.

Ti-Mediated Reduction of 5,9-Tetradecadiyne. The reaction was run in the usual manner. After flash chromatography (hexane), the ^{13}C NMR spectrum of the product was identical with that of an authentic sample of (5*Z*)-tetradec-5-en-9-yne (in ppm from internal Me_4Si): 13.54, 13.90, 18.37, 19.13, 21.86, 22.28, 26.95, 27.02, 31.15, 31.83, 79.62, 80.28, 127.95, 131.00.

Isolation of Zirconacyclopentadienes. The cyclization was carried out in the usual manner, but the resultant mixture was filtered to remove unreacted magnesium and the solvent THF was removed in vacuo. The residue was taken up in hexane and filtered to free it from the magnesium chloride–THF complex and oligomeric side products. Removal of the hexane afforded the product metallacycles free of any apparent impurities by NMR. Compounds **6** and **7** were recrystallized by slow evaporation from hexane.

Structural Details. Crystals of all three compounds were mounted on glass fibers and placed on a Syntex P3 diffractometer (graphite monochromator, Mo Kα, λ = 0.71069 Å) at −100 °C. The crystal system, space group, and approximate unit-cell dimensions of each crystal were determined during a preliminary investigation. The unit-cell dimensions were refined from the Bragg angles of 50 computer-centered reflections. Intensity data were collected by the ω-scan technique ($4° < 2\theta < 55°$): scan width of 1°, variable scan rate of 2.0–5.0° min^{-1}, background measurements at both ends of scan, total background time equal to scan time. The intensities of four standard reflections were monitored periodically; only statistical fluctuations were noted except in the case of compound **6** in which a sudden, unexplained change of 20.9% occurred midway through the data acquisition.

Table V. Crystal Data

compd	**5**	**6**	**7**
formula	$C_{14}H_{20}O_2$	$C_{18}H_{20}Zr$	$C_{26}H_{36}Zr$
M_r	220.31	327.58	439.80
crystal dimension, mm		0.36 × 0.21 × 0.36	0.35 × 0.17 × 0.41
crystal system	monoclinic	triclinic	monoclinic
space group	$P2_1/c$	$P\bar{1}$	$P2_1/c$
unit cell			
a, Å	14.963 (3)	12.827 (2)	11.711 (2)
b, Å	9.142 (2)	15.245 (2)	9.986 (1)
c, Å	8.834 (2)	7.926 (1)	19.052 (2)
α, deg		92.75 (1)	
β, deg	96.80	94.47 (1)	92.65 (1)
γ, deg		108.87 (1)	
V, Å^3	1199.9	1457.7	2225.7
Z	4	4	4
calcd density, g cm^{-3}	1.219	1.493	1.312
absorption coeff, cm^{-1}	0.74	7.25	4.9
empirical absorption correction	no	yes	yes
no. of independent reflections	2759	6713	5391
reflections with $I > 2(I)$	1021	5290	3997
no. of variables	225	463	406
hydrogen atoms	located	located	some calcd
R	0.064	0.028	0.034
R_w	0.056	0.031	0.035
peaks in final difference Fourier (e Å^{-3})	<0.28	0.79–0.95 (5, near Zr)	0.51 (2, near Zr)

Table VI. Orbital Parameters for Extended Hückel Calculations

orbital		H_{ii}	exponent
Pt	6s	−9.00	2.554
	6p	−5.48	2.554
	5d	−12.59	6.013 (0.633)
Zr	5s	−9.87	1.817
	5p	−6.76	1.776
	4d	−11.18	3.835 (0.621)
			1.505 (0.580)
P	3s	−18.6	1.600
	3p	−14.0	1.600
C	2s	−21.4	1.625
	2p	−11.4	1.625
H	1s	−13.6	1.300

The crystal data and a summary of the refinement for the structures are given in Table V. The solution and refinement of the structure were carried out on a PDP-11 computer using local modifications of the programs supplied by the Enraf-Nonius Corp.[29] The atomic scattering factors were taken from the tabulations of Cromer and Waber,[30a] and the anomalous dispersion corrections were by Cromer.[30b] In the least-squares refinement, the function minimized was $\sum(w|F_o| - |F_c|)^2$ with the weights, w, assigned as $1/\sigma^2(F_o)$. The standard deviations of the observed structure factors, $\sigma(F_o)$, were based on counting statistics and an "ignorance factor", p, of 0.02.[31]

