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Diastereoselection and diastereofacial selection in 5-(3,4) ene cyclizations: Recent studies and applications in organic synthesis

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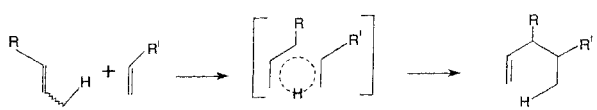
Abstract

Stereoselectivities in the thermal and Lewis acid-catalysed 5-(3,4) ene cyclizations of 1,6-dienes activated by one or two electron-withdrawing groups on the enophile are studied. Inadequacy of Houk's force field model to explain the preponderance of *trans* products is discussed. High diastereoface selectivity is observed in ene cyclizations of 1,6-dienes carrying a silyloxy group in the tether. The ene adducts with a strategically placed trimethylsilyl group in the olefinic side chain are of value as exemplified by the synthesis of (±)-hirsutene and (±)-methyl cucurbate.

Key words: Ene cyclization, stereochemical control, force field model, cyclopentanoid allylsilanes, natural product synthesis.

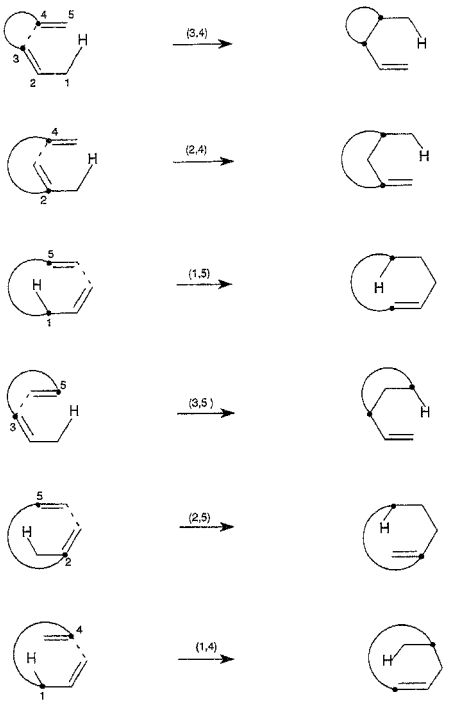
1. Introduction

Although the ene reaction has been around for over five decades, it has become part of the mainstream of organic chemistry only in recent years. In particular, the intramolecular variant of this reaction has emerged as an efficient tool for the preparation of carbo- and heterocyclic cyclopentanes in a regio- and stereoselective manner. Formally, the ene reaction represents a concerted six-electron process involving the transfer of a proton from an olefin carrying an allylic hydrogen, which acts as a donor (ene) to a double or triple bond (enophile), which acts as acceptor, to form a 1:1 adduct (Scheme 1).



SCHEME 1.

In the intramolecular case where R and R' are joined, six different modes of cyclization are possible depending on the positioning of the tether linking the one donor and acceptor (Scheme 2)[1]. Of these, (3.4) ene reactions are by far the most studied, especially for five-membered ring-forming reactions.



SCHEME 2.

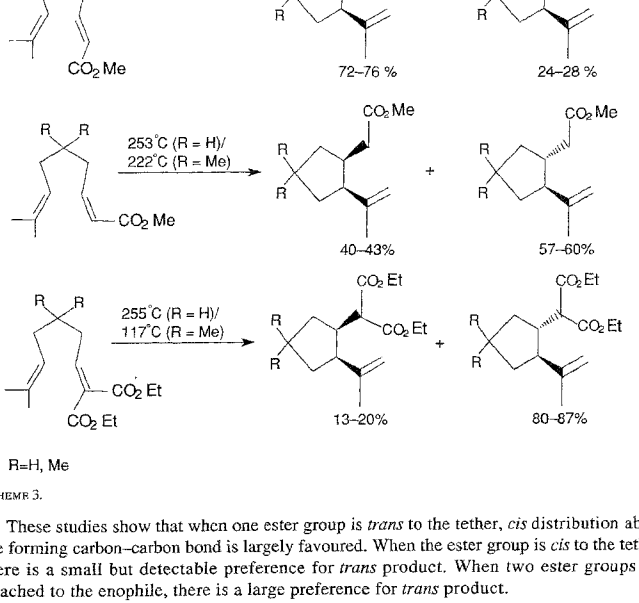
The various facets of intramolecular ene reactions including thermal, Lewis acid-catalysed and metallo-ene processes have been comprehensively reviewed[1–5]. However, in spite of the notable advances in this area. It is apparent that the stereochemistry of intramolecular ene reactions has not been fully explored compared with the mechanistically related intramolecular Diels–Alder reactions. In order for the intramolecular ene reaction to become an accepted basic strategy for the construction of complex molecules, it is important to have data regarding structural features which primarily influence the rate of cyclization and structural features which primarily influence transition state selection leading to stereoselectivity. These considerations led us to initiate a systematic study of the ene reactions in the mid-1980s. The present paper summarizes the significant progress made in the area of thermal and Lewis

