Stereoisomerism in the Cycloadducts from 4-Alkyl-1-vinylcyclohexenes with Maleic Anhydride, Sulfur Dioxide, and Methylphosphonous Dichloride[1]

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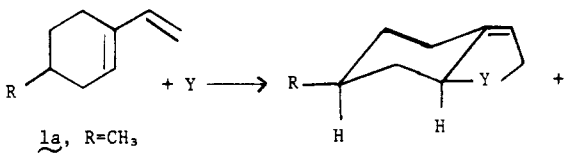
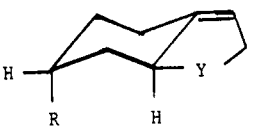
Cycloaddition of 4-methyl-1-vinylcyclohexene with the dienophiles of the title gave adducts which consisted of a mixture of diastereoisomers. The ^{13}C NMR spectra of the mixtures revealed the isomerism to arise from equatorial (syn isomer) or axial (anti isomer) disposition of the methyl group relative to the newly created chiral carbon of the cyclohexane ring. In every case, the predominating isomer was that with an *axial* methyl. Such isomers also were formed when these dienophiles were reacted with 4-*tert*-butyl-1-vinylcyclohexene. In some cycloadditions conducted over prolonged reaction periods, changes in the isomer ratio occurred, and the favored product became the thermodynamically more stable syn form. In the cycloaddition with CH_3PCl_2, some rearrangement of the double bond in the cycloadduct to the ring-fusion position occurred. All of the six possible isomers (hexahydrophosphindole derivatives) were formed on hydrolysis of the adduct mixtures.

1-Vinylcyclohexenes are well-known participants in Diels–Alder and related cycloaddition reactions. A stereochemical point in their use that does not appear to have been addressed previously with experimentation is the steric disposition in the cyclic product of a ring substituent when present in the 4-position of the diene, as in **1**. This



1a, R=CH_3
1b, R=$C(CH_3)_3$

2 (syn)

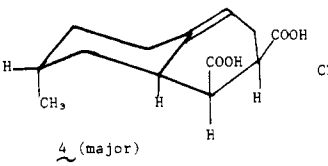


3 (anti)

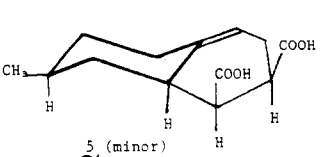
makes a given conformation of the diene have two different faces; a dienophile Y can become attached to either face, resulting in two isomeric products. If the assumptions are made that the original six-membered ring adopts the chair shape in the product and that the newly formed ring (especially if five-membered) demands for steric reasons the equatorial position at the sp^3 carbon to which it is attached, then the isomeric structures may be represented by **2** (designated syn) and **3** (designated anti). The syn isomer then has an equatorial disposition for the substituent, and the anti an axial disposition, although a large 4-substiuent may cause twisting of the chair in the latter case to relieve the crowding. However, a search of the literature has so far not revealed any prior observation of such isomers.

We have performed several cycloadditions to such dienes as **1** with R = CH_3 using a diverse group of dienophiles consisting of maleic anhydride, sulfur dioxide, and methylphosphonous dichloride (CH_3PCl_2). In every case, the product was found by NMR spectroscopic measurements to be a mixture of the isomers, *with the more crowded anti form in predominance.* It is not at all obvious that this should be the favored steric path for these cycloadditions. However, the force controlling the stereochemical outcome of these reactions is not trivial, for it will be seen that isomers form even when a *tert*-butyl group is present.

Maleic Anhydride as Dienophile. A cycloadduct formed readily from 4-methyl-1-vinylcyclohexene (**1a**) and maleic anhydride. That a mixture of isomers was obtained was immediately suggested by the ^{13}C NMR spectrum, which had two complete sets of signals in the approximate ratio of 2:1; both were consistent with the adduct structure. Hydrolysis to the diacid was accomplished with preservation of the isomers. Attempts to separate the mixture by chromatography have not yet been successful, although some enrichment of the major isomer was achieved by fractional crystallization from chloroform. That the mixture did consist of isomers was confirmed by the elemental analysis giving the correct values for the dicarboxylic acid. The most important difference in the ^{13}C spectra of the isomers occurred in the CH_3 signal, which is readily recognized from its upfield position. That the most upfield signal for each isomer was properly associated with the methyl carbon was convincingly demonstrated by applying the technique of insensitive nucleus enhancement by polarization transfer (INEPT program; see footnote 21 for details) which caused changes in the intensity of the methine carbons and inverted the signals for methylene carbons, without affecting methyl carbons. The difference in chemical shifts of the methyl signals in the isomers is just that known[2] to be associated with the axial–equatorial character of a methyl of a six-membered ring. Thus, the steric compression[3] of the axial methyl of *cis*-1-methyl-4-*tert*-butylcyclohexane absorbs at δ 17.49, while the less-crowded equatorial methyl of the trans isomer absorbs at δ 22.75. The signals for the diacid isomers match these values closely (major, δ 16.7; minor, δ 22.3). This leads to the assignment of structures **4** and **5** for the isomers, with



4 (major)



5 (minor)

the half-chair conformation of the cyclohexene ring and its carboxyls not being specified. These structures assume that the dienophile approached the diene with the usual orientation that allows secondary π-orbital interactions,[4]

(1) Taken in part from the Ph.D. Dissertation of J.E.M., Duke University, 1979.

(2) Schneider, H.-J.; Hoppen, V. *J. Am. Chem. Soc.* **1978**, *43*, 3866.
(3) The nature of the cause of upfield shifting when steric compression occurs between γ-related carbons is not well understood.
(4) Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537.

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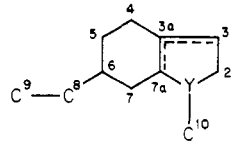
Table I. ^{13}C NMR Spectral Data[a] of Sulfur and Phosphorus[b] Compounds



