On the Reaction of a Dioxenylmolybdenum Carbene Complex with Enynes: Studies of the Intramolecular Diels−Alder Reaction

Daniel F. Harvey* and Ellen M. Grenzer

Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0358

Received July 21, 1995[⊗]

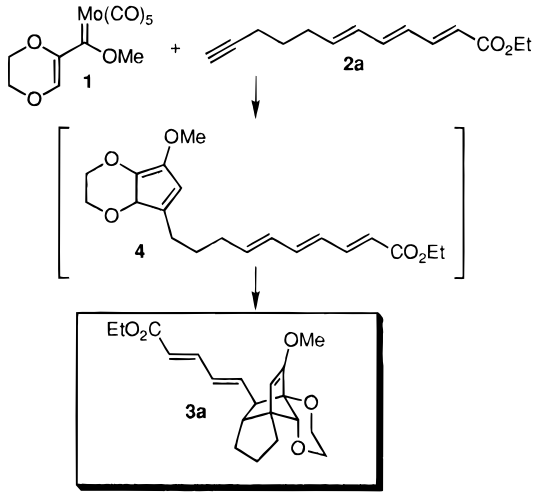
Dioxenylmolybdenum carbene complex **1** has been found to readily react with enynes to form tetracyclic products. The tetracyclic products of this reaction appear to be generated via intramolecular [4 + 2] cycloaddition of an initially formed trialkoxycyclopentadiene derivative. Studies which help to define the generality of this reaction are reported, and the involvement of the metal in the cyclization process is discussed.

We recently reported that vinylmolybdenum carbene complexes, such as **1**, react with trienyne **2a** to give tetracyclic products such as **3a**.[1] This process has been suggested to involve in situ generation of a cyclopentadiene intermediate (**4**) which undergoes subsequent intramolecular Diels−Alder reaction to form **3a**. We were particularly intrigued by the high yield and excellent stereoselectivity obtained in this process and sought to determine the generality of this reaction as well as probe in more detail the mechanism of the [4 + 2] cycloaddition reaction.

The intramolecular Diels−Alder reaction has been extensively investigated with respect to both its mechanism and its utilization in the synthesis of complex natural products.[2] In particular, intramolecular Diels−Alder reactions utilizing cyclopentadiene derivatives as the diene component have been studied and applied to the synthesis of a variety of natural products.[3] In general, these studies have involved initial preparation of cyclopentadiene/dienophile substrates and subsequent thermolysis to form the cycloaddition product.

In the reaction outlined in Scheme 1, the cyclopentadiene intermediate was generated in situ and could not be isolated, though in some cases products derived from hydrolysis of the enol ether unit of the alkoxycyclopentadiene were obtained.[1] In many cases, [4 + 2] cycloaddition occurred smoothly under the reaction conditions. It was somewhat surprising that this [4 + 2] cycloaddition occurred since the thermolysis conditions employed (67 °C) are relatively mild in comparison to previous reports.[2b,c,3] Additionally, the fact that the cycloaddition had occurred on the face of the cyclopentadiene syn to the alkoxy substituent also attracted our interest. This approach of the dienophile appears to occur from the more sterically hindered face of the substituted cyclopentadiene derivative. Studies to explore the generality of these observations are presented, and the possibility that the intramolecular Diels−Alder reaction may be mediated by the metal is discussed herein.

Scheme 1



Results

Molybdenum carbene complex **1** was prepared as previously described.[1] All substrates were prepared from commercially available material using standard procedures, details of which are described in the Experimental Section. The conditions employed for the cyclization reactions were based on previous studies of reactions of various vinylcarbene complexes with enyne substrates.[1,4] So that differences in the reaction conditions would not be a complicating variable, all of the cyclization reactions were performed in tetrahydrofuran (THF) for 2 h either at reflux at atmospheric pressure or in a sealed vial at 100 °C. The product distribution remained unchanged, and only a slight variation in yield was observed when the same reactions were performed under both reflux and sealed vial conditions. Conditions which gave the highest yields are reported. A slight excess (1.1−1.2 equiv) of the carbene complex was employed.

The influence of the triene unit on the [4 + 2] cycloaddition step was investigated by comparing the reactivity of **2a** to the reactivity of dienyne **2b** and enyne

⊗ Abstract published in *Advance ACS Abstracts,* December 15, 1995.

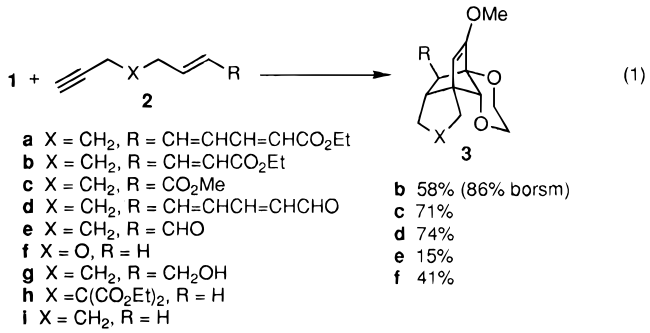
(1) Harvey, D. F.; Grenzer, E. M.; Gantzel, P. *J. Am. Chem. Soc.* **1994**, 116, 6719−6732.

(2) For reviews, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550. (b) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183−234. (c) Ciganek, E. *Org. React.* **1984**, *32*, 1−374.

(3) (a) Corey, E. J.; Glass, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 2600−2606. (b) Brieger, G.; Anderson, D. R. *J. Org. Chem.* **1971**, *36*, 243−244. (c) Breitholle, E. G.; Fallis, A. G. *Can J. Chem.* **1976**, *54*, 1991, 1993. (d) Landry, D. W. *Tetrahedron* **1983**, *39*, 2761−2768. (e) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F.; Banks, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 2149−2153. (f) Snowden, R. L. *Tetrahedron* **1986**, *42*, 3277−3290. (g) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855−856. (h) Stille, J. R.; Grubbs, R. H. *J. Org. Chem.* **1989**, *54*, 434−444. (i) Sternbach, D. D.; Ensinger, C. L. *J. Org. Chem.* **1990**, *55*, 2725−2736. (j) Himeda, Y.; Hiratani, K.; Hatanaka, M.; Ueda, I. *J. Chem. Soc., Chem. Commun.* **1992**, 1684−1685. (j) Fallis, A. G.; Lei, B. *J. Org. Chem.* **1993**, *58*, 2186−2195.

(4) Lund, K. P. Ph.D. dissertation, UCSD, 1992.

