Perhaps, the weakest point of our approach concerns the term $\Gamma(x,y,z)$ accounting for intermolecular interactions. The expression of $\Gamma(x,y,z)$ in (6) implicitly supposes that the SS, SQ, and QQ species are statistically distributed, whereas the cooperativity should favor the formation of like-species domains. The larger the interaction parameter γ, the more pronounced this defect is. Actually, this deficiency is present in the original Slichter and Drickamer's model from which we drew inspiration.

To conclude, we want to point out that it is not quite correct to attribute the step 1, below T_c, to the SS $\leftrightarrow$ SQ process, and the step 2, above T_c, to the SQ $\leftrightarrow$ QQ process. Each step involves SS, SQ, and QQ species, even if the proportions of QQ in step 1 and SS in step 2 are weak. According to our calculation (see Figure 13), z is equal to 0.043 at 163 K, and y is equal to 0.051 at 197 K.

The long term goal of our work dealing with polynuclear species incorporating spin-transition ions is to tune the shape of the signal provided by the $\chi_M T$ versus T plot.[55] This would be required to control both the intra- and intermolecular interactions. Molecular and crystal engineerings are involved in such a project, together with theoretical studies.

(55) Zarembowitch, J.; Kahn, O. *New J. Chem.* **1991**, *15*, 181.

Control over the Relative Stereochemistry at C4 and C5 of 4,5-Dihydrooxepins through the Cope Rearrangement of 2,3-Divinyl Epoxides and a Conformational Analysis of This Ring System

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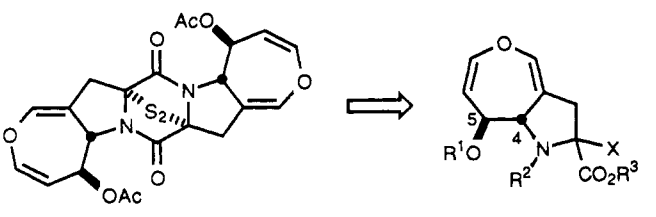
Abstract: The Cope rearrangement of *cis*-2,3-divinyl epoxides was used to control the relative stereochemistry at C4 and C5 of 4,5-dihydrooxepins. Wadsworth–Horner–Emmons olefination of either (4*E*)-*cis*-2,3-epoxy-5-(trimethylsilyl)-4-pentenal (**3**) or (5*E*)-*cis*-3,4-epoxy-6-(trimethylsilyl)-5-hexen-2-one (**4**) provided the cis epoxides used in this study. The termini of their 1,5-dienes were thereby substituted at one end with a trimethylsilyl group with fixed *E* stereochemistry and at the other with either a carboalkoxy or cyano substituent as both the *Z* and *E* isomers. The rearrangements were carried out within a temperature range of 95–135 °C, and all of the rearrangements were stereospecific, each leading to a single 4,5-dihydrooxepin. Based on a presumed boatlike transition state for these rearrangements, the (1*E*,5*E*)-*cis*-3,4-epoxy-1,5-hexadienes **5a–e** led to the *cis*-4,5-dihydrooxepins **7a–e**, and the (1*E*,5*Z*)-*cis*-3,4-epoxy-1,5-hexadienes **6a,c–e** led to the *trans*-4,5-dihydrooxepins **8a,c–e**. In general, those 1,5-dienes containing a *Z* double bond rearranged slower than the corresponding *E* isomers. A solvent affect was found in the [3,3] sigmatropic rearrangement of substrates containing *Z*-α,β-unsaturated esters, CH_3CN being a more effective solvent than CCl_4. It was further found that *Z*-α,β-unsaturated nitiriles rearranged more cleanly than the corresponding esters. The relative stereochemistry at C4 and C5 can greatly affect the subsequent reactivity of the oxepin nucleus, as illustrated by the greater kinetic acidity of the cis isomer of 4-carbomethoxy-5-(trimethylsilyl)-4,5-dihydrooxepin (**7a**) compared to that of its trans isomer **8a**. The ester of the former compound was easily deprotonated at −70 °C in THF by $LiN(TMS)_2$ and the resultant enolate alkylated at the α carbon by MeI, conditions that led to the complete recovery of the trans isomer. These results are consistent with the assignment of cis and trans stereochemistry of these oxepins. From their ^1H NMR spectra, all of the *trans*-4,5-dihydrooxepins appeared to be similar to each other in terms of their coupling patterns and constants, but the *cis*-4,5-dihydrooxepins could be divided up into two groups on the basis of their coupling constants. For three of the oxepins, *cis*-4,5-dihydrooxepins **7a** and **7c** and *trans*-4,5-dihydrooxepin **8a**, the assignment of their coupling patterns was confirmed by 2-D NMR. The minimum-energy conformations of these three oxepins were determined by molecular mechanics calculations. The conformational preferences were explicable in terms of two steric interactions: allylic $A^{1,2}$ strain and the gauche interaction at C4 and C5.

Introduction

Aranotin acetate (**1**) is a fungal metabolite exhibiting antiviral activity and containing two 4,5-dihydrooxepin nuclei that are identical both in their functionality and in their absolute stereochemistry.[2] One possible retrosynthetic analysis of this molecule, involving a disconnection of the epidithiapiperazinedione moiety, leads to the advanced intermediate **2**, which could also be used as an intermediate for a number of other structurally related fungal metabolites.[3] One of the problems inherent in the synthesis of



1 aranotin acetate 2 X=H or SR[4]

2 is the control of the relative stereochemistry at C4 and C5 of the 4,5-dihydrooxepin ring. The preparation of 4,5-dihydrooxepins

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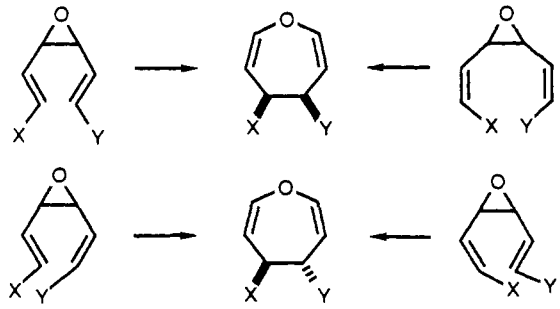
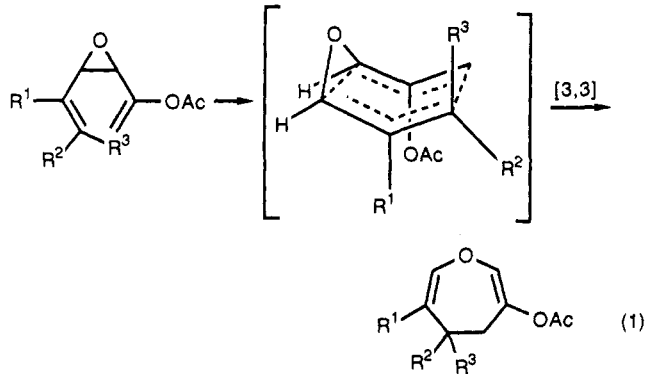
Scheme I



through [3,3] sigmatropic rearrangement of *cis*-2,3-divinyl epoxides[4] (eq 1) is well suited for application to this problem. If

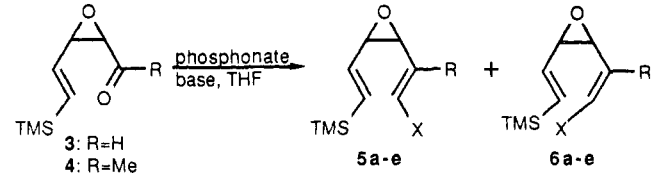


(1)

one assumes that this Cope rearrangement is concerted, then the only viable manifold for the rearrangement is the boatlike transition state shown below. This hypothesis is consistent with the observation that a substrate with the *Z* alkene stereochemistry rearranged slower than the corresponding epoxide with the *E* alkene stereochemistry.[4h,5] This observation is presumably the result of greater steric strain in the transition state for the *Z* isomer (R^3 = alkyl, R^2 = H) than for the *E* isomer (R^3 = H, R^2 = alkyl). If both double bonds are unsymmetrically substituted at the termini of the 1,5-diene, then stereocenters at both C4 and C5 of the oxepin ring will be generated following the Cope rearrangement. Furthermore, it should be possible by simply controlling the stereochemistry of the alkene geometries in the 1,5-diene to obtain either of the two possible stereoisomers in the oxepin product. As illustrated in Scheme I, for either the *cis*- or *trans*-4,5-dihydrooxepin, there are two possibilities for matching the double-bond geometries of the 1,5-diene to give an oxepin with the same relative stereochemistry at C4 and C5.[6] For synthesizing *cis*-4,5-dihydrooxepins, the divinyl epoxide wherein both double bonds are *E* is likely to be the better choice, as there should be less steric strain in its boatlike transition state than in the corresponding transition state wherein both double bonds are *Z* in the divinyl epoxide.[7] For generating *trans*-4,5-dihydrooxepins, the two possibilities are more closely matched, since they both involve pairing one *Z* double bond with one *E*.

Previous methodologies for preparing divinyl epoxides have not allowed for a straightforward investigation into this question of control over the relative stereochemistry at C4 and C5 of 4,5-dihydrooxepins,[8] but extension of our original procedure[4h] for preparing *cis*-2,3-divinyl epoxides makes pairs of complimentary divinyl epoxides readily available. We report herein our investigation into this strategy.

Table I. Preparation of *cis*-2,3-Divinyl Epoxides through Wadsworth–Horner–Emmons Olefination[a]



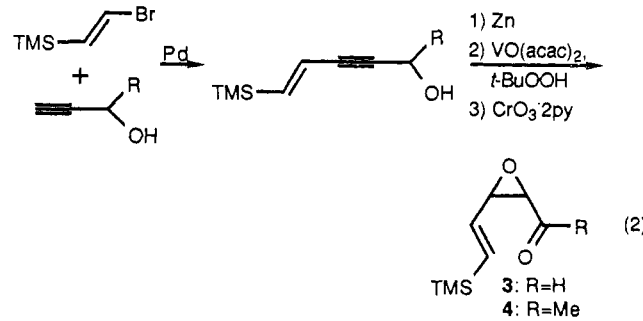
3: R=H
4: R=Me

	R	X	ratio **5**:**6**	yield, %
a	H	CO_2Me	1:3.3	83
b	H	CO_2Et	12:1	83
c	Me	CO_2Et	1:3	70
d	H	CN	1.8:1	67
e	Me	CN	1.5:1	67

[a] See text and experimental section for details on the phosphonate reagent and reaction conditions used in each example.

Results and Discussion

Synthesis and Rearrangement of *cis*-2,3-Divinyl Epoxides. One way to put this analysis into practice is to prepare and rearrange pairs of 1,5-dienes wherein one double bond is always *E*, while the stereochemistry of the other alkene is varied. For this purpose, use was made of aldehyde **3** and methyl ketone **4**, both of which were readily available (eq 2) from (*E*)-(2-bromovinyl)trimethylsilane through a sequence of reactions that began with Sonogashira coupling[9] with either propargyl alcohol or 3-butyn-2-ol. Each of the resultant enynols underwent Rieke zinc re-



(2)

(1) Author to whom correspondence should be sent concerning the molecular mechanics calculations and the low-temperature, 1-D, and 2-D NMR data obtained at 300 MHz.

(2) Neuss, N.; Boeck, L. D.; Brannon, D. R.; Cline, J. C.; DeLong, D. C.; Gorman, M.; Huckstep, L. L.; Lively, D. H.; Mabe, J.; Marsh, M. M.; Molloy, B. B.; Nagarajan, R.; Nelson, J. D.; Stark, W. M. *Antimicrob. Agents Chemother.* **1968**, 213–219.