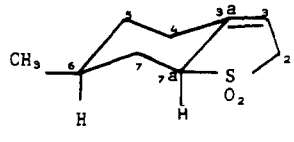
compd	Y	chemical shift, δ						
		C-2	C-3	C-3a	C-7a	C-8	C-10	C-4,5,7[a]
6	SO_2	56.4	115.8	149.8	63.8	21.8		30.6, 33.4, 33.9
7	SO_2	55.9	113.1	140.3	60.1	16.9		25.9, 26.6, 30.6
8	SO_2	48.3	29.7	144.7	135.6	21.0		25.9, 27.5, 28.0
9[c]	SO_2	56.3	114.7	140.6	61.4	32.9		22.0, 23.2, 26.6
11	$P^+CH_3Cl^-$	34.8 (46.9)	115.13 (7.80)	142.23 (13.67)	40.6 (48.8)	16.5	15.07 (43.0)	
13	$P(O)CH_3$	32.06 (65.43)	116.17 (11.70)	142.58 (14.15)	38.07 (70.31)	16.18	12.35 (65.43)	
14	$P(O)CH_3$	33.40 (62.50)	115.59 (11.70)	143.91 (11.75)	38.07 (70.31)	16.83	16.76 (62.50)	
15	$P(O)CH_3$	24.50 (70.31)	31.22 (8.80)	154.28 (30.27)	129.56 (95.70)	21.25	15.50 (65.43)	
16	$P(O)CH_3$	24.50 (70.31)	31.22 (8.80)	154.28 (30.27)	129.56 (95.70)	21.25	15.76 (65.43)	

[a] The C-6 signal was generally not observed. C-4, C-5, and C-7 were in close proximity and not routinely assignable with confidence. The complexity in this region of the spectra of the phosphorus compounds (due to ^{31}P-^{13}C coupling) prevented firm assignments of chemical shifts to individual carbons. [b] Values in parentheses are ^{31}P-^{13}C coupling constants in hertz. [c] C-9, δ 27.4; C-6, δ 41.5.

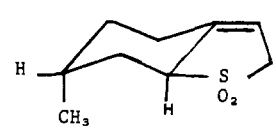
but even if the opposite approach had occurred, the ^{13}C NMR spectra require that the products still differ by the axial and equatorial character of the methyl.[5]

The cycloaddition of 4-*tert*-butyl-1-vinylcyclohexene (**1b**) with maleic anhydride has been reported by other workers[6] to occur in refluxing toluene, but no mention was made of the presence of isomers in the cycloadduct. On the basis of the complexity of the ^{13}C NMR spectrum of the product we obtained on carrying out this reaction at room temperature, it is believed that syn and anti isomers can be formed in this case also. This was most clearly seen in the well-resolved sp^2 carbon region (major isomer, C-1 at δ 118.5 and C-8a at δ 142.9; minor isomer, C-1 at δ 115.8 and C-8a at δ 140.5). This system, however, lacks the useful indicator of stereochemistry that was provided by the 6-methyl group in compounds formed from diene **1a**. The formation of isomers with a 6-*tert*-butyl substituent is more clearly established in the reaction of diene **1b** with SO_2, as is discussed in the next section.

Sulfur Dioxide as Dienophile. The stereochemical consequences of the cycloaddition are also clearly seen when SO_2 is used as the dienophile. This [4 + 2] cheletropic reaction is known to be concerted and to occur in the disrotatory manner.[7] Products **6** and **7** would then



6 (syn)

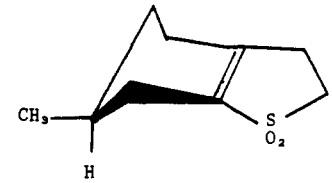


7 (anti)

result from diene **1a**. The reaction was conducted in the usual way[8] at room temperature in methanol. The recovered adduct, a liquid, was examined by ^{13}C NMR, and it was immediately obvious that isomers were present from the two sets of signals in the approximate ratio of 3:1. The isomer in predominance had the spectral characteristics (Table I) associated with the interactions resulting from an axial 6-substituent (**7**). Specifically, upfield shifts occur for the methyl carbon, its carbon of attachment (C-6), and the carbons (C-4, C-7a) bearing the axial protons that are the cause of the nonbonded interaction. Even carbons C-5 and C-7 show upfield shifting from the crowding. All of these effects have been documented many times for isomers of carbocyclic and heterocyclic systems differing in the axial–equatorial disposition of a substituent.[9] Again the methyl signal is especially useful as an indicator of the isomerism, since the signal is easily located and significantly different in the two isomers. The shifts observed (**6**, δ 21.85; **7**, δ 16.85) are very similar to those already noted for the hydrolyzed maleic anhydride adducts.

The ^1H NMR spectrum (100 MHz) was singularly uninformative about the isomerism; only one CH_3 doublet and one olefinic proton signal (δ 5.8) were present.

3-Sulfolenes are relatively unstable, suffering retrocycloaddition or double-bond rearrangement to the conjugated positon.[8] Adducts **6** and **7** were therefore purposely rearranged to give a stable form for purification and analysis. When the mixture of **6** and **7** was allowed to stand with KOH, both were converted to the new structure **8**, for which no diastereoisomers exist. Judging from the



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position of the methyl ^{13}C NMR signal (δ 20.98), this

(5) Experiments with tetracyanoethylene as the dienophile, which would give adducts where the approach of the reactants is immaterial to their structure, have also given an isomer mixture with similar differences in CH_3 signals (major, δ 16.50; minor, δ, 21.83).

(6) Andreev, V. M.; Kugatova-Shemyakina, G. P.; Smirnova, G. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, 408.

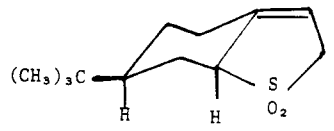
(7) Block, E. "Reactions of Organosulfur Compounds"; Academic Press: New York, 1978; (a) p 268, (b) pp 274–276.

(8) Turk, S. D.; Cobb, R. L. In "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967; Chapter 2.

(9) Wilson, N. K.; Stothers, J. B. *Top. Stereochem.* **1974**, *8*, 1.

substituent has likely adopted the equatorial position in the half-chair.

From the reaction of 4-*tert*-butyl-1-vinylcyclohexene with SO_2 at room temperature for a short period (40 min), isomeric adducts **9** and **10** were again formed. This was



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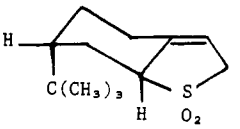

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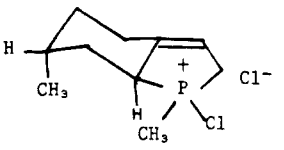
revealed by the complexity of the ^{13}C NMR spectrum. Signals for the methyls of two *tert*-butyls clearly stood out (δ 27.25 and 27.61, 2:1). After a longer reaction period (3 days), the spectrum simplified to that of a single product. This product was a recrystallizable solid that gave the correct elemental analysis and ^1H and ^{13}C NMR spectra for the expected cycloadduct, and it was assigned the syn structure **9**. The spectral changes on employing a longer reaction period are explained by the well-known reversibility[7b] of the SO_2–diene reaction; the fastest formed anti isomer (**10**) equilibrates through the starting materials to the more stable syn isomer **9**. This important observation establishes that the formation of the more crowded anti isomer is a kinetically, not thermodynamically, favored process.