0022-3263/96/1961-0159$12.00/0

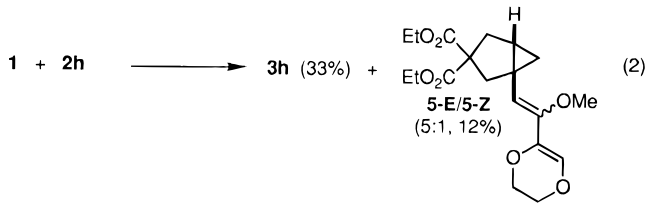


2c. Both of these substrates were found to readily participate in the expected [4 + 2] cyclization reaction. Dienyne substrate **2b** gave **3b** in 58% yield with 33% of **2b** recovered (86% yield of **3b** based on recovered starting material), while enyne **2c** produced **3c** in 71% yield.

Utilizing a terminal aldehyde to activate the dienophile component gave mixed results. Trienal **2d** behaved similarly to the corresponding ester, **2a**, producing **3d** in 74% yield. However, only 15% of **3e** was obtained upon treatment of enal **2e** with **1**. No other isolable products were obtained from this reaction, but a significant amount of apparently oligomeric/polymeric material appeared to be produced. Polymerization of the enal substrate could occur in a manner similar to the well-precedented polymerization of acrolein. The additional conjugation present in trienal **2d** may discourage this polymerization from occurring, thus allowing the desired cyclization pathway to occur.

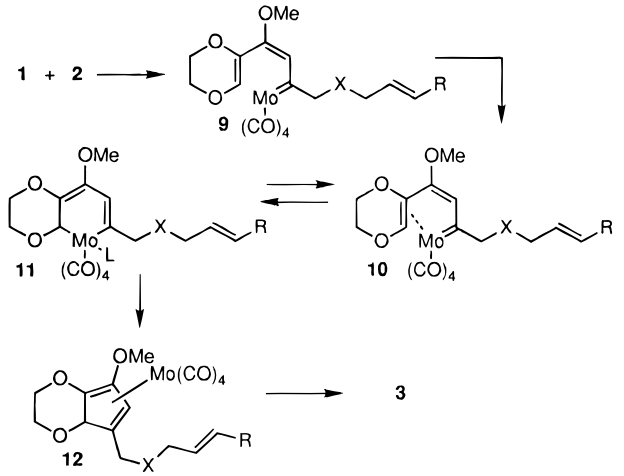
Substrates without electron-withdrawing substituents on the alkene component were also investigated. Allyl propargyl ether **2f**, which had previously been found to react with alkyl-substituted molybdenum carbene complexes via cyclopropanation-based pathways,[5] produced **3** in 41% yield. However, allylic alcohol **2g** produced no isolable products, with **2g** being recovered in 40% yield.

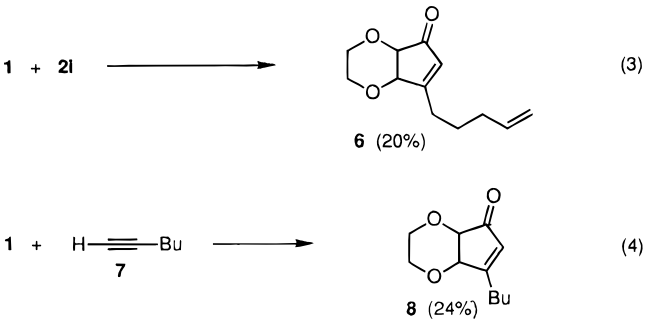
Intramolecular cyclization reactions are often facilitated by the presence of substituents on the linkage between the functional groups involved in the reaction.[6] This effect has been previously observed in our studies of molybdenum carbene based cyclopropanation pathways.[4,7] Treatment of enyne **2h** with complex **1** gave Diels–Alder cyclization product **3h** in 33% yield and vinylcyclopropanes **5-*E*** and **5-*Z*** in 12% yield as a 5:1 (*E*:*Z*) mixture of enol ether isomers.



6-Hepten-1-yne, **2i**, was the only enyne substrate investigated that did not undergo subsequent intramolecular Diels–Alder cyclization. Instead, cyclopentenone **6**, resulting from hydrolysis of the corresponding methyl enol ether, was produced in 20% yield. This is similar to the reactivity observed with 1-hexyne from which cyclopentenone **8** was obtained in 24% yield.

Scheme 2





Discussion

Cyclopentadiene Formation. The formation of cyclopentadienes from vinylmolybdenum carbene complexes is thought to involve the reaction pathway outlined in Scheme 2.[1] Initial loss of carbon monoxide from **1** followed by reaction of the resulting coordinatively unsaturated metal complex with the alkyne produces vinylcarbene intermediate **9**. Although the metal center of **9** may fill its vacant coordination site in several ways,[1] it most likely coordinates to the 4,5-alkene resulting in η^1,η^1,η^2-coordination as in **10**. From **10**, electrocyclic ring closure, which may require assistance by an auxiliary ligand, L, in order to maintain an 18e$^-$-environment around the metal center, then gives metallacyclohexadiene **11**. Subsequent reductive elimination then produces cyclopentadiene complex **12**. In the absence of an appropriate dienophile, decomplexation and hydrolysis of the enol ether moiety of **12** occurs to give the corresponding cyclopentenone (such as **6** and **8**). When an appropriate dienophile is present, intramolecular Diels–Alder reaction and decomplexation leads to the tetracyclic product **3**.

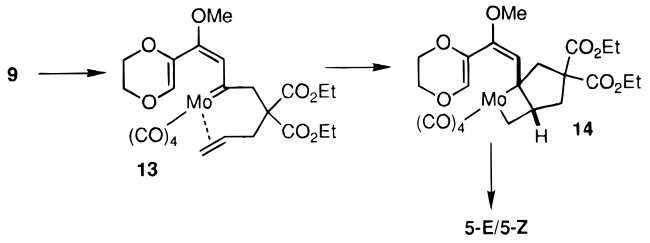
Products derived from cyclopentadiene intermediates were the only products obtained in all but one case. Enyne **2h**, bearing *gem*-carbethoxy groups on the tether between the alkyne and the alkene, gave a mixture of cyclopentadiene-derived cyclization product **3h** and cyclopropanation products **5-*E*/5-*Z***. The *gem*-carbethoxy substituents facilitate coordination of the tethered alkene to intermediate, **9**, allowing formation of **13** to effectively compete with electrocyclic ring closure to form **11**. From **13**, [2 + 2] cyclization to give metallacyclobutane **14**

(5) (a) Harvey, D. F.; Lund, K. P.; Neil, D. A. *Tetrahedron Lett.* **1991**, *32*, 6311–6314. (b) Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424–8434.