(3) (a) Seya, H.; Nozawa, K.; Nakajima, S.; Kawai, K.; Udagawa, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 109–116. (b) Seya, H.; Nozawa, K.; Udagawa, S.; Nakajima, S.; Kawai, K. *Chem. Pharm. Bull.* **1986**, *34*, 2411–2416. (c) Kawahara, N.; Nozawa, K.; Yamazaki, M.; Nakajima, S.; Kawai, K. *Chem. Pharm. Bull.* **1990**, *38*, 73–78. (d) Kawahara, N.; Nozawa, K.; Yamazaki, M.; Nakajima, S.; Kawai, K. *Heterocycles* **1990**, *30*, 507–515.

(4) (a) Braun, R. A. *J. Org. Chem.* **1963**, *28*, 1383–1384. (b) Stogryn, E. L.; Gianni, M. H.; Passannante, A. J. *J. Org. Chem.* **1964**, *29*, 1275–1276. (c) Vogel, E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385–401. (d) Pommelet, J. C.; Manisse, N.; Chuche, J. *Tetrahedron* **1972**, *28*, 3929–3941. (e) Balci, M.; Sütbeyaz, Y. *Tetrahedron Lett.* **1983**, *24*, 4135–4138. (f) Sütbeyaz, Y.; Secen, H.; Balci, M. *J. Org. Chem.* **1988**, *53*, 2312–2317. (g) Hudlicky, T.; Fleming, A.; Lovelace, T. C. *Tetrahedron* **1989**, *45*, 3021–3037. (h) Clark, D. C.; Chou, W.-N.; White, J. B. *J. Org. Chem.* **1990**, *55*, 3975–3977. (i) Chou, W.-N.; White, J. B. *Tetrahedron Lett.* **1991**, *32*, 157–160.

(5) To avoid confusion with nomenclature in this paper, the terms cis and trans will be used exclusively for differentiating geometric isomers of epoxides and oxepins, and the terms *E* and *Z* will be used as descriptors of alkene geometry.

(6) It should be noted that if the divinyl epoxides in Scheme I are enantiomerically pure, then the products from each pair of dienes with inverted olefinic geometries would be enantiomers of each other.

(7) 1,2-Divinylcyclopropanes, which generally undergo more facile Cope rearrangement than the corresponding 2,3-divinyl epoxides (for a lead reference, see: Stogryn, E. L.; Brois, S. J. *J. Am. Chem. Soc.* **1967**, *89*, 605–609), fail to undergo thermally induced [3,3] sigmatropic rearrangement when both double bonds of the 1,5-diene are cis. For the example of *cis,cis,cis*-1,2-di(prop-1-enyl)cyclopropane, see: (a) Baldwin, J. E.; Ullenius, C. *J. Am. Chem. Soc.* **1974**, *96*, 1542–1547. (b) Schneider, M. P.; Rau, A. *J. Am. Chem. Soc.* **1979**, *101*, 4426–4427.

(8) There are two published examples of Cope rearrangements of divinyl epoxides that lead to 4,5-disubstituted 4,5-dihydrooxepins. See ref 4d,f.

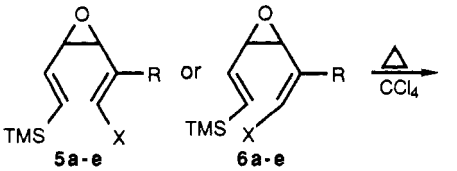
(9) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.

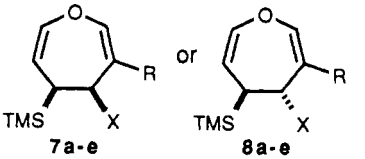
duction to give the product from cis reduction of the alkyne.[10] Selective epoxidation of the allyl alcohol double bond followed by Collins oxidation of the alcohol provided *cis*-epoxy aldehyde **3** and cis-epoxy ketone **4**. The *cis*-2,3-divinyl epoxides **5** and **6** examined in this study were then obtained by Wadsworth–Horner–Emmons olefination of **3** and **4** (Table I).

Because of its potential usefulness in future synthetic endeavors and ease of introduction with control over the olefinic stereochemistry, a carboalkoxy group was the first substituent examined as a match with the TMS group at the termini of the 1,5-diene. Olefination of aldehyde **3** with bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate[11] led to mixtures of the *E* and *Z* methyl esters **5a** and **6a** that favored the *Z* isomer **6a**, whereas olefination with triethyl phosphonoacetate led to predominantly the ethyl *E*-α,β-unsaturated ester **5b**. The assignment of olefinic stereochemistry, which is important to the eventual assignment of relative stereochemistry in the products from Cope rearrangement, was in agreement with the known *E* and *Z* selectivity of the two phosphonate anions used in this study.[12] Furthermore, the *E* stereochemistry of the α,β-unsaturated esters in **5a** and **5b** was consistent with the large vicinal olefinic coupling constant (J = 15.8 Hz) for this double bond.[13] Each ester was easily separated from its olefinic isomer by flash chromatography, thereby avoiding any ambiguity in the interpretation of the stereochemical outcome of its rearrangement. In the event, it was found that both *E*-α,β-unsaturated esters **5a** and **5b** underwent very clean Cope rearrangement in CCl_4 to each give a single product whose structures were assigned as the *cis*-4,5-dihydrooxepins **7a** and **7b**, respectively. Rearrangement of the *Z*-α,β-unsaturated ester **6a** in CCl_4 required more vigorous conditions (130 °C, 24 h, 62%) and was not as clean a reaction, but it also led to a single identifiable oxepin, which was assigned the trans stereochemistry of **8a**. It was later found that the efficiency of the Cope rearrangement of esters with the *Z* configuration was solvent dependent (vide infra). In the case of **6a**, rearrangement in CH_3CN led to a significant improvement in yield and a much cleaner reaction. To the extent that it could be determined by both NMR and TLC, there was no crossover in the rearrangements of **5a,b**, **6a**, or any of the other divinyl epoxides examined in this study (see Table II); i.e., each rearrangement was stereospecific.

From their ^1H and ^{13}C NMR spectra it was clear that the *cis*-oxepins **7a** and **7b** differed only in the alkoxy group of the ester, while the *trans*-oxepin **8a** was a diastereomer of **7a**. The assignment of the relative stereochemistry at C4 and C5 of **7a,b** and **8a** rests in part on the presumption of a boatlike transition state in these Cope rearrangements, and is supported by the effect of the TMS group on the reactivity of the adjacent ester group. The cis ester **7a** was faster moving on silica gel than the corresponding trans ester **8a**, consistent with the carboalkoxy group being sterically more hindered when syn to the TMS group. There was also a notable difference in the kinetic acidity of the ester groups in **7a** and **8a**. Deprotonation of **7a** was easily achieved at low temperature and the resultant enolate underwent alkylation with methyl iodide to give oxepin **9** as a single diastereomer based on its ^{13}C NMR spectrum. The trans ester **8a** was recovered unchanged when subjected to the same reaction conditions and even proved resistant to deprotonation by $LiN(TMS)_2$ at 0 °C. Indeed, the difference in reactivity between these two esters was sufficiently great that a 50:50 mixture of **7a** and **8a** was cleanly converted at −75 °C to a mixture of **9** and recovered **8a**. The assignment of relative stereochemistry at C4 and C5 of **9** was consistent both with the expectation of alkylation from the less hindered face of the ester enolate away from the TMS group and with the experimental observation that quenching of the enolate derived from **7a** with methanol led to the recovery of **7a**. Quenching with methanol-*d* led to incorporation of deuterium at C4 of the oxepin ring and isolation of **10**, whose ^{13}C NMR spectrum, with the exception of the expected change at C4, was identical with that of **7a**.

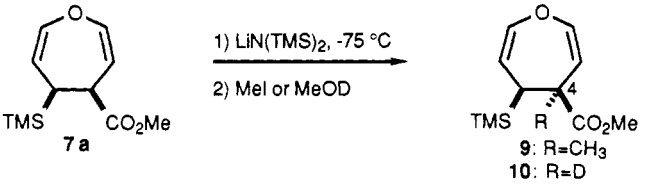
Table II. Preparation of *cis*- and *trans*-4,5-Dihydrooxepins through Cope Rearrangement of *cis*-2,3-Divinyl Epoxides



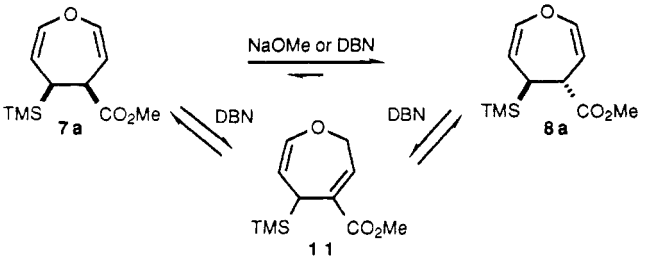


	R	X	T, °C	t, h	yield of **7** from **5**, %	T, °C	t, h	yield of **8** from **6**, %
a	H	CO_2Me	100	12	84	135	15	82[a]
b	H	CO_2Et	95	20	77			*b*
c	Me	CO_2Et	125	21	89	135	15	82[a]
d	H	CN	105	13	79	135	21	74
e	Me	CN	125	5	85	125	24	85

[a] The rearrangements of **6a** and **6c** were best conducted in acetonitrile or benzene; see text for details. [b] **6b** was formed as a minor product in the preparation of **5b** and was not subjected to Cope rearrangement.



Given our interest in preparing *trans*-4,5-dihydrooxepins and the milder conditions necessary to effect the Cope rearrangement to generate the *cis*-4,5-dihydrooxepins, the base-catalyzed equilibration of oxepin **7a** was studied to determine if the *trans*-oxepin might be available from its cis isomer. It appeared that the trans isomer **8a** was thermodynamically more stable than **7a**, although the results were complicated by relatively low mass recovery (≤50%) and the fact that the cis isomer is presumably more reactive toward the base and may have been selectively destroyed in comparison to the trans isomer. Treatment with NaOMe (1.2 equiv, THF, 0 °C–room temperature) of either **7a** or **8a** led to an approximately 4:1 mixture in favor of *trans*-4,5-dihydrooxepin **8a**. Equilibration of either **7a** or **8a** with DBN (1 equiv, THF, room temperature) led to ratios of approximately 1:6–10 of **7a** and **8a**, along with variable amounts of the conjugated isomer **11**.



The feasibility of directly incorporating through the Cope rearrangement an alkyl substituent at C3 of the oxepin nucleus was also investigated. To this end, methyl ketone **4** was olefinated with triethyl phosphonoacetate to give a mixture of the isomeric β,β-disubstituted α,β-unsaturated esters **5c** and **6c** (Table I). These esters were separated by HPLC and the assignment of *E* olefinic stereochemistry to **5c** was based on the chemical shift of

(10) Chou, W.-N.; Clark, D. L.; White, J. B. *Tetrahedron Lett.* **1991**, *32*, 299–302.
(11) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
(12) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
(13) The corresponding vicinal coupling constant in the ^1H NMR spectra of **6a,b** could not be determined at 200 MHz.

its vinyl methyl group being upfield in the ^{13}C NMR spectrum and downfield in the ^{1}H NMR spectrum (δ 16.1 and 2.13) compared to the corresponding shifts for **6c** (δ 21.6 and 1.94).[14] Cope rearrangement of the *E* isomer **5c** (125 °C, 21 h, 89%) took place cleanly to give the *cis*-4,5-dihydrooxepin **7c**,[15] but Cope rearrangement of the *Z* isomer **6c** proved problematic at first. It was discovered that, unlike the other pairs of isomeric 1,5-dienes in this study, the *Z* isomer **6c** was actually more reactive (i.e., less stable) in CCl_4 than was the *E* isomer **5c**. Heating divinyl epoxide **6c** at 70 °C in CCl_4 led to slow decomposition and the formation of small amounts of several unidentified products. None of these products appeared to be the desired product **8c**, nor was **8c** detected as a transient intermediate by TLC. Heating **6c** in the range 105–135 °C in CCl_4 or CCl_4/Et_3N[4i] also led to manifold products, but variable amounts of the product from Cope rearrangement, oxepin **8c**, were isolated and identified by ^{1}H NMR. Although not a synthetically useful result, the hint of a temperature dependence in this rearrangement led to an examination of the other experimental variable in these reactions, the solvent. It was discovered that 4,5-dihydrooxepin **8c** could be obtained in good yield from **6c** in either acetonitrile or benzene (135 °C, 15 h, 82%). The Cope rearrangement of **6c** also worked to a lesser extent in THF (135 °C, 15 h, 71%) but gave little or no oxepin **8c** in anhydrous ethanol, hexane, CH_2Cl_2, or diethyl ether. This solvent effect was limited to the *Z* isomer **6a** (vide supra) and **6c**, as the Cope rearrangement of the *E* isomer **5c** showed no improvement when either acetonitrile or benzene (135 °C, 15 h, 85%) was substituted for CCl_4.