The assumption is made in drawing structure **10** that the cyclohexylidene ring retains its normal[10] chair shape and that it is not twisted to relieve the nonbonded interactions of the axial *tert*-butyl group. There are reports in the recent literature[11] that *tert*-butyl groups can occupy axial positions of six-membered rings, and one such structure is based on the cyclohexylidene ring.[10]

Methylphosphonous Dichloride as a Dienophile. The cycloadducts from P(III) halides and dienes are generally precipitated as solids or oils when the reaction mixture is allowed to stand. The phosphorus atom in the cycloadducts has phosphonium ion character, although this form is in rapid equilibrium with a small amount of the initially formed pentacovalent form.[12a] In cases where the newly formed ring is fused to another ring, a new chiral carbon is created, but the rapid equilibration about phosphorus eliminates the possibility of this atom also acting as a chiral center so as to create observable cis and trans isomers. In the hydrolysis products (phosphine oxides), however, the chirality is fixed at phosphorus, and cis/trans isomerism can be observed.[12] The cycloadduct with 4-methyl-1-vinylcyclohexene can be expected to have the same possibility of syn and anti isomers as noted for the case of SO_2 as the dienophile. When this diene was reacted with CH_3PCl_2 in a concentrated hexane solution for a relatively short period (14 h), the solid that precipitated had only one ^{31}P NMR signal (δ 120), and thus only one of the two possible isomers **11** and **12** had been formed. That the double bond had not migrated was confirmed by the ^1H NMR spectrum, which exhibited a single olefinic proton (δ 5.74, $^3J_{PH}$ = 36 Hz). This product had exclusively an axial *C*-methyl group as revealed by the ^{13}C NMR signal at δ 16.50. No absorption was present in the characteristic region for an equatorial *C*-methyl. The cycloadduct is therefore assigned structure **11**, where the phosphorus is



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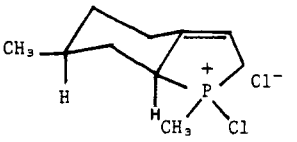

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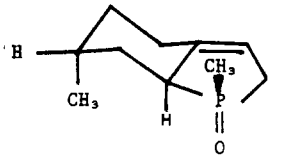
expressed without a chiral preference.

When adduct **11** was hydrolyzed, the expected two isomeric oxides **13** and **14** were formed. The mixture gave



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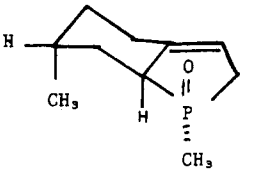

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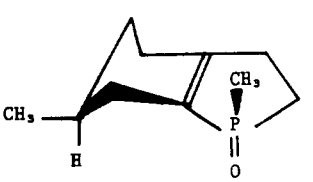
the correct elemental analysis and exact mass for M^+ but was not separable by chromatography. Both isomers possessed an axial *C*-methyl as indicated by the ^{13}C NMR signals at δ 16.18 and 16.83. The major isomer in the 2:1 mixture was assigned structure **13**, where the *P*-methyl and the ring carbon (C-7) attached to the α-position of the phospholene ring are cis to each other. This follows from the relatively upfield position (δ 12.35) of the crowded *P*-methyl in this isomer; that with a trans ring substituent (**14**), being less crowded, has a more downfield position (δ 16.76) for the *P*-methyl signal. These relations have been used for a number of other cyclic phospholene oxides (for example, ref 13).

Rearrangements of the double bond into the fusion position, as in **15** and **16**, would allow the ring conformation



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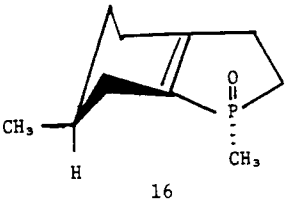

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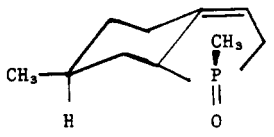
to change and the *C*-methyl to adopt the less crowded equatorial disposition. The ^{13}C NMR spectrum should reflect this change, just as was noted for the corresponding sulfone. The rearrangement was promoted by conducting the cycloaddition in refluxing hexane.[13] Hydrolysis of the gummy cycloadduct gave a mixture of oxides **15** and **16**; no olefinic ^1H signal was observed, proving that the rearrangement was complete. The ^{31}P NMR spectrum (δ 65.07 and 65.30, 1:1) proved that isomers were present. The ^{13}C NMR spectra for the isomers were virtually identical, except for the PCH_3 signals ($\Delta\delta$ 0.26). The *C*-methyl absorption at δ 21.25 was consistent with its equatorial character.

When the room-temperature cycloaddition was performed over a long period of time (26 days) and then hydrolysis performed, the reaction mixture was quite complicated, containing six ^{31}P NMR signals in the characteristic phospholene oxide region. Signals expected for isomers **13** and **14**, as well as for **15** and **16**, were present, the latter from double-bond migration during the

(10) Johnson, F.; Zito, S. W.; Sarma, R.; McKeever, B. M. *Tetrahedron Lett.* **1978**, 753.
(11) Vierhapper, F. W. *Tetrahedron Lett.* **1981**, *22*, 5161.
(12) Quin, L. D. "The Heterocyclic Chemistry of Phosphorus"; Wiley-Interscience: New York, 1981; (a) Chapter 2, (b) Chapter 7.
(13) Symmes, C., Jr.; Quin, L. D. *J. Org. Chem.* **1976**, *41*, 238.

long standing period. Two new signals (δ 68.55 and 61.49) were suggested to arise from the isomers with equatorial *C*-methyls (**17** and **18**). The appearance in the cyclo-



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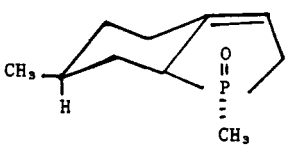

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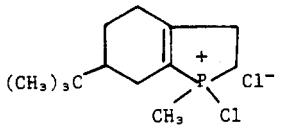
addition mixture when these two forms were allowed to stand may imply that the initially formed cycloadducts with an axial *C*-methyl are the products of kinetic control and undergo equilibration through retrocycloaddition to the thermodynamically more stable equatorial forms. While this is consistent with the similar observation made in the sulfone case, reversibility in the McCormack cycloaddition, while not unknown,[14] is certainly a far less commonly encountered phenomenon. An alternative explanation is simply that the rates of formation of the isomeric cycloadducts **11** and **12** are greatly different, with the latter being the slower to form; its concentration could have been too low to be detected in the short reaction period experiment. The kinetically favored anti isomer **11**, being the more crowded, would probably rearrange the faster to the $\Delta^{3a,7a}$ form, thus allowing some relative buildup of the concentration of **12**. In another experiment, the ^{31}P NMR spectrum was obtained directly on the cycloadduct from an aged (73 days) mixture; three signals were present, at δ 120 for **11**, at δ 116 for its isomer **12**, and at δ 105 for the double-bond rearrangement product, in the ratio 6:1:2. The more upfield signal was assigned to the rearranged isomer on the basis of known spectra–structure relations for such systems.[12b]