acid-catalysed 5-(3,4) ene cyclizations. The work is presented in a chronological fashion as it progressed and some discussion of other very relevant studies is also included.

2. Diastereoselection in 5-(3,4) ene cyclizations

2.1. Unusual formation of trans-1,2-disubstituted cyclopentanes

In general, (3,4) ene cyclizations exhibit high level of diasteroselection over two ring-stereogenic centres. *Cis* diastereomers are usually obtained predominantly or exclusively in 5-membered ring-forming processes. Some sporadic examples involving educts featuring a heteroatom in the tether are also known where either total lack of selectivity[6–8] or predominant or exclusive *trans* selectivity[8–10] have also been recorded. As part of a synthetic approach toward cyclopentanoid natural products, we have recently investigated the effects of electron-withdrawing groups and geminal substituents on the diastereoselectivities and rates of thermal 5-(3-4) ene cyclizations. The results are summarized in Scheme 3[11].

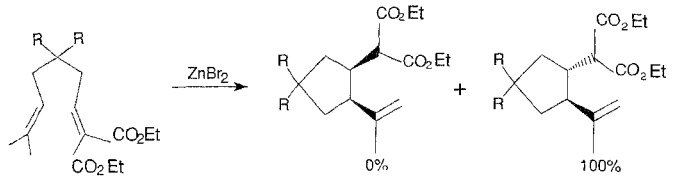


R=H, Me

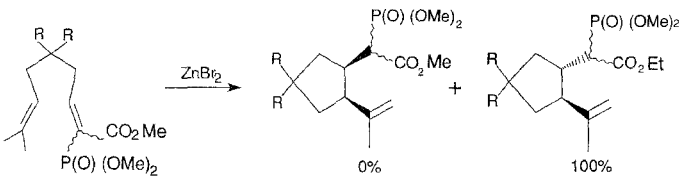
SCHEME 3.

These studies show that when one ester group is *trans* to the tether, *cis* distribution about the forming carbon–carbon bond is largely favoured. When the ester group is *cis* to the tether, there is a small but detectable preference for *trans* product. When two ester groups are attached to the enophile, there is a large preference for *trans* product.

When the same alkylidene malonates (*cf.* Scheme 3) and related 2-phosphonoacrylates were exposed to anhydrous $ZnBr_2$ in methylene chloride at ambient temperature, exclusive formation of *trans*-1,2-disubstituted cyclopentanes were observed (Scheme 4)[12]. This structural unit is present in many well-known natural products such as prostaglandins, brefeldin and chokol-A. Furthermore, the propensity of 2-phosphonoacrylate moiety to act as active enophilic partner in intramolecular ene reactions was demonstrated for the first time. In addition, the organophosphonates produced in the ene reactions were shown to be useful intermediates for the synthesis of α, β-unsaturated esters *via* the phosphonate modification of the Wittig reaction (Scheme 5)[12].



R=H, Me



R=H, Me

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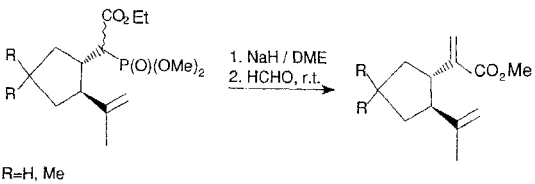
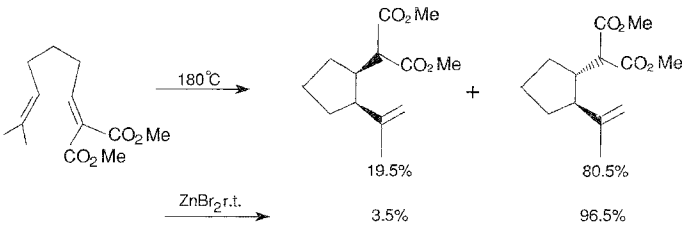


R=H, Me

SCHEME 5.