The Cope rearrangement is expected to be relatively slower for *Z*-α,β-unsaturated esters **6a,c** compared to the *E* isomers **5a,c** due to greater steric interactions in the transition state for the former, which increases the likelihood that alternative reaction pathways can successfully compete with the Cope rearrangement for the *Z* isomers. One alternative reaction pathway that is geometrically possible for the *Z* isomers but not for *E* isomers is intramolecular attack by the carbonyl oxygen atom of the ester on the epoxide, leading to cleavage of the C–O bond of the epoxide closest to the ester. Such a reaction pathway may also explain why **6a** more cleanly undergoes the Cope rearrangement (in CCl_4) than does **6c**. The vinyl methyl group in **6c** would provide additional stabilization of the oxonium ion portion of the zwitterionic intermediate from nucleophilic attack on the epoxide by the ester and thereby lower the transition-state barrier of this reaction pathway for **6c** compared to **6a**. Another possible reaction pathway is the heterolytic opening of the epoxide carbon–carbon bond to generate an intermediate carbonyl ylide, the negative end of the resulting dipole being stabilized by resonance with the ester.[16] Such an intermediate generated from **6c** might further react with either unreacted **6c** or **8c**, leading to a loss in yield of the product from Cope rearrangement. In one reaction run in CCl_4, the inclusion of a dipolarophile (2 equiv of dimethyl acetylenedicarboxylate) led to a significant improvement in the yield of **8c** from **6c** (135 °C, 15 h, 75%) and the isolation of, among other unidentified products, a small amount (<5%) of the adduct identified from its ^{1}H NMR spectrum as that from [3 + 2] cycloaddition of the carbonyl ylide of the epoxide with the dipolarophile.[16] The better yields observed in the Cope rearrangement of **6a** and **6c** in CH_3CN may be the result of trapping of a carbonyl ylide intermediate by the solvent.

(14) (a) For a lead reference concerning the assignment of stereochemistry from the ^{13}C NMR data for α,β-unsaturated esters, see: Séquin, U. *Tetrahedron Lett.* **1979**, 1833–1836. (b) For a lead reference concerning the assignment of stereochemistry from the ^{1}H NMR data for α,β-unsaturated esters, see: Burrell, J. W. K.; Garwood, R. F.; Jackman, L. M.; Oskay, E.; Weedon, B. C. L. *J. Chem. Soc. C* **1966**, 2144–2154.

(15) *cis*-Oxepin **7c** was not as easily deprotonated as *cis*-oxepin **7a**, as alkylation under the same conditions described for the preparation of **9** led mostly to recovery of **7c** and about a 5% yield of a compound identified from its ^{1}H NMR spectrum as the product from methylation at C4. *trans*-Oxepin **8c** was recovered unchanged when subjected to the same conditions.

(16) The corresponding trans epoxides of **5a** and **6a** react predominantly through such intermediates to give low yields in CCl_4 of **7a** and **8a**, respectively. See: Chou, W. N.; White, J. B. The Use of *trans*-2,3-Divinyl Epoxides as Precursors to Carbonyl Ylides. *Tetrahedron Lett.* **1991**, *32*, 7637–7640.

The difficulties associated with the Cope rearrangement of the *Z*-α,β-unsaturated esters **6a** and **6c** compared to their *E* isomers **5a** and **5c** lent an impetus for a search for an alternative to the carboalkoxy group that would minimize the differences in reactivity between the *E* and *Z* isomers. The cyano group, being similar to an ester in terms of the possible synthetic transformations available to it following the Cope rearrangement but smaller in size, seemed an ideal choice for this purpose. Olefination of aldehyde **3** or methyl ketone **4** with diethyl cyanomethylphosphonate led to separable mixtures of the *E* and *Z* isomeric α,β-unsaturated nitriles (Table I). The *E* stereochemistry of the α,β-unsaturated nitrile **5d** was clear from its larger olefinic coupling constant (J_{alkene} = 16.2 Hz) compared to that of its isomer **6d** (J_{alkene} = 11.2 Hz). The *E* olefinic stereochemistry was assigned to **5e** on the basis of the same (albeit smaller) upfield shift in the ^{13}C NMR spectrum and downfield shift in the ^{1}H NMR spectrum for the vinyl methyl group (δ 18.3 and 2.04) relative to the corresponding shifts for **6e** (δ 20.8 and 1.91) that had been observed for the corresponding esters **5d** and **6d**.[14] All four of these α,β-unsaturated nitriles underwent [3,3] sigmatropic rearrangement in CCl_4 to give the expected products **7d,e** and **8d,e** in good yield (Table II). Although there was no improvement in the comparative reactivity of a *Z* isomer versus its *E* isomer from what had already been observed in the ester series (in each case the *E*-α,β-unsaturated nitrile rearranged under milder conditions than the corresponding *Z*-α,β-unsaturated nitrile), the nitriles did differ in one respect from the esters. The Cope rearrangements of the *Z*-α,β-unsaturated nitriles **6d,e** in CCl_4 were clean reactions, unlike the reactions of the *Z*-α,β-unsaturated esters **6a** and **6c** in this solvent, and may therefore be a more reliable way of making trans-4,5-disubstituted 4,5-dihydrooxepins. If the problem with the Cope rearrangements of the *Z* isomers of the esters is a competitive intramolecular attack by the carboalkoxy group on the epoxide (vida supra), then it may be that the advantage of the cyano group is not its smaller size but its linearity, which prevents it from participating in a similar reaction. The use of an aldehyde in place of an ester at the terminus of the 1,5-diene was also investigated. Olefination of aldehyde **3** with (formylmethylene)triphenylphosphorane led to the expected *E*-α,β-unsaturated aldehyde. However, attempted thermal Cope rearrangement in CCl_4, CH_3CN, or benzene led to a mixture of products, in contrast to a previous report[4e,f] of the successful Cope rearrangement of a carboxaldehyde-substituted divinyl epoxide. In our example, the problem may be with the stability of the oxepin product itself, as one of the isolated products appears to be derived in part by migration of the C2–C3 π bond into conjugation with the aldehyde.

Conformational Analysis of 4,5-Disubstituted 4,5-Dihydrooxepins

Introduction. In examining the NMR spectral data of the 4,5-dihydrooxepins **7a–e** and **8a,c–e** for patterns that were characteristic of the relative stereochemistry at C4 and C5, it was found that the chemical shifts of the hydrogens at C4 and C5 in the *cis*-4,5-dihydrooxepin series were always downfield of those in the corresponding *trans*-4,5-dihydrooxepins, although the J_{45} vicinal coupling constants in the ^{1}H NMR spectra were remarkably not indicative of the relative stereochemistry at C4 and C5. In a previous study of 4,5-disubstituted *trans*-4,5-dihydrooxepins, which were prepared by nucleophilic addition to *sym*-oxepin oxide,[17] it had been observed that the J_{45} coupling constants fell within the range 7.2–8.7 Hz. In contrast, the J_{45} coupling constants for all of the 4,5-dihydrooxepins prepared in this study, both cis and trans, were considerably smaller (2.2–3.6 Hz) and showed no discernible trends. However, it was possible to sort these molecules into three groups on the basis of their J_{24}, J_{56}, J_{57}, and, were relevant, J_{34} coupling constants. All of the trans isomers **8a,c–e** had similar values for both J_{56} (8.3–8.9 Hz) and, for **8a** and **8d**, J_{34} (8.1–8.4 Hz), but the cis isomers **7a–e** could

(17) Rastetter, W. H.; Chancellor, T.; Richard, T. J. *J. Org. Chem.* **1982**, *47*, 1509–1512.

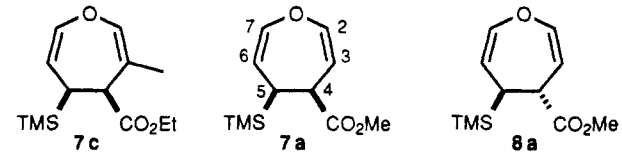
be differentiated into two groups. **7a,b,d** were similar to the trans isomers in having relatively large J_{56} coupling constants (7.7–8.9 Hz) but differed from **8a** and **8d** in having smaller J_{34} coupling constants (3.4–4.7 Hz) and differed from all of the other oxepins in having substantial J_{24} coupling constants (2.3–2.8 Hz). The cis isomers **7c** and **7e**, which differ from the cis isomers **7a,b,d** by being substituted at C3 with a methyl group, were distinguished from all of the oxepins both by their smaller values for J_{56} (4.9–6.4 Hz) and by their significant J_{57} coupling constants (1.7–2.4 Hz). Given the lack of any previous work on the conformational analysis of 4,5-disubstituted 4,5-dihydrooxepins, a study was undertaken of these molecules that involved the determination of their minimum-energy conformations as established by molecular mechanics calculations and a comparison of the calculated values of their vicinal coupling constants with the experimentally observed ones. One compound from each of the three groups, the cis isomers **7a** and **7c** and the trans isomer **8a**, was included in this study.

Experimental Methods and Definition of Terms. The ^1H and ^{13}C NMR spectra of oxepins **7a**, **7c**, and **8a** were taken at 300 and 75 MHz, respectively. A combination of 1-D and 2-D methods was used to determine all parameters. The proton coupling constants were checked in all cases by a full six-spin simulation. Homo- and heteronuclear correlation spectra were used to confirm the overall coupling pattern and the relation of various carbons to their associated protons.

Molecular modeling and mechanics calculations were carried out on a Macintosh IIci with the program PCMODEL.[18] This program consists of several parts. The MMX force field utilized in the molecular mechanics portion of this program is a modified form of the 1977 Allinger MM2 force field. For π-electron-containing systems, the carbon–carbon bond lengths are adjusted by π-bond order following a SCF MO calculation. During the subsequent refinement, the program periodically returns to the MO portion and updates these bond lengths. The final minimized energy is given in terms of a relative MMX energy as well as in heats of formation and strain energy. While the experimental procedure produced **7c** as the ethyl ester, for the sake of consistency in comparing its heat of formation with those of the methyl esters **7a** and **8a**, the molecular mechanics calculations for **7c** assumed it to be the methyl ester. That the conformation of the methyl ester should be approximately the same as that of the ethyl ester is supported by a comparison of the NMR data for the methyl ester **7a** and the ethyl ester **7b**, which showed no significant differences in their chemical shifts or coupling constants. The authors of PCMODEL warn specifically that the MMX energies should only be used in comparing different conformers of the same molecule. The program includes a dihedral driver option for either one or two bonds and allows estimations of vicinal NMR proton coupling constants for H–C(sp^3)–C(sp^3)–H fragments by the Haasnoot, de Leeuw, and Altona[19] modification of the Karplus equation and for H–C(sp^3)–C(sp^2)–H couplings by the equation of Garbisch.[20]

Examination of Fieser models (Aldrich) of the three dihydrooxepins established that they can exist only in various boat and twist-boat conformers. Since the boat forms involve total eclipsing of all bonds at C4 and C5, they are unlikely to be minimum-energy conformations, but they may represent barriers between such conformations. The extremes of the angles[21] of rotation about the H–C4–C5–H bond, which correspond to the two staggered arrangements of substituents about the C4–C5 bond, were estimated from the models to be +60° to −60° for compounds **7a** and **7c** and −60° to 180° for compound **8a**, and these angles were used as limits for the dihedral driver program. Bond rotations between these limits were taken in 10-deg increments. The terms equatorial and axial will be used to distinguish between the two possible positions of the substituents at C4 and C5 when the substituents are completely staggered at the extremes of the dihedral angle for H–C4–C5–H. The term axial will denote a substituent that is nearly perpendicular to the plane of the oxepin ring, while the term equatorial will refer to a substituent staggered between the two substituents on the adjacent sp^3 hybridized carbon atom. This means that for the two fully staggered conformations of *cis*-oxepins **7a** and **7c**, one of the two non-hydrogen substituents at C4 and C5 is axial and the other is equatorial. For the trans isomer **8a**, the two non-hydrogen substituents are either both axial or both equatorial. For all three of these molecules, two sets of calculations were required based on the two possible positions of the divinyl ether oxygen atom with respect to the rest of the ring and the substituents at C4 and C5. The terms syn and anti will be used to differentiate these two sets of calculations and will refer to the relative position of the divinyl ether oxygen with respect to the TMS group at C5. Flipping the oxygen atom of the ring "up" and "down" (syn and anti based on the relative stereochemistry shown for **7a**, **7c**, and **8a**) affects the dihedral angles H–C3–C4–H and H–C5–C6–H but does not require simultaneous rotation about the C4–C5 bond.