(6) For a recent discussion of this effect, see: Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319–7322 and references cited therein.

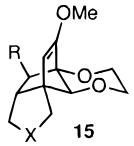
(7) (a) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066–5068. (b) Backenstrass, F. Unpublished results.

Scheme 3



followed by reductive elimination produces **5-*E*/5-*Z*** (Scheme 3).

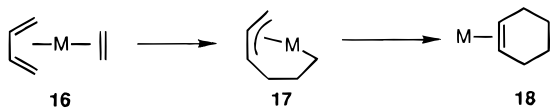
The Intramolecular Diels−Alder Reaction. Though the cyclization of **4** to **3** appears to be the result of a facile intramolecular Diels−Alder reaction, several observations suggested that this might not be the case. As mentioned previously, the dienophile has approached from what appears to be the more sterically hindered face of the diene, leading to **3** rather than **15**. Additionally,



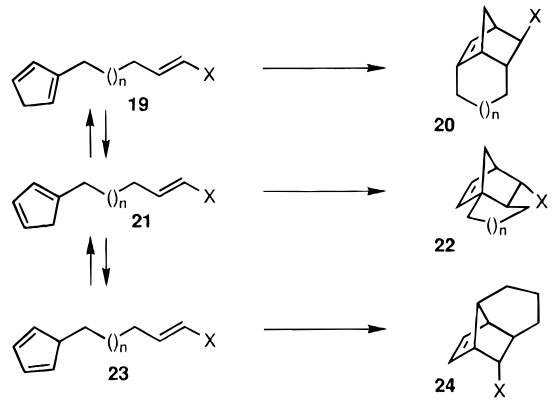
we have not been able to isolate the proposed intermediate, cyclopentadiene **4**. In cases where the [4 + 2] cyclization reaction has not occurred, only cyclopentenones have been obtained, but in significantly lower yield than when cyclization to give **3** has occurred (e.g., 72% vs. 20%). Additionally, on the basis of previous reports,[2,3] we anticipated that the intramolecular Diels−Alder reaction of decomplexed **4** would require somewhat higher temperatures than utilized in these studies. The possibility that the metal might be involved in mediating not only cyclopentadiene formation but also the [4 + 2] cycloaddition reaction was therefore considered.

The Diels−Alder reaction has been catalyzed by several different types of metal complexes.[8,9] Though detailed studies of the mechanism of this process have not been carried out, it is generally presumed to involve the intermediacy of an η^3,η^1-complex such as **17**.[10] Subsequent reductive elimination leads to **18**, which upon decomplexation, generates the cyclohexene product (Scheme 4).

Scheme 4

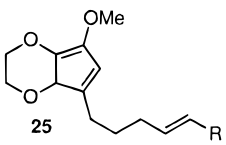


Scheme 5



Numerous studies of the intramolecular Diels−Alder reaction of cyclopentadiene derivatives have previously been reported.[2,3] Upon thermolysis, substituted cyclopentadienes rapidly isomerize via 1,5-hydrogen shifts providing access to **19**, **21**, and **23**. Upon [4 + 2] cycloaddition, **19**, **21**, and **23** produce **20**, **22**, and **24**, respectively (Scheme 5). With a three-atom tether between the cyclopentadiene and the dienophile, cyclization occurs exclusively through the 1-substituted derivative, **21**, leading to exo-tricyclic product, **22**. The endo-analog of **22** contains a strained trans-fused bicyclo[3.3.0]octane ring system and is considerably less stable than **22**. Secondary orbital interactions have also been used to rationalize the product distribution.[2a] In order to minimize nonbonded interactions, an unsymmetric transition state is assumed. Bonding is thought to initially occur preferentially between the termini with the largest HOMO−LUMO coefficients, C_x and C_y. In our studies, exo-cycloaddition products analogous to **22** were obtained in all cases.

In conventional intramolecular Diels−Alder cycloaddition reactions of cyclopentadiene derivatives, though slightly higher thermolysis temperatures are often employed, the dienophile need not be activated by an electron-withdrawing substituent and the diene does not require electron-donating substituents for [4 + 2] cycloaddition to smoothly occur.[3a,b] It was therefore surprising that reaction of complex **1** with unactivated enyne **2i** did not produce the [4 + 2] cycloaddition product. Instead, hydrolysis product **6** was obtained in 20% yield. The yield for this reaction is similar to the 24% yield for the reaction of **1** with 1-hexyne, which lacks the tethered alkene necessary for intramolecular cyclization.



There are several possible explanations for this observation. Formation of cyclopentadiene **25** may be occuring in high yield, but isolation is not facile because the cyclopentadiene remains complexed to the metal. An η^4-cyclopentadiene intermediate, such as **12**, could undergo

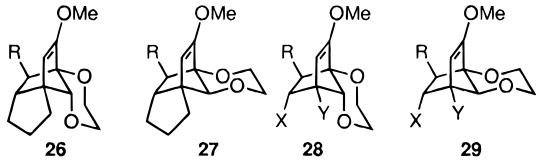
(8) For examples of metal-catalyzed [4 + 2] cycloadditions, see: (a) Carbonaro, A.; Greco, A.; Dall'Asta, G. *J. Org. Chem.* **1968**, *33*, 3948−3950. (b) Genet, J. P.; Ficini, J. *Tetrahedron Lett.* **1979**, 1499−1502. (c) Dieck, H. T.; Diercks, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 778−779. (d) Mach, K.; Antropiusova, H.; Petrusova, L.; Turecek, F.; Hanus, V. *J. Organomet. Chem.* **1985**, *289*, 331−339. (e) Matsuda, I.; Shibata, M.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1987**, *28*, 3361−3362. (f) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432−6434. (g) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965−4966. (h) Lautens, M.; Tam, W.; Edwards, L. G. *J. Org. Chem.* **1992**, *57*, 8−9. (i) McKinstry L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145−6154. (j) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843−1844.

(9) For examples of other types of metal-promoted cycloaddition reactions, see: (a) Wender, P. A.; Ihle, N. C.; Corriea, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904−5906. (b) Chaffee, K.; Sheridan, J. B.; Aistars, A. *Organometallics* **1992**, *11*, 18−19. (c) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579−585. (d) Kreiter, C. G.; Lehr, K. *J. Organomet. Chem.* **1993**, *454*, 199−207. (e) Wang, C.; Sheridan, J. B.; Chung, H.-J.; Cote, M. L.; Lalancette, R. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 8966−8972.