In an independent, but comprehensive study, Tietze *et al*[13] have also found a large preference for *trans* product in a similar system (Scheme 6).



SCHEME 6.

The preponderance of *trans* products in the above-mentioned examples (Schemes 3 & 4) is unusual in the light of recent theoretical studies[14] on intramolecular ene reactions which predict the formations of *cis*-1,2-disubstituted cyclopentanes from 1,6-dienes.

Loncharich and Houk[14] reported the RHF/3-21G transition structure of the parent ene reaction between propene and ethene as shown in Fig.1. The transition state geometry resembles that proposed by Hoffmann[15], although the C–H–C angle is 156°, not 180°. The transition structure is characterized as an envelope conformation. Detailed examination of the transition structure (Fig. 1) has led to an understanding for the preference of the substituents about the new carbon–carbon bond to be *cis* upon five-membered ring formation in intramolecular ene reactions with unactivated enophiles. It has been shown that the dihedral angles H–C–C–H (where the hydrogens are to be replaced by the tether and the carbons are

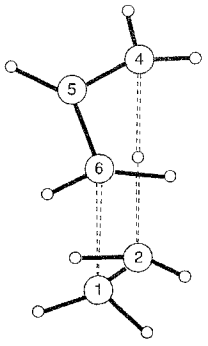


Fig. 1. A view of the RHF/3-21G transition structure of the propene ethene ene reaction (from Loncharich and Houk[14]).

those of the forming carbon–carbon bond) corresponding to the *cis* product are 38 and 39° while the dihedral angles corresponding to the *trans* product are 77 and 154° (Fig. 2)[14]. Using molecular mechanics it has been shown that a stretched cyclopentane prefers to have a C–C–C–C dihedral angle of 0° about the stretched bond[14]. In forming the cyclopentane, the *cis* transition structures (NC, XC) require much less adjustment of the parent transition structure upon substitution of the tether than does the *trans* transition structures (NT, XT). Thus, the transition structures leading to the *cis* product are more stable than those leading to the *trans* product and hence the *cis* product should be the preferred product. This is in accord with experimental results.

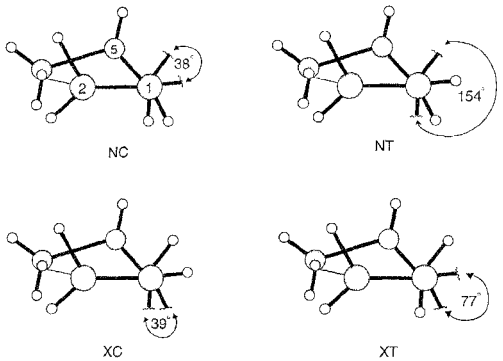
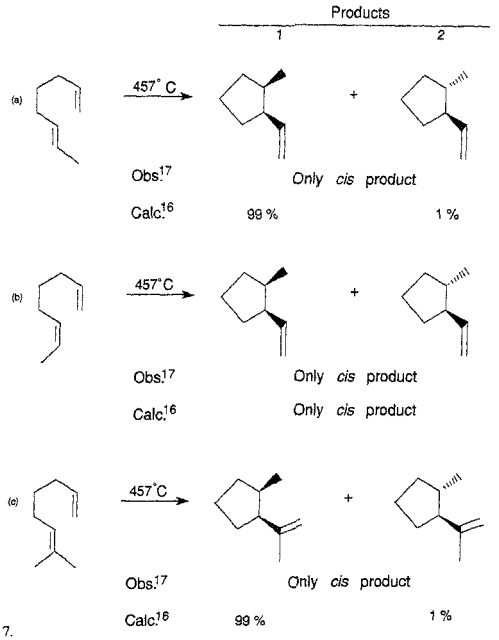


Fig. 2. Four transition structures of an intramolecular ene reaction with an achiral tether where the broken bonds indicate the site of attachment of the tether. Each T.S. is identified by a two-letter acronym, with the first letter indicating whether the tether is *exo* or *endo* at C1 with respect to C5, while the second letter indicates the resulting *cis* or *trans* stereochemistry about the forming carbon–carbon bond (from Loncharich and Houk[14]).

A further development[16] in this area is a modification of Allinger's MM2 force field which models the transition structures of intramolecular ene reactions and qualitatively predicts the ratios of the products formed in reactions of substituted compounds. Scheme 7 and Table I give results where the rigid transition structure model reproduces the stereochemical trends observed for some intramolecular 5-(3,4) ene cyclizations.