4-*tert*-Butyl-1-vinylcyclohexene also underwent the cycloaddition reaction with CH_3PCl_2. When the product was collected after a 32-day reaction period, it consisted only of a single compound with ^{31}P δ 106.5. This value, as well as the spectral characteristics of its hydrolysis product (no olefinic proton), indicated the cycloadduct to have undergone rearrangement to **19** and that the hydrolysis



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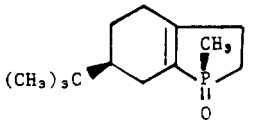

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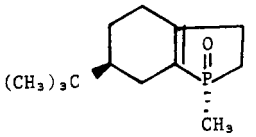

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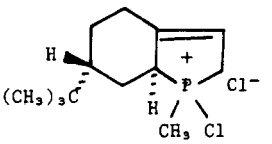
products would have structures **20** and **21**. The markedly greater tendency for the initial cycloadduct to rearrange, relative to the methyl analogue, can be attributed to the greater strain associated with the *tert*-butyl series. When the cycloaddition was monitored regularly by following ^{31}P NMR changes in a $CDCl_3$ reaction medium, it was observed that the adduct initially detected (as measured after 6 h) had a ^{31}P shift of δ 126, a value which is similar to that (δ 120) found for the initially formed *P*-methyl adduct with the anti substituent (**11**) and which is therefore attributed to **22**. Signals later appeared at δ 120 and 108; the former



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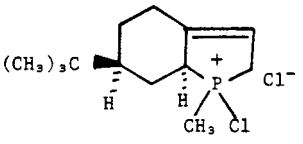


23

is attributed to the syn isomer **23**, analogous to **12**, and the latter to the rearranged structure **19** already observed on long standing. Anti isomer **22** reached a peak concentration at about 140 h and then diminished; isomers **23** and **19** grew steadily in concentration, with the latter at the faster rate. After 240 h, the mixture consisted of nearly equal amounts of **22** and **19**, with **23** at about one-third their concentration. The final measurement was made after 34 days; anti isomer **22** had nearly vanished, and the product consisted of 18% of the syn isomer **23** and 82% of the rearranged form **19**. These observations clearly indicate that the initial anti product is unstable and decomposes by retrocycloaddition or double-bond migration. The preferred formation of the adduct with the *tert*-butyl group in an axial position (or shifted from this following a conformational change to a twist form) is a surprising observation.

Hydrolysis of a mixture of the three chlorophosphonium chlorides **19**, **22**, and **23** gave a mixture of six phospholene oxides as determined by ^{31}P NMR (with overlap of the two signals for isomeric oxides **20** and **21** at δ 66.6). If the same sequence of shifts holds as that found for the 6-methyl series, then the most downfield signal (δ 75.0), along with δ 63.6, may be associated with the anti isomers; the syn isomers are suggested to have shifts of δ 70.4 and 62.9. Insufficient work has been done to claim these as definite assignments, however.

Discussion

The experiments described above are definitive in showing that syn and anti isomers are formed in the cycloaddition of various dienophiles with 4-substituted 1-vinylcyclohexenes and that for the 4-methyl compounds the predominating isomer has the more crowded anti structure, presumably with an axial CH_3. In those reactions where isomer equilibration has been promoted, the anti form is converted to the more stable syn form. Isomer formation occurs also when *tert*-butyl is the 4-substituent of the 1-vinylcyclohexene, and, indeed, in the cycloaddition with CH_3PCl_2, where ^{31}P NMR can be employed as an additional structural analysis tool, the fastest formed isomer is that with the *anti tert*-butyl structure.

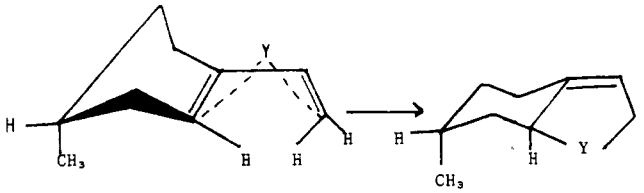
In developing an understanding for this unusual kinetic effect, it needs to be remembered that the equilibration between the two half-chair conformations of a cyclohexene occurs much more rapidly than between the chairs in cyclohexane; 4-substituted cyclohexenes have values for $\Delta G^{\ddagger}$ of 5.2–6.2 kcal/mol at −165 °C.[15] Furthermore, there is a considerably smaller preference exerted by a 4-substituent for the equatorial position. Thus, for 4-methyl, $\Delta G°$ has been reported[16] to be only 0.86 kcal/mol, corresponding to an equilibrium mixture consisting of 19% of the axial

(14) Scott, G. D.; Hammond, P. J.; Hall, C. D.; Bramblett, J. D. *J. Chem. Soc., Perkin Trans. 2* **1977**, 882.

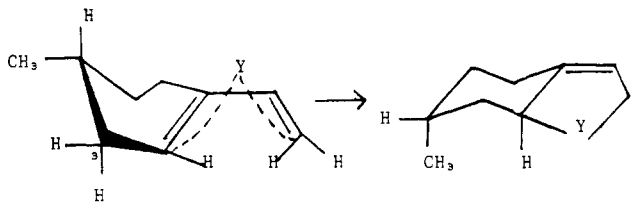
(15) Jensen, F. R.; Bushweller, C. H. "Advances in Alicyclic Chemistry"; Hart, H., Karabatsos, G. J., Eds.; Academic Press: New York, 1971; Vol. 3, pp 190–194.

(16) Fernandez-Gomez, F.; Lysenkov, V. I.; Ulyanova, O. D.; Pentin, Y. A.; Bardyshev, I. I. *Zh. Fiz. Khim.* **1977**, *51*, 2710; *Chem. Abstr.* **1978**, *88*, 21988.

conformer. These conformational properties make it unsafe to predict which conformer is the faster reacting and hence to perform a meaningful analysis of the structural factors that lead to the kinetic preference for an anti product. It seems clear, however, that if the axial conformer is the more reactive, an olefinic dienophile will approach from the opposite, less-crowded face, thus giving the observed anti product. It is less obvious why the



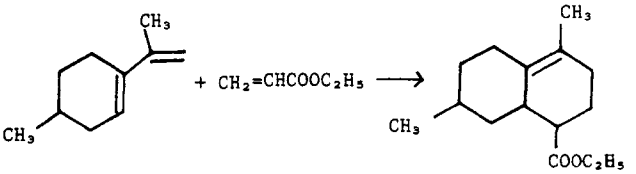
equatorial conformer would give primarily the anti isomer, for no strong directive effect can be discerned. Two features of the equatorial form might be considered in this regard. First, an axial H at C-3 could offer weak interference to approach toward the face to which it is approximately orthogonal. This would lead to a preference for attack at the opposite face; after conformational strain minimization the anti form **3** would result.