(10) For the intermediacy of related η^3,η^1-complexes in iron-mediated triene cyclization reactions, see: Takacs, J. M.; Myoung, Y.-C.; Anderson, L. G. *J. Org. Chem.* **1994**, *59*, 6928−6942, and references therein.

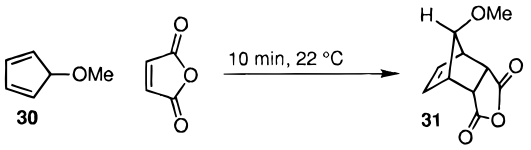
C−H insertion to give an η^5-cyclopentadienylmolybdenum hydride complex which would not be expected to survive our isolation procedure.[11] Alternatively, coordination of a tethered alkene may be necessary for smooth formation of the cyclopentadiene ring to occur. Alkene coordination to a coordinatively unsaturated intermediate, such as **11**, might be necessary before reductive elimination to the cyclopentadiene can occur. Since **2i** lacks the activating electron-withdrawing group of the other dienophiles, it is expected to not coordinate as well to the electron-rich coordinatively unsaturated metal center. Related coordination effects have previously been proposed to influence the reactivity of group VI carbene complex-based reactions.[1,12]

The fact that the oxygen substituent of the dioxane ring of **3** was syn to the dienophile bridge suggested that the "contrasteric" product had been produced. MMX and AM1 semiempirical calculations performed on conformational models designed to approach the transition state indicate that there is minimal energy difference between approach of the dienophile syn and anti to the cyclopentadiene substituent (0.48 kcal/mol and 0.23 kcal/mol, respectively). However, calculations performed on the products indicate that **27**, resulting from approach of the dienophile anti to the cyclopentadiene substituent, is favored energetically by 3.53 kcal/mol (MMXE) and 3.37 kcal/mol (AM1) over the syn-addition product **26**. This suggests that the contrasteric kinetic product, **26**, is formed preferentially over the thermodynamically more stable isomer **27**. The tether between the alkyne and alkene does not apear to play a role in determining which stereoisomer is thermodynamically preferred. Calculations performed on structures where the tether has been replaced with various combinations of H and Me groups in the X and Y positions (**28** and **29**) still produce approximately a 3 kcal/mol difference in energy favoring **29** over **28**.



26 **27** **28** **29**

This contrasteric effect has been observed before in intermolecular Diels−Alder reactions of cyclopentadienes.[13] Macauley and Fallis have found that cyclopentadienes with OH, OMe, NH_2, NHAc, and Cl substituents at C_5 react preferentially to form syn adducts.[13b] For example, treatment of 5-methoxycyclopentadiene (**30**) with maleic anhydride for 10 min at 22 °C gave exclusively the syn adduct **31**. The stabilities of the syn and anti transition states were compared in order to explain this result.[14] The transition state was suggested to be stabilized by σ electron donation by the filled orbitals of the bonds vicinal to the vacant σ^{*} orbital associated with the σ-bond being formed in the reaction. Thus, dienophile addition should occur preferentially antiperiplanar to the C−H bond since it is a better σ-donor than the heteroatom substituent. This hypothesis was originally put forth by Cieplak to explain the stereochemistry of nucleophilic additions to cyclohexanone[14] and applied to other systems by Cieplak, Tait and Johnson.[15] The basic concept of hyperconjugative σ-assistance is also supported by ab initio calculations[16] and AM1 calculations performed on the transition states for syn and anti attack.[17] Alternatively, the orbital mixing rule has been utilized to rationalize these experimental results.[18] Other models have been proposed to account for the diastereoselectivity seen in nucleophilic additions to carbonyl compounds, such as the frontier orbital model,[19] the Anh−Eisenstein hypothesis,[20] and the Felkin torsional model.[21]



30 **31** (5)

Recently, Poirier and colleagues have performed additional computational studies on this reaction and suggest that the deformation energy of the cyclopentadiene is the factor most responsible for determining the preferred mode of addition in this reaction.[22] It is expected that deformation of the cyclopentadiene derivatives toward **32** would be preferred over **33**. This would be preferred electronically because it orients the better σ-donor with the conjugated π-system of the diene and sterically because it avoids developing 1,3-diaxial interactions across the 1,4-dioxane ring system.

32 **33**

Although there is no striking evidence for the intramolecular Diels−Alder reaction being metal-mediated, the possibility must be considered as it could also explain the observed facial selectivity.

Cyclopentadiene complex **12** is expected to exist in the η^4-state as shown (see Scheme 6). Metal coordination can occur either syn (**12a**) or anti (**12b**) to the alkoxy substituent. Previous studies suggest that as reductive elimination of the metallacyclohexadiene occurs and the cyclopentadiene ring is formed, the metal will coordinate syn to the alkoxy substituent as in **12a**.[23] Other modes

(11) Davis, R.; Kane-Maguire, L. A. P. In *Comprehensive Organometallic Chemistry;* Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds; Pergamon Press: Emsford, NY, 1982; Vol. 3, pp 1176−1203 and references cited therein.

(12) (a) Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813−5832. (b) Yamashita, A. *Tetrahedron Lett.* **1986**, *27*, 5915−5918. (c) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9−56. (d) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 8916−8921.

(13) (a) Chung, W. S.; Turro, N. J.; Srivastava, S.; Li, H.; Le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882−7883. (b) Macauley, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136−1144. (c) Halterman, R. L.; McCarthy, B. A.; McEvoy, M. A. *J. Org. Chem.* **1992**, *57*, 5585−5589.

(14) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552.

(15) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447−8462.

(16) (a) Taira, K.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 7825−7831. (b) Yang, J.-C.; Gorenstein, D. G. *Tetrahedron* **1987**, *43*, 479−486.

(17) Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *33*, 651−654.

(18) Ishida, M.; Benuja, Y.; Inagaki, S.; Kato, S. *J. Am. Chem. Soc.* **1990**, *112*, 8980−8982.