In the case of (Z)-1,6-octadiene, only the XC and NT transition structures are possible. XC is much more stable (Fig. 2). For (E)-1,6-octadiene, the NC and XT transition structures lead to two possible products. NC is more stable by 6.6 kcal/mol. In the case of 7-methyl-1,6-octadiene, all four transition structures are possible. NC and XC are separated by 0.6 KCal/mol. XC is more stable. XT is the only low-energy *trans* transition structure possible, but it is still 5.6 kcal/mol higher in energy compared to XC. In all these cases theoretical predictions tally well with experimental results.



SCHEME 7.

The force field, however, gives very poor results with activated enophiles. For example, reactions of a number of 1,6-dienes were examined by Thomas *et al* [16] (Scheme 8, Table II). Although the force field predicts that the products with *cis* stereochemistry about the new carbon–carbon bond should be the major product in all the cases, results (*cf.* Scheme 3) from this laboratory[11]) indicate this not to be true.

These results obviously imply that the geometries of the transition structures for the ene reaction of alkenes with activated enophiles are different from the transition structure of the propene ethene reaction. These discrepancies led Thomas *et al*[16] to undertake a detailed *ab initio* MO calculations on the ene reaction of acrylonitrile with propene to understand how the geometry of the transition structure changes on going from unactivated enophile to an activated enophile. *Thomas et al*[16] *have concluded that a flexible model needs to be developed in place of the rigid model in order to explain stereoselectivities of 5-(3,4) ene cyclizations with activated enophiles.*

Table I

Steric and relative energies (kcal/mol) of transition structures for 5-(3,4) ene cyclizations of unactivated 1,6-dienes[16]

Educt	*Transn struct*	*Steric energy*	*Rel energy*	*Product*
(a) (*E*)-1,6-Octadiene	NC	7.9	0.0	1
	XT	14.5	6.6	2
(b) (*Z*) 1,6-Octadiene	NT	106 3	97.7	2
	XC	8.6	0 0	1
(c) 7-Methyl-1,6-octadiene	NC	9.2	0.6	1
	NT	106.2	97 6	2
	XC	8.6	0 0	1
	XT	14.2	5.6	2

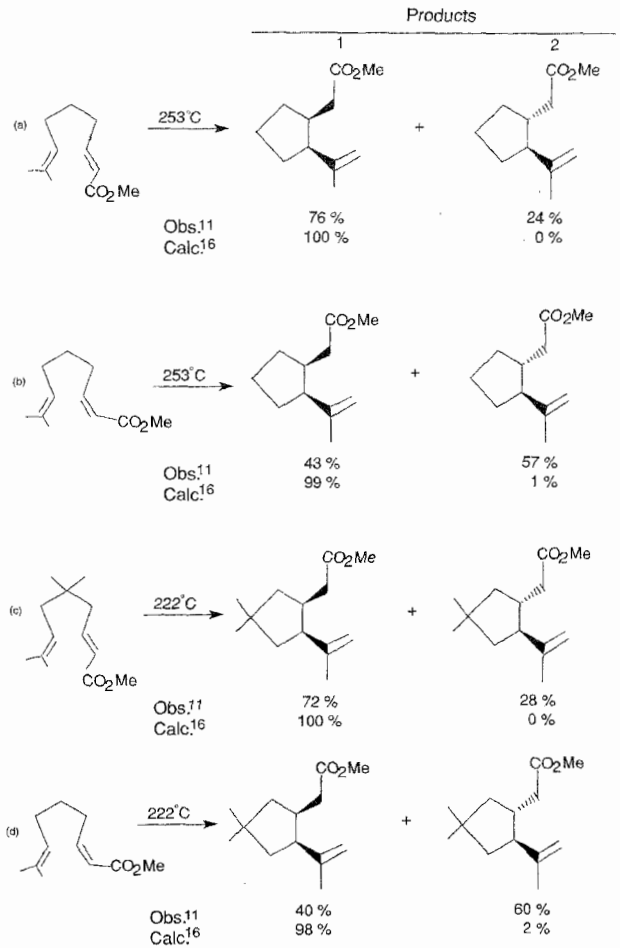
Table II

Steric and relative energies (kcal/mol) of transition structures for 5-(3,4) ene cyclizations of activated 1,6-dienes[16]