A second effect, associated with the same axial H at C-3, as well as the axial H at C-6, might arise from a weak but directed distortion of the π orbitals of the diene. The importance of interactions of σ and π frontier molecular orbitals in giving stereospecificity to reactions has received recent emphasis.[17] In the 1-vinylcyclohexenes, the axial HC-3 and HC-6 bonds are nearly orthogonal to the nodal plane of the diene, and thus properly oriented for consideration of possible interaction of their bonding and antibonding σ orbitals with the π orbitals of the diene. In the diene HOMO, the atomic p_z orbital of C-2 will be affected by the bonding orbital of axial HC-3; since this orbital is of opposite phase,[18] a distortion of the diene's orbital to the anti face occurs to minimize the antibonding nature of the interaction. The net effect of this interaction is to enrich the electron density in the π orbitals of the diene in a stereospecific way, thus influencing the establishment of bonds to the approaching dienophile. Whether or not the magnitude of such orbital interaction is sufficient to steer the stereochemical course of the cycloaddition into a situation of considerable nonbonded interaction remains unknown.

It may be significant that both two-atom and one-atom dienophiles gave similar stereochemical results, since the approach of the species to the diene may not follow the same path and need not be equally affected by steric hindrance effects. This may add emphasis to the orbital distortion argument, since it should apply to cycloadditions with both types of dienophiles.

Regardless of the origin of the directive effect operating in 4-substituted 1-vinylcyclohexenes, there are some important practical consequences of it. Other workers in the past have conducted Diels–Alder reactions with such dienes, but until the advent of ^{13}C NMR there was no simple technique available for determining the orientation of this substituent in the product. Even ^1H NMR can fail to detect the presence of the isomers. To select a case in illustration,[19] a cycloaddition of mentha-3,8-diene with methyl acrylate was recently performed in a synthesis of the sesquiterpene cadin-1(10)-en-11-ol (see below). It was



recognized that isomers could be formed but they were not detected, and the stereochemistry of the product was not assigned. A ^{13}C NMR spectrum of the cycloadduct should provide instant clarification of the structure, with the chemical shift of the *C*-methyl signal as the indicator.

In other work in this laboratory,[20] 1-vinylcyclohexenes with 4-alkoxy substituents were used in the cycloaddition with P(III) halides. No strong directional effect seemed to operate in these cases, and substantial amounts of the isomers with axial and equatorial substitution were obtained. Whether or not this is connected with a difference in the degree of biasing of the conformational equilibrium by this smaller group or with a secondary polar interaction with the dienophile, or some other cause, cannot at present be determined. The result does clearly indicate the need for caution and experimental verification in the assignment of stereochemistry to the cycloadducts from all types of 4-substitued 1-vinylcyclohexenes.

Experimental Section[21]

Cycloaddition of 4-Methyl-1-vinylcyclohexene with Maleic Anhydride and Hydrolysis of the Adduct. Maleic anhydride (0.8 g, 0.008 mol) and 1.0 g (0.008 mol) of diene **1a**[22] were combined in a small flask. A small spot on the flask was warmed by touching it to a hot plate, causing initiation of the exothermic cycloaddition which proceeded to completion with no further forcing. The resulting thick oil was washed several times with hexane to extract the product from a small amount of maleic anhydride. Concentration of the solution gave a crude product: ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6 Hz, $CHCH_3$), 3.23–3.5 (m, 2 H, CHCOR), 5.3–5.8 (m, 1 H, C=CH); ^{13}C NMR ($CDCl_3$) for major isomer ratio 2:1 δ 19.8, 22.5, 27.0, 29.8, 30.4, 31.6, 33.5, 39.8 and 43.9 (possibly C-3, C-4), 117.1 (C-1), 141.3 (C-8a), 172.1 and 174.3 (both C=O); ^{13}C NMR for minor isomer δ 20.8, 22.1, 33.0, 34.0, 34.8, 38.2, 38.7, 40.8 and 42.8 (possibly C-3, C-4), 115.5 (C-1), 139.0 (C-8a), 171.8 and 173.8 (both C=O).

The oily material was added slowly to boiling water, and the mixture was refluxed for several minutes. The process was repeated on the residual oily residue with fresh water. The solution was acidified with HCl, which helped prevent the formation of emulsions, and the solution was extracted with four 30-mL portions of $CHCl_3$. The extracts were dried ($MgSO_4$) and con-

(17) (a) Liotta, C. L. *Tetrahedron Lett.* **1975**, 519, 523. (b) Burgess, E. M.; Liotta, C. L. *J. Org. Chem.* **1981**, *46*, 1703.

(18) Selection of the proper orbitals was based on the methods outlined in the literature: Jorgensen, W. L.; Salem, L. "The Organic Chemist's Book of Orbitals"; Academic Press: New York, 1973.

(19) Buttery, R. G.; Ling, J. C. *J. Agric. Food Chem.* **1977**, *25*, 291.

(20) MacDiarmid, J. E.; Quin, L. D. *J. Org. Chem.* **1981**, *46*, 1451.

(21) Melting points were taken on a Mel-Temp apparatus and are corrected; boiling points are uncorrected. NMR spectra were taken as follows: ^1H, JEOL MH-100 spectrometer, internal Me_4Si reference, $CDCl_3$ solutions; ^{31}P, Bruker HFX-10 at 36.43 MHz, FT proton decoupled, 85% H_3PO_4 external reference with negative signs upfield, $CDCl_3$ solutions; ^{13}C, JEOL FX-60 at 15.0 MHz, FT proton decoupled, internal Me_4Si as reference in $CDCl_3$ solutions and as a lock, except for **5** and **6**, where a JEOL FX 90Q was used with similar conditions. This instrument was used for the INEPT program of G. A. Morris and R. Freeman (*J. Am. Chem. Soc.* **1979**, *101*, 760. See also: Morris, G. A. *Ibid.* **1980**, *102*, 428). CH enhancement occurs at 0.25J and CH_2 inversion at 0.75J.