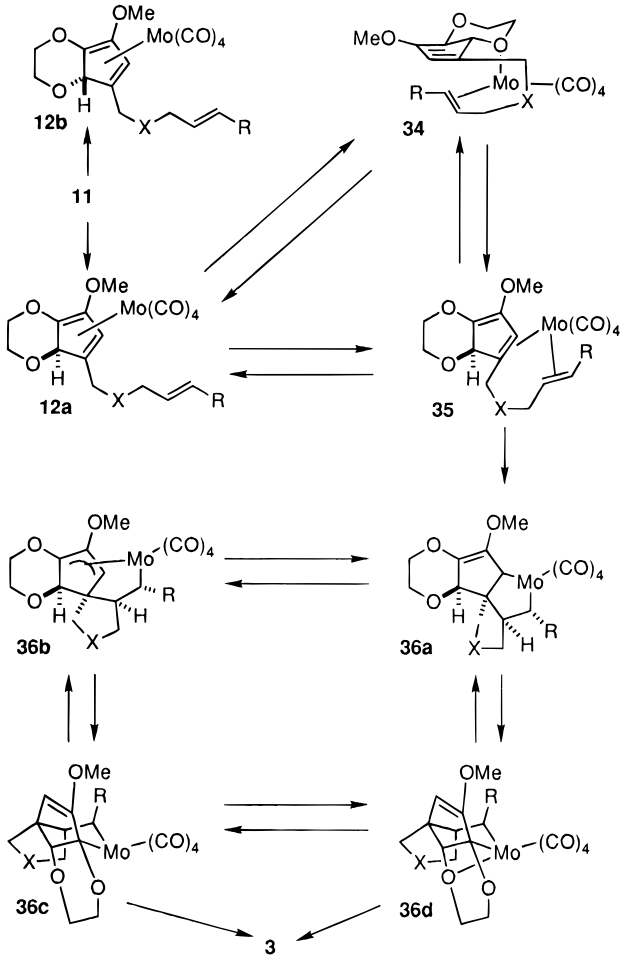
(19) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146−1149.

(20) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456−458.

(21) Wu, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908−910.

(22) Poirier, R. A.; Pye, C. C.; Xidos, J. D.; Burnell, D. J. *J. Org. Chem.* **1995**, *60*, 2328−2329.

Scheme 6



of metal coordination to the cyclopentadiene intermediate are possible, but are all anticipated to be less stable than **12a** and **12b**. Coordination of the metal to the side chain could lead to η^2,η^1-complex **34** or η^2,η^2-complex **35**.

Complex **34** serves to orient the diene and the dienophile toward [4 + 2] cycloaddition syn to the alkoxy substituent, but metal-directed cyclization form such an intermediate is unlikely. Before a strictly thermal cycloaddition process can occur, the olefin must dissociate from the metal, and the alkoxy-coordination directing effect is lost since the noncoordinated olefin is free to react with either face of the diene. Alternatively, metal coordination to the alkene, as in **34**, might activate it toward cycloaddition with the diene in a fashion analogous to the manner that many Lewis acids catalyze formal [4 + 2] cycloaddition reactions. However, this would require addition of the diene from the face of the alkene anti to the metal, a mode of addition that for steric reasons appears to be highly unfavorable.

From **35**, cyclization can occur via the general metal-catalyzed cycloaddition mechanism outlined in Scheme 4. Oxidative cyclization leads to intermediate **36**, which can exist either as the 16-electron η^1,η^1-complex **36a**, the 18-electron η^1,η^3-complex **36b**, the 16-electron η^1,η^1-complex **36c**, or the 18-electron η^1,η^1,η^1-ether complex **36d**. From **36b**, **36c**, or **36d**, reductive elimination can occur to give **3**. In this fashion, the stereochemistry of cyclopentadiene complex **12a** could control the facial selectivity of the cycloaddition reaction.

(23) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293−9319.

Conclusion

Reaction of carbene complex **1** with 1,6-enynes leads to tetracyclic products with the general structure **3**. Though this reaction clearly occurs via formation of a trialkoxycyclopentadiene, such as **4**, it is not clear whether the subsequent [4 + 2] cyclization reaction is simply a thermal cycloaddition reaction or a metal-mediated process. With substrates wherein the intramolecular cyclization pathway is less favorable or not possible, the yield of cyclopentadiene-derived products is low, suggesting that the metal remains bound to the cyclopentadiene product and can be involved in subsequent cyclization reactions. Calculations suggest that the intramolecular cyclization reaction is not reversible under the reaction conditions as the contrasteric kinetic product is produced preferentially over the thermodynamically more favorable one. This contrasteric effect has been observed previously with Diels−Alder reactions of cyclopentadiene derivatives, and hyperconjugative σ-assistance, as well as other factors, have been invoked to explain these results. In our case, the observation that substrates lacking a tethered alkene do not produce good yields of cyclopentadiene products, or hydrolysis products derived therefrom, suggests that $Mo(CO)_4$−cyclopentadiene products, such as **12**, are intermediates in this reaction. The observed stereochemical outcome when cycloaddition products are obtained can also be accounted for by the metal-mediated cyclization pathway summarized in Scheme 6.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on 500 or 300 MHz spectrometers. IR spectra were recorded on a FT-IR spectrophotometer. Low-resolution mass spectra were recorded on a HP 5970 mass-selective detector (20 eV) interfaced with a HP 5890 gas chromatograph equipped with a 12 m × 0.2 mm HP-1 fused silica capillary column. High-resolution mass spectra were performed at the UC Riverside Mass Spectrometry Facility on a VG-ZABZFHF or VG-7070EHF mass spectrometer. Elemental analyses were performed by Oneida Laboratories, Inc. Column chromatography was performed with Fisher Scientific Florisil (100−200 mesh) or silica gel (200−425 mesh) with a gradient elution ethyl acetate/hexane solvent system unless otherwise indicated. All reagents were obtained from commercial suppliers and used as received unless otherwise indicated. Benzene and tetrahydrofuran (THF) were distilled from potassium/benzophenone ketyl under a nitrogen atmosphere. Diethyl ether was distilled from sodium/benzophenone ketyl under a nitrogen atmosphere. Dichloromethane and acetonitrile were distilled from calcium hydride under a nitrogen atmosphere.

General Procedure. A solution of enyne and the carbene complex in THF was heated at either 67 °C under a nitrogen atmosphere in flame-dried glassware or at 100 °C behind a blast shield in a thick-walled glass vial with a teflon screw cap (sealed vial conditions). After being cooled to room temperature, the crude reaction mixture was concentrated in vacuo and chromatographed immediately.