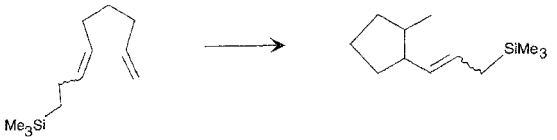
	Educt	*Transn struct*	*Steric energy*	*Rel energy*	*Product*
(a)	(*E*)-8-Methyl-2,7-octadienoic acid 1-methyl ester	NC	44.3	0.0	1
		NT	144.6	100.3	2
		XC	48.5	4.2	1
		XT	52.6	8.3	2
(b)	(*Z*)-8-Methyl-2,7-octadienoic acid 1-methyl ester	NC	47.5	0.0	1
		NT	143.5	96.0	2
		XC	48.3	0.8	1
		XT	51.6	4 1	2
(c)	(*E*)-5,8,8-Trimethyl 2,7-octadienoic acid 1-methyl ester	NC	45.7	0 0	1
		NT	147.2	101 5	2
		XC	51.1	5.4	1
		XT	53.6	7.9	2
(d)	(*Z*)-5,8,8-Trimethyl 2,7-octadienoic acid 1-methyl ester	NC	49.3	0.0	1
		NT	146.3	97 0	2
		XC	50 6	1.3	1
		XT	52.7	3.4	2

2.2. *Cyclopentanoid allylsilanes in synthesis*

(3,4) ene cyclizations usually lead to 1,2-disubstituted ring systems containing at least one double bond in the side chain. When the newly created olefinic unit is 1,1-disubstituted (*e.g.*, isopropenyl group), direct elaboration of the ene product is possible, namely, *via* a Prins reaction or a Friedel–Crafts reaction as has been done in the elegant total synthesis of several polycyclic natural products[18,19]. In an effort to make direct use of the otherwise unreactive π bond, we were intrigued by the idea of introducing a TMS group in a strategic position on the 1,6-diene and to effect its cyclization leading to the ene product which now incorporates a reactive as well as highly versatile allylsilane group in the side chain (Scheme 9).

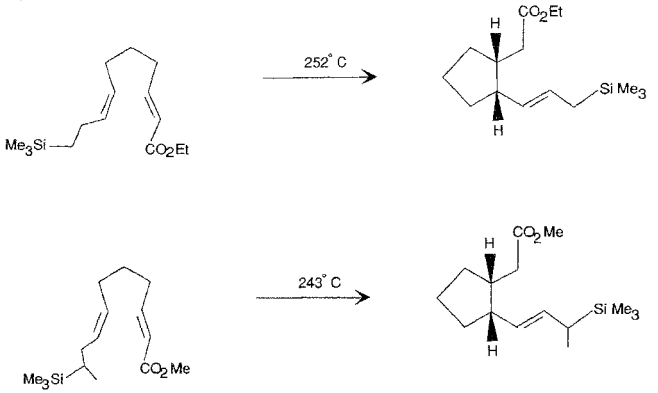

Products
1
2
(a)
253°C
CO2Me
CO2Me
+
Obs.[11]
Calc.[16]
76 %
100 %
24 %
0 %
(b)
253°C
CO2Me
CO2Me
+
Obs.[11]
Calc.[16]
43 %
99 %
57 %
1 %
(c)
222°C
CO2Me
CO2Me
+
Obs.[11]
Calc.[16]
72 %
100 %
28 %
0 %
(d)
222°C
CO2Me
CO2Me
+
Obs.[11]
Calc.[16]
40 %
98 %
60 %
2 %

SCHEME 8



SCHEME 9.

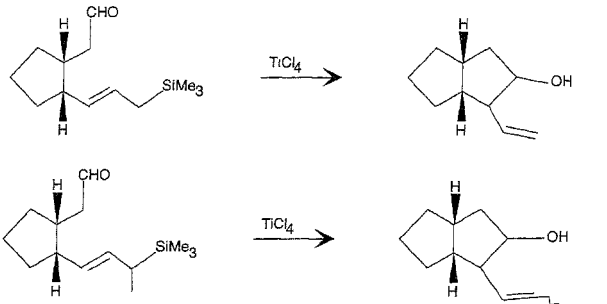
This goal was realized when a series of 1,6-dienes containing a homoallylsilane unit as the ene donor underwent highly diastereoselective cyclization to give the desired cyclopentanoid allylsilanes in high yield (Scheme 10)[20]. As the reactions were run at considerably lower temperatures (< 500°C), there was no untoward scrambling[21] of the allylsilane moiety in the ene product.