For compound **7**, C(7) and C(8) were disordered. Initial refinement of the occupation factors suggested that values of 0.55 for C(7) and C(8) and of 0.45 for C(7)′ and C(8)′ were appropriate. Difference maps around these atoms indicated that only four hydrogen positions were appropriate: one of the two equatorial hydrogens was shared by C(7)

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and C(7)′ and the other by C(8) and C(8)′. One of the two axial positions was nearly shared by C(7) and C(8)′ while the other was shared by C(7)′ and C(8). The hydrogens were thus assigned occupancies of 1.0. Since the electron density was dominated by those hydrogens attached to C(7) and C(8), the refined hydrogen positions are biased: the bond distances and angles are better for contacts with C(7) and C(8) than with C(7)′ and C(8)′.

Molecular Orbital Calculations. Calculations were performed by using the TRIBBLE package,[32] an extended Hückel method incorporating two-body repulsion corrections as introduced by Anderson.[33] Orbital exponents and H_{ii} values for H, C, and Zr were taken from ref 34, those for P and Pt from ref 35 (see Table VI). Double-ζ wave functions were used for the d-orbitals of Pt and Zr, with coefficients given in parentheses.

Supplementary Material Available: Final positional parameters (as fractional coordinates) and tables of thermal parameters (10 pages); tables of structure factor amplitudes (observed and calculated) (56 pages). Ordering information is given on any current masthead page.

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Proline Signals in Ultraviolet Resonance Raman Spectra of Proteins: Cis-Trans Isomerism in Polyproline and Ribonuclease A

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Abstract: The Raman spectrum of aqueous polyproline excited at 200 or 218 nm is dominated by a single band at ~1465 cm^{-1}, assigned to the imide C-N stretching vibration. It is analogous to the amide II′ band at ~1465 cm^{-1} of polypeptides in D_2O, which is also enhanced strongly at 200 nm. The amide II′ band loses much more intensity between 200- and 218-nm excitation (×5.6) than does the polyproline band (×1.2). This difference is attributable to a red shift of the imide vs. amide $\pi-\pi^*$ electronic transition: the first UV absorption band maximizes at 192 nm for poly-L-lysine but at 203 nm for polyproline. Because of this effect, proline residues are readily detected in protein ultraviolet Raman spectra excited at 218 nm. For example, histidine-rich glycoprotein (HRG) shows a major band at 1457 cm^{-1} due to the high proline content, 16.6% of the residues; this is much stronger than the 1547-cm^{-1} band arising from the amide II mode of the remaining residues. When polyproline is dissolved in 1:9 H_2O-propanol containing ~0.15 M $HClO_4$, a 1435-cm^{-1} band grows in at the expense of the original 1465-cm^{-1} band. This spectral change is associated with the transition from polyproline II to polyproline I, which contain trans and cis imide bonds, respectively. The frequency shift is in the same direction as that seen for the amide II mode of cis peptides. Ribonuclease A shows a band at 1458 cm^{-1} in its 218 nm excited Raman spectrum, attributable to its four proline residues, two of which are in the cis conformation. When the protein is incubated at pH 1.5 this band shifts to 1466 cm^{-1}; the upshift is consistent with the expected conversion to a higher percentage of prolines in the trans conformation in the unfolded protein. UVRR spectroscopy offers a direct probe of proline conformation in protein structural studies.

Because its side chain ties back on itself to form a secondary linkage (Figure 1) proline is an important structural determinant in proteins. The absence of a hydrogen atom on the imide nitrogen atom eliminates H-bonded interactions, while the presence of the ring constrains the rotation angle of the N-C^α bond.[1] Proline residues are frequently found at bends in the polypeptide chain.[2] On the other hand cis and trans isomers about the N-C(O) bond are much closer in energy for proline than for other amino acids. Steric constraints normally destabilize the cis peptide bond by a factor of ~10^3 over the normal trans conformation, but for proline the steric inhibition is relieved by the ring structure, and the trans:cis equilibrium ratio is reduced to ~4.[3] There are several examples of cis proline residues in protein structures,[4] but there are only four instances of cis peptides not involving proline (three in carboxypeptidase A and one in dihydrofolate reductase).[5] This conformational flexibility of the proline imide bond may be an important element in protein dynamics. It has been argued, for example, that the proline-rich region of immunoglobins might regulate antigen binding by mediating a structural transition in the hinge region of the protein.[6] Cis/trans isomerization about the proline imide bond is believed to be the rate-limiting step in the denaturation of a number of proteins and may be a key step in protein folding in general.[3b,7] A widely accepted model is that

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