Ethyl (2*E*)-3-(13-Methoxy-8,11-dioxotetracyclo[5.5.2.-0^{1,5}.0^{7,12}]tetradec-13-en-6-yl)-2-propenoate (3b). To a solution of dienyne **2b**[7a] (50.0 mg, 0.259 mmol) in THF (16 mL) was added complex **1** (91.8 mg, 0.285 mmol). The reaction was heated in a sealed vial at 100 °C for 2 h, cooled to room temperature, concentrated in vacuo to approximately 1 mL, and immediately chromatographed on silica gel to give **3b** (48.0 mg, 58%) as well as recovered dienyne **2b** (16.3 mg, 33%); 86% yield of **3b** based on recovered starting material. **3b**: ^{1}H NMR (300 MHz, C_6D_6) δ 0.97 (t, J = 7.2 Hz, 3H), 1.46−1.56 (m, 1H), 1.61−2.02 (m, 6H), 2.92 (s, 1H), 3.04−3.12 (m, 4H containing 3.10 (s, 3H)), 3.18−3.22 (m, 2H), 3.54 (dd, J = 8.2, 3.3 Hz,

1H), 3.66 (ddd, J = 12.2, 10.3, 5.6 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 4.37 (s, 1H), 6.12 (d, J = 15.4 Hz, 1H), 7.19 (dd, J = 15.8, 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 25.2, 27.1, 28.8, 41.6, 55.8, 56.6, 57.2, 60.0, 60.8, 66.4, 88.8, 89.4, 100.0, 122.4, 149.1, 158.1, 166.3; IR (CH_2Cl_2) 2964, 2939, 2905, 2872, 1710, 1649, 1607, 1461, 1449, 1374 cm^{-1}; LRMS *m/e* 321 (4), 320 (M^+, 17), 247 (14), 233 (14), 215 (20), 207 (30), 167 (100); HRMS (EI) calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1617. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.73; H, 7.38.

Methyl 13-Methoxy-8,11-dioxotetracyclo[5.5.2.0^{1,5}.0^{7,12}]-tetradec-13-ene-6-carboxylate (3c). To a solution of methyl (2*E*)-2-octen-7-ynoate (**2c**)[5b] (38.0 mg, 0.250 mmol) in THF (100 mL) was added complex **1** (96.7 mg, 0.300 mmol). The reaction was heated at 67 °C for 2 h, cooled to room temperature, concentrated in vacuo to approximately 1 mL, and immediately chromatographed on silica gel to give **3c** (50.0 mg, 71%): ^{1}H NMR (500 MHz, C_6D_6) δ 1.55−1.61 (m, 1H), 1.65−1.72 (m, 1H), 1.78−1.88 (m, 2H), 1.90−2.00 (m, 2H), 2.55-2.60 (m, 1H), 2.94 (s, 1H), 3.15−3.24 (m, 3H), 3.27 (s, 3H), 3.45 (s, 3H), 3.75 (d, J = 4.4 Hz, 1H), 3.97−4.03 (m, 1H), 4.54 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 27.1, 28.8, 42.6, 51.8, 53.7, 56.0, 56.6, 60.8, 66.3, 89.2, 89.9, 100.0, 157.1, 174.1; IR ($CDCl_3$) 2966, 2954, 1727, 1610, 1460, 1449, 1437, 1376 cm^{-1}; LRMS, EI, *m/e* (%) 281 (2), 280 (M^+, 14), 221 (4), 207 (20), 167 (100); HRMS (EI) calcd for $C_{15}H_{20}O_5$ (M^+) 280.1311, found 280.1305. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.26.

(2*E*,4*E*,6*E*)-2,4,6-Dodecatrien-11-yn-1-al (2d). To a solution of ethyl (2*E*,4*E*,6*E*)-2,4,6-dodecatrien-11-ynoate[1] (138.6 mg, 0.635 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DIBAL in CH_2Cl_2 (1.33 mL, 1.33 mmol, 1.0 M). The resulting mixture was stirred at −78 °C for 20 min and then allowed to warm to 0 °C. The reaction was quenched with H_2O (0.5 mL) followed by 10% H_2SO_4 (0.5 mL). The mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2. The organic phases were combined, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated to give crude (2*E*,4*E*,6*E*)-2,4,6-dodecatrien-11-yn-1-ol (111.0 mg, 99%), which was taken on without further purification.

Oxalyl chloride (66.0 mL, 0.755 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to −60 °C. DMSO (108.0 mL, 1.51 mmol) was slowly added followed, after 5 min, by (2*E*,4*E*,6*E*)-2,4,6-dodecatrien-11-yn-1-ol (121.0 mg, 0.686 mmol). Stirring was continued for an additional 30 min at −60 °C. Triethylamine (498.0 mL, 3.57 mmol) was then added, and the solution was allowed to warm to room temperature. The reaction mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2. The organic phases were combined, washed with H_2O followed by saturated NaCl solution, dried over $MgSO_4$, and chromatographed on silica gel to give (2E,4E,6E)-2,4,6-dodecatrien-11-yn-1-al (**2d**) (74.0 mg, 62%) and recovered alcohol (1.7 mg, 1.5%). **2d**: ^{1}H NMR (300 MHz, C_6D_6) δ 1.32 (p, J = 7.1 Hz, 2H), 1.79 (t, J = 2.6 Hz, 1H), 1.89 (dt, J = 7.0, 2.6 Hz, 2H), 1.96 (q, J = 7.3 Hz, 2H), 5.48 (dt, J = 14.7, 7.1 Hz, 1H), 5.74 (dd, J = 15.0, 8.4 Hz, 1H), 5.79 (dd, J = 10.9, 8.4 Hz, 1H), 5.97 (dd, J = 15.2, 8.0 Hz, 1H), 6.06 (dd, J = 15.0, 10.9 Hz, 1H), 6.44 (dd, J = 15.1, 11.1 Hz, 1H), 9.43 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 17.9, 27.8, 31.8, 69.4, 83.6, 128.7, 130.9, 131.5, 139.6, 141.8, 150.8, 192.1; IR (CH_2Cl_2) 1681, 1613 cm^{-1}; LRMS, EI, *m/e* (%) 175 (1), 174 (M^+, 11), 146 (10), 145 (24), 144 (9), 132 (12), 131 (43), 130 (18), 118 (48), 117 (85), 115 (43), 9 1(100); HRMS (EI) Calcd for $C_{12}H_{14}O$ 174.1045, found 174.1038.