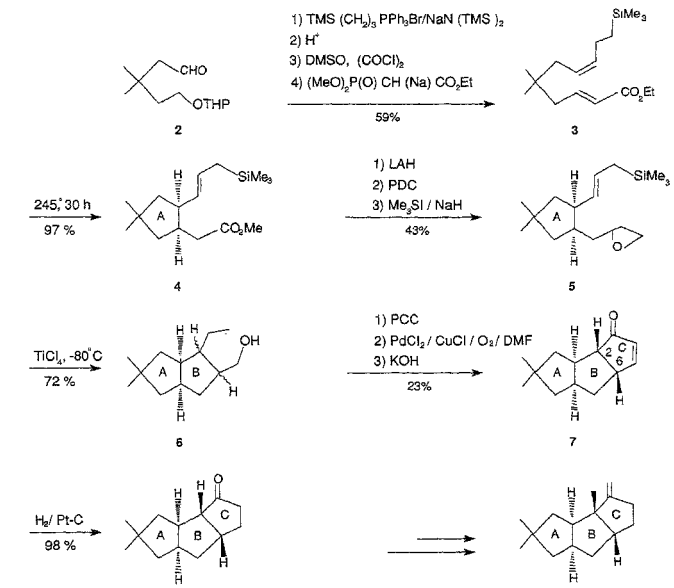
SCHEME 10.

The reactivity of the allylsilane group in the ene products was nicely demonstrated by smooth ring closure of the derived aldehydes to functionalized diquinanes (Scheme 11)[20].

After these initial studies it was the challenge of natural product synthesis which spurred the most relevant exploration of the utility of cyclopentanoid allylsilanes in synthesis . We selected hirsutene **1** (Scheme 12) as the initial target molecule[22,23]. Incidentally, hirsutene has served as a prototype for the synthesis of linear polyquinanes and has frequently been used to illustrate newer methods for construction of condensed cyclopentane rings. To this end, in the first key step **3**→**4**, the cyclopentanoid allylsilane was formed with high stereochemical control. Conversion of **4** to **5** set the stage for the $TiCl_4$-induced epoxy-allylsilane ring closure which furnished **6** as a mixture (42: 50: 8) of stereoisomers. Lack of diastereoselection in this



SCHEME 11.



SCHEME 12.

case was of little importance since the remaining closure of ring C was accomplished by an intramolecular aldolization with thermodynamic control over the configuration at C2 and/or C6. Therefore, the mixture **6** was channelized efficiently into the well-known hirsutene intermediate **8**, thus completing a formal synthesis of (±)-hirsutene (**1**)[22,23]

3. Diastereofacial selection in 5-(3,4) ene cyclizations

When the ene educt contains one or more chiral centres on the tether, a new complexity is introduced, Rather than just two (*cis vs trans*) possible products from the cyclization, there are now four. Thomas *et al*[16] have made a theoretical study of the topological influence over developing stereogenic centres in the 5-(3,4) ene reaction of a number of 1,6-dienes (Scheme 13, Table III). It is clear that the force field correctly predicts the major product as well as the order of preference of the minor products in the case of unactivated enophiles as before (*cf.* Scheme 7 and Table I).

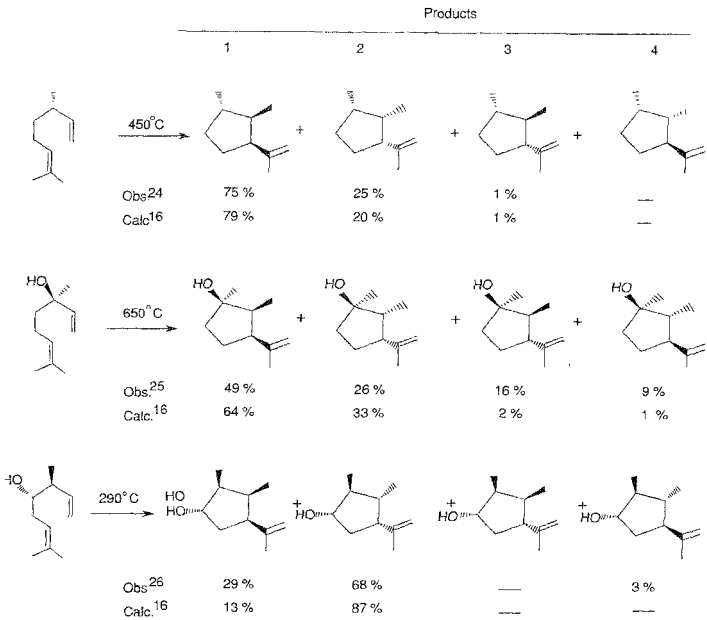
Analysis of the eight possible transition structures for the ene reaction of (3*S*)-3,7-dimethyl 1,6-octadiene (Scheme 13) provides an explanation of why one product is favoured over another. Transition structures NC and NCB indicate the attack of alkene on different faces of the enophile (Fig. 3). NC gives the major and NCB the minor *cis* products. The striking difference between these transition structures is that in NC the methyl group on the tether is pseudoequatorial, while in NCB it is pseudoaxial. Obviously, NC is the lower energy transition structure. For the other pairs of transition structures the situation remains much the same. XTB with a pseudoequatorial methyl group is the lowest energy transition structure leading to a *trans* product, whereas in XT the methyl group is pseudoaxial.