(22) Vig, O. P.; Singh, G.; Chung, O. P.; Matta, K. L. *Indian J. Chem.* **1969**, *7*, 434.

centrated. The resulitng oil was characterized by ^{13}C NMR as a 2:1 mixture favoring **4**. The ^{13}C NMR ($CDCl_3$) at 22.5 MHz[23] with the INEPT program gave the following. For **4** (major): CH_3, δ 16.89; CH_2, δ 24.43, 28.90, 31.35, 35.40; CH, δ 27.23, 32.84, 41.30, 44.16; C-1 δ 118.23; C-7a, δ 136.58; C=O, δ 179.55, 180.33. For **5** (minor, not completely observed): CH_3, δ 22.29; CH_2, δ 34.74, 38.60; CH, δ 25.68, 38.08, 42.61; C-1, δ 118.3; C-7a, δ 135.99; C=O, δ 176.69, 177.23. Addition of some $CHCl_3$ gave, after overnight standing, a crystalline product that was further enriched in **4**: mp 166–167 °C dec (with CO_2 evolution); ^1H NMR ($CDCl_3$) δ 1.02 (d, J = 7 Hz, CH_3), 5.4 (m, 1 H, C=CH), 11.6 (s, 2 H, COOH). The solution remaining from the fractional crystallization was enriched in **5** to a 1:1 ratio: ^1H NMR ($CDCl_3$) for **5** δ 0.89 (d, J = 6 Hz, $CHCH_3$), other signals mixed with those for **4**. The sample enriched in **4** was used for analysis.

Anal. Calcd for $C_{13}H_{17}O_4$: C, 65.53; H, 7.61. Found: C, 65.36; H, 7.68.

Cycloaddition of 4-Methyl-1-vinylcyclohexene with Tetracyanoethylene. A solution of 0.5 g (0.004 mol) of TCNE in 10 mL of THF, cooled in ice, was treated with 0.5 g (0.004 mol) of diene **1a** washed in with 5 mL of THF. The initially yellow solution turned rust-orange. It was stirred in the ice bath for 1 h, whereupon the color reverted to yellow. The solution was concentrated under vacuum without warming to leave 1.0 g of brown residue. Trituration of this residue with hexane left 0.7 g of solid. Extraction of the solid with a mixture of $CHCl_3$ and hexane left 0.2 g of tan solid which appeared to be unreacted TCNE by ^1H NMR. Concentration of the hexane and $CHCl_3$–hexane washings yielded 0.7 g (68%) of a light brown solid which gave the spectral features for a mixture of adducts: ^1H NMR ($CDCl_3$) δ 1.18 (d, J = 8 Hz, $CHCH_3$), 5.56 (m, C=CH); ^{13}C NMR ($CDCl_3$), two sets of signals with one in predominance, major δ 113.2 (C-1), 32.1 (C-2), 38.2 (C-3), 45.1 (C-4), 34.8 (C-5), 26.7 (C-6), 30.3 (C-7), 28.3 (C-8), 136.5 (C-9), 38.5 (C-10), 16.5 (C-CH_3); minor δ 111.4 (C-1), 136.0 (C-9), 21.8 (C-CH_3), others not resolved. The adduct has not been successfully purified.

Reaction of 4-*tert*-Butyl-1-vinylcyclohexene with Maleic Anhydride. Maleic anhydride (1.2 g, 0.012 mol), 2 g (0.012 mol) of diene **1b**[24] and 3 mL of benzene gave a homogeneous solution, which solidified after 1.5 h. The solid was broken up in hexane and the resulting shiny white crystals (1.3 g, 40.7%) were filtered off: mp 134–144 °C (lit.[4] 151–151.5 °C, for material obtained by 6-h reflux in toluene, isomer ratio unknown); ^{13}C NMR ($CDCl_3$; two isomers in 2:1 ratio) δ 27.6 (major, $C(CH_3)_3$), 27.42 (minor, $C(CH_3)_3$), 118.5 (major, C-1), 115.8 (minor, C-1), 142.9 (major, C-9), 140.5 (minor, C-9), 172.3 and 174.65 (major, $(-CO)_2O$), 172.9 (minor, $(-CO)_2O$, other half not resolved), other signals (major) 24.0, 24.5, 30.3, 33.0, 33.6, 41.2, 42.0, 45.1.

Cycloaddition of 4-Methyl-1-vinylcyclohexene with SO_2. A mixture of diene **1a** (4.2 g, 0.34 mol), 0.1 g of hydroquinone (as a polymerization inhibitor), and 3 mL of methanol were combined in a heavy-walled glass reaction bottle and chilled in dry ice. Sulfur dioxide (3 mL, 4.3 g, 0.067 mol) was condensed into a graduated cylinder chilled in dry ice–acetone and added to the prechilled reaction bottle, which was then closed with a securely fastened rubber stopper. The mixture was permitted to stand at room temperature for 3 days, by which time it had acquired an olive color. The SO_2 was vented, and the solution was concentrated by rotary evaporation under high vacuum without heating (to avoid retrocycloaddition) to leave 4.5 g of a brown liquid. This was dissolved in ethyl ether, decolorized with Norite, dried ($MgSO_4$), and reconcentrated without warming by rotary evaporation to leave 3.6 g (56.2%) of **6** and **7** in about a 1:3 ratio: ^1H NMR ($CDCl_3$) δ 1.12 (d, J = 7 Hz, $CHCH_3$), 3.5–4.1 (m, $CHSO_2CH_2$), 5.8 (br s, C=CH); ^{13}C NMR (Table I).

6-Methyl-Δ$^{3a(7a)}$-hexahydrobenzo[*b*]thiophene 1,1-Dioxide (8). A 0.8-g (0.04 mol) sample of a mixture of **6** and **7** with 2 mL of 10% aqueous KOH and 3 mL of ethanol was allowed to stand for 3 days. The mixture was concentrated to remove ethanol; acidification with 10% HCl caused precipitation of a yellow solid. The mixture was extracted with ethyl ether, which dissolved the solid, and the extracts were decolorized with Norite and filtered to leave a colorless solution. The solution was concentrated to yield a slightly yellow solid which was recrystallized from water to give 0.3 g (37.5%) of **8** as white needles: mp 86.5–86.8 °C; ^1H NMR ($CDCl_3$) δ 1.12 (d, J = 6 Hz, $CHCH_3$), 3.30 (t, J = 6 Hz, $SO_2CH_2CH_2$); ^{13}C NMR (Table I).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.03; H, 7.58. Found: C, 58.15; H, 7.75.