Table III. ^1H and ^{13}C NMR Chemical Shifts[a,b] for 4,5-Dihydrooxepins **7c**, **7a**, and **8a**



	7c		7a		8a	
position	^1H, δ	^{13}C, δ	^1H, δ	^{13}C, δ	^1H, δ	^{13}C, δ
2	6.21	139.8	6.15	143.3	6.23	144.2
3		116.0	5.42	106.3	4.85	102.5
4	3.32	50.5	3.78	45.6	3.34	45.3
5	2.12	28.6	2.43	34.7	2.10	32.9
6	4.80	108.1	4.91	110.0	4.93	108.0
7	6.27	143.7	6.15	141.4	6.16	139.6
CO_2		172.6		173.1		174.5

[a] Supplementary ^1H NMR (^{13}C NMR) chemical shifts (δ): (**7c**) OCH_2CH_3 4.13 (60.6) and 1.26 (14.1), vinylic CH_3 1.68 (21.0); (**7a**) OCH_3 3.70 (53.3); (**8a**) OCH_3 3.64 (52.4). [b] Spectra were obtained at 300 MHz (75 MHz) in $CDCl_3$ using internal tetramethylsilane as reference.

Table IV. Experimentally Observed Coupling Constants (Hz) for 4,5-Dihydrooxepins **7c**, **7a**, and **8a**

	J_{23}	J_{24}	J_{34}	J_{35}	J_{45}	J_{46}	J_{56}	J_{57}	J_{67}
7c[a]					2.8	*b*	4.9	2.4	6.8
7a	7.6	2.5	3.4	0.8	3.6	*b*	8.9		7.7
8a	7.8		8.4	0.8	2.3	0.3	8.9		7.7

[a] The coupling constant between the H at C.2 and the methyl group at C.3 was 1.46 Hz. [b] Correlation was observed in the COSY experiment, but only as a line broadening in the 1-D spectrum.

Results and Discussion. The proton coupling patterns for **7a**, **7c**, and **8a** were all first order so that coupling constants were available by direct analysis. The reasonable assumption was made that the chemical shifts for both the protons and carbons at position 5 would be upfield from those at position 4 and that the chemical shifts for the olefinic positions α to the ring oxygen would be downfield from their neighboring olefinic positions β to the ring oxygen. The NMR parameters at room temperature are given in Tables III and IV. Proton spectra for **7a**, **7c**, and **8a** were also determined at 20° intervals from 20 °C down to −60 °C. Trivial changes in some chemical shifts were the only alterations noted, which can be attributed to the small concentration changes that occur upon cooling. From this low temperature ^1H NMR study, it can be inferred that these molecules have either a single low-energy conformation or, more likely, relatively small barriers between low-energy conformations.

(18) This program was written by K. E. Gilbert and J. J. Gajewski and is available from Serena Software, Bloomington, IN.

(19) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.

(20) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5561–5564.

(21) In sighting down the bond connecting C*n* with C*n*+1, the sign of the dihedral angle is defined as being positive when the angle carved out by going from H–C*n* to H–C*n*+1 is clockwise and negative when counterclockwise.

Table V. Minimum MMX Energies with Their Dihedral Angles and Calculated Vicinal Coupling Constants for **7c**,[a] **7a**, and **8a**

	conformation[b]		MMX,	H–C3–C4–H	H–C4–C5–H	H–C5–C6–h
	$SiMe_3$	CO_2Me	kcal/mol	(J_{34})[c]	(J_{45})[c]	(J_{56})[c]
7c[a]						
syn	ax	eq	6.47	−84°[d]	60° (3.01)	−5° (6.57)
syn	eq	ax	3.66	−3°[d]	−60° (2.69)	73° (2.92)
anti	ax	eq	4.73	−131°[d]	60° (3.01)	46° (4.5)
anti	eq	ax	3.33	50°[d]	−60° (2.68)	131° (4.33)
7a						
syn	ax	eq	6.10	−76° (2.81)	58° (3.02)	−2° (6.59)
syn	eq	ax	4.85	2° (6.59)	−60° (2.71)	74° (2.89)
anti	ax	eq	4.42	−130° (6.38)	60° (2.98)	46° (4.49)
anti	eq	ax	5.36	−48° (4.35)	−60° (2.70)	132° (6.62)
8a						
syn	ax	ax	6.22	38° (5.06)	−58° (2.93)	−3° (6.59)
syn	eq	eq	6.21	129° (6.16)	180° (14.1)	61° (3.50)
anti	ax	ax	3.26	−3° (6.59)	−60° (2.60)	42° (4.83)
anti	eq	eq	6.21	66° (3.27)	−179° (14.1)	131° (6.42)

[a] The calculations on **7c** were actually carried out on the methyl ester; see reference 20. [b] The terms syn, anti, axial (ax), and equatorial (eq) are defined in the text. [c] The calculated values of the vicinal coupling constants in units of hertz are given in parentheses following the value of the corresponding dihedral angle. [d] The value given for the dihedral angle for H–C3–C4–H for **7c** is actually the dihedral angle for Me–C3–C4–H.

The minimum MMX energies and the dihedral angles along the C3–C4, C4–C5, and C5–C6 bonds for both the syn and anti series, as well as the calculated J_{34}, J_{45}, and J_{56} vicinal coupling constants, are provided in Table V. For each of these molecules, the minima in energy were found either at or within a few degrees of the fully staggered conformations about the C4–C5 bond. For the *cis*-oxepin **7c**, the maxima in MMX energy when fully eclipsed about the C4–C5 in the syn and anti series was calculated to be 12.9 and 23.7 kcal/mol,[22] respectively. The energy barrier for flipping the divinyl ether oxygen atom from the minimum syn to the minimum anti conformation was estimated to be about 3.5 kcal/mol based on a calculated MMX energy of 6.8 kcal/mol for the conformation in which the molecule was fixed about the ether oxygen in a half-chair. This barrier is too small[23] to be detected by ^1H NMR over the 80-deg temperature range examined (+20 to −60 °C) and is consistent with **7c** being conformationally mobile with the principal motion being the syn–anti interconversion rather than pseudorotation about the C4–C5 bond. It should be noted from Table V that the minimum-energy conformation in both the syn and anti series of calculations of **7c** places the TMS group in an equatorial position and the ester group in an axial position. The barriers to rotation about the C4–C5 bond for the anti and syn series of *cis*-oxepin **7a** were 15.6 and 10 kcal/mol, respectively. The oxygen flipping barrier from the syn to anti manifolds was again a lower energy process, costing about 5 kcal/mol. **7a** differs principally from **7c** in showing less of a conformational preference, as there are conformations with the TMS group equatorial and the ester group axial, or vice versa, that are approximately equal in energy. For **8a**, the conformation in which both the TMS and ester groups are axially oriented and the divinyl ether oxygen is anti to the TMS group is significantly lower in energy than the other minimum-energy conformations. It was observed for **8a** that the energy smoothly increased upon rotation about the C4–C5 bond from this lowest energy conformation (the eclipsed conformer has a torsion angle of −120°), reaching a maximum when both substituents were equatorial and gauche to each other. The barrier for anti to syn inversion of the divinyl ether oxygen was 3.7 kcal/mol.

In examining the values for the vicinal coupling constants in Table V, it is the calculated values for J_{45} that are most helpful in confirming the predicted conformational preferences from the MMX energies by matching the experimental values in Table IV. The observed J_{45} of 2.76 Hz for **7c** is in excellent agreement with the calculated values for either the anti (2.68 Hz) or syn (2.69 Hz) minimum-energy conformers wherein the TMS group is equatorial and the ester group is axial, although the calculated values for J_{45} in the alternative minimum-energy conformations with the TMS group axial and the ester group equatorial (3.01 Hz) are not that much larger. The observed value for J_{45} of 3.60 Hz for **7a** (Table IV) is higher than that calculated for any of the minimum-energy conformations given in Table V (2.70–3.02 Hz), but relatively small changes in the H–C4–C5–H dihedral angle lead to larger calculated values for J_{45} (vide infra). Furthermore, the J_{45} for **7a** is the one most likely to represent an averaged value between the two extremes of staggered configurations about the C4–C5 bond, based on the MMX energies. Among the three oxepins in this study, it is the calculated values for J_{45} for the *trans*-oxepin **8a** that are most confirmatory of the results from the molecular mechanics calculations. The value for J_{45} for the predicted lowest energy conformation of **8a** wherein both substituents at C4 and C5 are axial (2.60 Hz) is the one closest in value to that observed experimentally (2.29 Hz). The predicted higher energy conformations wherein the TMS and ester groups are both equatorial (H–C4–C5–H = 180°) have calculated coupling constants for J_{45} of 14.1 Hz. These values are clearly consistent with the observed value for J_{45} and such conformations can be ruled out as major contributors to the overall structure of the *trans*-oxepins.

For the *cis*-oxepin **7c**, the observed value for J_{56} of 4.9 Hz can be rationalized as an averaged value among its three lowest energy conformations. For oxepins **7a** and **8a**, however, the discrepancies between the observed and calculated values for J_{34} and J_{56} are much larger. In order to match the large experimental value for J_{56} (8.9 Hz) in the *cis*-oxepin **7a** with a calculated value, a torsion angle (or an averaged torsion angle) for H–C5–C6–H of about 145° is required. It is possible to obtain such an angle by starting from the minimum-energy anti conformer with the TMS group equatorial (MMX energy of 5.36 kcal/mol, Table V) and altering and fixing the H–C4–C5–H and H–C5–C6–H torsion angles at −54° and +144°, respectively, before the energy is minimized. This leads to a conformation with calculated values for J_{34} (−55°), J_{45}, and J_{56} of 4.01, 3.82, and 8.70 Hz, respectively, which are fairly close to the experimental values in Table IV, but at a cost of an additional 1.4 kcal/mol in energy. The large experimental coupling constants for J_{34} and J_{56} (8.4 and 8.9 Hz, respectively) for *trans*-oxepin **8a** are even more difficult to rationalize with calculated values. It is impossible to achieve the required large torsion angles for H–C3–C4–H and H–C5–C6–H simultaneously by any reasonable distortion from the calculated energy minima in Table V or by considering any of various conformations achievable with the Fieser models. Furthermore, there is no conceivable averaging process that would allow for such large values. The inconsistencies between the experimental and the calculated values for the J_{34} and J_{56} coupling constants point to limitations in the use of these calculated values, which stem from

(22) At a H–C4–C5–H torsion angle of 0 °C in the anti series for **7c**, the carboalkoxy group eclipses both the TMS group at C5 and the methyl group at C3, which could explain the unusually high MMX value for this conformation.