Diastereoface selectivity in 5-(3,4) ene reactions for both carbo- and heterocyclization has been studied on 1,6-dienes carrying an activated enophile[1]. In general, steric, rather than stereoelectronic effects, determine the extent of diastereofacial selectivity or induced diastereoselectivity (*cf.* Scheme 13, Table III). Impressive applications of stereodirecting bias of a preexisting stereogenic centre in 5-(3,4) ene cyclizations have also been recorded in the area of natural product synthesis[1]. Although most reports so far have dealt with the influence of a methyl substituent on the tether, the influence of an oxygen substituent as a stereodirecting resident group in the ene and/or enophilic compartment has not been

Table III

Steric and relative energies (kcal/mol) of transition structures for 5-(3,4) ene cyclizations of unactivated 1,6-dienes

Educt	*Transn struct*	*Steric energy*	*Rel energy*	*Product*
(3*S*)-3,7-Dimethyl-	NC	9.0	0.0	1
1,6-octadiene	NCB	10.9	1.9	2
	NT	105.1	96.1	3
	NTB	109.5	100.5	4
	XC	11.3	2.3	2
	XCB	9.2	0.2	1
	XT	16 3	7.3	4
	XTB	14.1	5.1	3



SCHEME 13.

systematically investigated. It seems likely that reports on mechanistically related Diels–Alder reactions which indicate that lesser steric bulk of an alkoxy group makes it less effective than an alkyl group for diastereoinduction[4] have discouraged work in this area.

Prompted by the ubiquitous occurrence of hydroxyl-bearing chiral centres in cyclopentanoid natural products, we have recently studied this facet of 5-(3,4) ene cyclizations[27]. The results are summarized in Scheme 14. In this work, silicon protection of the hydroxyl group was deemed important for two reasons. Firstly, in the thermolytic runs the free hydroxyl group caused extensive decomposition of the starting dienes. Secondly, the hydroxyl group is sterically very small when compared to a methyl group which has been used in previous studies of diastereoface selectivity in 5-(3,4) ene cyclizations[1]. For example, the A value for a methyl group is 1.8[28] while that for a hydroxyl group is 0.5[29] in non-aqueous solutions. It