(2*E*,4*E*)-5-(13-Methoxy-8,11-dioxotetracyclo[5.5.2.0^{1,5}.0^{7,12}]-tetradec-13-en-6-yl)-2,4-pentadienal (3d). To a solution of (2*E*,4*E*,6*E*)-2,4,6-dodecatrien-11-yn-1-al (**2d**) (35.0 mg, 0.201 mmol) in THF (80 mL) was added complex **1** (77.7 mg, 0.241 mmol). The reaction was heated at 67 °C for 2 h, cooled to room temperature, concentrated in vacuo to approximately 1 mL, and immediately chromatographed on Florisil to give **3d** (44.7 mg, 74%): ^{1}H NMR (500 MHz, C_6D_6) δ 1.55−1.60 (m, 1H), 1.67−1.73 (m, 2H), 1.78−1.83 (m, 1H), 1.86−1.92 (m, 1H), 1.93−1.99 (m, 1H), 2.01−2.06 (m, 1H), 2.95 (s, 1H), 3.10−3.15 (m, 1H), 3.16 (s, 3H), 3.24−3.27 (m, 2H), 3.49 (dd, J = 4.4 Hz, 1H), 3.71−3.77 (m, 1H), 4.44 (s, 1H), 5.97 (dd, J = 15.4, 8.0 Hz, 1H), 6.00 (dd, J = 14.9, 7.6 Hz, 1H), 6.06 (dd, 15.1, J = 10.2 Hz, 1H), 6.49 (dd, J = 15.1, 10.2 Hz, 1H), 9.36 (d, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 25.7, 27.6, 29.3, 42.8, 55.3, 56.7, 57.7, 60.4, 66.5, 89.6, 90.0, 100.0, 129.7, 130.6, 146.7, 151.5, 159.5, 192.6; IR (CH_2Cl_2) 2959, 2934, 2901, 2872, 1684, 1637, 1605 cm^{-1}; LRMS, EI, *m/e* (%) 302 (M^+, 4), 243 (7), 168 (13), 167 (100); HRMS (EI) Calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1504.

1-(13-Methoxy-8,11-dioxotetracyclo[5.5.2.0.^{1,57,12}]tetradec-13-en-6-yl)methanal (3e). To a solution of (2*E*)-2-octen-7-ynal (**2e**)[24] (30.0 mg, 0.246 mmol) in THF (100 mL) was added complex **1** (95.0 mg, 0.295 mmol). The reaction was heated at 67 °C for 2h, cooled to room temperature, concentrated in vacuo to approximately 1 mL, and immediately chromatographed on Florisil to give **3e** (9.3 mg, 15%): ^{1}H NMR (300 MHz, C_6D_6) δ 1.46−1.56 (m, 1H), 1.60−2.02 (m, 5H), 2.27 (ddt, J = 9.9, 4.3, 1.0 Hz, 1H), 2.86 (d, J = 0.9 Hz, 1H), 3.06 (s, 3H), 3.12−3.17 (m, 1H), 3.24−3.34 (m, 1H), 3.51 (dd, J = 3.8, 2.9 Hz, 1H), 3.73 (ddd, J = 12.2, 8.6, 6.8 Hz, 1H), 4.36 (s, 1H), 9.78 (d, J = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 25.5, 27.5, 28.8, 50.8, 52.1, 55.3, 57.0, 60.6, 66.3, 89.1, 90.0, 100.2, 158.3, 201.5; IR (neat) 2956, 2934, 2871, 1717, 1642, 1606, 1462 cm^{-1}; LRMS, EI, *m/e* (%) 251 (2), 250 (M^+, 7), 233 (16), 222 (14), 221 (15), 207 (18), 168 (15), 167 (100), 165 (13), 154 (46), 139 (12), 137 (22), 91 (45).

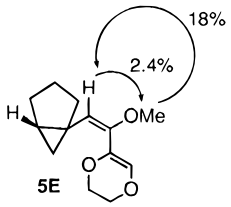
13-Methoxy-3,8,11-trioxotetracyclo[5.5.2.0^{1,5}.0^{7,12}]tetradec-13-ene (3f). To a solution of 4-oxa-6-hepten-1-yne (**2f**)[5b] (47.6 mg, 0.500 mmol) in THF (16 mL) was added complex **1** (161.1 mg, 0.500 mmol). The reaction was heated in a sealed vial at 100 °C for 2 h, cooled to room temperature, concentrated in vacuo to approximately 1 mL, and immediately chromatographed on silica gel to give **3f** (45.8 mg, 41%): ^{1}H NMR (500 MHz, C_6D_6) δ 1.25 (dd, J = 11.4, 9.0 Hz, 1H), 2.02−2.09 (m, 1H), 2.33 (dd, J = 11.7, 4.4 Hz, 1H), 2.87 (s, 1H), 3.10 (d, J = 3.4 Hz, 1H), 3.13 (s, 3H), 3.20−3.22 (m, 1H), 3.23 (d, J = 2.9 Hz, 1H), 3.70 (ddd, J = 16.6, 11.7, 4.6 Hz, 1H), 3.77 (d, J = 8.8 Hz, 1H), 3.96 (t, J = 7.8 Hz, 1H), 4.02 (dd, J = 10.8, 7.3 Hz, 1H), 4.10 (d, J = 8.8 Hz, 1H), 4.28 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 23.0, 50.9, 55.5, 58.4, 60.5, 66.3, 66.5, 70.6, 86.8, 88.0, 96.0, 161.9; IR (CH_2Cl_2) 2957, 2933, 2889, 1604, 1460, 1448 cm^{-1}; LRMS, EI, *m/e* (%) 225 (15), 224 (M^+, 100), 193 (16), 168 (35), 167 (41), 153 (48), 137 (34); HRMS (EI) Calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1054. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.24; H, 7.00.

3,3-Dicarbomethoxy-13-methoxy-8,11-dioxotetracyclo-[5.5.2.0^{1,5}.0^{7,12}]tetra-dec-13-ene (3h) and (5β)-1β-(2-Methoxy-2-(1,4-dioxen-2-yl)-1-ethenyl)-3,3-dicarbomethoxybicyclo[3.1.0]hexane (5). To a solution of dimethyl hept-6-en-1-yne-4,4-dicarboxylate (**2h**)[25] (75.7 mg, 0.360 mmol) in THF (16 mL) was added complex **1** (116.0 mg, 0.360 mmol). The reaction was heated in a sealed vial at 100 °C for 2 h, cooled to room temperature, concentrated in vacuo to approximately 1 mL, and immediately chromatographed on Florisil to give **3h** (40.5 mg, 33%) and **5** (14.2 mg, 12%, 5:1 mixture of enol ether isomers). The major enol ether isomer of **5** was assigned *E* geometry on the basis of NOE enhancements of 2.4% to the vinyl methoxy from the vinyl hydrogen and 18% enhancement to the vinyl hydrogen from the vinyl methoxy. **3h**: ^{1}H NMR (500 MHz, C_6D_6) δ 1.38 (dd, J = 11.2, 8.8 Hz, 1H), 2.17−2.24 (m, 1H), 2.39 (dd, J = 11.7, 4.4 Hz, 1H), 2.63 (dd, J = 12.7, 6.8 Hz, 1H), 2.69 (d, J = 14.6 Hz, 1H), 2.868 (t, J = 12.5 Hz, 1H), 2.874 (d, J = 14.6 Hz, 1H), 2.88 (s, 1H), 3.07−3.10 (m, 1H), 3.11 (s, 3H), 3.19−3.20 (m, 1H), 3.21−3.22 (m, 1H), 3.34 (s, 3H), 3.35 (s, 3H), 3.71 (ddd, J = 12.2, 10.4, 5.2 Hz, 1H), 4.50 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 25.9, 33.6, 38.2, 49.9, 52.1, 52.3, 55.4, 56.9, 60.5, 63.5, 66.7, 86.3, 88.9, 99.1, 161.5, 171.6, 173.7; IR ($CDCl_3$) 2955, 2937, 2904, 1731, 1607, 1460, 1449, 1436 cm^{-1}; LRMS, EI, *m/e* (%) 339 (2), 338 (M^+, 9), 307 (5), 279 (9), 168 (12), 167 (100), 166 (12); HRMS (EI) calcd for $C_{17}H_{22}O_7$ (M^+) 338.1366, found 338.1379. **5**: ^{1}H NMR (500 MHz, C_6D_6) major isomer only (**5E**)