(23) Lambert, J. B.; Nienhuis, R. J.; Keepers, J. W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 487–500.

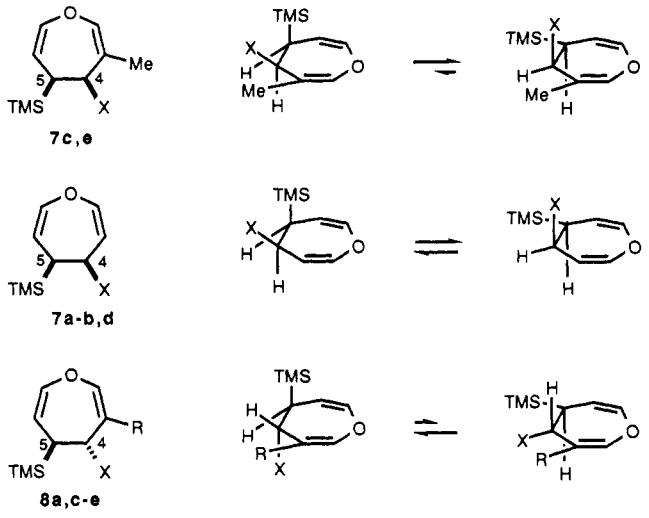


Figure 1. Conformational analyses of 4,5-dihydrooxepins **7** and **8**.

a lack of understanding of the effect of structural features in the molecules and the NMR parameters. The Garbisch relation,[20] unlike the relation of Altoona et al.,[19] does not take into account the effects of substituent electronegativity. Of equal significance is the lack of understanding about the effect of distortion in the H–C(sp^2)–C(sp^3) bond angles, which were observed to vary over a range of 116–121° in the MMX calculations on compounds **7a**, **8a**, and **7c**, upon the coupling constant. The discrepencies between the experimental and predicted values of the H–C(sp^2)–C(sp^3)–H coupling constants points out an area of research in need of further refinement.

The oxepins prepared in this study were originally divided into three groups on the basis of their ^{1}H NMR spectra (see the Introduction to this section). The differences between these three groups in their conformational preferences as established by the molecular mechanics calculations performed on oxepins **7a**, **7c**, and **8a** are explicable on the basis of two steric considerations within the oxepin ring. To illustrate these two considerations, the equilibrium between the two staggered configurations about the C4–C5 bond for each of the three groups is shown in Figure 1 with the structures drawn flat both to emphasize the differences in the equatorial and axial disposition of the substituents at C4 and C5 and to simplify the analysis by ignoring the relatively low-energy syn to anti interconversion of the oxygen atom of the ring. The reason for the *cis*-oxepins being differentiated into two groups is based on the presence or absence of a methyl substituent at C3 of the oxepin nucleus. From an examination of models for **7c,e**, the placement of the nonhydrogen substituent at C4 in the equatorial position leads to $A^{1,2}$ strain[24] with the methyl group at C3, leading to a preference for the substituent at C4 to be axial. For *cis*-oxepins lacking the conformationally biasing methyl group at C3 (**7a,b,d**), there is less of a preference for which of the two nonhydrogen substituents at C4 and C5 is axial and which is equatorial and a more nearly equal population of the two staggered conformations about the C4–C5 bond. The clearcut preference for *trans*-4,5-dihydrooxepin **8a** to place both of its nonhydrogen substituents at C4 and C5 in axial positions instead of in equatorial positions can be rationalized as avoidance of the gauche interaction between the TMS and ester groups when both are equatorial. Placing a substituent in an axial position at C4 or C5 would not appear from an examination of models to lead to significant steric interactions about the ring, since C2, C3, C6, and C7 are all sp^2 hybridized and trigonal. In the *trans*-oxepin series with a methyl group at C3 these two steric considerations reinforce the preference for diaxial orientation, since placing the nonhydrogen substituent at C4 in an equatorial position would lead to both a gauche interaction with the equatorial TMS group at C5 and $A^{1,2}$ strain with the methyl group at C3. The larger J_{45} coupling constants observed for the trans-4,5-disubstituted 4,5-dihydrooxepins prepared by Rastetter, Chancellor, and Richard[17] (7.2–8.5 Hz), which bear a hydroxyl group at C4, an amino or thio substituent at C5, and hydrogen atoms at C3 and C6, indicate that in their compounds both substituents either are equatorially oriented or at least spend more time equatorially oriented than is the case for the *trans*-oxepins **8a,c–e**. This difference could be due to the greater steric bulk of the TMS group in our *trans*-oxepins, which may increase the cost of the gauche interaction at C4–C5 relative to other interactions within the *trans*-4,5-dihydrooxepin ring system and the absence of $A^{1,2}$ strain in their compounds. It is of interest to note that the observed J_{45} vicinal coupling constants for the 4,5-disubstituted *trans*-4,5-dihydrooxepin rings of aranotin acetate **1**[2] and related natural products[3] are in the range 8.1–8.6 Hz, which is similar to the range observed by Rastetter for his *trans*-oxepins[17] and significantly larger than the range observed for the *trans*-oxepins prepared in this study (2.3–3.0 Hz). However, it is clear from models that the pyrollidine ring fused to C3 and C4 of the oxepin ring of these natural products greatly restricts rotation about the C4–C5 bond of the oxepin ring, preventing the nonhydrogen substituents at C4 and C5 to be diaxial.

(24) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413.

Conclusion

In conclusion, either the cis or trans isomers of 4,5-disubstituted 4,5-dihydrooxepins can be made stereospecifically in excellent yield and in a predictable manner by controlling the olefinic geometry in the *cis*-2,3-divinyl epoxide precursors used in the Cope rearrangement. The *E,E*-1,5-dienes rearranged more facilely than their *E,Z* counterparts, as expected for a boatlike transition state for these [3,3] sigmatropic rearrangements. It also proved possible to carry an alkyl substituent through the Cope rearrangement, leading to substitution at C3 of the oxepin ring. A solvent effect on the efficiency of the Cope rearrangement was observed for those 1,5-dienes containing a *Z*-α,β-unsaturated ester, and the corresponding *trans*-4,5-dihydrooxepins were made more reliably by using a cyano group in place of a carboalkoxy substituent. From molecular mechanics calculations on representative examples of these 4,5-dihydrooxepins, differences in the conformational preferences among these molecules can be explained by avoidance of $A^{1,2}$ strain by non-hydrogen substituents at C3 and C4 (or C5 and C6) and, for trans-4,5-dihydrooxepins, a gauche interaction at C4 and C5. Studies to incorporate the nitrogen and oxygen substituents at C4 and C5, respectively, as required for a synthesis of the oxepin portion of the aranotin family of natural products, are in progress and will be reported in due course.

Experimental Section

General. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran (THF) were distilled under nitrogen from sodium/benzophenone. Dichloromethane was distilled from P_2O_5. Benzene was distilled from sodium. Carbon tetrachloride was purchased as an HPLC-grade solvent and used without further purification. Diisopropylamine 1,1,1,3,3,3-hexamethyldisilazane, and triethylamine were distilled from CaH_2 and stored over KOH. Reactions involving organometallic reagents or $LiAlH_4$ were carried out under argon (balloon) in oven-dried glassware. Reactions were monitored by thin-layer chromatography (TLC) using Whatman precoated glass plates of 250-μm thickness silica gel with a fluorescent indicator. TLC plates were visualized by staining with *p*-anisaldehyde/H_2SO_4/CH_3CO_2H/ethanol and heating on a hot plate. Flash chromatography was carried out by using American Matrex silica gel (35–70 μm, 60-Å pore) or Florisil (100–200 mesh, Fisher Scientific). HPLC was carried by using a Rainan Dynamax Macro-HPLC silica gel column (21.4-mm i.d. × 25-cm length). IR spectra were recorded on a Perkin-Elmer 1310 IR spectrophotometer. Bands are characterized as strong (s), medium (m), or weak (w) and are in units of cm^{-1}. ^{1}H NMR spectra were recorded as solutions in $CDCl_3$ on a Nicolet NT-200 WB. Chemical shifts are expressed in parts per million (δ units) relative to internal tetramethylsilane (0.0 δ) or $CHCl_3$ (7.26 δ). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad), coupling constant(s), and integration. ^{13}C NMR spectra were determined as solutions in $CDCl_3$ on a Nicolet NT-200 WB and the chemical shifts are reported in parts per million (δ units) relative to the center peak of $CDCl_3$ (77.0 δ). Low-resolution mass spectra (EI) were

obtained on a GC-Finnegan TSQ 70 quadrupole mass spectrometer. Exact masses were obtained by peak matching.

(*E*)-5-(Trimethylsilyl)-5-penten-3-yn-1-ol. To trimethylsilylacetylene (3.21 g, 32.7 mmol) and benzoyl peroxide (44 mg, 0.18 mmol, 0.5 mol %) cooled in an ice bath was bubbled HBr gas. From the ^{1}H NMR spectra (60 MHz) after about 1 h it was determined that most of the acetylene had been consumed. The reaction was diluted in ether (50 mL), carefully washed with saturated $NaHCO_3$ (30 mL) and then with saturated NaCl (30 mL), and dried over $MgSO_4$. Filtration and evaporation gave crude (*E*)-(2-bromoethenyl)trimethylsilane[25] (3.85 g, 21.5 mmol), which is about 55–60% pure. The mixture includes, among other things, some of the cis alkene isomer, but this impurity is unreactive compared to the trans isomer in the Sonogashira coupling. To the crude (*E*)-(2-bromoethenyl)trimethylsilane prepared above (3.54 g) in diisopropylamine (45 mL) at room temperature was added $(PhCN)_2PdCl_2$ (63.3 mg, 0.166 mmol), Ph_3P (86.9 mg, 0.331 mmol), and CuI (44.8 mg, 0.236 mmol). The mixture was degassed with a stream of argon for 5 min. Propargyl alcohol (2.89 mL, 49.7 mmol) was added and the reaction was stirred at room temperature. After 1 h, the reaction was diluted in ether (100 mL), washed with H_2O (4 × 40 mL) and saturated NaCl (40 mL), and dried over $MgSO_4$. Following filtration and evaporation, the residue was purified by flash chromatography or silica gel (hexanes/ethyl acetate 12:1) to give (*E*)-5-(trimethylsilyl)-5-penten-3-yn-1-ol (1.72 g, 11.1 mmol, 37% from (trimethylsilyl)acetylene) as a colorless liquid: IR (film) 3340 (br), 2980 (s), 2210 (w), 1570 (s), 1245 (s), 1210 (m), 1145 (m), 1010 (s), 975 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.43 (d, J = 19.3 Hz, 1 H), 5.93 (dd, J = 19.3, 1.7 Hz, 1 H), 4.32 (br s, 2 H), 2.25 (s, 1 H, OH), −1.76 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 146.2, 122.6, 87.6, 85.8, 51.4, −1.76. Anal. Calcd for $C_8H_{14}OSi$: C, 62.28; H, 9.15. Found: C, 61.80; H, 9.50.

(3*Z*,5*E*)-5-(Trimethylsilyl)-3,5-pentadien-1-ol.[10] $ZnBr_2$ (3.01 g) in a 100-mL round-bottom flask was placed under vacuum and fused with the aid of a Bunsen burner to give, upon cooling, 2.89 g (12.8 mmol). THF (30 mL) was added, and the solid dissolved with the aid of magnetic stirring. Potassium metal (860 mg, 22.0 mmol), cut into 15 pieces, was added. Following 3 h at reflux, the enynol (906 mg, 5.87 mmol) in MeOH (20 mL) was added dropwise, followed by the addition of H_2O (4 mL). After 20 min, the reaction was allowed to cool and was then filtered through Celite into H_2O (40 mL). The Celite was washed with ether (40 mL) and the aqueous layer was separated and extracted with ether (3 × 35 mL). The combined organic layers were washed with 10% NH_4Cl (2 × 40 mL) and saturated NaCl (40 mL), dried with $MgSO_4$, filtered, and evaporated to give the dienol as a greater than 19:1 ratio in favor of the product from cis reduction (816 mg, 5.22 mmol) in 89% yield as a colorless liquid: IR (film) 3330 (br), 2950 (s), 1570 (m), 1245 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.78 (ddd, J = 18.2, 10.7, 1.0 Hz, 1 H), 6.08 (tq, J = 10.7, 1.1 Hz, 1 H), 5.93 (d, J = 18.2 Hz, 1 H), 5.59 (dtt, J = 10.9, 6.9, 0.9 Hz, 1 H), 4.35 (dd, J = 6.9, 1.3 Hz, 2 H), 1.87 (s, 1 H, OH), 0.083 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 138.0, 136.9, 133.3, 129.8, 58.7, −1.40.