***syn*-6-*tert*-Butyl-Δ^3-hexahydrobenzo[*b*]thiophene 1,1-Dioxide (9).** As in the preparation of **6** and **7**, a mixture of diene **1b** (3.0 g, 0.018 mol), 0.1 g of hydroquinone, and 20 mL of methanol was treated with 3 mL (0.067 mol) of liquid SO_2 and allowed to stand for 2.5 days. The solution was concentrated without warming; the residue was taken up in ethyl ether, decolorized with Norite, and reconcentrated, and the single product (**9**) then crystallized by addition of hexane as fine white needles: mp 86.7–87.7 °C; ^1H NMR ($CDCl_3$) δ 0.96 (s, $C(CH_3)_3$), 1.2–2.7 (m, 7 H of carbocyclic ring), 3.5–4.0 (m, 3 H, $CHSO_2CH_2$), 5.75 (br s, 1 H, C=CH); ^{13}C NMR (Table I).

Anal. Calcd for $C_{12}H_{20}O_2S$: C, 63.12; H, 8.83; S, 14.04. Found: C, 63.41; H, 9.07; S, 14.31.

When the diene (1 g, 0.006 mol), a trace of hydroquinone, and 3 mL (0.067 mol) of liquid SO_2 were allowed to stand at room temperature for 40 min and the solution was then mixed with hexane, the precipitated solid had a ^{13}C spectrum which showed signals for **9** and for an isomer (**10**) in a 2:1 ratio. The CH_3 groups gave the most easily recognized signals at δ 27.25 and 27.61, respectively.

Cycloaddition of 4-Methyl-1-vinylcyclohexene with CH_3PCl_2 and Hydrolysis of the Cycloadduct. A mixture of 5.0 g (0.04 mol) of diene **1a**, 1 mL of hexane, 0.1 g of copper stearate, and 5.5 mL of (0.06 mol) of CH_3PCl_2 was allowed to stand for 14 h at room temperature. In a glovebag with an N_2 atmosphere the solids were removed, and the remaining liquid was returned to the reaction vessel for further reaction. The solid (**11**) was washed with hexane and filtered: ^1H NMR ($CDCl_3$) δ 1.21 (d, J = 7 Hz, $CHCH_3$), 3.3 (d, J = 14 Hz, PCH_3), 5.74 (d, $^3J_{PH}$ = 36 Hz, HC-3); ^{31}P NMR ($CDCl_3$) δ 120; ^{13}C NMR (Table I). Adduct **11** was hydrolyzed with $NaHCO_3$–ice-cold water. The aqueous solution was extracted with several small portions of $CHCl_3$, and the organic extract was dried ($MgSO_4$) and concentrated under vacuum without heating to give 0.9 g (11.9%) of **13** and **14** as a slightly yellow oil: ^1H NMR δ 1.02 (d, J = 6 Hz, R_2CHCH_3), 1.46 (d, $^2J_{PH}$ = 13 Hz, PCH_3 for major isomer **13**), 5.40 (d, $^3J_{PH}$ = 27.6 Hz, HC-3); ^{31}P NMR ($CDCl_3$) δ 70.8 (**15**), 62.9 (**16**) (ratio 2:1); ^{13}C NMR (Table I); mass spectrum, m/e 184.1017 (M^+, calcd 184.1016).

Anal. Calcd for $C_{10}H_{17}OP$: C, 65.20; H, 9.30; P, 16.31. Found: C, 65.17; H, 9.46; P, 16.83.

Cycloaddition with Rearrangement of 4-Methyl-1-vinylcyclohexene and CH_3PCl_2. A mixture of 3.0 g (0.025 mol) of diene **1a**, 0.1 g of copper stearate, 3 mL (0.034 mol) of CH_3PCl_2, and 25 mL of hexane was refluxed for 53 h and after being cooled to room temperature was poured carefully into cold water. The solution was neutralized with $NaHCO_3$, and the aqueous layer was extracted with several small portions of $CHCl_3$. The organic extracts were dried ($MgSO_4$) and concentrated, and the residue was distilled. There was obtained 2.2 g (49%) of oxides **15** and **16** as a clear liquid which solidified on standing overnight: ^1H NMR ($CDCl_3$) δ 1.05 (d, $^3J_{H,H}$ = 6 Hz, $CHCH_3$), 1.60 (d, $^2J_{P,H}$ = 12 Hz, PCH_3); ^{31}P NMR ($CDCl_3$) δ 65.1, 65.3 (1:1); ^{13}C NMR (Table I). The hygroscopicity of the compound interfered with elemental analysis; mass spectrum, m/e 184.1015 (M^+; calcd for $C_{10}H_{17}OP$ 184.1017.

Detection of *syn*-1-Chloro-1,6-dimethyl-Δ^3-hexahydrophosphindolium Chloride (12) and Its Hydrolysis to Oxides 15 and 16. In a 5-mm NMR tube were placed 0.5 mL (0.0036 mol) of diene **1a**, 0.5 mL (0.0036 mol) of CH_3PCl_2, a trace of copper stearate, and 0.35 mL of $CDCl_3$. After 73 days, signals were present in a 6:1:2 ratio for **11**, its syn isomer **12**, and the rearranged isomer at ^{31}P δ 120, 116, and 105, respectively.

In another experiment, a mixture of 16.2 g (0.13 mol) of diene **1a**, 13 mL (0.14 mol) of CH_3PCl_2, 0.3 g of copper stearate, and 50 mL of hexane was allowed to stand at room temperature for 26 days. The solid adduct was recovered by filtration and hy-

(23) Obtained on an aged sample that had acquired some extra signals. Only those signals matching the 15-MHz spectrum taken on a fresh specimen are recorded.

(24) Paquette, L. A.; Melega, W. P.; Kramer, J. D. *Tetrahedron Lett.* **1976**, 4033.

drolyzed by addition to a solution of $NaHCO_3$ in ice–water. The solution was extracted with six 100-mL portions of $CHCl_3$. The extracts were dried ($MgSO_4$) and concentrated to leave a residue of 16.6 g (68%) of a mixture of isomeric phospholene oxides. The mixture was distilled at 132–135 °C (0.7 mm). ^{31}P NMR signals for the mixture were recorded at δ 70.48 (**13**, major), 68.55 (**17**, minor), 65.37 (**15** or **16**, major), 65.17 (**15** or **16**, major), 62.78 (**14**, intermediate), and 61.49 (**18**, minor).

Cycloadditions of 4-*tert*-Butyl-1-vinylcyclohexene with CH_3PCl_2. Copper stearate (0.2 g), 10.5 g (0.064 mol) of diene **1b**, 6.25 mL (0.07 mol) of CH_3PCl_2, and 200 mL of hexane were combined and allowed to stand for 32 days at room temperature. The solid adduct was then collected by filtration (^{31}P signal in $CDCl_3$ at δ 106.5) and hydrolyzed with $NaHCO_3$–ice-cold water. The aqueous solution was extracted continuously with $CHCl_3$ overnight. The resulting $CHCl_3$ extract was dried ($MgSO_4$) and concentrated by rotary evaporation to yield 1.5 g (10%) of **20** and **21** as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.95 (s, $C(CH_3)_3$), 1.63 (d, $^2J_{PH}$ = 12 Hz, PCH_3); ^{31}P NMR ($CDCl_3$) δ 66.2, 66.6 (1:1).