(24) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 6264−62666

(25) Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676−2678.

δ 0.65−0.68 (m, 1H), 0.73 (t, J = 4.9 Hz, 1H), 1.37 (dt, J = 8.6, 4.4 Hz, 1H), 2.76 (dd, J = 13.7, 1.5 Hz, 1H), 2.79 (d, J = 14.2 Hz, 1H), 2.88 (dd, J = 13.7, 4.9 Hz, 1H), 3.11 (s, 3H), 3.24 (s, 3H), 3.34 (s, 3H), 3.55−3.57 (m, 2H), 3.71 (ddd, J = 7.3, 4.4, 2.9 Hz, 1H), 3.78 (ddd, J = 7.8, 4.9, 3.4 Hz, 1H), 4.73 (s, 1H), 6.66 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6) major isomer only (**5E**) δ 17.8, 26.9, 27.3, 37.0, 43.1, 52.2, 52.3, 54.6, 60.1, 64.2, 64.3, 103.0, 128.7, 133.9, 153.0, 172.4, 173.5; IR (CH_2Cl_2) 3063, 3031, 3002, 2981, 2955, 2909, 2881, 2843, 1731 cm^{-1}; LRMS, EI, *m/e* (%) 338 (M^+, 9), 307 (29), 247 (24), 219 (8), 188 (15), 187 (11), 91 (33), 77 (19), 59 (100); HRMS (EI) Calcd for $C_{17}H_{22}O_7$ 338.1366, found 338.1371.



5*H*-2,3,4a,7a-Tetrahydro-5-oxo-7-(4-pentenyl)cyclopenta-1,4-dioxin (6). To a solution of 6-hepten-1-yne (**2i**)[26] (28.2 mg, 0.300 mmol) in THF (30 mL) was added complex **1** (116.0 mg, 0.360 mmol). The reaction was heated at 67 °C for 2 h, cooled to room temperature, concentrated in vacuo to approximately 1 mL, and immediately chromatographed on silica gel to give **6** (12.6 mg, 20%): ^{1}H NMR (500 MHz, C_6D_6) δ 1.21−1.28 (m, 2H), 1.77 (q, J = 7.3 Hz, 2H), 1.85 (dt, J = 15.6, 6.8 Hz, 1H), 2.05 (dt, J = 15.6, 7.3 Hz, 1H), 3.04 (dt, J = 11.2, 2.9 Hz, 1H), 3.13 (dt, J = 11.7, 2.4 Hz, 1H), 3.16−3.21 (m, 1H), 3.45 (ddd, J = 11.7, 9.6, 2.4 Hz, 1H), 3.72 (d, J = 4.4 Hz, 1H), 3.83 (d, J = 4.9 Hz, 1H), 4.91−4.95 (m, 2H), 5.55−5.63 (m, 1H), 5.76 (t, J = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 30.8, 33.2, 63.2, 72.2, 74.6, 115.6, 129.5, 137.5, 175.1, 203.3; IR ($CDCl_3$) 3054, 2987, 1728, 1421 cm^{-1}; LRMS, EI, *m/e* (%) 208 (M^+, 6), 207 (2), 165 (24), 152 (32), 139 (13), 126 (48), 108 (37), 86 (78), 82 (43), 81 (27), 79 (30), 73 (100); HRMS (EI) Calcd for $C_{12}H_{15}O_3$ 207.1021, found 207.1015.

5*H*-2,3,4a,7a-Tetrahydro-5-oxo-7-pentylcyclopenta-1,4-dioxin (8). To a solution of 1-hexyne (**7**) (25.0 mg, 0.304 mmol) in THF (30 mL) was added complex **1** (117.6 mg, 0.365 mmol). The reaction was heated at 67 °C for 2 h, cooled to room temperature, concentrated in vacuo to approximately 1 mL, and immediately chromatographed on Florisil to give **8** (14.5 mg, 24%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.40 (sextet, J = 7.3 Hz, 2H), 1.54−1.63 (m, 2H), 2.39 (dt, J = 16.1, 7.8 Hz, 1H), 2.53 (dt, J = 16.1, 7.8 Hz, 1H), 3.60−3.72 (m, 4H), 4.08 (d, J = 4.9 Hz, 1H), 4.50 (d, J = 4.9 Hz, 1H), 6.10 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 22.4, 28.3, 31.2, 63.2, 72.2, 74.6, 129.4, 175.6, 203.4; IR (CH_2Cl_2) 2960, 2930, 2872, 1732 cm^{-1}; LRMS, EI, *m/e* (%) 196 (M^+, 8), 195 (11), 154 (54), 139 (24), 126 (85), 95 (28), 86 (100), 82 (100), 81 (35), 79 (16); HRMS (EI) Calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1102.

Acknowledgment. We thank Professor Jay Siegel for helpful discussions. We are grateful for support from the National Institutes of Health (Grant GM 39972) and the Alfred P. Sloan Foundation. Fellowship support to E.M.G. from the Graduate Assistance in Areas of National Need (GAANN) Program of the Department of Education, Eli Lilly, and Syntex is gratefully acknowledged. The 500 MHz NMR spectrometer was purchased with assistance from the National Institutes of Health (RR04733) and the National Science Foundation (CHE 8814866). Mass spectra were obtained with the assistance of Dr. Richard Kondrat and associates at the University of California at Riverside Mass Spectroscopy Facility.

Supporting Information Available: ^{13}C NMR spectra (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9513370

(26) Wulff, W. D.; Kaesler, R. W. *Organometallics* **1985**, *4*, 1461−1463.