(4*E*)-*cis*-2,3-Epoxy-5-(trimethylsilyl)pent-4-enal (3). To the dienol (210 mg, 1.34 mmol) in CH_2Cl_2 (5 mL) was added $VO(acac)_2$ (7.1 mg, 0.027 mmol, 2 mol %). The reaction was cooled in an ice bath and *t*-BuOOH (3 M in 2,2,4-trimethylpentane, 0.76 mL, 2.28 mmol, 1.7 equiv) was added. After 10 min, the cold bath was removed and the reaction was stirred at room temperature for 1 h. Ten percent NH_4Cl (15 mL) was added and the reaction was extracted with ether (3 × 12 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and saturated NaCl (20 mL) and dried over $MgSO_4$. Filtration and evaporation were followed by flash chromatography on Florisil (hexanes/ethyl acetate 25:1 → 15:1 → 10:1) to give the epoxy alcohol (193 mg, 1.12 mmol, 84%) as a colorless liquid. To CrO_3 (816 mg, 8.16 mmol, 8 equiv) in CH_2Cl_2 (30 mL) at 0 °C was added pyridine (1.32 mL, 16.3 mmol, 16 equiv). The alcohol (175 mg, 1.02 mmol) in CH_2Cl_2 (1 mL) was added and the ice bath removed. After 30 min, the reaction was filtered through a column of Florisil, and the column was washed with ether (50 mL). The filtrate was washed with $CuSO_4$ (2 × 20 mL), saturated $NaHCO_3$ (20 mL), and saturated NaCl (20 mL) and dried over $MgSO_4$. The residue from filtration and evaporation was purified by flash chromatography on Florisil (hexanes/ethyl acetate 30:1) to give the epoxy aldehyde (124 mg, 0.728 mmol, 71%) as a colorless liquid: IR (film) 2955 (s), 2845 (s), 1720 (s), 1615 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 9.42 (d, J = 5.4 Hz, 1 H), 6.39 (d, J = 18.7 Hz, 1 H), 5.91 (dd, J = 18.7, 7.5 Hz, 1 H), 3.73 (dd, J = 7.3, 4.7 Hz, 1 H), 3.48 (t, J = 5.2 Hz, 1 H), 0.08 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 198.4, 140.6, 136.5, 60.2, 59.5, −1.67; mass spectrum, m/e 170.0753 (M$^+$ calcd for $C_8H_{14}O_2Si$ 170.0763), 169, 155, 129, 111, 110, 81 (base), 73. Anal. Calcd for $C_8H_{14}O_2Si$: C, 56.43; H, 8.29. Found: C, 56.64; H, 8.73.

Methyl (2*E*,6*E*)- and (2*Z*,6*E*)-*cis*-4,5-Epoxy-7-(trimethylsilyl)-2,6-heptadienoate (5a and 6a). KH (35% by weight in mineral oil, 127 mg, 3.16 mmol, 1.4 equiv) was washed with hexanes (3 × 2 mL) and suspended in THF (20 mL). $HN(TMS)_2$ (0.71 mL, 3.38 mmol, 1.5 equiv) was added and the reaction was stirred for 30 min at room temperature before the addition of 18-crown-6 (3.58 g, 13.5 mmol, 6 equiv). After an additional 30 min, the reaction was cooled to −75 °C and bis(2,2,2-trifluoroethyl)[(methoxycarbonyl)methyl]phosphonate (0.48 mL, 2.71 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise. After 15 min, aldehyde **3** (384 mg, 2.26 mmol) in THF (1.5 mL) was added dropwise. After 20 min, the reaction was quenched with 10% NH_4Cl and diluted in ether (50 mL). The reaction was washed with 10% NH_4Cl (2 × 25 mL) and saturated NaCl (25 mL) and dried over $MgSO_4$. Following filtration and evaporation, the residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 50:1) to give (in order of elution) **6a** (327 mg, 1.45 mmol) and **5a** (98 mg, 0.433 mmol) in a combined yield of 83%. Substitution of NaH for $KN(TMS)_2$/18-crown-6 gave a comparable yield of a 2:1 mixture of **6a** to **5a**. For **5a**: IR (film) 2960 (s), 1720 (s), 1645 (m), 1615 (w), 1435 (m), 1400 (w), 1360 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.78 (dd, J = 15.8, 6.5 Hz, 1 H), 6.26 (d, J = 19.1 Hz, 1 H), 6.18 (d, J = 16.1 Hz, 1 H), 5.80 (dd, J = 18.8, 6.9 Hz, 1 H), 3.76 (s, 3 H), 3.64–3.69 (m, 2 H), 0.08 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 165.9, 141.8, 139.4, 137.8, 125.1, 61.0, 57.1, 51.7, −1.55; mass spectrum, m/e 226.1024 (M$^+$ calcd for $C_{11}H_{18}O_3Si$ 226.1025), 211, 167, 151, 98 (base), 73. Anal. Calcd for $C_{11}H_{18}O_3Si$: C, 58.37; H, 8.02. Found: C, 57.88; H, 8.58. For **6a**: IR (film) 2960 (s), 1720 (s), 1640 (s), 1620 (m), 1440 (s), 1415 (m), 1320 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.24 (dd, J = 18.7, 0.6 Hz, 1 H), 6.02–6.05 (m, 2 H), 5.78 (dd, J = 18.6, 7.1 Hz, 1 H), 4.64 (m, 1 H), 3.74 (s, 3 H), 3.69 (dd, J = 7.1, 4.7 Hz, 1 H), 0.06 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 166.1, 144.2, 138.8, 138.6, 124.2, 60.9, 55.2, 51.5, −1.53; mass spectrum, m/e 226.1007 (M$^+$ calcd for $C_{11}H_{18}O_3Si$ 226.1025), 167, 151, 121, 94, 73 (base).

Ethyl (2*E*,6*E*)-*cis*-4,5-Epoxy-7-(trimethylsilyl)-2,6-heptadienoate (5b). To NaH (60% dispersion in mineral oil, 53 mg, 1.33 mmol, 1.1 equiv) that had been washed with hexanes (3 × 2 mL) and suspended in THF (10 mL) at room temperature was added dropwise triethyl phosphonoacetate (0.288 mL, 1.45 mmol, 1.2 equiv). After 10 min, the reaction was cooled in an ice bath and aldehyde **3** (205 mg, 1.21 mmol) in THF (1 mL) was added. Following stirring for 20 min, the reaction was quenched with 10% NH_4Cl (20 mL) and extracted with ether (3 × 15 mL). The combined organic layers were washed with saturated NaCl (30 mL), dried with $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate 30:1) to give **5b** (222 mg, 0.935 mmol) as well as some of the *Z* isomer (18 mg, 0.075 mmol) for a combined yield of 83%: IR (neat) 2960 (m), 1720 (s), 1650 (m), 1615 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.75 (dd, J = 15.8, 7.0 Hz, 1 H), 6.24 (d, J = 18.9 Hz, 1 H), 6.15 (d, J = 15.9 Hz, 1 H), 5.80 (dd, J = 18.7, 6.7 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 3.60–3.70 (m, 2 H), 1.27 (t, J = 7.1 Hz, 3 H), 0.06 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 165.3, 141.4, 139.0, 137.8, 125.6, 60.8, 60.5, 57.1, 14.2, −1.58; mass spectrum, m/e 240 (M$^+$), 225, 211, 167, 151, 112, 84 (base), 73. Anal. Calcd for $C_{12}H_{20}O_3Si$: C, 59.96; H, 8.39. Found: C, 59.75; H, 8.65.

Ethyl (2*E*,6*E*)- and (2*Z*,6*E*)-*cis*-4,5-Epoxy-3-methyl-7-(trimethylsilyl)-2,6-heptadienoate (5c and 6c). NaH (60% dispersion in mineral oil, 128 mg, 3.19 mmol, 1.2 equiv) was washed with hexanes (3 × 2 mL) and suspended in THF (20 mL). Triethyl phosphonoacetate (0.63 mL, 3.19 mmol, 1.2 equiv) was added and, after 20 min, methyl ketone **4**[4h] (490 mg, 2.66 mmol) in THF (2 mL) was added. After 13 h of stirring at room temperature, the reaction was diluted with ether (50 mL), washed with 10% NH_4Cl (2 × 20 mL) and saturated NaCl (30 mL), and dried over $MgSO_4$. Filtration and evaporation were followed by flash chromatography on Florisil (hexanes/ethyl acetate 60:1) and further purification by HPLC (hexanes/ethyl acetate 16:1) to give (in order of elution) **5c** (120 mg, 0.472 mmol) and **6c** (357 mg, 1.40 mmol) in a combined yield of 70%. For **5c**: IR (film) 2960 (m), 1715 (s), 1655 (m), 1610 (w), 1320 (m), 1250 (m), 1210 (s), 1150 (s), 1090 (w), 1040 (m), 985 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.24 (d, J = 18.7 Hz, 1 H), 5.93 (d, 1.1 Hz, 1 H), 5.65 (dd, J = 18.8, 6.7 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.56–3.64 (m, 2 H), 2.13 (d, J = 1.2 Hz, 3 H), 1.28 (t, J = 7.2, 3 H), 0.04 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 166.3, 150.6, 139.6, 137.4, 116.7, 61.0, 60.4, 59.8, 16.1, 14.3, −1.56; mass spectrum, m/e 254.1328 (M$^+$ calcd for $C_{13}H_{22}O_3Si$ 254.1338), 239, 225, 181, 165, 126, 98 (base), 73. For **6c**: IR (film) 2955 (m), 1710 (s), 1635 (m), 1245 (s), 1220 (s), 1145 (s), 1095 (w), 1045 (m), 980 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.19 (d, J = 18.8 Hz, 1 H), 5.87 (m, 1 H), 5.58 (dd, J = 18.7, 7.3 Hz, 1 H), 4.28 (dd, J = 4.6, 1.3 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 3.68 (dd, J = 7.4, 4.8 Hz, 1 H), 1.94 (br s, 3 H),

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1.26 (t, J = 7.2 Hz, 3 H), 0.04 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 165.6, 153.1, 139.2, 138.1, 119.3, 60.2, 59.9, 59.7, 21.6, 14.3, −1.53; mass spectrum, m/e 254.1330 (M^+ calcd for $C_{13}H_{22}O_3Si$ 254.1338), 239, 225, 181, 165, 135, 126, 98 (base), 75, 73. Anal. Calcd for $C_{13}H_{22}O_3Si$: C, 61.38; H, 8.72. Found: C, 61.66; H, 9.05.