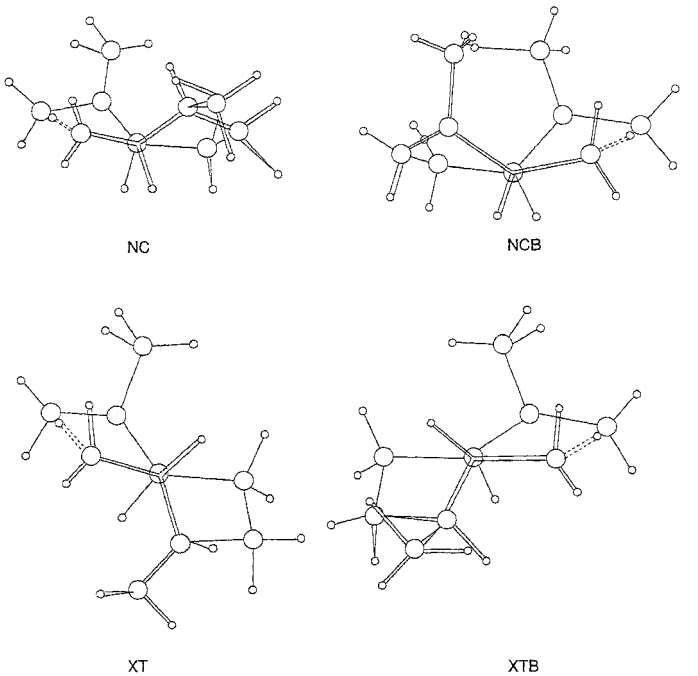
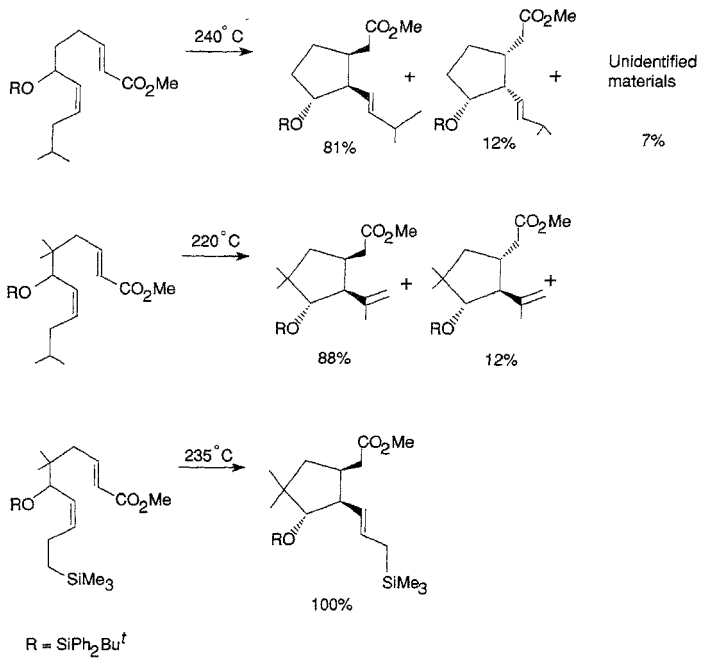


Fig. 3. Transition structure of the 5-(3,4) ene cyclization of (3*S*)-3,7-dimethyl-1, 6-octadiene.

was hoped that a bulky TBDPS group would not only prevent decomposition of ene educts but also enhance the stereoselectivity of the ene cyclization. This prognosis turned out to be correct. The most astonishing result was observed with the 1,6-diene carrying a strategically located TMS group which gave the cyclopentanoid allylsilane in nearly quantitative yield with 100% diastereoselective and 100% diastereoface selectivity!

A culmination of this type of 5-(3,4) ene cyclization methodology has been its ideal application to the diastereoselective and diastereoface selective synthesis of the potent plant growth regulator (±)-cucurbic acid **16**[13] as its methyl ester **15** (Scheme 15)[31].



SCHEME 14.

Thus, the crucial 5-(3,4) ene cyclization **10**→**11** occurred with high diastereoselectivity (99%) and diastereoface selectivity (90%). Protodesilylation gave **12** which was oxidatively cleaved to **13**. Wittig olefination under salt-free conditions furnished **14** which was desilylated to (±)-methyl cucurbate (**15**)[31]. During this step **14**→**15**, the minor stereoisomer carried over from **11** was eliminated presumably as a lactone.

Acknowledgement

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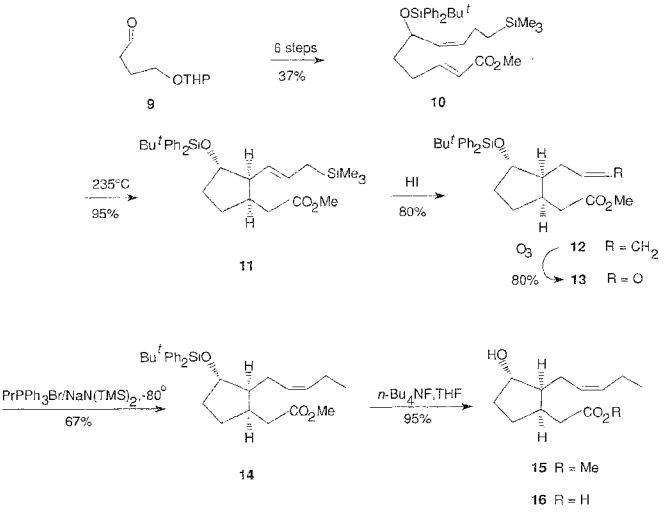

SCHEME 15.

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