Anal. Calcd for $C_{13}H_{23}OP$: C, 69.00; H, 10.24; P, 13.69. Found: C, 69.01; H, 10.47; P, 14.07.

In another experiment, 0.5 mL each of diene **1b**, CH_3PCl_2, and $CDCl_3$, with a trace of copper stearate, were mixed in a 5-mm NMR tube; the ^{31}P NMR spectrum was measured directly at intervals over a 240-h period. Some ^{31}P shifts observed are recorded in the text.

Registry No. **1a**, 23985-33-3; **1b**, 33800-81-6; **1b** maleic anhydride adduct (isomer 1), 82189-08-0; **1b** maleic anhydride adduct (isomer 2), 82189-09-1; **4**, 82149-59-5; **5**, 82149-60-8; **6**, 82149-61-9; **7**, 82149-62-0; **8**, 82149-63-1; **9**, 82149-64-2; **10**, 82149-65-3; **11**, 82167-35-9; **12**, 82189-51-3; **13**, 82149-66-4; **14**, 82189-10-4; **15**, 82149-67-5; **16**, 82149-68-6; **20**, 82149-69-7; **21**, 82149-70-0; SO_2, 7446-09-5; $MePCl_2$, 676-83-5; tetracyanoethylene, 670-54-2; maleic anhydride, 108-31-6.

Synthesis of Agarofurans by Cyclization of 10-Epieudesmene-3,11-diols

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The course of the direct cyclization of 10-epi- and 14-nor-10-epieudesm-4-ene-3,11-diols (**2**, **5**) to α-agarofuran (**1**) and its derivatives has been investigated in detail. The reaction of 10-epieudesm-4-ene-3α,11-diol (**9**) with Jones reagent, *p*-toluenesulfonic acid, diethyl azodicarboxylate–triphenylphosphine, or *p*-toluenesulfonyl chloride affords **1** in variable yields. The 3-epimer of diol **9** (**8**) also affords **1** under similar conditions. The 14-nor analogues of diols **8** and **9** (**12**, **13**) were prepared and have been found to afford 14-nor-α-agarofuran (**14**) with *p*-toluenesulfonic acid and to afford mixtures containing variable amounts of **14** with Jones reagent. The preparation in good yield of 14-nor-9-oxo-α-agarofuran (**4**), an intermediate in the synthesis of polyhydroxyagarofurans, is described. The stereochemistry of diols **8** and **9** has been confirmed, and a variety of minor reaction products from the cyclizations reactions have been characterized.

Following the clarification of the structure and first synthesis of α-agarofuran (**1** Chart I) by Barrett and Buchi,[1] several other syntheses have been described.[2] Among the more convenient of these is the direct conversion of a 10-epieudesm-4-ene-3,11-diol of unspecified stereochemistry (**2**) to α-agarofuran by treatment with either mild acid[2b] or Jones reagent.[2d] In recent work from this laboratory, the latter procedure was used successfully for the preparation of 9-oxo-α-agarofuran (**3**), a key intermediate in the synthesis of polyhydroxyagarofurans derived from plants of the family Celastraceae. However, the conversion of the corresponding triol to 14-nor-9-oxo-α-agarofuran (**4**), a possible intermediate in an alternative approach to the natural products, proceeded in only 15% yield.[3] On the basis of the data available there appeared to be no a priori reason for the differences in the course of the reactions leading to oxoagarofurans **3** and **4**; however, there had also been no definitive study of the stereoelectronic aspects of these cyclizations. In order to gain some insight into the course of these reactions as a function of the stereochemistry of the allylic hydroxyl group at C-3 and the substitution of C-4, we undertook an investigation of the behavior of both isomers of 10-epieudesmene-3,11-diol (**2**) and 14-nor-10-epieudesmene-3,11-diol (**5**) toward mild acid and Jones reagent. The results of this study are summarized in Table I.

Table I. Conversion of 10-Epieudesmene-3,11-diols to Agarofurans

		products (% yield[a])	
diol	reaction conditions	agarofuran	other
9	Jones reagent	**1** (34)	**10** (27)
9	HOTs, benzene	**1** (56)	**11** (28)
9	DEAD, triphenylphosphine[b]	**1** (48)	
9	TsCl, pyridine	**1** (63)	
8	Jones reagent	**1** (35)	**10** (19)
8	HOTs, benzene	**1** (75)	**11** (21)
12	Jones reagent	**14** (5)	**15** (14)
12	HOTs, benzene	**14** (60)	**16** (15)
12	DEAD, triphenylphosphine[b]	**14** (53)	
13	Jones reagent	**14** (39)	**17** (47)
13	HOTs	**14** (49)	**16** (44)

[a] Isolated yields. [b] Reference 13.

Metal hydride reducation of enone **6**, or the corresponding 11,12-epoxide, has been reported to afford mixtures of the epimeric 3-ols,[2a,b,5] one of which has been isolated and tentatively assigned 3α (quasi-equatorial) stereochemistry.[5] Precedent in similar systems would seem

(1) Barrett, H. C.; Buchi, G. *J. Am. Chem. Soc.* **1967**, *89*, 5665.

(2) (a) Marshall, J. A.; Pike, M. T. *J. Org. Chem.* **1968**, *33*, 435. (b) Asselin, A.; Mongrain, M.; Deslongchamps, P. *Can. J. Chem.* **1968**, *46*, 2817. (c) Heathcock, C. H.; Kelly, T. R. *Chem. Commun.* **1968**, 267. (d) Huffman, J. W.; Miller, C. A.; Pinder, A. R. *J. Org. Chem.* **1976**, *41*, 3705. (e) Buchi, G.; Wuest, H. *Ibid.* **1979**, *44*, 546.

(3) Huffman, J. W.; Hillenbrand, G. F. *Tetrahedron Suppl.* **1981**, *No. 9*, 269.

(4) Some years ago, an investigation of these reactions as a function of the stereochemistry at C-3 was said to be forthcoming;[2b] however, to the best of our knowledge, the results have not been reported.

(5) Miller, C. A. Ph.D. Dissertation, Clemson University, 1976. The authors are indebted to Dr. A. R. Pinder for making available to them various samples and spectra of Dr. Miller's samples.

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