(2*E*,6*E*)- and (2*Z*,6*E*)-*cis*-4,5-Epoxy-7-(trimethylsilyl)-2,6-heptadienenitrile (5d and 6d). NaH (60% dispersion in mineral oil, 62 mg, 1.54 mmol, 1.1 equiv) was washed with hexanes (3 × 2 mL). Diethyl (cyanomethyl)phosphonate (0.27 mL, 1.68 mmol, 1.2 equiv) was added over 5 min and, after 15 min, the reaction was cooled to −5 °C and aldehyde **3** (239 mg, 1.40 mmol) in THF (1 mL) was added. After 20 min, the reaction was diluted with ether (40 mL), washed with 10% NH_4Cl (20 mL) and saturated NaCl (20 mL), and dried over $MgSO_4$. Filtration and evaporation were followed by flash chromatography on silica gel (pentane/ethyl acetate 30:1) to give (in order of elution) **6d** (65 mg, 0.336 mmol) and **5d** (116 mg, 0.600 mmol) in an overall yield of 67%. For **5d**: IR (film) 2960 (s), 2215 (s), 1630 (m), 1620 (m), 1400 (m), 1355 (s), 1300 (w), 1245 (s), 1210 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.58 (dd, J = 16.1, 5.8 Hz, 1 H), 6.28 (d, J = 19.0 Hz, 1 H), 5.72 (dd, J = 18.8, 6.4 Hz, 1 H), 5.69 (dd, J = 16.3, 0.7 Hz, 1 H), 3.63–3.72 (m, 2 H), 0.09 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 148.0, 140.3, 136.6, 116.4, 103.5, 61.0, 57.0, −1.61; mass spectrum, m/e 193.0916 (M^+ calcd for $C_{10}H_{15}NOSi$ 193.0923), 151, 94 (base), 73. Anal. Calcd for $C_{10}H_{15}NOSi$: C, 62.12; H, 7.82; N, 7.24. Found: C, 61.74; H, 8.02; N, 6.60. For **6d**: IR (film) 2960 (s), 2220 (s), 1615 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.30 (d, J = 18.7 Hz, 1 H), 6.29 (dd, J = 11.2, 8.8 Hz, 1 H), 5.80 (dd, J = 18.7, 6.6 Hz, 1 H), 5.62 (d, J = 11.1 Hz, 1 H), 4.00 (dd, J = 8.8, 4.6 Hz, 1 H), 3.76 (dd, J = 6.6, 4.4 Hz, 1 H), 0.08 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 148.4, 139.5, 137.3, 115.0, 104.1, 60.6, 56.2, −1.56; mass spectrum, m/e 193.0914 (M^+ calcd for $C_{10}H_{15}NOSi$ 193.0914), 178, 151, 97, 73 (base). Anal. Calcd for $C_{10}H_{15}NOSi$: C, 62.12; H, 7.82; N, 7.24. Found: C, 61.84; H, 7.84; N, 6.51.

(2*E*,6*E*)- and (2*Z*,6*E*)-*cis*-4,5-Epoxy-3-methyl-7-(trimethylsilyl)-2,6-heptadienenitrile (5e and 6e). Methyl ketone **4**[4h] (300 mg, 1.63 mmol) was olefinated as described for the preparation of **5d** and **6d**, except that the reaction was stirred at room temperature. The mixture of **5e** and **6e** was purified by HPLC (hexanes/ethyl acetate 10:1) to give (in order of elution) **5e** (136 mg, 0.655 mmol) and **6e** (91 g, 0.437 mmol) in a combined yield of 67%. For **5e**: IR (film) 2955 (s), 2220 (s), 1635 (m), 1615 (m), 1245 (s), 985 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.26 (d, J = 18.5 Hz, 1 H), 5.51 (dd, J = 18.7, 7.2 Hz, 1 H), 5.42 (m, 1 H), 3.59–3.64 (m, 2 H), 2.04 (d, J = 1 Hz, 3 H), 0.05 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 156.7, 140.8, 136.2, 116.1, 96.6, 60.6, 59.6, 18.3, −1.63; mass spectrum, m/e 207.1089 (M^+ calcd for $C_{11}H_{17}NOSi$ 207.1079), 206, 192, 165, 118, 108, 97, 91, 80, 75, 73 (base). For **6e**: IR (film) 2955 (s), 2220 (s), 1615 (m), 1245 (s), 985 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.30 (d, J = 18.8 Hz, 1 H), 5.67 (dd, J = 18.8, 7.0 Hz, 1 H), 5.35–5.38 (m, 1 H), 3.90–3.92 (m, 1 H), 3.65–3.72 (m, 1 H), 1.91 (d, J = 1.6 Hz, 3 H), 0.07 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 158.1, 139.7, 137.4, 115.5, 97.7, 59.6, 58.7, 20.8, −1.60; mass spectrum, m/e 207.1063 (M^+ calcd for $C_{11}H_{17}NOSi$ 207.1079), 192, 165, 108, 73 (base).

General procedure for the Cope rearrangements of **5a–e** and **6a,c–e**. The divinyl epoxide was dissolved in the indicated solvent, degassed, and heated in a resealable vial at the indicated temperature for the indicated time (see Table II). The solvent was evaporated and the residue purified by flash chromatography on silica gel (hexanes or pentane/ethyl acetate) to give the 4,5-dihydrooxepins **7a–e** and **8a,c–e**.

Methyl *cis*-5-(Trimethylsilyl)-4,5-dihydrooxepin-4-carboxylate (7a). **5a** (53 mg, 0.235 mmol) in CCl_4 (2 mL) gave, following purification (60:1), **7a** (44.6 mg, 0.197 mmol) in 84% yield as a colorless liquid: IR (film) 2955 (m), 1735 (s), 1660 (w), 1640 (m), 1435 (w), 1350 (w), 1300 (m), 1285 (m), 1245 (s), 1195 (m), 1180 (m), 1140 (m), 1105 (w), 1020 (m), 840 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.16 (dd, J = 7.6, 2.5 Hz, 1 H), 6.15 (d, J = 7.7 Hz, 1 H), 5.42 (dd, J = 7.5, 3.4 Hz, 1 H), 4.90 (dd, J = 8.7, 7.8 Hz, 1 H), 3.78 (q, J = 3.4 Hz, 1 H), 3.70 (s, 3 H), 2.42 (dd, J = 8.9, 3.6 Hz, 1 H), −0.01 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 173.1, 141.9, 139.9, 108.6, 105.3, 51.9, 44.2, 33.2, −1.43; mass spectrum, m/e 226.1024 (M^+ calcd for $C_{11}H_{18}O_3Si$ 226.1024), 211, 167, 151, 121, 94, 73 (base).

Methyl *trans*-5-(Trimethylsilyl)-4,5-dihydrooxepin-4-carboxylate (8a). **6a** (69.8 mg, 0.309 mmol) in CH_3CN (1.5 mL) gave, following purification (40:1), **8a** (57 mg, 0.252 mmol) in 82% as a colorless liquid: IR (film) 2960 (s), 1730 (s), 1650 (s), 1435 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.23 (d, J = 7.8 Hz, 1 H), 6.16 (d, J = 7.6 Hz, 1 H), 4.92 (t, J = 8.0 Hz, 1 H), 4.85 (t, J = 7.8 Hz, 1 H), 3.68 (s, 3 H), 3.34 (dd, J = 8.3, 2.2 Hz, 1 H), 2.10 (ddd, J = 8.9, 2.3, 0.9 Hz, 1 H), 0.04 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 174.3, 144.0, 139.4, 107.7, 102.2, 52.2, 45.0, 32.7, −2.4; mass spectrum, m/e 226.1024 (M^+ calcd for $C_{11}H_{18}O_3Si$ 226.1025), 211, 167, 151, 94, 73 (base).

Ethyl *cis*-5-(Trimethylsilyl)-4,5-dihydrooxepin-4-carboxylate (7b). **5b** (164 mg, 0.683 mmol) in CCl_4 (2.5 mL) gave, following purification (50:1), **7b** (126 mg, 0.525 mmol) in 77% as a colorless liquid; IR (film) 2960 (s), 1730 (s), 1640 (m), 1600 (m) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.16 (d, J = 7.6 Hz, 1 H), 6.15 (d, J = 7.7 Hz, 1 H), 5.42 (dd, J = 7.6, 3.4 Hz, 1 H), 4.91 (dd, J = 8.8, 8.0 Hz, 1 H), 4.02–4.28 (m, 2 H), 3.77 (dd, J = 8.9, 3.5 Hz, 1 H), 2.43 (dd, J = 8.9, 3.5 Hz, 1 H), 1.29 (t, J = 7.1 Hz, 3 H), 0.00 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 172.6, 141.8, 139.9, 108.6, 105.5, 60.9, 44.4, 33.2, 14.1, −1.34; mass spectrum, m/e 240 (M^+), 225, 211, 167, 151, 73 (base).

Ethyl *cis*-3-Methyl-5-(trimethylsilyl)-4,5-dihydrooxepin-4-carboxylate (7c). **5c** (161 mg, 0.633 mmol) in CCl_4 (3 mL) gave, following purification (50:1), **7c** (143 mg, 0.562 mmol) in 89% yield as a colorless liquid; IR (film) 2960 (m), 1735 (s), 1640 (m), 1250 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.27 (dd, J = 6.8, 2.4 Hz, 1 H), 6.21 (q, J = 1.4 Hz, 1 H), 4.80 (dd, J = 6.7, 5.0 Hz, 1 H), 4.18 (dq, J = 10.8, 7.1 Hz, 1 H), 4.07 (dq, J = 10.8, 7.1 Hz, 1 H), 3.31 (d, J = 2.8 Hz, 1 H), 2.12 (dt, J = 5.1, 2.6 Hz, 1 H), 1.68 (d, J = 1.3 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 0.06 (s, 9 H); ^{13}C NMR (50.3 Hz, $CDCl_3$) 172.6, 143.7, 139.8, 116.0, 108.1, 60.6, 50.5, 28.5, 20.9, 14.2, −2.27; mass spectrum, m/e 254 (M^+), 239, 225, 181, 165, 135, 121, 108, 75, 73 (base).

Ethyl *trans*-3-Methyl-5-(trimethylsilyl)-4,5-dihydrooxepin-4-carboxylate (8c). **6c** (66 mg, 0.259 mmol) in CH_3CN or C_6H_6 (1.5 mL) gave, following purification (50:1), **8c** (54 mg, 0.212 mmol) in 82% as a colorless liquid: IR (film) 2950 (s), 1720 (s), 1650 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.16 (br d, J = 1.2 Hz, 1 H), 6.09 (d, J = 7.6 Hz, 1 H), 4.78 (ddd, J = 8.5, 7.7, 0.8 Hz, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.16 (br d, J = 2.4 Hz, 1 H), 2.07 (dd, J = 8.7, 2.7 Hz, 1 H), 1.77 (br d, J = 1.4 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 0.06 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 173.5, 140.1, 139.2, 111.4, 106.4, 60.9, 50.2, 32.0, 22.2, 14.2, −1.99; mass spectrum, m/e 254.1337 (M^+ calcd for $C_{13}H_{22}O_3Si$ 254.1338), 225, 181, 165, 73 (base).

***cis*-5-(Trimethylsilyl)-4,5-dihydrooxepin-4-carbonitrile (7d).** **5d** (73 mg, 0.378 mmol) in CCl_4 (1.5 mL) gave, following purification (25:1), **7d** (58 mg, 0.300 mmol) in 79% yield as a relatively unstable yellow liquid: IR (film) 2960 (s), 2220 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.17–6.24 (m, 2 H), 4.95 (dd, J = 7.4, 4.8 Hz, 1 H), 4.89 (t, J = 7.7 Hz, 1 H), 3.88 (ddd, J = 4.6, 3.3, 2.4 Hz, 1 H), 2.22 (dd, J = 8.1, 3.4 Hz, 1 H), 0.17 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 143.9, 141.6, 120.8, 108.2, 103.5, 32.7, 30.6, −1.59; mass spectrum, m/e 193 (M^+), 151, 73, 66 (base).

***trans*-5-(Trimethylsilyl)-4,5-dihydrooxepin-4-carbonitrile (8d).** **6d** (40 mg, 0.207 mmol) in CCl_4 (1 mL) gave, following purification (25:1), **8d** (29.6 mg, 0.153 mmol) in 74% yield as a liquid that solidified upon cooling: IR (film) 2960 (s), 2215 (s), 1650 (s), 1340 (s), 1315 (s), 1295 (m), 1250 (s), 1155 (m), 1125 (s), 1085 (w) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.28 (d, J = 7.6 Hz, 1 H), 6.27 (d, J = 7.5 Hz, 1 H), 5.01 (t, J = 8.2 Hz, 1 H), 4.86 (t, J = 7.9 Hz, 1 H), 3.44 (dd, J = 8.1, 3.0 Hz, 1 H), 2.12 (dd, J = 8.8, 2.9 Hz, 1 H), 0.064 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 146.0, 140.6, 121.2, 107.1, 100.0, 34.4, 30.5, −2.44; mass spectrum, m/e 193.0924 (M^+ calcd for $C_{10}H_{15}NOSi$ 193.0923), 151, 73 (base).

***cis*-3-Methyl-5-(trimethylsilyl)-4,5-dihydrooxepin-4-carbonitrile (7e).** **5e** (40.5 mg, 0.195 mmol) in CCl_4 (1.5 mL) gave, following purification (30:1), **7e** (34.4 mg, 0.166 mmol) in 85% yield as an unstable liquid: IR (film) 2955 (s), 2240 (m), 1665 (s), 1640 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.26 (dd, J = 7.2, 1.7 Hz, 1 H), 6.18 (br s, 1 H), 4.81 (t, J = 6.7 Hz, 1 H), 3.69 (br d, J = 2.4 Hz, 1 H), 2.17 (dt, J = 6.1, 2.2 Hz, 1 H), 1.80 (br d, $J \leq$ 1.3 Hz, 3 H), 0.17 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 143.2, 140.8, 119.7, 113.3, 107.5, 35.4, 30.6, 19.6, −2.12; mass spectrum, m/e 207.1075 (M^+ calcd for $C_{11}H_{17}NOSi$ 207.1079), 192, 165, 108, 80, 79, 73 (base).

***trans*-3-Methyl-5-(trimethylsilyl)-4,5-dihydrooxepin-4-carbonitrile (8e).** **6e** (124 mg, 0.598 mmol) in CCl_4 (2.5 mL) gave, following purification (30:1), **8e** (105 mg, 0.508 mmol) in 85% yield as a colorless liquid: IR (film) 2955 (s), 2230 (m), 1670 (s), 1655 (s), 1440 (m), 1385 (m), 1340 (m), 1295 (s), 1250 (s), 1195 (s), 1160 (s), 1130 (s), 1065 (m), 1030 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 6.23 (d, J = 7.6 Hz, 1 H), 6.16 (br d, J = 1.3 Hz, 1 H), 4.91 (t, J = 8.3 Hz, 1 H), 3.27 (br d, J = 3 Hz, 1 H), 2.05 (dd, J = 8.8, 3.0 Hz, 1 H), 1.78 (br d, J = 1.2 Hz, 3 H), 0.07 (s, 9 H); ^{13}C NMR (50.3 Hz, $CDCl_3$) 141.6, 140.7, 120.9, 109.1, 106.3, 35.8, 33.0, 20.8, −2.09; mass spectrum, m/e 207.1069 (M^+ calcd for $C_{11}H_{17}NOSi$ 207.1079), 192, 165, 108, 80, 79, 73 (base).

Methyl (4*S,5*S**)-4-Methyl-5-(trimethylsilyl)-4,5-dihydrooxepin-4-carboxylate (9).** To hexamethyldisilazane (0.28 mL, 1.33 mmol, 4 equiv) in THF (4 mL) cooled in an ice bath was added *n*-BuLi (2.5 M in hexane, 0.53 mL, 1.33 mmol, 4 equiv). After 1 h, the solution was cooled to −75 °C and **7a** (75 mg, 0.331 mmol) in THF (0.5 mL) was added. After 1 h, methyl iodide (filtered through basic alumina, 0.103 mL, 1.66

mmol, 5 equiv) was added. After 30 min, the reaction was quenched with 10% NH_4Cl (0.5 mL) and allowed to warm to room temperature. The reaction was diluted in ether (20 mL), washed with 10% NH_4Cl (2 × 10 mL) and saturated NaCl (10 mL), dried over $MgSO_4$, filtered, and evaporated. Purification by flash chromatography on silica gel (pentane/ethyl acetate 60:1) gave **9** (55.4, 0.230 mmol) in 70% yield as a colorless liquid: IR (film) 2530 (s), 1715 (s), 1645 (m), 1630 (m), 1435 (m), 1420 (m), 1320 (s), 1285 (s), 1230 (s), 1190 (s), 1140 (s), 1100 (s) cm^{-1}; ^1H NMR (50.3 MHz, $CDCl_3$) 6.14 (d, J = 7.6 Hz, 1 H), 6.04 (d, J = 8.0 Hz, 1 H), 5.62 (dd, J = 8.2, 1.0 Hz, 1 H), 4.84 (dd, J = 9.3, 7.6 Hz, 1 H), 3.70 (s, 3 H), 2.17 (dd, J = 9.4, 1.0 Hz, 1 H), 1.47 (s, 3 H), −0.04 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 176.4, 140.4, 139.0, 110.0, 106.0, 52.0, 48.0, 39.2, 31.2, −1.57; mass spectrum, m/e 240.1179 (M^+ calcd for $C_{12}H_{20}O_3Si$ 240.1182), 225, 181, 165, 135, 121, 108, 73 (base).

Methyl *cis*-5-(Trimethylsilyl)-4,5-dihydrooxepin-4-carboxylate-4-*d* (10). **10** was prepared under similar conditions to those described for **9** with the substitution of methanol-*d* for methyl iodide; ^1H NMR (200 MHz, $CDCl_3$) 6.16 (d, J = 7.6 Hz, 1 H), 6.15 (d, J = 7.6 Hz, 1 H), 5.40 (d, J = 7.4 Hz, 1 H), 4.90 (t, J = 8.4 Hz, 1 H), 3.70 (s, 3 H), 2.41 (d, J = 8.8 Hz, 1 H), −0.06 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 173.1, 141.9, 139.9, 108.5, 105.2, 51.9, 43.8, (middle line of triplet), 33.1, −1.44.

Methyl 5-(Trimethylsilyl)-2,5-dihydrooxepin-4-carboxylate (11). IR (film) 2950 (m), 1715 (s), 1645 (m), 1430 (m), 1245 (s), 1125 (s), 1040 (m), 1020 (m) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 6.92 (t, J = 5.6 Hz, 1 H), 6.35 (dd, J = 7.1, 0.9 Hz, 1 H), 4.68 (m, 1 H), 4.66 (t, J = 7.4 Hz, 1 H), 4.31 (dd, J = 15.3, 5.6 Hz, 1 H), 3.74 (s, 3 H), 3.19 (br d, J = 7.4 Hz, 1 H), 0.075 (s, 9 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 167.8, 145.8. 137.4, 134.4, 108.6, 66.6, 52.1, 32.1, −1.98; mass spectrum, m/e 226.1024 (M^+ calcd for $C_{11}H_{18}O_3Si$ 226.1025), 225, 211, 195, 167, 151, 122, 73 (base).

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Coordination Compounds of Polyoxovanadates with a Hexametalate Core. Chemical and Structural Characterization of $[V^V_6O_{13}\{(OCH_2)_3CR\}_2]^{2-}$, $[V^V_6O_{11}(OH)_2\{(OCH_2)_3CR\}_2]$, $[V^{IV}_4V^V_2O_9(OH)_4\{(OCH_2)_3CR\}_2]^{2-}$, and $[V^{IV}_6O_7(OH)_6\{(OCH_2)_3CR\}_2]^{2-}$

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Abstract: Reactions of the tris(hydroxymethyl)methane-derived ligands, $(HOCH_2)_3CR$, R = NO_2, CH_2OH, and CH_3, with $[(C_4H_9)_4N]_3[H_3V_{10}O_{28}]$ in CH_3CN yield the polyoxovanadate coordination complexes $[(C_4H_9)_4N]_2[V_6O_{13}\{(OCH_2)_3CR\}_2]$ (R = NO_2, **1**; CH_2OH, **2**; CH_3, **3**). Complexes of this general class are electrochemically active, displaying a reversible one-electron reduction in the range −0.67 to −1.20 V, relative to the ferrocene/ferrocenium couple. The reduced species $[V^{IV}V^V_5O_{13}\{(OCH_2)_3CNO_2\}_2]^{3-}$ exhibits an eight-line EPR spectrum at 4.2 K, approximately centered at **g** = 1.95. Broadening of EPR spectral features as the temperature is raised from 4.2 to 83 K is evidence for increased motion of the unpaired electron consistent with thermally induced electron transfer between V^{IV} and V^V states. In contrast, chemical reductions of $[(C_4H_9)_4N]_2[V_6O_{13}\{(OCH_2)_3CCH_3\}_2]$ with organohydrazines yield the reduced, hydroxy-bridged species $[(C_4H_9)_4N]_2[V^{IV}_4V^V_2O_9(OH)_4\{(OCH_2)_3CCH_3\}_2]$ (**6**) and $[(C_4H_9)_4N]_2[V^{IV}_6O_7(OH)_6\{(OCH_2)_3CCH_3\}_2]\cdot 2CH_2Cl_2\cdot 0.5C_6H_5NNC_6H_5$ (**7**). The protonation sites have been established by X-ray crystallography. Protonation and reduction can be decoupled such that reaction of **3** with $HBF_4\cdot O(C_2H_5)_2$ yields the diprotonated species $[V_6O_{11}(OH)_2\{CH_3C(CH_2O)_3\}_2]$ (**5**) wherein the site of protonation has been established by X-ray crystallography as two of the bridging oxo groups. Crystal data are as follows. **1**: triclinic $P\bar{1}$; a = 11.470 (2) Å, b = 12.149 (2) Å, c = 12.433 (2) Å, α = 63.24 (1)°, β = 63.45 (1)°, γ = 79.31 (1)°, V = 1383.5 (5) Å^3, Z = 1, D_{calcd} = 1.55 g cm^{-3}; structure solution and refinement (in all cases: Mo Kα, λ = 0.710 73 Å) converged at R = 0.049. **2**·DMF: monoclinic $P2_1/c$, a = 12.003 (2) Å, b = 16.900 (3) Å, c = 16.769 (3) Å, β = 106.95 (1)°, V = 3253.8 (11) Å^3, Z = 2, D_{calcd} = 1.37 g cm^{-3}; R = 0.054. **3**: triclinic $P\bar{1}$, a = 11.460 (2) Å, b = 12.237 (2) Å, c = 12.331 (2) Å, α = 62.88 (1)°, β = 63.50 (1)°, γ = 77.52 (1)°, V = 1377.4 (5) Å^3, Z = 1, D_{calcd} = 1.49 g cm^{-3}; R = 0.055. **5**·2DMF·$(C_2H_5)_2O$: triclinic $P\bar{1}$, a = 10.362 (3) Å, b = 10.513 (3) Å, c = 10.366 (2) Å, α = 116.33 (1)°, β = 93.56 (1)°, γ = 62.40 (1)°, V = 882.2 (7) Å^3, Z = 1, D_{calcd} = 1.83 g cm^{-3}; R = 0.043. **6**: triclinic $P\bar{1}$, a = 11.534 (2) Å, b = 12.161 (3) Å, c = 12.483 (4) Å, α = 62.86 (2)°, β = 63.15 (2)°, γ = 78.87 (2)°, V = 1389.7 (7) Å^3, Z = 1, D_{calcd} = 1.48 g cm^{-3}; R = 0.043. **7**: triclinic $P\bar{1}$, a = 13.613 (3) Å, b = 16.090 (4) Å, c = 16.077 (4) Å, α = 86.36 (1)°, β = 80.71 (2)°, γ = 80.46 (1)°, V = 3424.1 (12) Å^3, Z = 2, D_{calcd} = 1.45 g cm^{-3}; R = 0.042.

Polyoxometalates are a class of soluble molecular oxides which incorporate structural characteristics of the more complex solid oxide surfaces used in a variety of heterogeneous catalysis processes.[1-3] This structural analogy between polyoxometalates and

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